# PHOTOCHEMICAL ACCESS TO FOUR MEMBERED HETEROCYCLES

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***Abstract***. *The preparation of strained heterocycles is a significant scientific goal to which organic photochemistry has given a strong contribution since its bird in early XX century. In particular, the seminal work of Emanuele Paternò in 1920s (reworded by George Büchi in early 50's) provided a useful and versatile approach to oxygen containing four membered rings, that in the last years has been re-discovered and extended to the preparation of a wide range of derivatives, including thietanes and azetidine. Reactions can be performed under mild and appealing conditions that involve the use of visible light and continuous flow photoreactors. The most recent advances in this field are resumed in the present chapter.*

**Contents**



## 1. Introduction

Molecules that contain a four membered heterocycle core (such as oxetane, 1,2-dioxetane, azetidine thietane and azetidine) exhibit a wide range of biological activities, and several examples are illustrated in the following sections. Due to the strained structures, such cyclic systems have found also application as building blocks and semi-synthesis products since they have been used as substrates in a wide range of reactions, including ring reorganization (*e.g.* enlargement)[1] and ring opening[2] processes.

Replacement of one or more carbon atoms from cyclobutane structural motif with suitable heteroatom from 2nd and 3rd period of periodic table is on the basis for more than few generations of four-membered ring heterocycles (Figure 1). Indeed, the substitution of one or more carbon atom with a heteroatom furnish to such elusive systems different chemical and biological properties in comparison to the homocarbocyclic analogues.

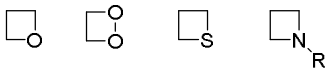



**Figure 1.** Main saturated four membered ring heterocycles.

From the stereo-electronic point of view, the four membered rings are less strained in comparison to the well-known three membered rings[3] in accordance with minimization of the ring strain thanks to the ring deformation for four membered ring systems (Figure 2).

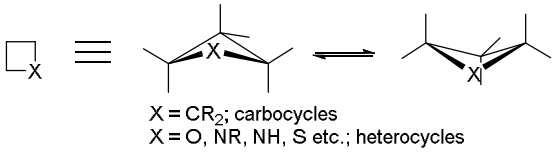



**Figure 2.** General conformation for a four-membered ring.

The thermodynamic features that are directly linked to the were directly linked to the heteroatom(s) present in the ring, have also been reported in the literature. Moreover, from the spectroscopic point of view, the vibrational infrared frequencies for four membered ring heterocycles are affected by value of bond angle strain and shifted toward higher frequencies occur. The C−H stretching vibrations of small ring compounds have higher frequency values from 2900 to 3080 $cm^{-1}$. The stretching frequency of C−H bonds of aziridine and azetidine are 3047 and 2966 $cm^{-1}$ respectively.[4] In the same manner, oxygen and sulfur containing heterocycles exhibit the same influence on the C−H bond stretching value, that was measured in 2928 $cm^{-1}$ and 2959 $cm^{-1}$ for the oxetane and thietane, respectively. The carbon-heteroatom stretching (C−N) frequency present also a higher value. The 2*H*-azirines show C−N stretching frequency at 1800 $cm^{-1}$, while acyclic imines show peaks at 1650 $cm^{-1}$.[5]

As highlighted by Schmidt and co-workers in their review,[6] the synthetic approaches to four membered heterocycles can be classified into three main categories, namely cyclization *via* either carbon-heteroatom or carbon-carbon bond formation, ring rearrangement, and cycloaddition.[7] In this context, photochemistry gave a fundamental contribution in the twentieth century, when innovative strategies for the building of such strained structures *via* photoinduced [2+2]-cycloaddition as well as Norrish-Yang rearrangement have been proposed. Such approaches have been recently revised based on the impressive number of visible light-driven protocols developed in the last decade.

Aim of the present chapter is thus provide the reader with a set of recent photochemical and photocatalyzed approaches to four membered heterocycles proposed in the literature.

## 2. Photochemical synthesis of oxygen containing four membered rings

### 2.1. Photochemical synthesis of oxetanes

The oxetane moiety is a common motif in natural bioactive compounds (some of them illustrated in Figure 3) and as building block widely used in organic synthesis.[8] Furthermore, such strained core has been employed in pharmaceutic research to replace *gem*-dimethyl and carbonyl moiety, and its incorporation has proved to improve several physicochemical properties, including solubility.

As highlighted in a recent and exhaustive review published by D'Auria,[9] the Paternò-Büchi [2+2]-cycloaddition is still the elective approach to build an oxetane core. Recent application of such synthetic platform ranges from material sciences (*e.g.* the cross-linking of styrene-isoprene-styrene copolymer[10] to biology (including the determination of lipids and glycerolipids *via* a Paternò Büchi tagging approach.[11] Also, the nature of excited states and intermediates involved in the formation of both C−O and C−C bonds in the oxetane core still fascinate the researchers.[12] As concerning the recent applications in synthesis, we should mention, among others, the preparation of fluorinated scaffolds from the corresponding alkenes[13] and the multistep enantioselective preparation of hexahydro‑4*H*‑furopyranol, which are P2 Ligand for HIV‑1 Protease Inhibitors.[14] However, UV-light irradiation and a large-excess of the alkene partners (that are even employed also as the reaction medium) are general required[15] and a poor regioselectivity was often observed.

A peculiar strategy has been described by Buendia *et al.* for having access to angular tricyclic 4:4:4 oxetane-containing architectures **1a-c**. Such structures have been obtained through a triple cascade photochemical reaction that involves a [2+2]-cycloaddition between simple alkenes and vinyl ketone derivatives followed by a Paternò-Büchi reaction (Scheme 1).[16]

The use visible and solar light to promote the formation of carbon-carbon and carbon-heteroatom bonds under mild conditions and by using a cheaper and sustainable energy source has attracted in the last decade the scientific community. Most progresses in this field have been certainly based on the impressive contribution of photoredox catalysis and photocatalysis (including photosensitization) to this topic.[17] In this context, as other traditional photochemical reactions, also Paternò-Büchi cycloadditions experienced a perhaps unexpected renaissance. Schindler and co-workers reported a Paternò-Büchi approach to the preparation of oxetanes **3a-c** upon visible light irradiation in the presence of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ as the triplet photosensitizer. By adopting such approach, arylglioxalate esters have been employed as starting substrate for the preparation of differently substituted derivatives, that were obtained in up to quantitative yield (Scheme 2).[18] Notably, Yoon and coworkers demonstrated that when the same process is

performed in the presence of a Lewis acid (*e.g.* $Y(OTf)_3$), an homoallyl alcohol is formed instead of the oxetane *via* a photoredox pathway.[19]

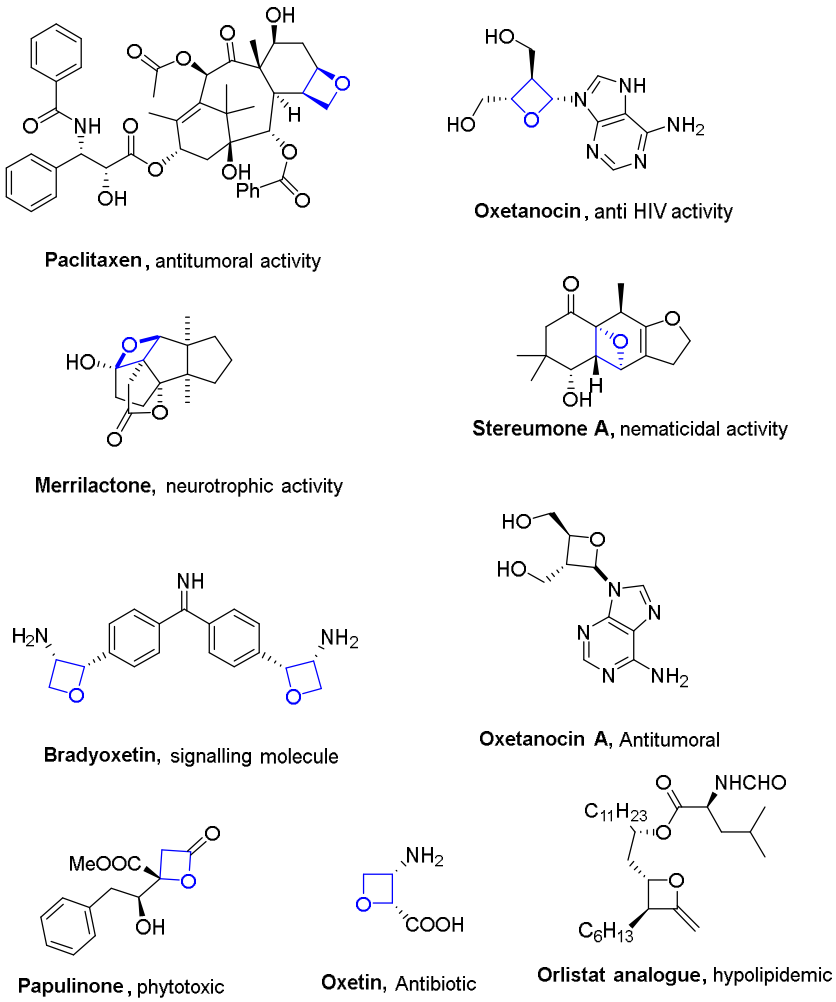
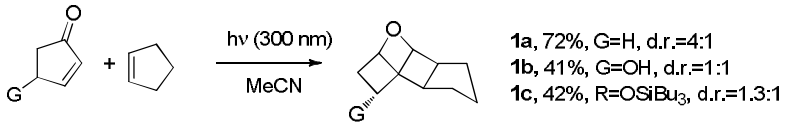
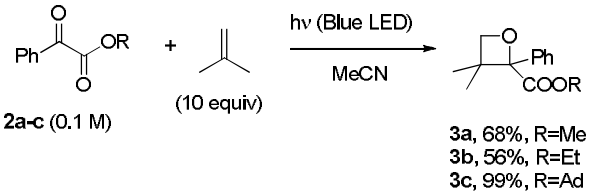



**Figure 3.** Oxetane containing bioactive compounds.

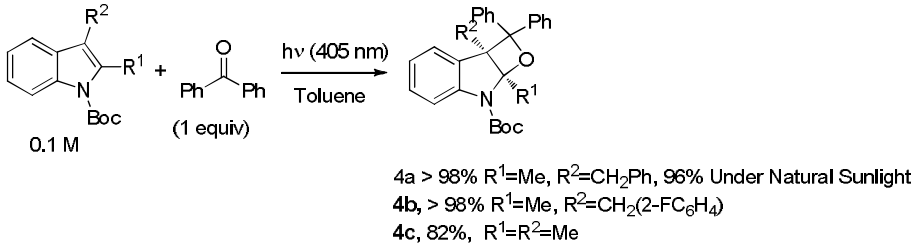



**Scheme 1.** Synthesis of tricyclic 4:4:4 oxetane-containing derivatives **1a-c**.

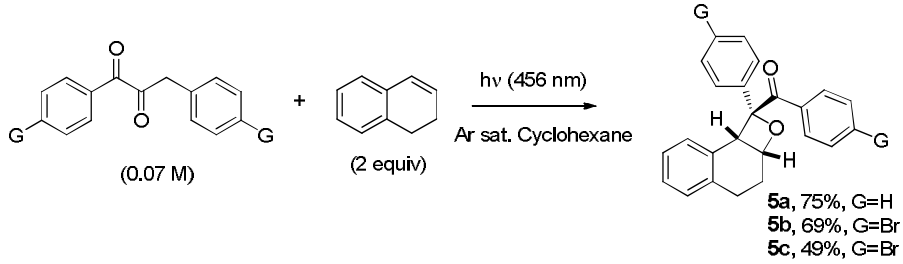



**Scheme 2.** Ir(III) sensitized [2+2]-cycloaddition.

Most recently, however, the interest for the development of (photo)catalyst-free, visible light-promoted protocols has increased. In this case, one of the reactants should be able to absorb in the visible light region. As an example, the Paternò-Büchi cycloaddition has been exploited in dearomatization procedures, for the building of the tetrahydrooxeto[2,3-b]indole scaffold in compounds **4a-c** upon visible or natural sunlight irradiation of indoles in the presence of aromatic ketones. The obtained compounds exhibit up to three contiguous all-substituted stereocenters, and have been obtained in satisfactory yields and high both regio and diasteroselectivity; despite polar medium (*e.g.* acetone) can be used, toluene gave the best results (see some representative examples in Scheme 3).[20] The protocol has been optimized in gram-scale under microfluidic conditions.[21] Analogously, Tinelli *et al.* recently described the preparation of oxetanes **5** in a stereoselective fashion *via* the [2+2]-photocycloaddition between benzils and cyclic olefins (Scheme 4). Interestingly, the use of visible light was found essential for a positive outcome of the process, since irradiation at as shorter wavelengths resulted to a partial decomposition of the desired product. However, when acyclic olefins are used, the predicted oxetane is formed along with several by products, deriving from [4+2]-cycloadditions and hydrogen atom abstraction side-paths.[22]




**Scheme 3.** Visible light driven preparation of tetrahydrooxeto[2,3-b]indoles.

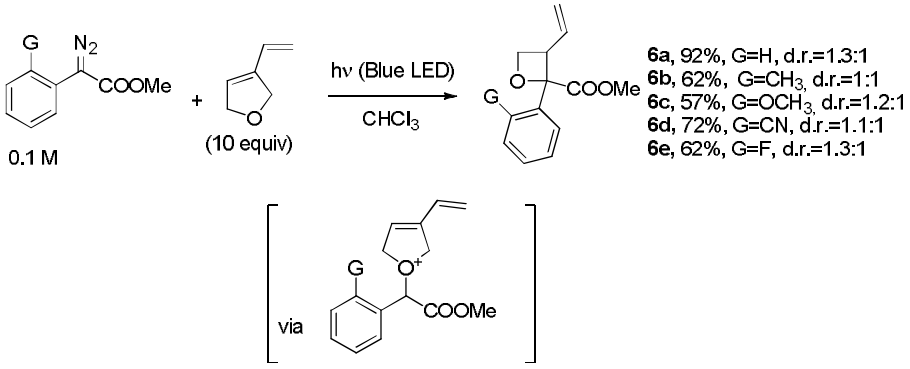



**Scheme 4.** Visible light promoted synthesis of oxetanes **5** from benzyls.

A synthetic approach alternative to [2+2]-cyclization was proposed by Qi *et al.*, who described the coupling between a 2,5-dihydrofuran moiety and diazo compounds, to give the desired 2-aryloxetanes **6a-e** in good to high yields *via* the initial formation of an oxonium ylide intermediate (Scheme 5). The reaction was optimized under both batch and flow conditions.[23]

The [2+2]-photocycloadditions between benzophenone and the olefin moiety in unsaturated lipids recently found application also in clinical analysis for the identification (and the quantification) of

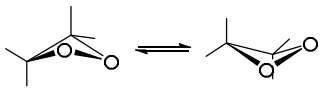
unsaturated fatty acid isomers.[24] The approach has been the subject of a combined q-TOF MS and computational analytic approach, which revealed the formation of a dimeric proton-bonded alkene and carbonyl substrates that can be activated upon visible light irradiation and led to the oxetane products.[25]




**Scheme 5.** Blue light catalyzed synthesis of 2-aryloxetanes **6a-e** *via* α-azoesters.

**2.2. Photochemical synthesis of dioxetanes**

The structure of dioxetanes is less strained in comparison to the corresponding three-membered ring systems such as dioxyranes; the two more stable conformers (which relative stability depends on the sterical hindrance of the substituents) are represented in Scheme 6.



**Scheme 6.** Stable conformations for 1,2-dioxetanes.

The first 1,2-dioxetane structure, namely 3,4-dimethyl-1,2-dioxetane, reported in literature in 1968, was described in a yellow benzene solution, whereas 3,3,4,4-tetramethyl-1,2-dioxetane was isolated some years later as a yellow-crystalline solid that sublimes at low temperatures and decomposes smoothly in benzene solution releasing a blue emission. The peculiar chemiluminescent behavior of 1,2-dioxetanes has been investigated by Turro and co-workers[26] and more recently by Yamaguchi and Saito.[27] The 1,2-dioxetane motif has been observed in different research field, including, among the other, material sciences (*e.g.* the adamantylideneadamantane 1,2-dioxetane, ADOX, (Figure 4).[28] Moreover, it is present as a mechanochemoluminescent unit in polymers of interest in medicinal chemistry,[29] where 1,2-dioxetane derivatives such as **II** (Figure 4) found applications as chemiluminescent probes for diagnosis.[30] Finally the 1,2-dioxetane systems were involved as intermediates in some *in vivo* processes, including the dioxetane pathway in isoprostanoid biochemistry.[31]

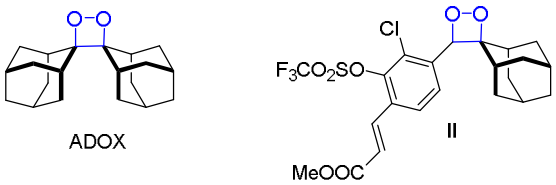
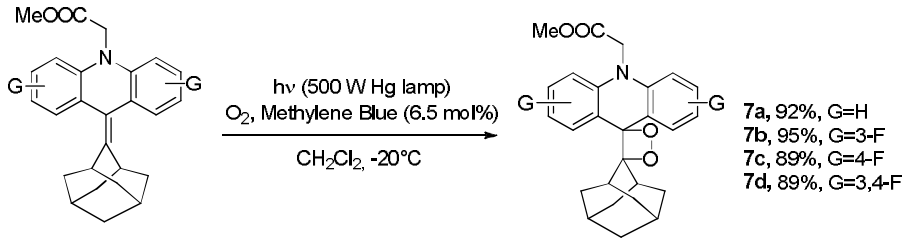



**Figure 4.** Chemiluminescent 1,2-dioxetanes.

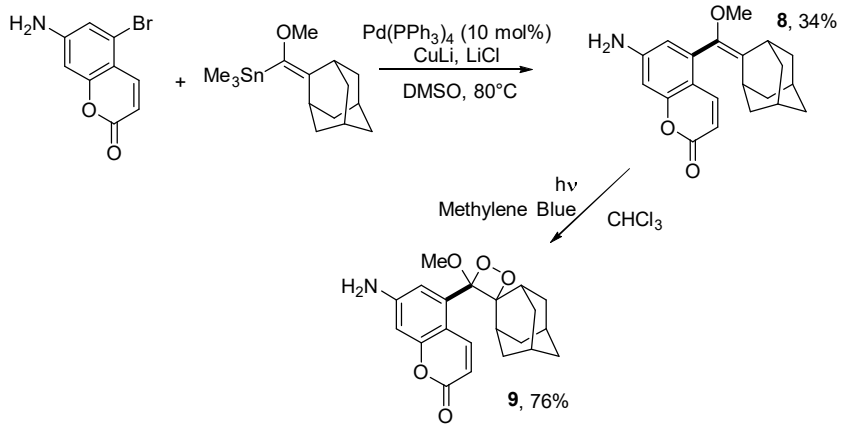
Early attempts devoted to the photochemical preparation of 1,2-dioxetanes have been conducted by Wynberg and co-workers.[32] In the adopted approach, the starting alkenes was irradiated in the presence of

methylene blue as the photosensitizer or treated with triphenylphosphite/ozone complex as source of singlet oxygen, to afford the desired cyclic peroxide in up to 85% yield. The photosensitized approach was then adopted by Adam and co-workers and extended to a variety of substituted olefins.[33] More recently, Roda *et al.* prepared a set of thermochemiluminescent, acridine-containing 1,2-dioxetanes *via* photooxygenation of the corresponding alkenes in dichloromethane at −20°C, using methylene blue as the photosensitizer[34] (**7a-d**, Scheme 7). A similar synthetic approach was previously adopted by the same research group employing a polymer-bound Bengal Rose as the heterogeneous photosensitizing system.[35]

In a similar way, Shabat and co-workers described the preparation and characterization of adamantyl-dioxetane luminophores *via* a two-step protocol that involves a Stille coupling followed by photooxygenation of the so-obtained aryl-adamantyl-enolether. In Scheme 8 is shown the representative synthesis of 7-aminocomarine 1,2-dioxetane **9**.[36]




**Scheme 7.** Synthesis of chemiluminescent 1,2-dioxetanes **7**.




**Scheme 8.** Two-step synthesis of 7-aminocomarine 1,2-dioxetane.

A dioxetane containing chemiluminescent probe was prepared by Sarbat *via* conjugation of a C-terminally activated Ub(1-75) with a Gly-enolether precursor followed by addition of photogenerated singlet oxygen in aqueous solvent.[37]

### 3. Photochemical synthesis of thietanes

Although less famous than other sulfur based heterocycles, thiethanes were proved to be present in several metabolites (see for instance thiathromboxane A2 produced during hemostasis, Figure 5). Furthermore, this core is present in food additives (including the sweetener Alitame) as well as in pesticides other bioactive compounds.

The synthetic strategies to such four-membered ring, which include, among the others, cyclic thioetherification and ring expansion/contraction, have been reviewed by Xu.[38] As in the case of oxetanes, [2+2]-photocycloaddition (the so-called thia-Paternò-Büchi reaction) is considered one of the most useful

approaches to have access to the thietane core, since the first report that appeared in 1969.[39] Recently, however, it was pointed out that the outcome of such photochemical process can be directed by tuning the concentration of the reactant. Indeed, the irradiation of thiobenzophenone (0.13 M) in the presence of an excess of acrylonitrile afforded the desired thietane in 43% yield (Scheme 9, path a); on the other hand, when the reaction was carried out under dilute conditions (0.025 M), the corresponding tetrahydrothiophene was the only product observed (Scheme 9, path b).[40]

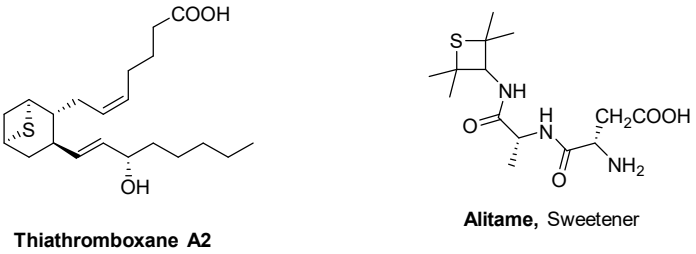
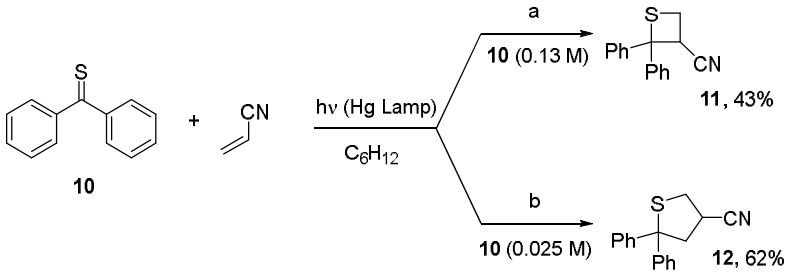
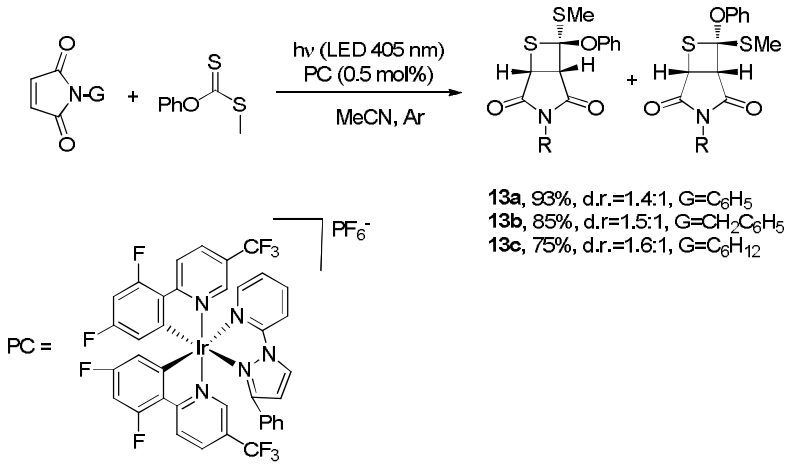



**Figure 5.** Examples of biologically active thietanes.




**Scheme 9.** Concentration dependent synthesis of thietanes and tetrahydrothiophenes.

Recently, great attention has been given to the development of visible light driven processes. For instance, He *et al.* described a Ir(III) photosensitized thia-Paternò-Büchi protocol for the gram-scale preparation of nitrogen-containing bicycles **13** (Scheme 10).[41]




**Scheme 10.** Triplet photosensitized synthesis of **13a-c**.

## 4. Synthesis of four-membered aza-heterocycles

As pointed out by Brandi *et al.* in their review,[42] azetidines and azetidones have received a rather limited attention in synthesis although their leading role in medicinal chemistry. However, apart from the interest for β-lactam rings in view of their use as antibacterial, the azetidine core was found in metabolites (*e.g.* monascumic acids or diazetidomonapyridone, Figure 6), as well as in bioactive compounds.

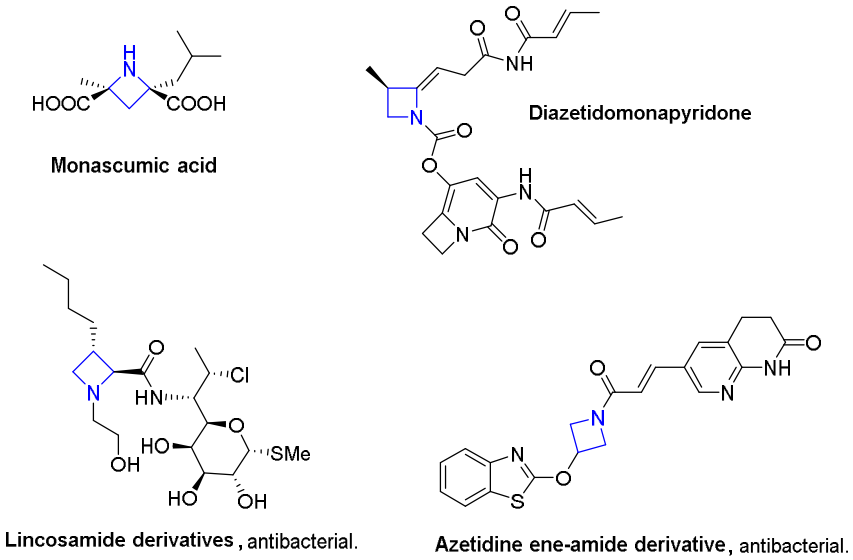



**Figure 6.** Metabolites with azetidine ring.

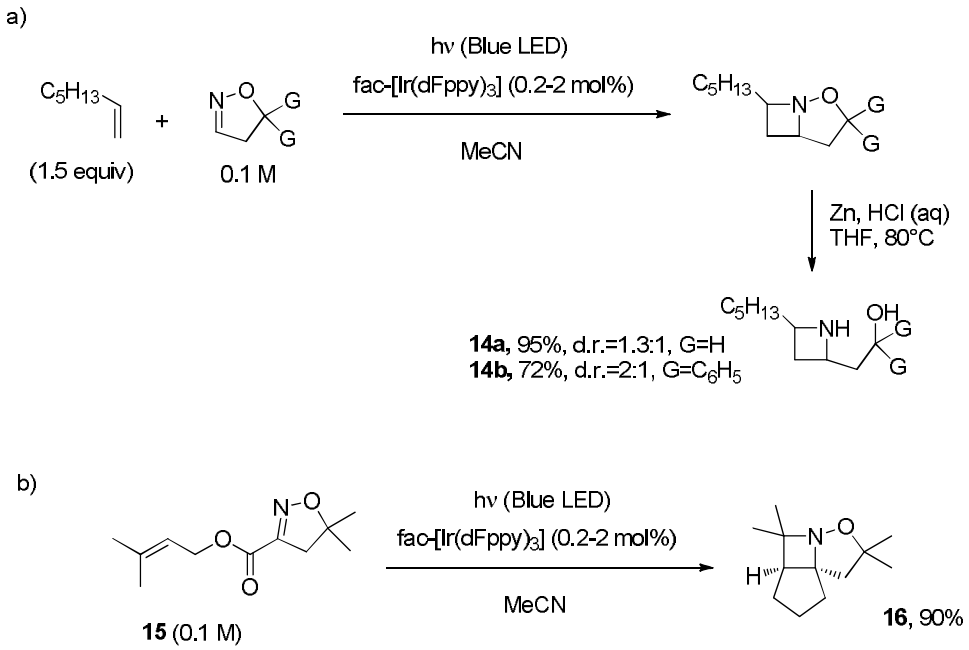
The aza-Paternò-Büchi cycloaddition occurring between an imine (or an imide) moiety and an olefin is considered one of the most useful tools to obtain these strained heterocycles.[43] Schindler and co-worker reported the preparation of 2-isoxazoline-containing derivatives *via* [2+2]-cycloaddition in the presence of *fac*-[Ir(dFppy)$_3$] as the photosensitizer. The obtained products can be smoothly converted under reductive conditions into free azetidines **14** in turn used for further functionalization (Scheme 11a). The same approach has been applied to the preparation of tricyclic azetidines *via* intramolecular cycloaddition occurring in the oxazole **15** (Scheme 11b).[44]

With the aim of further increasing the potentiality of organic photochemistry in enantioselective processes, the group of Bach proposed a visible light-driven stereoselective approach for aza Paternò-Büchi reactions to 2-arylazetidines **17a-d** using a chiral thioxantone as the photoorganocatalyst. The protocol has been successfully applied to both inter- and intramolecular reactions (Scheme 12).[45]

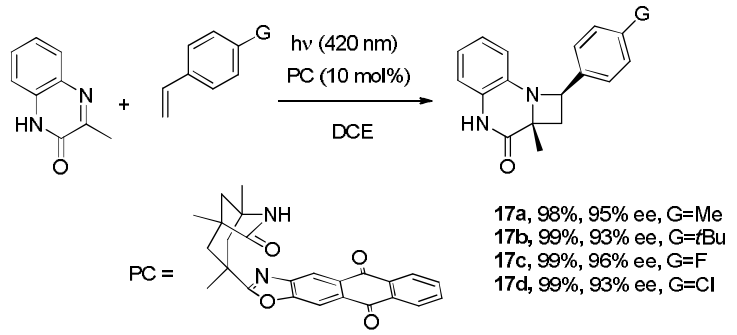
In some cases, a transition metal complex able to activate the olefin *via* a coordination-MLCT pathway was employed. The group of Schmidt exploited the copper-hydrotris(pyrazolyl)borate (Cu-Tp in Scheme 13) catalyzed photocycloadditions of non-conjugated imines and olefins to afford a variety of substituted azetidines **18.**[46] In this case, the formation of a Cu(I)-olefin complex able to absorb light has a key role in the synthesis. An analogous approach has been exploited for the preparation of oxetanes.[47]

Norrish-Yang cyclisation is a reasonable alternative to access azetidines *via* an intramolecular path. 3-Hydroxiazetidines **19** have been obtained in satisfactory yields and under continuous flow conditions from the corresponding sulfonamides, which afforded the diradical **20** in its turn generated *via* intramolecular hydrogen atom transfer followed by radical coupling. The adoption of the flow conditions led to a remarkable reduction of the reaction time from several hours (batch) down to few minutes (Scheme 14).[48]

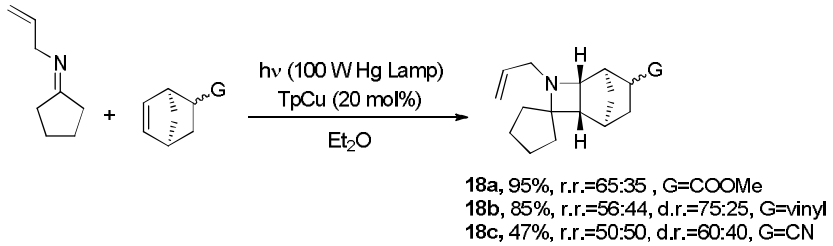
A Norrish-Yang type II photocyclization was also exploited for the preparation of β-lactam rings.[49]



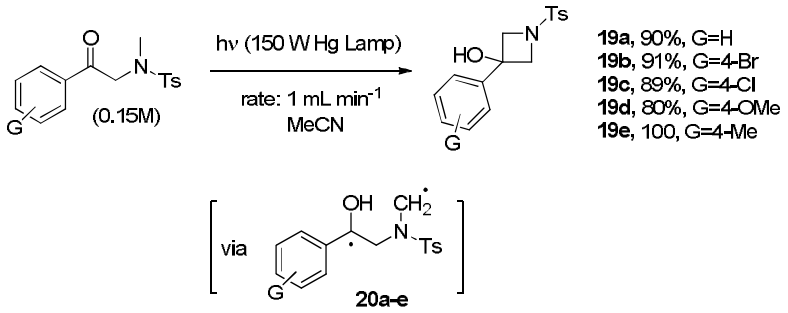

**Scheme 11.** Ir(III) photosensitized synthesis of derivatives **14** and b) o tricyclic compounds **16**.




**Scheme 12.** Enanthioselective photocatalyzed [2+2]-aza-Paternò-Büchi cycloadditions.




**Scheme 13.** Copper-hydrotris(pyrazolyl)borate (TpCu) catalyzed synthesis of bicyclic derivatives **18**.




**Scheme 14.** Photochemical synthesis of 3-hydroxyazetidines **19**.

**5. Conclusions**

A century after the first report on the photochemical [2+2]-cycloaddition between a carbonyl moiety and an alkene, the role of photochemistry in the preparation of four membered heterocycles has become predominant. The recent, impressive advances experienced by photochemistry, photoredox catalysis and photocatalysis spurred for the development of light-driven synthetic protocols that exhibit a large functional group tolerance and versatility. Furthermore, the simple set-up required by the described processes and the use of inexpensive and sustainable visible light as the energy source allows for an easy scalability of the processes and the adoption of continuous-flow conditions.

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