PHOTOCATALYZED PREPARATION OF OXYGENATED HETEROCYCLES

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Abstract. *The synthesis of heterocycles attracts attention among the scientific community, and photocatalytic protocols have emerged as a valuable tool in this area. This peculiar strategy relies on the photocatalyzed formation of ground state high-energy intermediates, affording the desired compounds upon a cyclization step, mostly involving an unsaturated or an aromatic moiety. This is particularly useful for the synthesis of oxygen containing heterocycles. Albeit the formation of oxygenated three or four-membered rings is quite rare, several strategies to build five and six-membered rings, as well as larger heterocyclic rings, are available and have been reported herein. Thus, the synthesis of oxygen heterocycles under the mild conditions typical of the photocatalytic approach represents an added value, in view of the pivotal role of these derivatives in the preparation of more complex target compounds.*

Contents

1. Introduction

Oxygenated heterocycles constitute one of the largest and most remarkable families of heterocyclic compounds, often underestimated both from the synthetic and applicative points of view. Nevertheless, the chemistry regarding their synthesis is as rich as their application in an extraordinary variety of chemical fields.

Indeed, furan ring systems are found in many naturally occurring compounds, either as fully unsaturated structures or as (partially) reduced forms. As an example, furfural, deriving from the acid-catalyzed hydrolysis of cereal waste, is cheaply available on large scale. Hence, the industrial method for preparing furans is unusual in its kind, because it is based on renewable starting materials rather than fossil fuels (or other pollutant sources). Several natural compounds containing a fully unsaturated furan ring are terpenoids, such as rosefuran, found in rose essential oil (Figure 1). On the other hand, the reduced form of furan is the typical key structure of pentose sugars, such as ribose and deoxyribose, well-known moieties present in nucleic acids. Moreover, the unsaturated lactone deriving from furan can be found in different structures, including ascorbic acid (vitamin C).[1,2]

Furans and the related benzo-condensed derivatives also constitute the core of several pharmaceutical compounds. Among the many examples, ranitidine (Zantac) is an important H2-histamine receptor antagonist. Antimicrobials, such as the APIs present in Furin and Niftran, also contain the furan ring. Besides, Lasix is one of the most popular drugs for the treatment of hypertension and hyperplasia (Figure 2).[3]

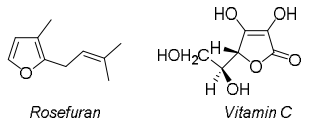


Figure 1. Structures of rosefuran and vitamin C.

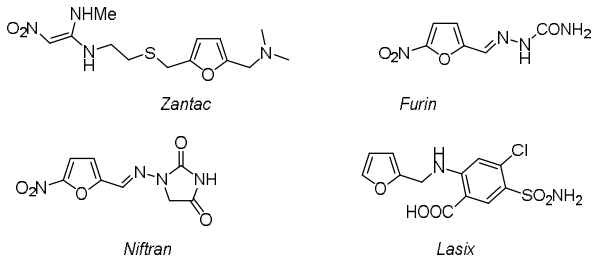


Figure 2. Structures of Active Pharmaceutical Ingredients (APIs) in Zantac, Furin, Niftran and Lasix.

Six-membered oxygenated heterocycles (tetrahydropyrans, chromanes, xanthones, flavanones, etc.) are a common structural motif found in natural products, too. Due to the rich array of functionalities and chiral centers that these heterocycles can incorporate, they are widely recognized as useful building blocks for the synthesis of biologically active compounds. Just to cite a few examples, both Kawain (an anticonvulsant) and Lovastatin (an HMG-CoA reductase inhibitor, Figure 3) contain the pyran-2-one moiety.

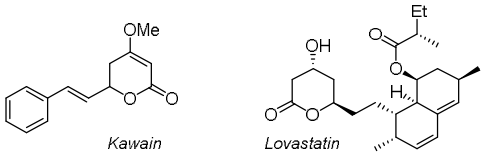


Figure 3. Structures of Kawain and Lovastatin.

As a consequence, the development of innovative catalytic methods for the preparation of pyran derivatives is of great interest.[4] Traditional methods for the asymmetric synthesis of six-membered oxygenated heterocycles include five-membered ring expansions, cycloadditions or cyclizations. Recently, asymmetric organocatalysis has become a very attractive methodology in this area.[5-9] Hence, several methods exploiting the enantioselective organocatalytic approach to six-membered oxygenated rings have appeared in the literature and they have been recently reviewed.[10] *Cis* and/or *trans*-2,6-disubstituted tetrahydropyrans **I** (THPs), substituted spiroketals **II**, or benzoannulated spiroketals **III** (Figure 4) are incorporated in a large number of natural and non-natural compounds possessing biological relevance. Consequently, the development of efficient tactics and methods to access THPs and spiroketals is a highly important goal.[11]

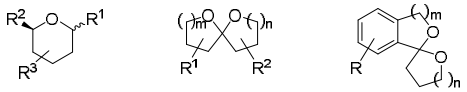


Figure 4. Structures of 2,6-disubstituted tetrahydropyrans **I**, spiroketals **II**, and benzoannulated spiroketals **III**.

The synthesis of these ubiquitous oxygenated heterocycles was recently achieved *via* chemo- and diastereoselective metal-catalyzed procedures. *Trans*-2,6- and *cis*-2,6-disubstituted THPs, along with benzoannulated spiroketals of various ring size, were obtained following an easy one-pot strategy.[11]

Six-membered oxygenated heterocycles fused to aromatic rings in a tricyclic scaffold give rise to the remarkable family of xanthones. Xanthones or 9*H*-xanthen-9-ones (dibenzo-γ-pirones) belong to an important class of oxygenated heterocycles whose role is well-known in medicinal chemistry. Indeed, recent reviews presented an array of biological and pharmacological effects attributed to both natural and synthetic xanthones.[12] The relevance of such derivatives as therapeutic agents, their use as pharmacological tools and their role as extract components in folk medicine attracted the attention of several research groups, interested in studying novel synthetic approaches to xanthones.[13]

Five- and six-membered heterocycles can be undoubtedly considered as the two pillars of cyclic organic compounds. It is worth mentioning the role of both smaller and larger oxygenated heterocycles. The well-known three-membered epoxy ring is widely used in organic synthesis due to the easy preparation and tendency to undergo C-O bond cleavage. The C-C bond fragmentation in oxiranes is, on the other hand, quite uncommon, but the ring expansion of epoxides fused with carbocyclic rings is a well-known strategy to prepare large heterocyclic rings.[14] Compared to the more common five- and six-membered oxygenated-rings, oxepanes represent a rare structure found in nature. Nevertheless, natural products with significant biological activities possess either one (or multiple) oxepane subunits fused to other oxygenated heterocycles. Therefore, a large number of methods have been designed to access these structures with a special attention on metal-catalyzed coupling reactions.[15]

Recently, homogeneous gold catalysis has revealed its vast potential in the synthesis of both oxygenated and nitrogen-containing rings. As an example, building such structures starting from alkynes following this strategy is a valuable, versatile and synthetically appealing method.[16] In the case of oxygenated heterocycles, external nucleophilic oxidants such as pyridine or quinoline *N*-oxides are usually employed in this procedure. The usual mechanism involves the generation of an alkenylgold intermediate (possibly evolving into a α-oxo gold carbene species), and allows a broad range of *N*- and *O*-heterocycles to become readily accessible (Figure 5).[17]

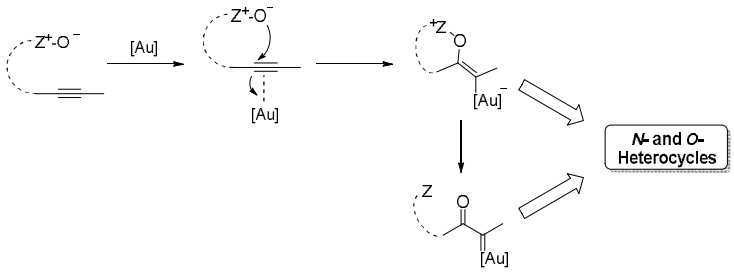
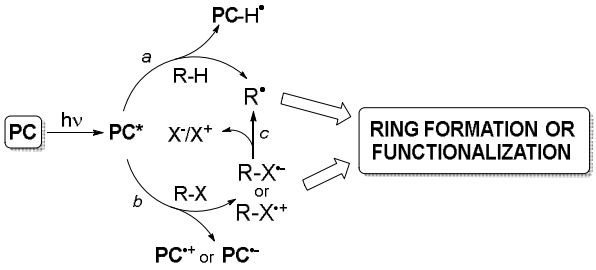


Figure 5. Gold-catalyzed synthesis of *N*- and *O*-heterocycles starting from C≡C triple bonds.

Photocatalytic methodologies are also at work in this field. These reactions make use of a *photo*catalyst (**PC**) activated by light absorption and are considered a green and sustainable approach in organic synthesis.[18-24] Moreover, the mild reaction conditions produce a reduced amount of waste. By using the photocatalytic approach, the straightforward formation of valuable reactive intermediates, such as radicals or radical ions,[25,26] is feasible. These intermediates have been employed for the preparation of heterocycles either *via* the functionalization of a pre-formed heterocyclic ring or through the formation of a ring *via* a cyclization step, as depicted in Scheme 1. Thus, the excited photocatalyst (**PC***) may cleave homolytically the C-H bond in various organic compounds acting as hydrogen donors (R-H, path *a*).[27] The resulting radicals are then used for the synthesis of heterocyclic scaffolds, although this approach has been rarely used. However, **PC*** is able to accept/donate electrons to a substrate R-X (path *b*) and either the resulting radical cations (or anions) or the radicals obtained from their fragmentation (with the concomitant

loss of X^+/X^-, path *c*) can be likewise used in organic synthesis. In the latter approach the presence of a redox-auxiliary group X has the role to facilitate the electron transfer step.[28,29]



Scheme 1. Main pathways for the preparation of heterocycles by a photocatalytic approach (**PC**=photocatalyst).

Photocatalysts may belong to different classes, including aromatic ketones, cyanoarenes, dyes or other organic compounds (*e.g.* pyrylium salts), as well as metal complexes (based on Ru^{II} or Ir^{III} derivatives),[18-24] and most of them are visible light absorbing species.

The redox potential values of representative **PC**s used in the synthesis of heterocycles are resumed in Table 1. The excited state of the **PC**s may oxidize (E^*_{RED} (**PC***/**PC**$^{\bullet-}$) up to +2.30 V *vs* SCE) or reduce (E^*_{OX} (**PC**$^{\bullet+}$/**PC***) up to −1.76 V *vs* SCE) the desired organic compounds, delivering the corresponding radical-ions or radicals (if the reagents are charged).

The photocatalyzed construction of heterocyclic rings was previously discussed in pertinent reviews.[30-38] Here, we aim to present some recent advances on the application of photocatalyzed approaches for the construction of mono-oxygenated heterocycles, as detailed below.

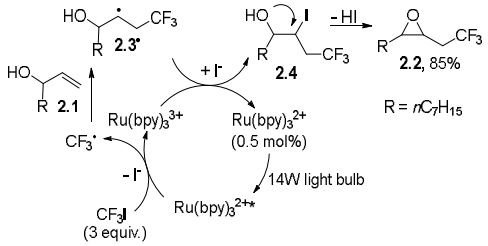
Table 1. Redox potentials (in V vs SCE) of selected photocatalysts (**PC**s).

Photocatalyst (PC)[a]	E_{RED} (PC/PC$^{\bullet-}$)	E_{OX} (PC$^{\bullet+}$/PC)	E^*_{RED} (PC*/PC$^{\bullet-}$)	E^*_{OX} (PC$^{\bullet+}$/PC*)	Ref.
Rose Bengal	–0.78	1.09	0.99	–0.68	20
Acr^+Mes	–0.43		2.08		20
Eosin Y	–1.14	0.72	1.18	–1.60	20
DCA	–0.89		1.97		20
DCN	–1.28		2.19		39
TPT^+	–0.35		2.30		24
T(p-OMe)PPT			1.74		40
T(p-F)PPT			2.28		41
Phenanthrene	–2.49	1.83	1.10	–1.76	20
mpg-C_3N_4	–1.39	1.22			42
$Ru(bpy)_3^{2+}$	–1.33	1.29	0.84	–0.86	30
$Ru(bpz)_3^{2+}$	–0.80	1.86	1.45	–0.26	30
$Ru(phen)_3^{2+}$	–1.36	1.26	0.82	–0.87	30
[(DPEphos)(bcp)Cu]PF_6				–1.02	43
fac-Ir(ppy)$_3$	–2.19	0.77	0.31	–1.73	30
[Ir[dF(CF_3ppy)]$_2$(dtbbpy)]PF_6			1.21		44
Ir(ppy)$_2$(dtbbpy)$^+$	–1.51	1.21	0.66	–0.96	30

[a]Acr^+Mes=9-mesityl-10-methylacridinium cation; DCA=9,10-dicyanoanthracene; DCN=1,4-dicyanonaphthalene; TPT^+=2,4,6-triphenylpyrylium cation; T(p-OMe)PPT=2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate; T(p-F)PPT=2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate; mpg-C_3N_4=mesoporous graphitic carbon nitride; bpy=(2,2′-bipyridine); bpz=2,2′-bipyrazine; phen=1,10-phenanthroline; ppy=2,2′-phenylpyridine.

2. Three- and four-membered rings

The synthesis of three-membered heterocycles under photocatalyzed conditions is rarely found in the literature. In one of such instances, epoxides were formed starting from the corresponding alkenes, using *t*BuOOH (or O_2) as oxygen source. Recent examples of this strategy include the Ru^{II} photocatalyzed reaction of styrenes with aromatic aldehydes for the synthesis of α,β-epoxy ketones[45] and the epoxidation of cyclic olefins with titanium dioxide-cobalt-ascorbic acid nanohybrid as photocatalyst.[46] In the latter case, epoxides were formed in very high yields (up to quantitative) and, noteworthy, the catalytic system could be reused (up to five times). A more versatile approach is shown in Scheme 2, where both CF_3-containing epoxides and aziridines were prepared starting from allyl alcohols and allyl amines, respectively.[47] In the example, the CF_3 radical generated by the Ru^{II}-photocatalyzed reduction of CF_3I adds to the double bond of the allyl alcohol **2.1**. A further oxidation, followed by iodide addition, allows the formation of the iodoalcohol **2.4**. An ensuing intramolecular cyclization forms the desired epoxide **2.2** in very good yields (Scheme 2).



Scheme 2. Synthesis of epoxides *via* the photocatalyzed trifluoromethylation of allylic alcohols.

Although the photochemical formation of oxetanes is well known in the literature (*e.g.* the Paternò-Büchi reaction), to our knowledge no related photocatalyzed syntheses have been described so far.

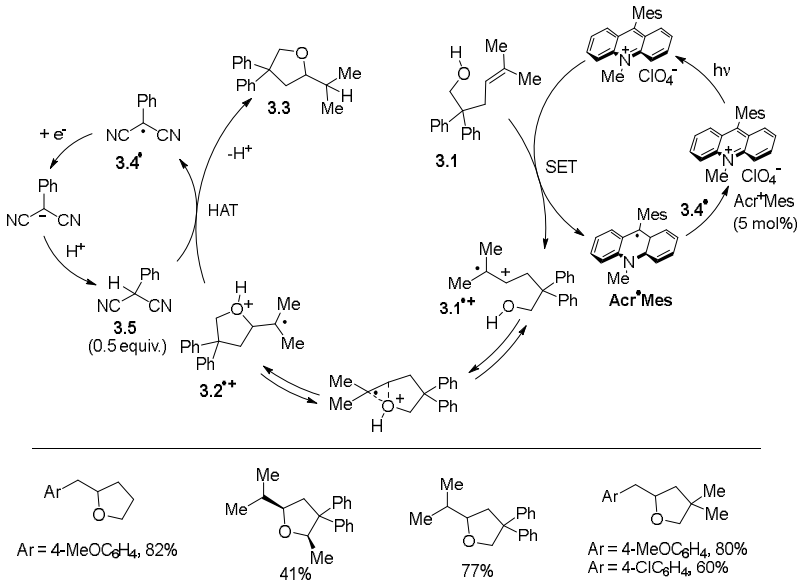
3. Five-membered rings

3.1. Tetrahydrofurans and dihydrobenzofurans

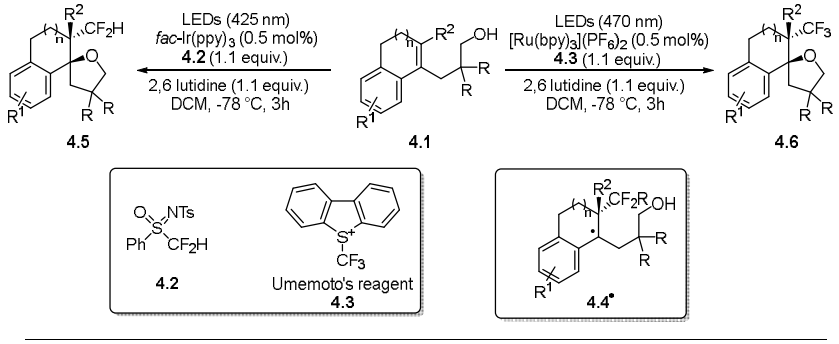
Natural compounds having medicinal or biological features, such as polyether antibiotics, marine macrolides and annonaceous acetogenins, contain the tetrahydrofuran ring and, accordingly, there is an urgent need to design photocatalytic reactions to access this core structure.[48,49]

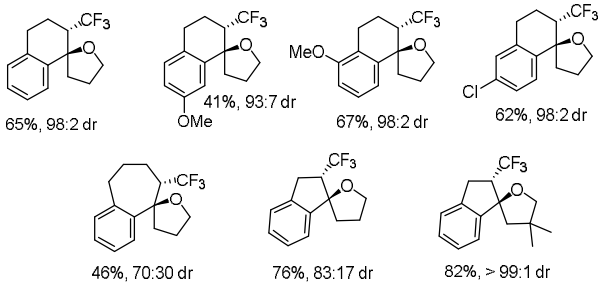
A possible approach involves the intramolecular anti-Markovnikov hydroetherification of alkenols.[50] In details, the oxidation of alkenol **3.1** (having oxidation potential <+2.0 V *vs* SCE) to $\mathbf{3.1}^{\bullet+}$ was carried out by using Acr^+Mes (E^*_{RED} ($\mathbf{PC}^*/\mathbf{PC}^{\bullet-}$)>+2.0 V *vs* SCE) as the photocatalyst[51] (Scheme 3). Tetrahydrofuran **3.3** was then obtained in a high yield when 2-phenylmalononitrile **3.5** was added as H-atom donor. The same group employed this approach to prepare again tetrahydrofurans from allylic alcohols and alkenes by a polar-radical-crossover cycloaddition (PRCC) reaction.[52]

Trifluoromethylated heterocycles have attracted considerable interest in various fields of chemistry, owing both to the importance of fluorine in medicinal chemistry and to the application of heterocycles in the pharmaceutical, agrochemical, and materials industries.[53-55] Indeed, the addition of fluorinated radicals onto the olefinic moiety of alkenols (*e.g.* cycloalkenylalkanols **4.1**) was recently reported. Compound **4.2** or the Umemoto's reagent **4.3** have been adopted as fluoromethylating agents to give intermediates $\mathbf{4.4}^{\bullet}$ *via* the addition of the fluorinated radical onto the unsaturated bond. Carbocation formation upon SET oxidation followed by intramolecular addition of the tethered nucleophilic alcohol gave rise to the predominant formation of the anti-fluoromethylated spiroethers **4.5** or **4.6** when working at low temperatures (Scheme 4).[56] The same approach was applied to the derivatization of styrenes bearing an alcoholic group (in this particular case, α-bromoesters were employed as radical source) to form tetrahydrofurans maintaining the same anti-diastereoselectivity in the cyclization step.[57]



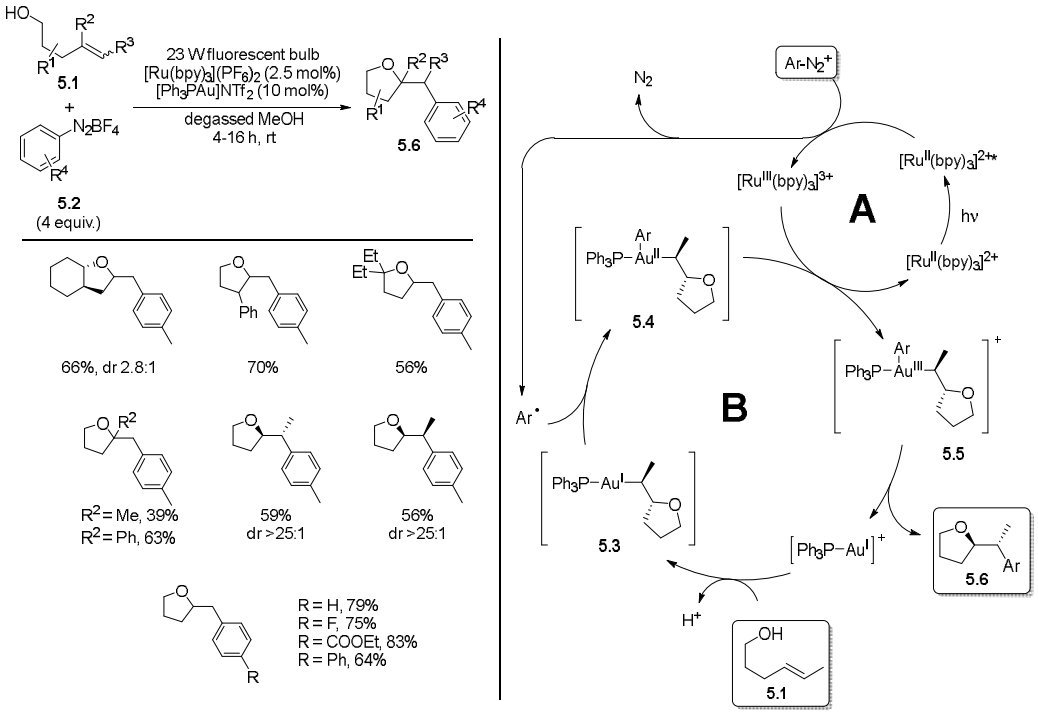
Scheme 3. Construction of the tetrahydrofuran ring by the photocatalyzed anti-Markovnikov hydroetherification of alkenols.





Scheme 4. Synthesis of fluoromethylated spiroethers from alkenols.

Moreover, the intramolecular oxyarylation of alkenols (*e.g.* substituted 4-penten-1-ols **5.1**) was recently reported to take place in the presence of arenediazonium salts **5.2** under a dual gold/photoredox catalysis procedure (Scheme 5).[58] The process starts with the complexation of the olefinic moiety in **5.1** by a cationic Au^{I} species to form the alkyl-$gold^{I}$ intermediate **5.3** in an anti-selective fashion (cycle **B**). An aryl radical (formed *via* the Ru^{II} photocatalyzed reduction of **5.2**, cycle **A**) was trapped by **5.3** and the resulting Au^{II} intermediate **5.4** restored the photocatalyst and benzyl tetrahydrofuran **5.6** was obtained *via* reductive elimination along with the starting Au^{I} catalyst.

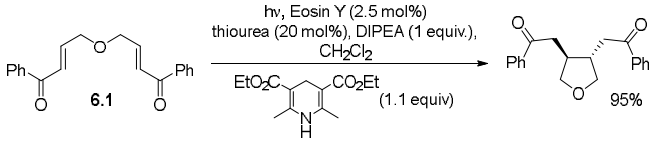


Scheme 5. Dual gold/photoredox catalysis for the preparation of benzyl tetrahydrofurans.

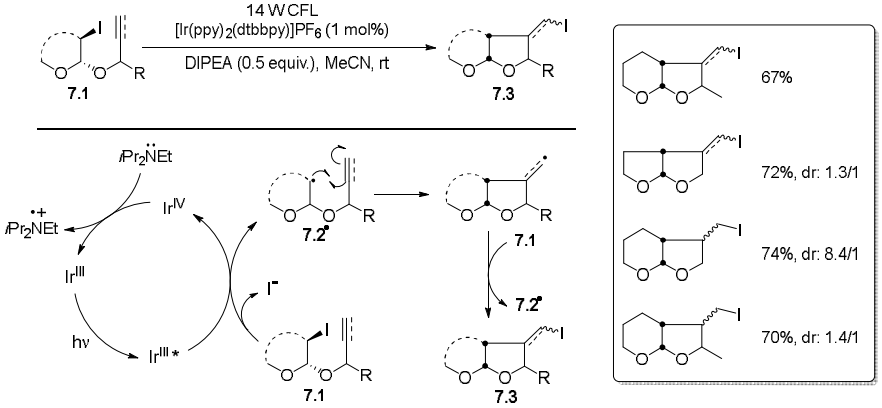
A different approach made use of phenylsulfanyl substituted aromatic alkanols. These compounds (E_{OX}=+0.72 V *vs* SCE) are easily oxidized by excited $Ru(bpy)_3^{2+}$ (E^*_{RED} (**PC***/**PC**$^{\bullet-}$)=+0.84 V *vs* SCE) causing the release of the phenylsulfanyl group. The benzyl cation thus formed was trapped by the alcoholic moiety leading to the desired oxygen containing heterocycle.[59]

The tetrahydrofuran core was likewise prepared by the photocatalyzed reduction of a bis-enone (**6.1**, Scheme 6).[60] A thiourea served as Lewis acid for the activation of the carbonyl, in turn favoring the Eosin Y photocatalyzed formation of the corresponding radical anion, that finally led to the desired tetrahydrofuran ring upon cyclization. The reaction was based on the umpolung of the α,β-unsaturated moiety and the mandatory presence of DIPEA and Hantzsch ester as reductive quenchers allowed the reaction to proceed in high yields and excellent diasteroselectivity.[60]

A photoredox atom-transfer Ueno-Stork reaction has been adopted for the preparation of biologically interesting oxabicyclic compounds (Scheme 7).[61] These derivatives were formed in the presence of an Ir based catalyst by irradiation (with a CFL lamp) of 2-iodoethyl propargyl (or allyl) ethers (*e.g.* **7.1**) with retention of the halogen functionality. The proposed mechanism (Scheme 7) involves the reduction of α-haloacetals **7.1** (E_{RED}=−0.55 V *vs* SCE) by the excited Ir^{III}* catalyst to afford radicals **7.2**$^{\bullet}$. Products **7.3** result after an atom transfer radical addition/cyclization (ATRA/ATRC) onto the double/triple bond.[61]

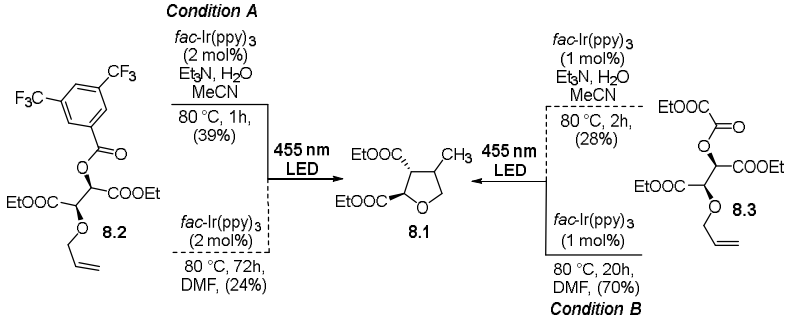


Scheme 6. Bis-enones as starting materials for the construction of the tetrahydrofuran ring.



Scheme 7. Oxabicyclic tetrahydrofurans from 2-iodoethyl propargyl (or allyl) ethers **7.1**.

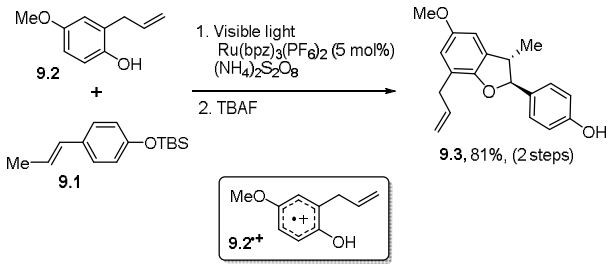
Interestingly, also valuable chiral tetrahydrofurans may be formed starting from substituted 1,2-diols by a visible-light-mediated deoxygenative cyclization (Scheme 8). This procedure involves a 5-*exo-trig* ring closure of a carbon bearing an oxygen based activating group onto an allyl ether moiety. Tartrate derivatives (in this case the activating group is the 3,5-bis(trifluoromethyl)benzoate scaffold in **8.2** or the ethyl oxalate in **8.3**), readily available in either enantiomerically pure form, were hence cyclized intramolecularly. Tetrahydrofuran **8.1** was formed in a diastereomeric ratio up to (>95:5) starting from both compound **8.2** (condition **A**) or **8.3** (condition **B**) under irradiation at 80 °C with or without the presence of a sacrificial amine, respectively. Both mechanisms likely involve an electron transfer from the excited Ir^{III}* photocatalyst to the activating group, followed by C-O bond mesolysis giving rise to an α-carboxyethyl radical that smoothly cyclizes.[62]



Scheme 8. Construction of tetrahydrofurans through deoxygenative cyclization.

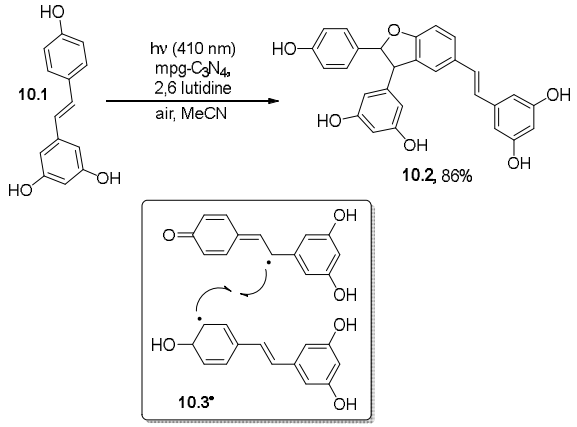
The photocatalytic approach was efficiently applied also for the construction of the 2,3-dihydrobenzofuran scaffold by means of a [3+2]-cycloaddition between two phenols promoted by $[Ru(bpz)_3](PF_6)_2$ (Scheme 9).[63] As an example, the initial oxidation of **9.2** gave the corresponding radical

cation **9.2**$^{\bullet+}$ that, upon reaction with **9.1** and treatment with TBAF, afforded **9.3**, a known member of the neolignan family, isolated from *Piper aequale*.



Scheme 9. Photocatalyzed [3+2]-cycloaddition reaction as a tool for the synthesis of 2,3-dihydrobenzofurans.

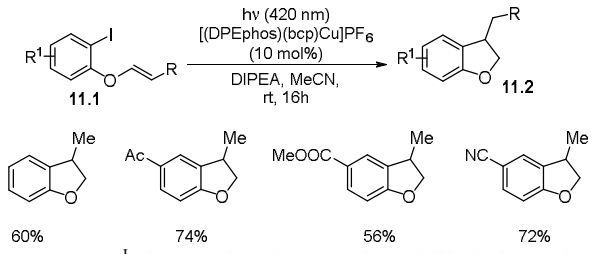
Another dihydrobenzofuran (δ-viniferin **10.2**) was smoothly prepared by a photocatalyzed dimerization of resveratrol **10.1** under air atmosphere. The mesoporous graphitic carbon nitride (mpg-C_3N_4) photocatalyzed oxidation of **10.1** furnished radical **10.3**$^{\bullet}$ that dimerized and gave rise to **10.2** in a very high yield (Scheme 10).[64] The presence of molecular oxygen was mandatory since it formed the hydroperoxy radical responsible for the generation of **10.3**$^{\bullet}$ from **10.1**.



Scheme 10. Photocatalyzed dimerization of resveratrol **10.1** to give δ-viniferin **10.2**.

A photoorganocatalyst, such as fluorescein, was used for the preparation of dihydrobenzofurans by means of an alkoxycarbonylation of *ortho*-allyl substituted benzenediazonium salts with the formation of methyl 2-(2,3-dihydrobenzofuran-3-yl)acetate.[65]

Photoredox transformations performed by visible light irradiation in the presence of catalytic amounts of a copper catalyst [(DPEphos)(bcp)Cu]PF_6 were applied to a range of unactivated aryl and alkyl halides. These compounds were smoothly activated through a $Cu^{I}/Cu^{I}*/Cu^{0}$ catalytic cycle. This complex efficiently catalyzes a series of radical processes, including reductions, cyclizations, and direct arylation of arenes. Scheme 11 shows the application of this protocol to the synthesis of dihydrobenzofurans **11.2**, obtained in very good yields from the corresponding aryl vinyl ethers **11.1**.[43]

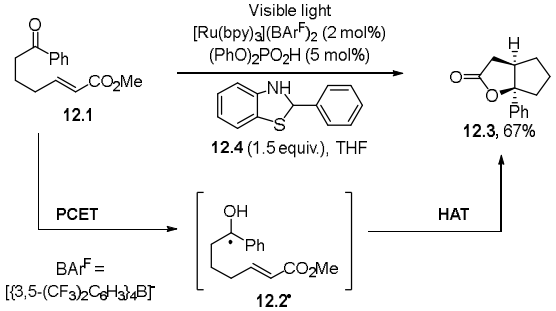


Scheme 11. Cu^{I} photocatalyzed preparation of dihydrobenzofurans.

3.2. γ-Lactones and butenolides

Photoredox catalysis represents an intriguing tool for the preparation of γ-lactones and butenolides, where the ring construction may follow two different pathways, *viz*. a direct cyclization of the substrate or the combination of two different reagents that triggers a cyclization event.

An interesting example pertaining to the first family involves the cyclization of the aryl ketone **12.1** promoted by a Proton-Coupled Electron Transfer (PCET) step (Scheme 12). In this work, the excited photoredox catalyst $Ru(bpy)_3^{2+}$ and a Brønsted acid operated a reductive PCET with subsequent formation of the long-lived ketyl radical intermediate **12.2**$^{\bullet}$. The cyclization of the latter onto the pendant alkene finally gave γ-butyrolactone **12.3** upon hydrogen atom transfer (HAT) from 2-phenylbenzothiazoline **12.4**. Notably, the reaction occurred with a high degree of diastereoselectivity, largely dictated by the rate of the HAT step.[66]



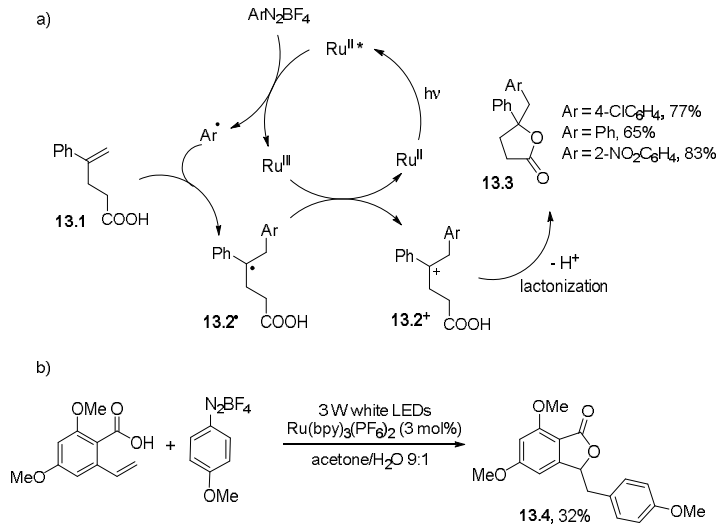
Scheme 12. Dual photoredox / Brønsted acid catalysis approach for the synthesis of γ-butyrolactones.

A different approach to the same targets involves the double functionalization of a C=C double bond occurring on irradiation with visible light *via* an arylation-lactonization sequence. The process is based on the use of arenediazonium salts and alkenoic carboxylic acids **13.1**. This strategy gives access to a library of diversely functionalized lactones with a sterically hindered γ-quaternary carbon. The proposed mechanism relies on the initial single electron reduction of the employed arenediazonium salt by the excited photocatalyst $Ru(bpy)_3^{2+}$* (Scheme 13a). The thus formed aryl radical added regioselectively to the alkene moiety of **13.1**, to give radical adduct **13.2**$^{\bullet}$. In the final step, the regeneration of the photocatalyst occurred through oxidation of **13.2**$^{\bullet}$ to **13.2**$^{+}$, that further underwent cyclization to give lactone **13.3**.[67] Noteworthy, this protocol could be adapted to the preparation of phthalide **13.4**, a naturally-occurring compound isolated from *Frullania falczloba* (Scheme 13b).[67]

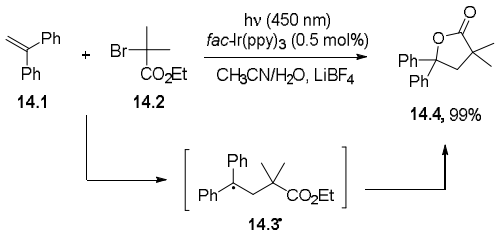
Another strategy for the synthesis of the γ-lactone core is based on the reaction of styrene **14.1** with α-bromoester **14.2** (Scheme 14). The process involved the intermediacy of radical **14.3**$^{\bullet}$, and the desired product **14.4** was formed *via* a hydroxylation/transesterification sequence.[68]

A different approach made use of *O*-benzyloxime acids and alkenes, resulting in the preparation of substituted α-benzyloxyamino-γ-butyrolactones. In this case, the suggested mechanism involved a polar

radical crossover cycloaddition (PRCC) sequence based on the use of an acridinium photocatalyst and a sub-stoichiometric amount of a redox-active co-catalyst.[69] Noteworthy, unsaturated acids could also be adopted, as demonstrated by the syntheses of methylenolactocin and protolichesterinic acid.[70]

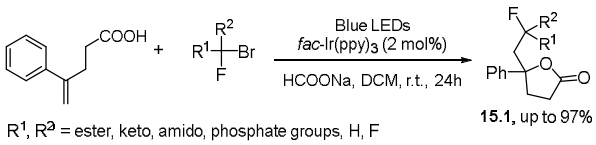


Scheme 13. a) Phototocatalytic arylation/lactonization sequence for the synthesis of sterically hindered γ,γ-disubstituted butyrolactones and b) application of this protocol to the synthesis of the naturally-occurring compound **13.4**.



Scheme 14. Intermolecular addition of α-bromoesters to styrenes for the photocatalyzed synthesis of γ-lactones.

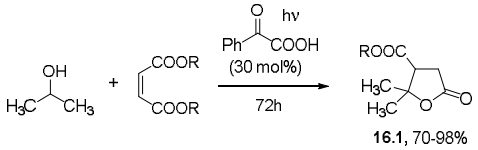
A cascade visible-light photocatalytic difluoroalkylation and intramolecular cyclization reaction has been developed as an easy method for the preparation of functionalized difluoroalkylated oxygen heterocycles (Scheme 15). The reaction was carried out under very mild conditions, affording fluorinated isobenzofuran-1-ones, γ-butyrolactones **15.1** and cyclic ethers with up to 97% chemical yields. As for the mechanism, the present strategy follows a mechanism similar to that reported above in Scheme 13.[71]



R¹, R² = ester, keto, amido, phosphate groups, H, F

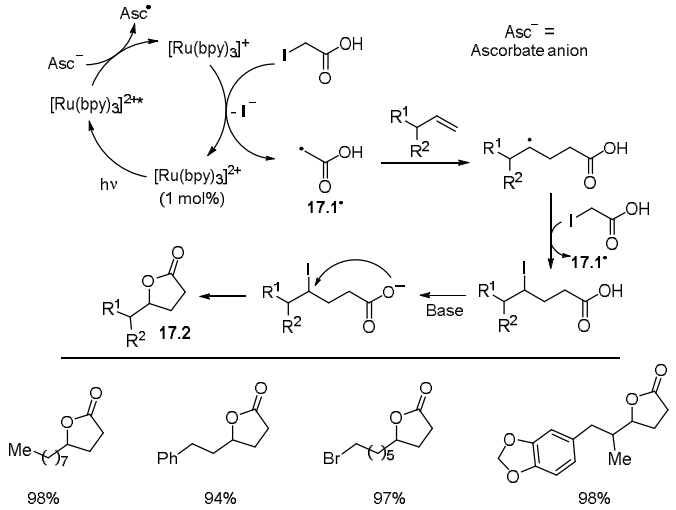
Scheme 15. Synthesis of fluorinated γ-butyrolactones.

A highly efficient and selective visible-light mediated protocol for the addition of alcohols to a plethora of Michael acceptors was recently investigated. The process is characterized by the use of phenylglyoxylic acid (30 mol%) as the photoorganocatalyst and common household bulbs as the light source. In the reaction, a cyclization step occurred leading to five-membered lactones **16.1** in excellent yields (Scheme 16). The proposed mechanism involved the initial formation of an exciplex between excited phenylglyoxylic acid and the α,β-unsaturated ester having a radical ion pair character. Hydrogen abstraction from the alcohol and addition of the resulting radical to the ester completed this simple, cheap and efficient photoorganocatalytic protocol for γ-lactones synthesis.[72]



Scheme 16. Photoorganocatalyzed synthesis of γ-lactones.

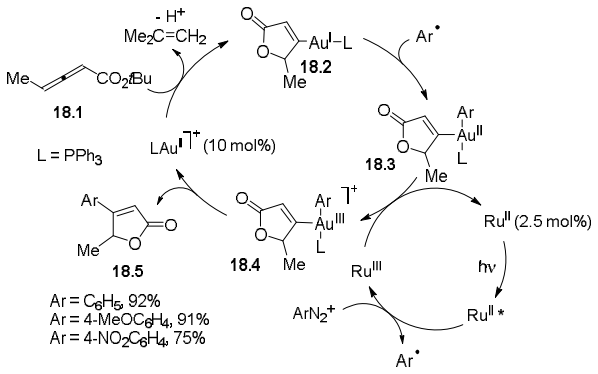
The atom-transfer radical addition (ATRA) process between olefins and haloalkanes constitutes a powerful and highly atom economical method for the one-step synthesis of C-C and C-X bonds. Taking advantage of the ATRA reaction, photocatalytic protocols for the synthesis of useful organic compounds, including the intramolecular preparation of γ-lactones, have been reported. Indeed, γ-lactones **17.2** could be prepared having recourse to several photocatalysts according to the mechanism reported in Scheme 17, albeit the highest yields were obtained with $[Ru(bpy)_3]Cl_2$. Different substituted olefins were competent substrates and the corresponding γ-lactones were smoothly obtained (Scheme 17).[73]



Scheme 17. Photocatalytic ATRA reaction for the synthesis of γ-lactones.

The preparation of γ-crotonolactone can be achieved through the formation of a new $C(sp^2)$–$C(sp^2)$ bond, in the reaction of *tert*-butyl allenoate **18.1** with arenediazonium salts. The process is based on a dual catalytic strategy, where an Au^I-Au^{III} cycle is merged with photoredox catalysis (Scheme 18). The reaction starts with the reaction of **18.1** with the Au^I complex leading to the complexed cyclic species **18.2**. The photocatalytically generated aryl radicals then lead to the formation of the Au^{II} species **18.3**, that is further

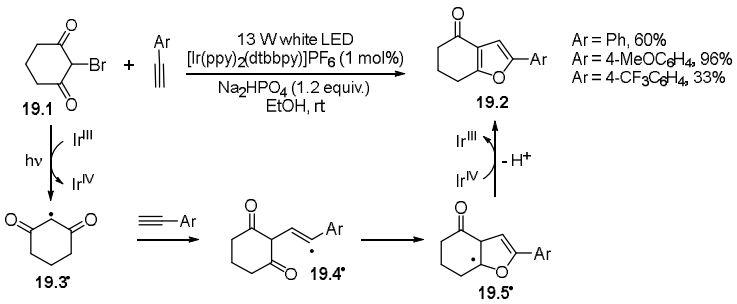
oxidized by Ru^{III} to the corresponding Au^{III} species. The catalytic cycle is completed *via* reductive elimination from **18.4** to give product **18.5**.[74]



Scheme 18. Preparation of lactones *via* dual catalytic photoredox-gold strategy.

3.3. Furans and benzofurans

Furans and the related benzo-condensed derivatives are important motifs in several different fields and many photoredox approaches have been developed for their synthesis. As an example, furans have been obtained through the coupling between 2-bromo-1,3-dicarbonyls (*e.g.* **19.1**) and alkynes in the presence of an Ir-complex as the photoredox catalyst (Scheme 19).

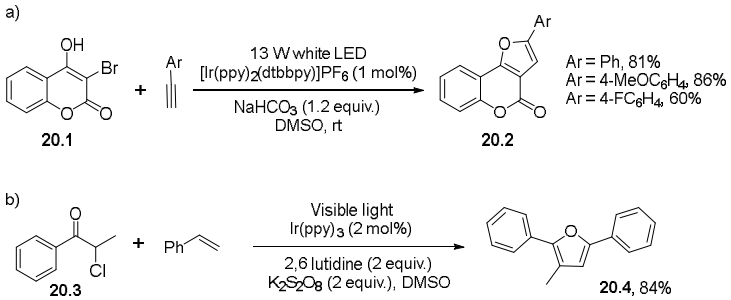


Scheme 19. Photocatalyzed synthesis of furan derivatives.

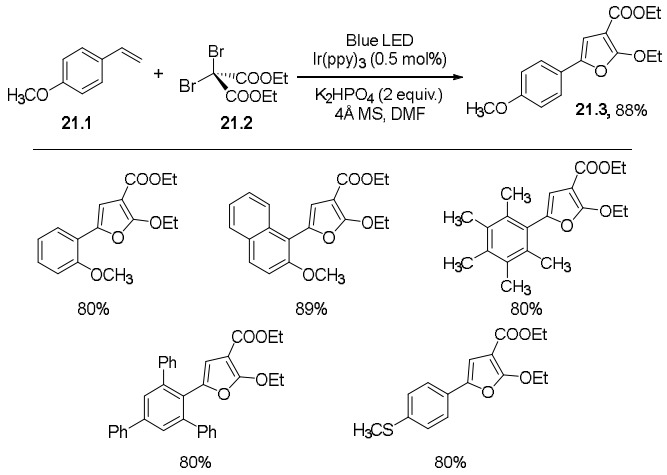
The mechanism is based on the initial photocatalytic activation of the dicarbonyl derivative to give **19.3**$^{\bullet}$ and then **19.4**$^{\bullet}$ upon addition onto the alkyne. A cyclization/oxidation sequence followed by deprotonation completes the catalytic cycle. Indeed, the desired products **19.2** were obtained in variable yields, depending on the electronic character of the substituents on the aryl group of the alkyne. In particular, electron-donating substituents consistently allowed to obtain higher yields.[75] Later, the protocol was extended to the preparation of furocoumarins **20.2** (Scheme 20a), where the furan ring was fused to a coumarin skeleton.[76] Furthermore, polysubstituted furans, such as **20.4**, have been prepared from styrenes and α-chloroaryl ketones (*e.g.* **20.3**) under oxidative conditions in the presence of $K_2S_2O_8$ (Scheme 20b).[77]

The redox neutral photocatalytic divergent radical 1,2-difunctionalization of a wide array of structurally different alkenes with *gem*-dibromides is the basis of a practical approach to the biologically important furan skeleton. To set the optimal conditions, the reaction of *p*-methoxystyrene **21.1** and *gem*-dibromomalonate **21.2** was chosen as the model reaction, wherein biologically important 2-arylated furan **21.3** was obtained in 88% yield (Scheme 21). The reaction is initiated by the addition of the

photogenerated monobromomalonate radical onto the double bond of the styrene. Indeed, electron-donating substituents on the aromatic ring are essential for this transformation.[78]

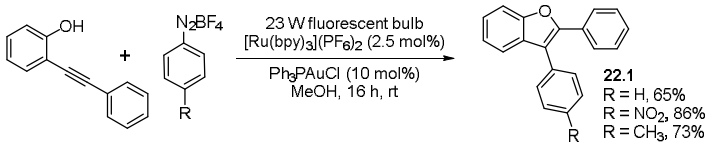


Scheme 20. Preparation of substituted furans from a) aryl alkynes and b) styrenes.



Scheme 21. Photocatalytic 1,2-difunctionalization of styrenes for the synthesis of furans.

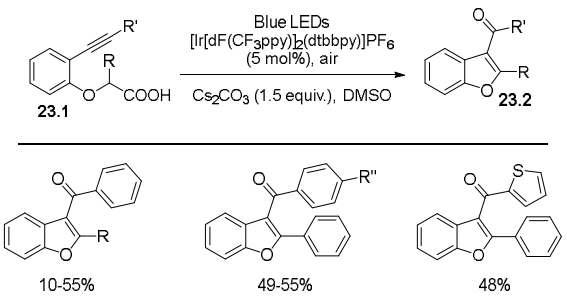
Dual photoredox / gold catalysis has been likewise demonstrated to be a reliable alternative for the preparation of benzofurans (Scheme 22). Indeed, diaryl substituted benzofurans, such as **22.1**, can be easily synthesized from arenediazonium salts and *o*-alkynylphenols. Interestingly, the outcome of the process strongly depends on the electronic character of the substituents on the aryl groups.[79]



Scheme 22. Synthesis of benzofurans *via* dual photoredox/gold catalysis.

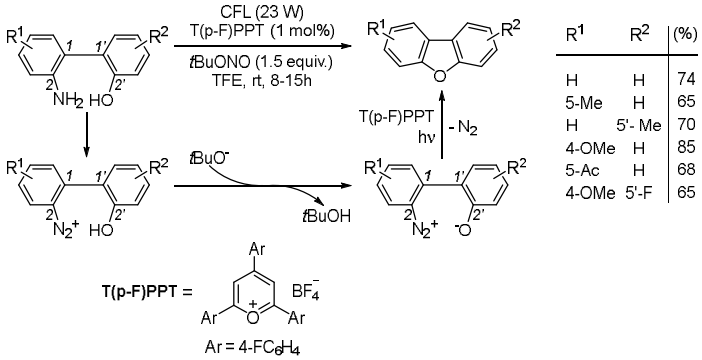
Heteroaromatic compounds, including 3-acylindoles, 3-acylbenzofurans and 3-acylbenzothiophenes, are present as pervasive structural motifs in numerous natural products and biologically active pharmaceutical molecules. A novel visible-light-driven intramolecular decarboxylative cyclization of *o*-alkynylated carboxylic acids in the presence of air, a base and a photocatalyst was adopted for the

synthesis of 3-acylbenzofurans. In this case, alkyl radicals generated *via* decarboxylation underwent intramolecular radical addition to the C≡C triple bond (*e.g.* in *o*-alkynylated phenoxyacetic acids **23.1**), followed by C-O bond formation, to give access to the corresponding carbonylated compounds **23.2** (Scheme 23). Interestingly, the same protocol could be likewise adopted for the synthesis of 3-acylindoles and 3-acylbenzothiophenes.[44]



Scheme 23. Photocatalyzed synthesis of 3-acylbenzofurans.

Dibenzofurans are naturally occurring molecules that have received considerable attention for a variety of practical applications, such as in the pharmaceutical and electronic fields.[80-83] An efficient and eco-friendly method for their synthesis relies on an intramolecular aryl-O bond formation, which involved the *in-situ* preparation of a diazonium salt. The transformation required a diazotizing agent and was promoted by the use of a photoorganocatalyst, *viz.* 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate (T(p-F)PPT), under visible-light irradiation, as depicted in Scheme 24.[84]



Scheme 24. Synthesis of dibenzofuran derivatives.

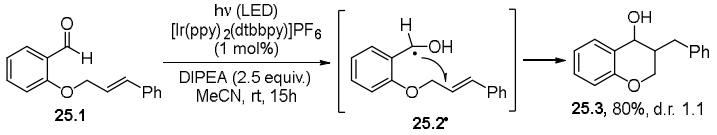
4. Six-membered rings

4.1. Chroman derivatives

The synthesis of chroman derivatives has been described to occur under several photocatalytic conditions. As an example, the visible light irradiation of substituted benzaldehyde **25.1** in the presence of an Ir^{III} based photocatalyst and an excess of DIPEA as the base resulted in the efficient formation of chromanol **25.3** *via* a PCET reaction occurring on **25.1** to give radical **25.2**$^{\bullet}$ followed by cyclization (Scheme 25).[85]

Eosin Y can be also used as the photoorganocatalyst to build the chromane core starting from phenols bearing a polyene unit (*e.g.* 2-geranylphenol) in hexafluoroisopropanol (HFIP). In this case, a radical cation intermediate at the terminal alkene moiety was initially generated and then involved in a stereoselective radical cascade cyclization leading to hexahydro-1*H*-xanthenes in variable yields.[86] Chromones were

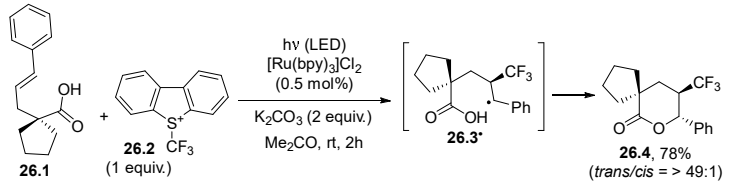
obtained as well *via* addition of a photogenerated fluorinated radical onto the double bond of an enaminone moiety, resulting in the formation of a C-O bond with the concomitant loss of a secondary amine.[87]



Scheme 25. Photoredox catalyzed synthesis of chromanol **25.3**.

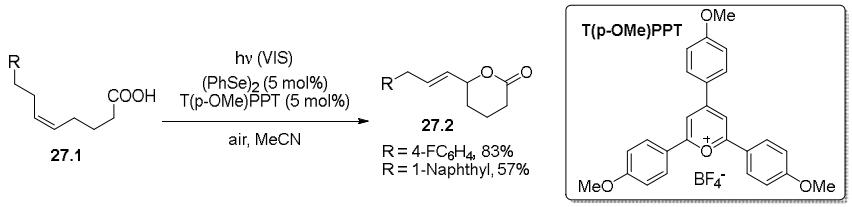
4.2. δ-Lactones and coumarins

The synthesis of lactones and coumarins usually made use of a cyclization reaction as the key-step. As an example, trapping of the $F_3C^{\bullet}$ radical (obtained *via* the photocatalyzed reduction of **26.2**, Scheme 26) by styrene **26.1** afforded the benzyl radical **26.3**$^{\bullet}$ that was thus oxidized to the corresponding cation, finally undergoing cyclization to the spiro derivative **26.4** in satisfactory yield and diastereoselectivity.[88]



Scheme 26. Photocatalyzed carbolactonization of alkenoic acid **26.1**.

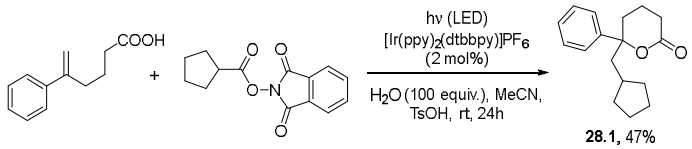
The aerobic dehydrogenative lactonization of alkenoic acids promoted by a cooperative non-metallic catalyst pair relies on the interplay between a photoredox and a selenium-π-acid catalyst, which allows for the regiocontrolled construction of five- and six-membered lactone rings in yields up to 96%.[40] Notable features of this method are the pronounced efficiency, good functional group tolerance, and high sustainability, since ambient air and visible light are adequate for the clean conversion of alkenoic acids into their respective lactones (Scheme 27). 2-Pyranone derivatives **27.2** were formed through oxidative lactonization of δ-alkenoic acids **27.1** photocatalyzed by a pyrylium salt with the intermediacy of a trimeric selenonium cation.[40]



Scheme 27. Photoorganocatalyzed synthesis of 2-pyranones.

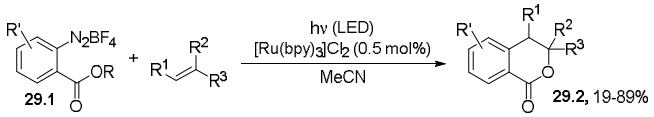
An efficient photoredox-catalyzed alkylation / lactonization reaction between unsaturated carboxylic acids and alkyl *N*-hydroxyphthalimide esters as alkylating reagents has been exploited for the synthesis of δ-lactones in moderate to good yields.[89] Such redox neutral procedure features mild conditions and operational simplicity and can be applied to the preparation of both five- and six-membered heterocyclic rings (an example in Scheme 28). A reasonable mechanism is based on the reduction of the *N*-hydroxyphthalimide ester by the excited photoredox catalyst $[Ir(ppy)_2(dtbbpy)]PF_6$ and fragmentation of the resulting radical anion to give an alkyl radical. The intermediate adds onto the C=C double bond of

styrene and the resulting radical adduct is then oxidized to the corresponding cation. The latter finally undergoes ring closure, delivering the reaction product (*e.g.* **28.1**) in good yields.[89]



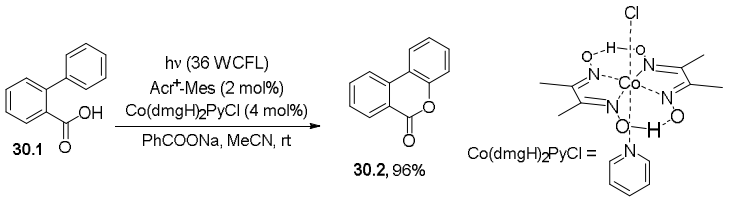
Scheme 28. Synthesis of δ-lactone **28.1**.

A different approach made use of the photocatalyzed arylation of substituted alkenes by 2-(alkoxycarbonyl)benzenediazonium tetrafluoroborate salts **29.1** to synthesize isochromanones **29.2** (Scheme 29). The advantage of using highly soluble esters rather than carboxylic acids as starting compounds became apparent when the reactions were performed under flow conditions.[90] The reaction was initiated by the addition of the (photogenerated) aryl radical onto the double bond.



Scheme 29. Synthesis of isochromanones.

The direct activation and functionalization of C-H bonds is considered one of the most significant challenges in sustainable organic synthesis. Therefore, an operationally simple, efficient and practical C-H functionalization/C-O bond forming strategy is highly desirable.[91,92] Biaryl lactones and their derivatives are key structural motifs widely present in natural bioactive compounds. In this field, the photoredox and cobalt co-catalyzed oxidant-free oxidative dehydrogenative C-O coupling between C-H/O-H bonds of 2-arylbenzoic acids was recently described, allowing for the convenient synthesis of lactones under mild conditions. The photoinduced dehydrogenative cross-coupling of **30.1** by using 9-mesityl-10-methylacridinium tetrafluoroborate ($Acr^{+}Mes\ BF_4^-$, 2 mol%) as the photocatalyst and $Co(dmgH)_2PyCl$ (4 mol%) as the co-catalyst efficiently led to the desired heterocycle (**30.2**, 96%) in the presence of PhCOONa as a base (Scheme 30). A variety of 2-arylbenzoic acids has thus been converted to the desired lactones in moderate to high yields. Different substituents on the aromatic rings, including electron-neutral and electron-rich groups, were tolerated. However, the yield dropped to 50% when using 2-arylbenzoic acids bearing the strong electron-withdrawing trifluoromethyl group.

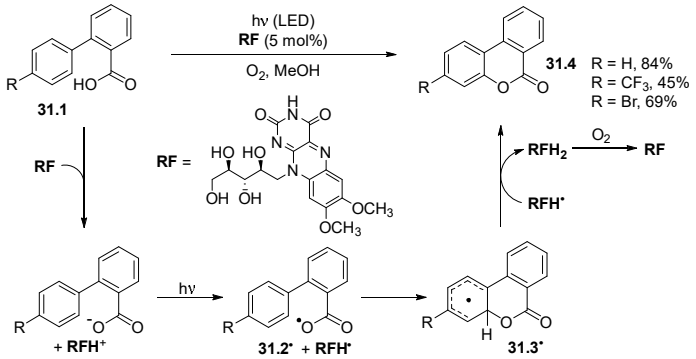


Scheme 30. Photocatalytic synthesis of 6*H*-benzo[*c*]chromen-6-one **30.2**.

Similar and excellent results were obtained by Lei and co-workers[93] and by Luo and co-workers,[94] pointing out the strong attention given by different research groups to this topic.

Alternatively, an operationally simple route to benzo-3,4-coumarins **31.4** from biaryl carboxylic acids **31.1** was described to occur without the need for substrate pre-functionalization. Complementary to classic lactonization strategies, this disconnection relies on the oxidation competence of photoactivated (−)-riboflavin (**RF**, vitamin B2) to generate the heterocyclic core. A photoinduced single electron transfer

(SET) from benzoic acid to the triplet excited state of (−)-riboflavin (E^*_{RED} (^{3}**RF***/**RF**$^{\bullet-}$)=+1.46 V *vs* SCE) was suggested as the key-step (Scheme 31). The catalytic cycle was likely initiated by the protonation of (−)-riboflavin. Subsequent SET process from the carboxylate anion to protonated riboflavin yielded the protonated flavin radical and the *O*-centered radicals **31.2**$^{\bullet}$, which can undergo rapid cyclization to intermediates **31.3**$^{\bullet}$. Final oxidation and re-aromatization released the products **31.4**, while the reduced (−)-riboflavin was in turn reoxidized by molecular oxygen.[95]



Scheme 31. Riboflavin-catalyzed synthesis of benzocoumarins.

Isochromanones and isochromenones were obtained *via* the addition of a photogenerated aryl radical bearing a COOH substituent in the *ortho*- position (in turn obtained *via* Ru^{II} photocatalyzed reduction of differently substituted arenediazonium salts derived from anthranilic acids) onto styrenes.[96] In alternative, the COOH group may be converted into an alkynoate (see compounds **32.1**, Scheme 32), wherein the cyclization step occurred following the radical addition of a α-oxy radical (generated from THF co-solvent) onto the C≡C triple bond. The resulting vinyl radicals **32.3**$^{\bullet}$ underwent cyclization affording, after oxidation of the radical adduct, the desired product.[97] Notably, α-oxy radicals were generated *via* photocatalyzed reduction of the peroxide TBHP and hydrogen atom abstraction operated by the resulting *t*BuO$^{\bullet}$ radical. Analogously, coumarins were prepared under metal-free conditions *via* the radical addition of sulfinic acids onto propiolates **32.1** in the presence of Eosin Y as the photocatalyst.[98]

4.3. Other oxygen heterocycles

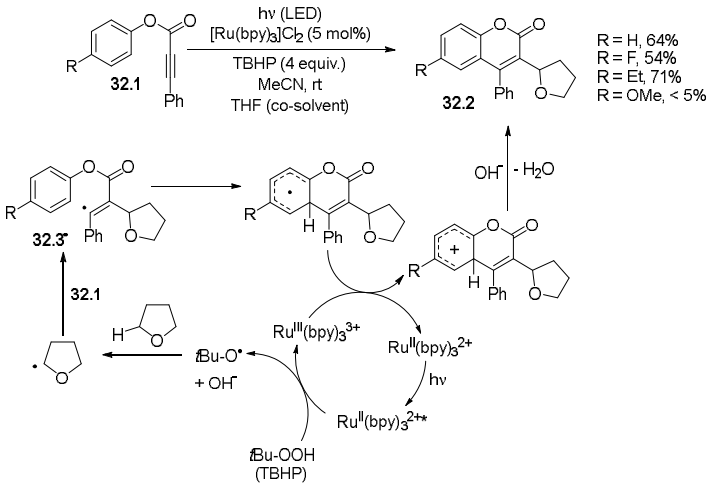
Tetrahydropyrans can be smoothly obtained *via* bromoetherification of alkenols in the presence of a Ru^{II} visible-light absorbing photocatalyst, that promotes the generation of bromine from CBr_4 (*via* the $Br_3C^{\bullet}$ radical). The subsequent trapping of Br_2 by an aromatic pentenol followed by cyclization led to the desired tetrahydropyran.[99]

A photocatalyzed ring enlargement/de-aromatization occurring on furan **33.1** and mimicking the Achmatowicz rearrangement was exploited for the synthesis of *2H*-pyran-3(*6H*)-one **33.3**. Indeed, light induced fragmentation of the persulfate anion led to the formation of oxocarbenium ion **33.2**$^{+}$, that, after loss of the X group, afforded **33.3**, a building block for bioactive compounds, including the bicyclic alkaloid monanchorin (Scheme 33).[100]

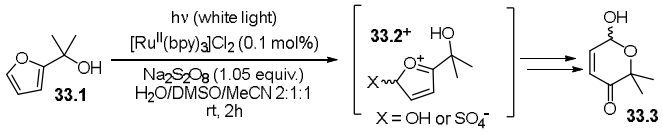
A general photoredox-catalyzed intramolecular cyclization was developed for the synthesis of trifluoromethylated oxygenated heterocycles. The reaction proceeded smoothly under mild photocatalytic conditions with high functional group tolerance and a broad substrate scope.

To extend the protocol, alkynols **34.1** were used in the presence of the Umemoto's reagent along with various photoredox catalysts (*e.g. fac*-Ir(ppy)$_3$) under visible light irradiation to form six-membered trifluoromethylated cyclic enol ethers **34.2** in more than 70% yield (Scheme 34).[101] The proposed mechanism involves the photogeneration of the $F_3C^{\bullet}$ radical, that is then trapped by **34.1** to form the corresponding vinyl radicals **34.3**$^{\bullet}$ stabilized by the adjacent aromatic ring. These radicals are then oxidized

to vinyl cations **34.3**$^+$, which can be attacked intramolecularly by the tethered heteroatom-based nucleophile to give the desired CF_3-substituted heterocycles.[101]



Scheme 32. Photocatalyzed synthesis of coumarins from aryl 3-phenylpropiolate esters.



Scheme 33. Preparation of the *2H*-pyran-3(*6H*)-one core.

5. Larger than six-membered rings

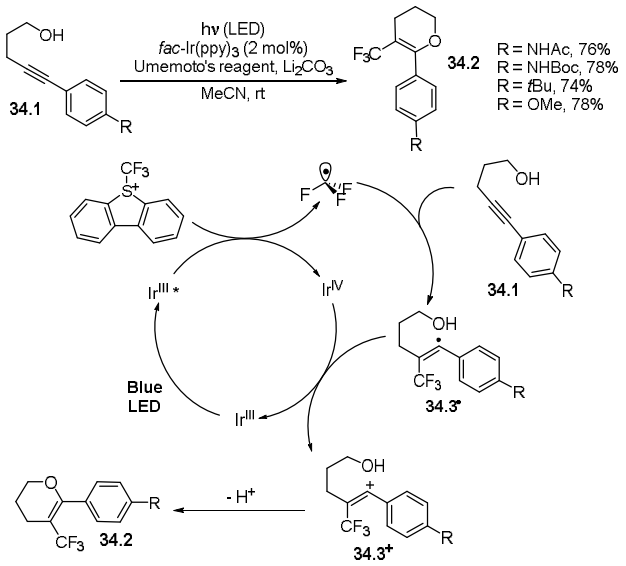
Only a couple of examples on the photocatalyzed construction of rings containing more than six atoms have been reported and most of them are related to (differently saturated) oxepine derivatives. These compounds, as representative seven-membered cyclic ethers, are widely encountered structural motifs in many natural products and pharmaceuticals with a variety of physiological and biological activities. Thus, the development of efficient strategies to easily assemble this significant scaffold has received considerable attention.[102,103]

An intramolecular cycloetherification was used for the synthesis of tetrahydrobenzo[*c*]oxepine **35.2** (58% yield).[104] In this case, excitation of 1,4-dicyanonaphthalene (DCN) caused the oxidation of anisole **35.1** that upon a deprotonation/oxidation sequence generated the carbocation **35.3**$^+$. Intramolecular nucleophilic addition of the -OH group completed the sequence (Scheme 35).[104]

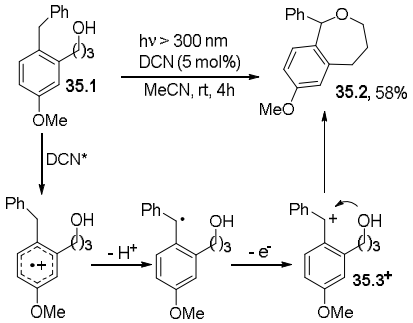
The reaction of (*E*)-1-(2-(allyloxy)aryl)-3-(dimethylamino)prop-2-en-1-ones **36.1** with $BrCF_2COOEt$ was investigated under irradiation with white LEDs (30 W, Scheme 36). Catalyst screening demonstrated that $[Ir(ppy)_2(dtbbpy)]PF_6$ was the premium choice.[105] Addition of the $^•CF_2COOEt$ radical onto the propenyl group followed by a radical addition cascade process furnished the final products **36.2** in 33-64% yield.

The first visible-light-driven hydrocarboxylation of alkynes, as well as carbocarboxylation, was recently described by using CO_2 *via* iridium/cobalt dual catalysis. These transformations provided access to various pharmaceutically important heterocycles in a one-pot procedure from readily available alkynes (*e.g.* **37.1**). Benzoxepinones, such as **37.2**, (but also coumarins and 2-quinolones) were directly accessed through a one-pot alkyne hydrocarboxylation/alkene isomerization/cyclization sequence. The Ir-based photocatalyst has the dual role to promote a SET process in alkyne hydrocarboxylation and an energy transfer process for the subsequent alkene isomerization (Scheme 37).[106] It is worth noting that the hydrocarboxylation

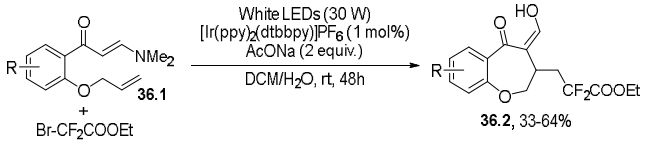
proceeded with CO_2 insertion preferentially at the alkyl-substituted site. The choice of phosphine ligand was crucial, since the adoption of other ligands resulted in complete suppression of the reaction.



Scheme 34. Synthesis of pyrans **34.2** from alkynols **34.1**.



Scheme 35. Photocatalyzed benzylic activation in anisole **35.1**.



Scheme 36. Synthesis of CF_2-containing benzoxepinones.

Scheme 37. Photocatalyzed synthesis of a benzo[*c*]oxepin-3(*1H*)-one.

6. Conclusions

This book chapter provides an up-to-date review of the diverse photoredox catalytic approaches for the generation of radicals that lead to oxygen containing heterocycles/heteroaromatics. Since both photocatalysis and the synthesis of heterocycles represent key topics in modern organic chemistry, this compendium provides a review of their merging. Albeit the formation of three and four-membered rings (epoxides, oxetanes) is quite rare, several photocatalytic strategies to build five and six-membered rings, as well as larger heterocyclic rings, have been reported and collected here. Moreover, the number and variety of examples clearly underline the maturity of photoredox catalysis in accomplishing the task of generating highly energetic intermediates under mild conditions, affording novel and, wherever possible, simpler ways to construct heterocycles. These photochemical protocols are expected to furnish in the near future intriguing routes to the synthesis of a large variety of heterocyclic compounds.

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