

Recent Developments in Arene Photocycloadditions

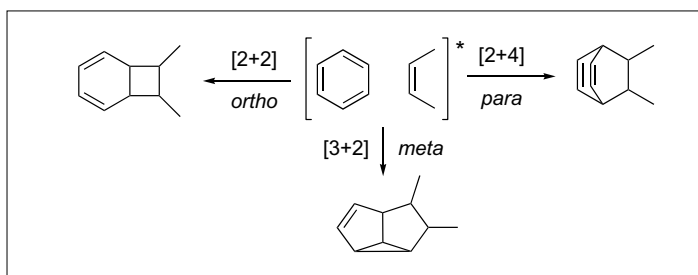
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Abstract: The photocycloaddition of alkenes with aromatic systems may proceed through three reaction modes, affording different types of products: *ortho*, *meta*, and *para*. These reactions generate a considerable increase in complexity, and yield products arduously attainable by classical synthetic steps. Whereas the *meta*-photocycloaddition has gained a lot of attention in the last decades because of its applicability in the total synthesis of numerous natural products, the *ortho*- and *para*-cycloadditions still have a great potential for further development. In this highlight, we review the latest advances in the field of photocycloaddition of alkenes to aromatic systems.

Keywords: Arene photocycloaddition · Lacifodilactone F

1. Introduction

Aromaticity is a fascinating property, which has been the subject of many studies that were undertaken from all sorts of perspectives. For the synthetic organic chemist, the extra stabilization of structures which feature cyclic arrays of $4n+2$ conjugated π -electrons has been a very useful concept, in terms of a driving force for molecules able to access such a state, or in terms of their resistance to aggressive reagents. The specific case of benzenoid substrates has been extensively studied in the past century, and synthetic transformations of such cores are now part of the standard synthetic toolbox (*e.g.* aromatic electrophilic or nucleophilic substitutions, metal-halogen exchanges, transition-metal catalyzed cross couplings *etc.*). On the other hand, the unusual stability of aromatic rings prevents them from engaging in typical reactions of alkenes.



Scheme 1.

For example, benzenoid substrates rarely undergo Diels-Alder [4+2] cycloaddition with olefins or dienes, *i.e.* as dienes or dienophiles. The ‘aromatic resonance energy’ of the ground state of benzenoid systems of *ca.* 20 kcal/mol may significantly raise activation barriers, thus preventing many processes from occurring thermally at synthetically relevant temperatures (<150 °C). On the other hand, it is well known that photoexcitation is capable of transmitting a substantial amount of energy to a substrate without thermal damage; it may therefore be expected that this process can trigger normally impossible reactions. This is indeed the case, *i.e.* excited aromatic compounds are for example capable of undergoing cycloadditions. The interest of such reactions is dual: it may be convenient to exploit the stability of aromatic structures in the initial phases of a synthetic plan, and *then* to convert the substrate into a more complex one by a process that is normally orthogonal to any other chemical reaction. Secondly, many of the structures that can be accessed by arene photocycloadditions are so complex that they cannot be assembled

efficiently by means of classical thermal reactions. We can distinguish three types of arene-alkene cycloadditions: *ortho*, *meta* and *para* (Scheme 1). These descriptors only indicate the connection points of the alkene to the aromatic molecule; attempts to draw reaction mechanisms by curly arrows are generally futile because, in their excited states, molecules often feature an electron distribution that cannot be conveniently represented by simple Lewis structures.

Since the first account of these cycloaddition by Büchi and Angus and Bryce-Smith (*ortho*),^[1] Wilzbach and Kaplan, and independently the Bryce-Smith group (*meta*),^[2] and Wilzbach and Kaplan (*para*),^[3] there has been a steady stream of work in this area, further boosted by the spectacular exploitation of such reactions in natural product synthesis by Wender and Howbert.^[4] The field has been reviewed on several occasions^[5,6] (the latest being the excellent review by Hoffmann^[7]). In this overview, we will focus on recent application of these reactions in the synthesis of complex molecules.

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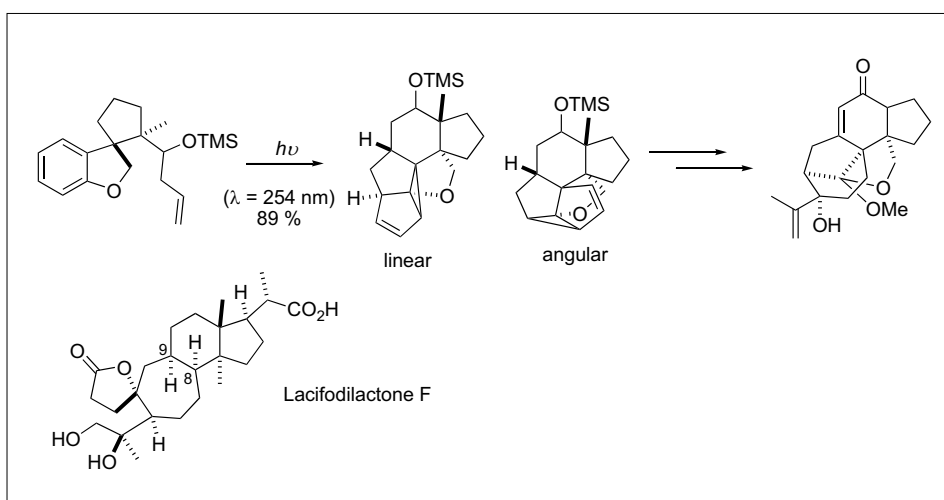
2. *meta*-Cycloaddition

Lacifodilactone F is a triterpenoid isolated recently from the Chinese herb *Schisandra*, bearing a 5,6,7-tricyclic skeleton. Wang and Chen achieved the construction of its core using a *meta*-photocycloaddition as the key step (Scheme 2).^[8] The first photocycloaddition attempts with less complex precursors only led to degradation; on the other hand, introduction of a trimethylsilyloxy group on the tether and an oxygen atom at the 1-position of the arene proved to be crucial. Surprisingly, the stereochemistry at the siloxyl center does not affect the *meta*-photocycloaddition; however silylation helps to orient the olefin group towards the arene moiety thus ensuring a high yield. The *exo* products are formed exclusively, through a boat-like conformation. The linearly and angularly fused products do not need further purification, and are further elaborated into the target molecule in four additional steps.

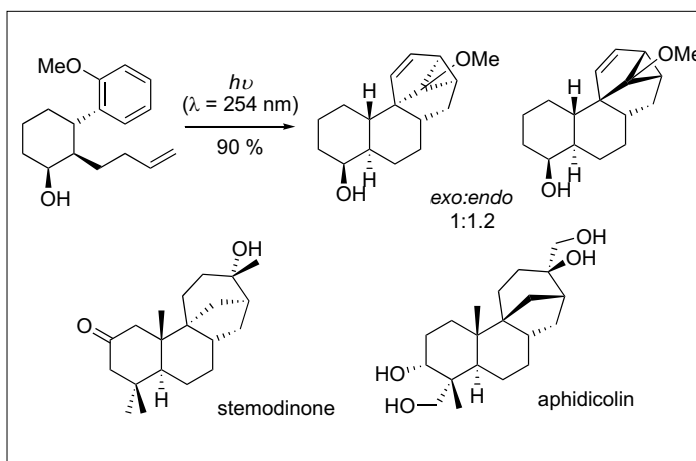
This flexible approach allows not only the construction of the 5,6,7-tricyclic skeleton with two adjacent quaternary centers, but also to access both configurations at the C(8) and C(9) positions of the lacifodilactone F.

The [3+2] *meta*-photocycloaddition was shown to take place through an *exo* rather than an *endo* exciplex. Additionally it was shown that tethers with four linking units give usually rise to very low quantum yields. This observation suggests that the biologically potent aphidicolin might be difficult to access *via* a *meta*-photocycloaddition reaction, since a four-carbon tether and an *endo* exciplex would be required to build up its core structure.^[9] Nevertheless, Russell and coworkers found that a cyclohexane ring on the tether helped to constrain the tether in a favorable conformation, and the photocycloadducts were obtained in good yields (although as a 1:1.2 mixture of *exo* and *endo* isomers) (Scheme 3). The core for either the aphidicolin or the stemodinone could be assembled in such a reaction.

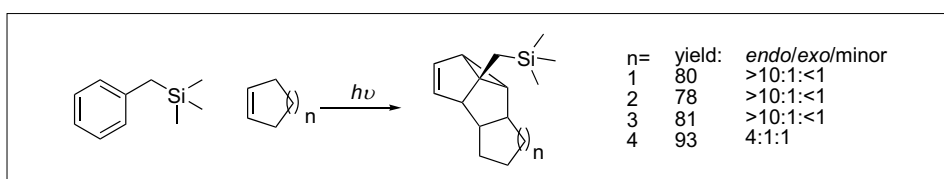
The intermolecular arene–olefin photocycloaddition is a great tool for rapidly increasing molecular complexity, but it suffers sometimes from idiosyncratic behavior and substrate-specificity. For example the reaction of anisole with cyclopentene furnishes the *endo meta*-photocycloaddition product in 80–85% yield, whereas the reaction with cyclohexene is much less stereoselective and efficient (only 20% yield). De Long *et al.* showed very recently that the yields of arenes with a benzylic silicon atom are much more reliable (Scheme 4).^[10] This probably arises from the β -silicon effect, a phenomenon well established for ground-state chemistry. Through hyperconjugation, the silicon atom at the β -position overlaps with the excited-state electron-deficient aromatic system, therefore minimizing the



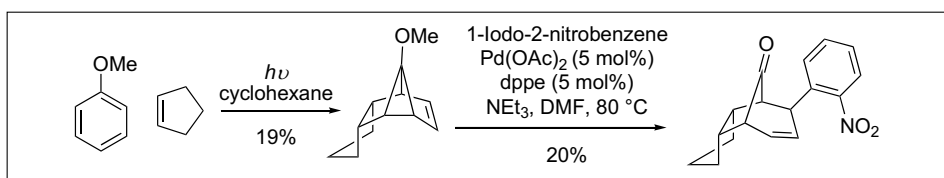
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

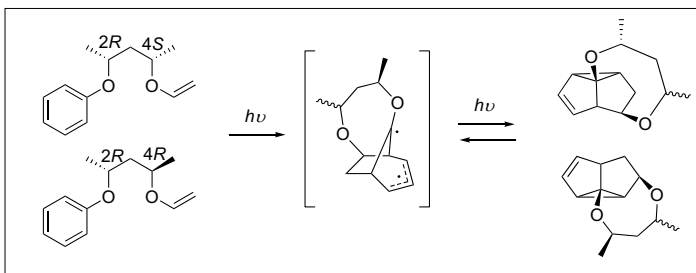
energy loss due to the broken aromaticity during the reaction. This allows the reaction of ring systems even larger than cyclopentene with aromatic rings, in high stereoselectivities and yields.

The reaction products of the *meta*-photocycloaddition are highly strained molecules and can undergo opening of the cyclopropylic ring with many reagents to

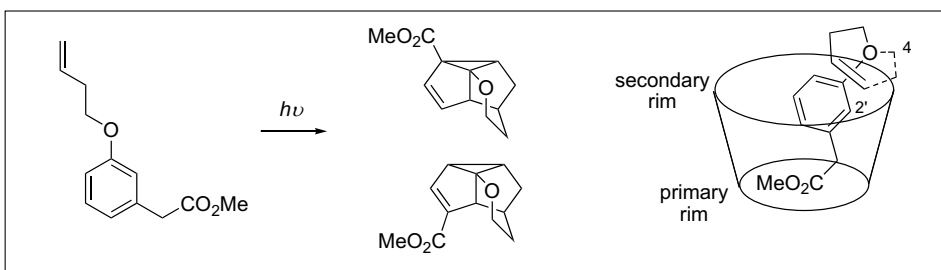
afford bicyclo[3.2.1] compounds. Electrophiles are known to add to electron-rich olefins and the resulting cationic intermediate fragments give bridged bicyclic compounds. Penkett and coworkers described recently the first carbocation-mediated reaction on *meta*-photocycloaddition products, coupled with a Heck-type reaction (Scheme 5).^[11]

3. Asymmetric *meta*-Cycloadditions

The reaction of an arene and an alkene in a *meta*-photocycloaddition reaction converts the flat (thus achiral) reaction sites into three-dimensional and potentially chiral moieties. Four new stereocenters are installed in this [3+2] cycloaddition. Therefore it is not surprising that investigations were undertaken to render this process asymmetric. The main strategy towards this goal was the introduction of a chiral tether for an intramolecular reaction. Sugimura and coworkers published recently very promising results with chiral 2,4-pentanediol (PD) tethers (Scheme 6).^[12] In this scenario, the vinyl ether adds to both *ortho* positions of the phenyl group. The face differentiation is excellent (controlled solely by the C(2) center), but a mixture of regioisomers is obtained (the ratio is then dependant on the configuration of the position 4, going from 70:1 for the *RR* to 2.7:1 for the *RS*). Related work was reported by Garcia and coworkers.^[13]

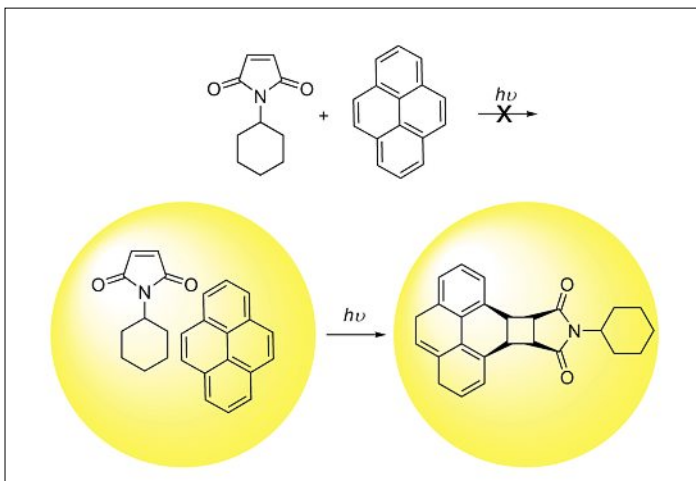


Scheme 6.



Scheme 7.

Another asymmetric approach was investigated by Van der Eycken and coworkers.^[14] They studied the intramolecular *meta*-photocycloaddition in the solid phase in the presence of cyclodextrin (Scheme 7). The *meta*-substituted arenes formed the [3+2]-photocycloadducts as a 1:1 mixture of two products. The presence of a CD host also led to the formation of the two products but in a ratio of 1:3. These two products show different enantiomeric enrichment, due to different types of interaction with the host: it was proposed that the vicinity of the protons H-C(2') and H-C(4) to the secondary rim of the CD was the main factor.

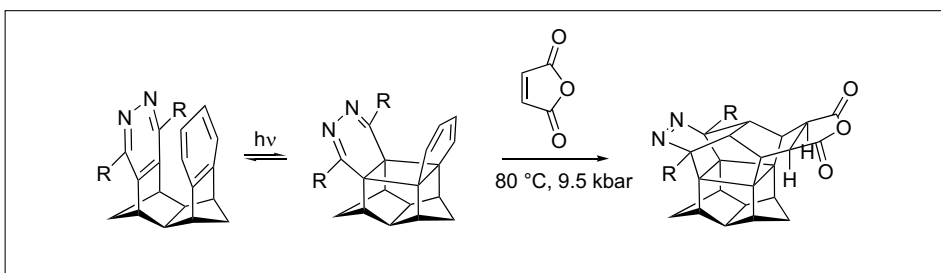


Scheme 8.

4. *ortho*-Cycloadditions

Fujita and coworkers first described the derivatization of higher and unreactive aromatic compounds *via* [2+2] photocycloadditions.^[15] The penanthrene, fluoranthrene and pyrene systems are known to be inert under ordinary photochemical conditions. However, in a self-assembled M_6L_4 -type coordination cage, which assembles six (en) Pd^{2+} and four *exo*-tridentate ligands to form a large hydrophobic cavity, penanthrene undergoes *ortho*-photocycloaddition quantitatively in the *syn* stereochemistry when irradiated in the presence of maleimide (Scheme 8). The cage-induced proximity of the two substrates reduces the entropy costs of the process.

After their very impressive total synthesis of pagodane, Prinzbach and coworkers published last year an approach to the synthesis of azapagodan-type cage molecules *via* a [6+6] photocycloaddition.^[16] At 254 nm (rayonet photoreactor) the cycloaddition forming the tetracyclic



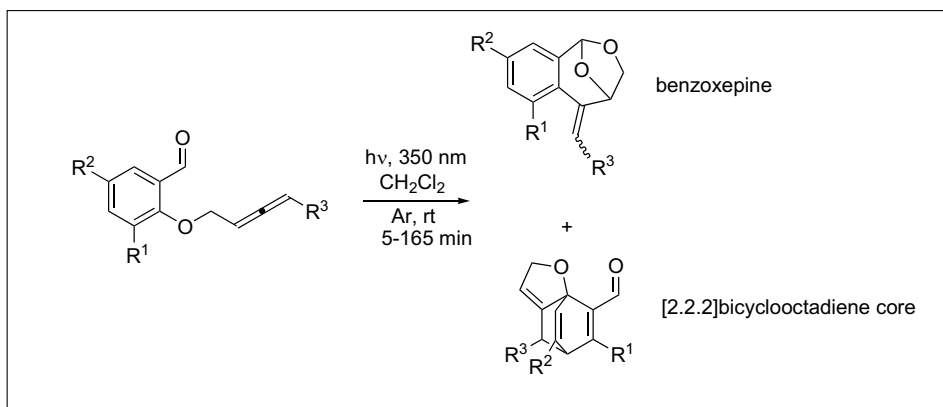
Scheme 9.

ring reaches a photostationary equilibrium of 2:1 (Scheme 9). Cycloreversion of the products could be induced by irradiation with polychromatic light in a pyrex vessel. After isolation, the obtained product could be further reacted with maleic anhydride to give the final 'domino' product in 10% yield, in a multiple [4+2] thermal Diels-Alder cascade.

5. *para*-Cycloadditions

There have been few examples of *para*-photocycloadditions, as their quantum yields are generally lower than those of other photoinduced processes. However, we recently found that allenes are capable of additions to arenes in the intramolecular [4+2] mode (Scheme 10).^[17] Thus, photolysis of

o-allyl salicylaldehydes gave a mixture of benzoxepines and *para*-cycloadducts, in variable ratios. Interestingly, steric bulk on the aromatic ring favors the *para*-mode, and up to 96% of products containing a [2.2.2] bicyclooctadiene core were isolated. This new reaction opens new synthetic prospects in such photocycloadditions, because of the simplicity of the reactant (very easily prepared by simple salicylaldehyde allylation), and the high complexity of the cycloadduct, which could be further elaborated towards natural targets.



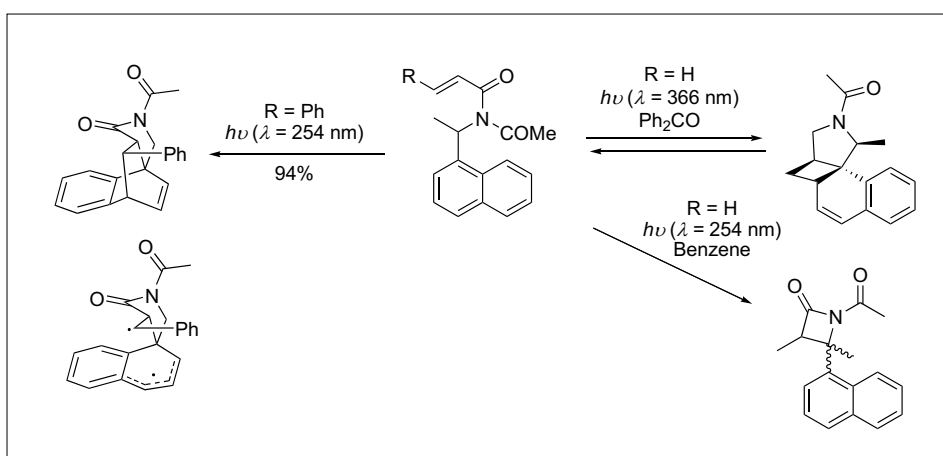
Scheme 10.

6. Condition-dependent Cycloaddition Modes

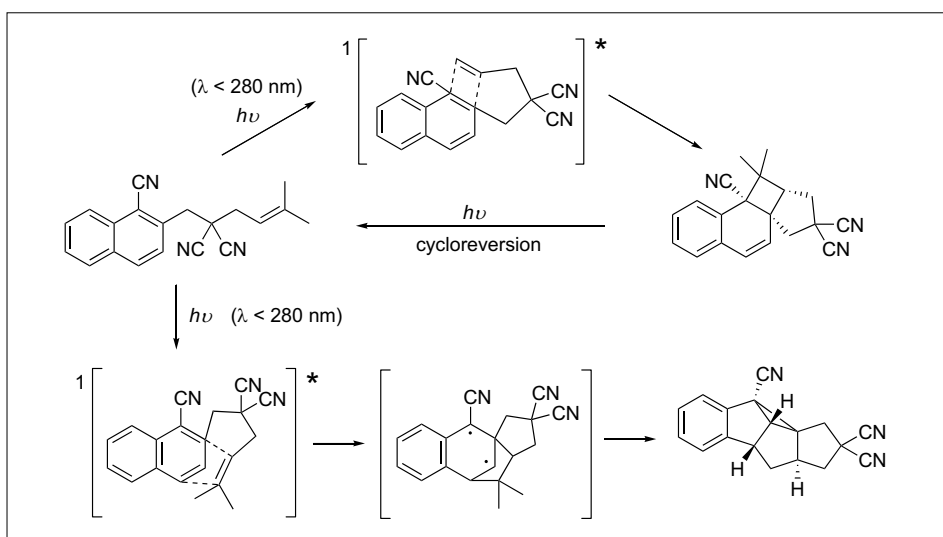
Bichromophoric compounds may undergo different photochemical reactions. Kohmoto *et al.* recently controlled photochemical reactions either by selective excitation of one of the chromophores, or by variation of substituents.^[18] Thus, *N*-(naphthylethyl)prop-2-enamides selectively reacted in three different intramolecular photochemical reactions: [2+2] or [4+2] cycloadditions, or Norrish-type-II cyclization (Scheme 11). While the [2+2] photocycloaddition could be selectively sensitized by benzophenone, the Norrish-type-II cyclization was the only product obtained with benzene sensitization. Kohmoto attributes this effect to a selective excitation of the naphthalene moiety by the excited benzophenone, whereas excited benzene transfers its energy preferentially to the enamine moiety. Substitution at the β -position of the unsaturated amide inhibits the Norrish-type-II cyclization, allowing the [4+2] photocycloaddition to take place in excellent yields. As a *supra-supra* [4+2] concerted reaction mode is normally photochemically forbidden and both *E* and *Z* precursors gave the same products, Kohmoto suggested that the reaction takes place *via* a biradical intermediate; the stereochemistry at the phenyl-substituted carbon is thus lost.

The formation of benzo- and benzopentacyclic compounds by the photocycloaddition of alkenes with naphthalene was recently studied by Mizuno and coworkers.^[19] They found that two different reactions can take place in such a system. During the initial stage (less than 20% conversion) mainly the *ortho*-photocycloadduct was detected (Scheme 12), whereas prolonged irradiation furnished the *meta*-cycloadduct as the sole product, in yields up to 84%. The *ortho*-photocycloaddition was shown to take place ten times faster than the *meta*-cycloaddition. However, due to its styrene-like character, the *ortho*-photocycloadduct can undergo a photoinduced cycloreversion under the reaction conditions, while the *meta*-cycloadduct is gradually accumulated.

Ohkura, Seki and coworkers studied



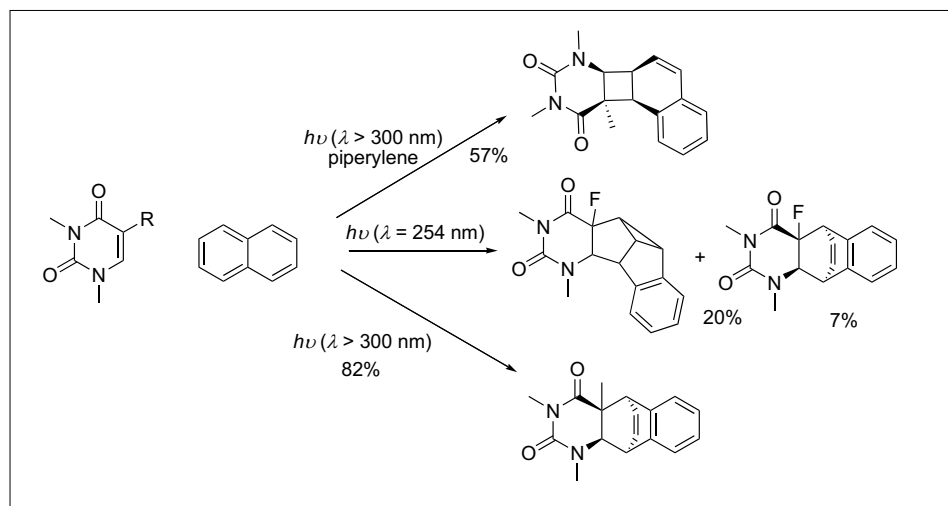
Scheme 11.



Scheme 12.

recently the reaction of differently substituted uracil moieties with naphthalenes.^[20] Different reaction modes were observed. While addition of piperylene to the reaction mixture irradiated at wavelengths above 300 nm led to preferential [2+2] photocycloaddition (Scheme 13), a high-yield photo-Diels-Alder reaction dominated in the

absence of a quencher. On the other hand, irradiation at 254 nm formed the *meta*-photocycloadduct in 20% yield, with small amounts of the *para*-cycloadduct as a side product. Very recently, a diastereoselective version of this reactions was published, using the chemotherapeutic furan-containing analogue *tegafur*.^[21]



Scheme 13.

7. Concluding Remarks

Half a century after the first observation of arene-alkene photocycloaddition, there is still considerable room for improvement, in particular with regard to the predictability of such processes. Indeed, sometimes very subtle changes in the reactant structure and/or the reactions conditions can switch the mode of cycloaddition between *ortho*, *meta*, and *para*, or even completely shut down the reaction. On the other hand, as it is still apparent from the few examples discussed above, the power of this process which allows the manipulation of aromatic rings, and even breaking the aromaticity under smooth conditions, constitutes a driving force for further studies and for the use of arene photocycloadditions in the synthesis of complex molecules. The elaboration of more carefully controlled reaction conditions, in particular with regard to the wavelength and the presence/absence of triplet sensitizers/quenchers, will definitely play a significant role in forthcoming explorations of this fascinating class of reactions.

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