

Photocycloadditions of benzene derivatives and their systematic application to organic synthesis

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ABSTRACT

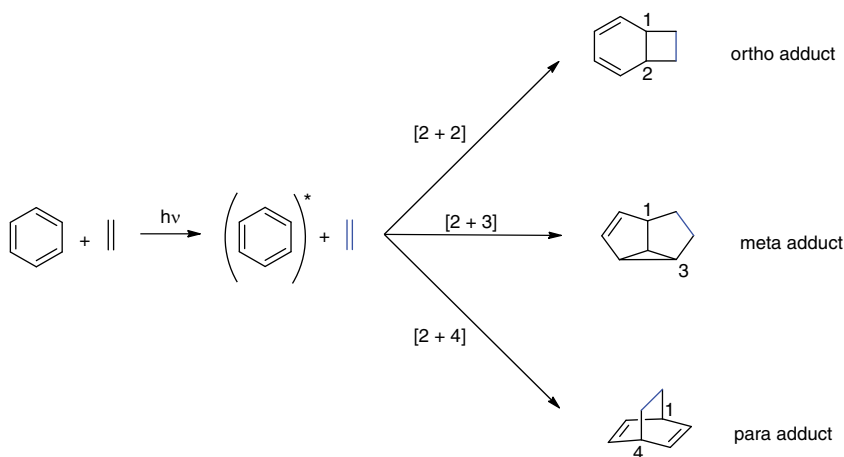
Photocycloadditions of benzene derivatives with alkenes play an important role as key steps in organic synthesis. Intramolecular reactions have been most frequently studied in this context. Often, meta or [2 + 3] photocycloadditions take place in competition with ortho or [2 + 2] additions. The influence of the substitution pattern and the spin multiplicity of the excited state on the outcome of these reactions is discussed. A topological analysis permitting a systematic application of the [2 + 3] photocycloadditions to the total synthesis of natural products is presented and a selection of corresponding syntheses is discussed. More recently the [2 + 2] photocycloaddition and consecutive rearrangements on organic synthesis have been published. Some approaches in the context of asymmetric synthesis have also been reported.

Keywords: aromatic compounds, meta or [2 + 3] photocycloaddition, molecular complexity, natural products, ortho or [2 + 2] photocycloaddition, photocycloaddition, spin multiplicity, terpenes, total synthesis.

Introduction

Photochemical reactions of simple compounds can generate a high degree of molecular complexity and diversity which is of high interest, for example, for the search of new biologically active compounds.^[1] The photochemical reactivity of organic compounds is significantly different from their ground state reactivity. This is due to the fact that photochemical or electronic excitation modifies the electronic configuration of such compounds.^[2,3] New compounds or compound families become easily available that cannot, or only with difficulty, be synthesised by more conventional methods of organic synthesis. Consequently, these reactions have become an important tool in organic synthesis.^[4–7] During recent years, photochemical reactions became also particularly attractive in chemical and pharmaceutical industries when searching for new biologically active compounds.^[8,9] Photocycloadditions of alkenes with electronically excited benzene derivatives are typical examples. While ground state reactions of such compounds are often characterised by a high tendency to regenerate aromaticity in the products, photochemical reactions are frequently characterised by a high tendency to lose aromatic character in the products. In this context, it should also be mentioned that photochemical excitation significantly affects the aromatic or anti-aromatic character.^[10–13] Thus benzene derivatives become anti-aromatic when they are photochemically excited. Consequently, the reactivity is significantly increased. For the same reason, product formation at the excited state potential energy surface is directed to structures which are less stable at the ground state potential energy surface. Thus, a high degree of molecular complexity is generated in one step with relatively simple starting compounds. In the context of sustainable chemistry, it should be pointed out that in these reactions the concept of the photon as a traceless reagent is realised.^[14]

Three different modes of photocycloaddition are possible between ground state alkenes and electronically excited benzene type compounds (Scheme 1). They provide efficient access to complex non-aromatic polycyclic compounds. Ortho ([2 + 2])



Scheme 1. Three modes of photocycloadditions of alkenes to electronically excited benzene derivatives.

photocycloadditions lead to bicyclo[4.2.0]octa-2,4-dienes, meta ([2 + 3]) photocycloadditions generate tricyclo[3.3.0.0]octa-3-enes and para ([2 + 4]) photocycloadditions give rise to bicyclo[2.2.2]octa-2,5-dienes.

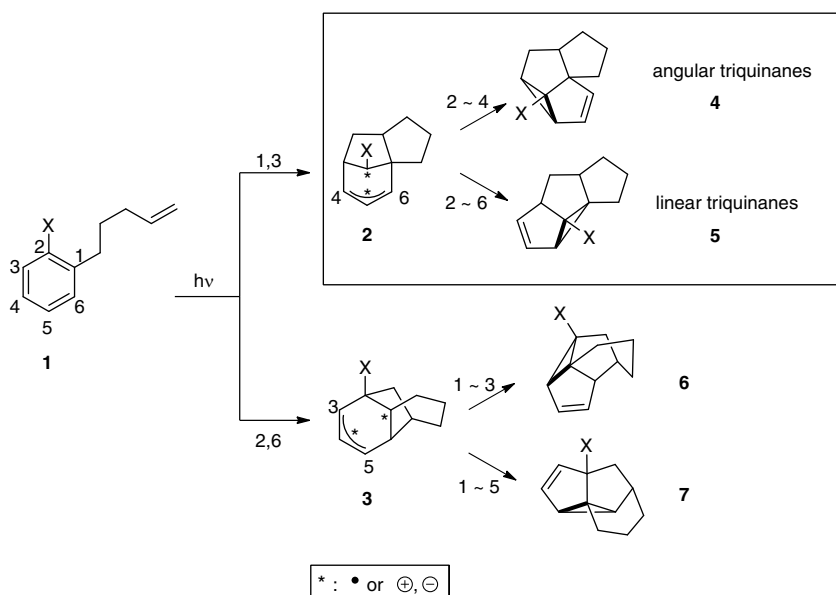
Despite promising recent studies,^[15–17] para photocycloadditions are rarely observed for benzene-like aromatic compounds. Ortho and meta photocycloadditions have been studied much more intensively since their discoveries, respectively, in 1957^[18,19] and 1966.^[20,21] However, many aspects, such as the competition between these modes, still need intensive investigation. Also, the influence of substituents or the influence of the spin multiplicity on this competition are not yet well understood. These are important topics when the reactions are systematically applied to organic synthesis. Mechanisms based on the formation of an exciplex have been proposed to explain the selectivity.^[22,23] The selectivity is strongly influenced by the nature of the substituents because they affect the electron-donating and accepting properties of the partners. A large electronic difference between the partners induced by the substituents directs the reaction towards the ortho photocycloaddition whereas a small difference favours the meta photocycloaddition.^[22,24] The substitution pattern may also cause an exergonic photochemical electron transfer between the reaction partners leading to non-cyclisation products. A common intermediate for all three photocycloadditions was later found in a computational study.^[25] It is easily accessible from the S_1 state and corresponds to a conical intersection between the S_1 and S_0 surfaces. Over the years, numerous reviews have described many aspects of these reactions, ranging from experimental conditions and mechanistic descriptions to applications in total synthesis.^[26–30] The present article gives an overview of historical and recent applications in total syntheses. Topological aspects are detailed as they are crucial for the planning of total syntheses. Furthermore, new insights on the competition between ortho and meta photocycloadditions at their singlet excited state are highlighted.

Meta photocycloaddition at the singlet state

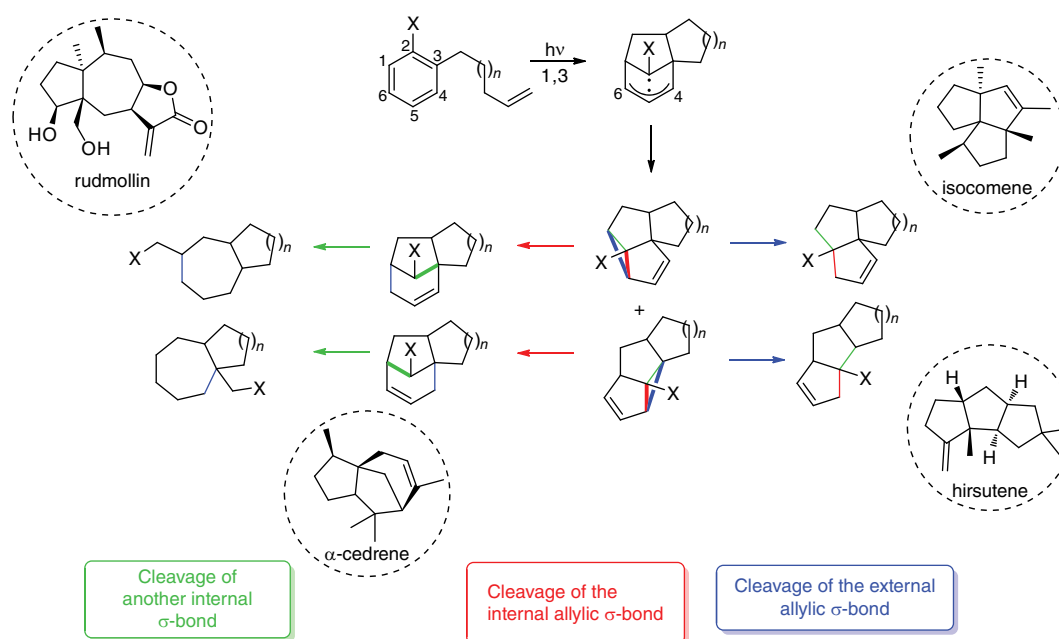
It was early established that the meta photocycloaddition occurs at the singlet excited state, based on the observed retention of configuration of the alkene partner and quenching experiments.^[31] The mechanism of the meta photocycloaddition is detailed for the intramolecular version in Scheme 2. The intramolecular [2 + 3] cycloaddition of the aromatic compound **1** excited to the singlet state to the alkene function can either occur at positions 1,3 or 2,6, to lead to intermediates **2** or **3** respectively. They also possess zwitterionic character due to the singlet multiplicity.^[32] After this initial formation of two σ -bonds, the charge or radical combination leads to two different products for each intermediate depending on the generated cyclopropane. The more common intermediate **2** usually yields angular triquinanes **4** or linear triquinanes **5**. Intermediate **3** gives structures **6** or **7**. Due to the zwitterionic character of the intermediates, electronic properties of substituent X have an influence on the regioselectivity. If X is electron-donating, it directs the addition towards positions 1,3 to form intermediate **2**, while positions 2,6 and intermediate **3** are preferred when X is electron-withdrawing.^[20,33,34] In the case of the absence of a strong donor or acceptor substituent X, compelling evidence showed the biradical nature of these intermediates.^[35,36]

Applications of meta photocycloadditions in total syntheses

The meta photocycloaddition gives access to many different scaffolds depending on the opening of the cyclopropane ring (Scheme 3). A topological analysis is helpful for a targeted application to the synthesis of natural compounds. On the one hand, cleavage of the external allylic σ -bond (blue) leads to either angular triquinanes like isocomene, or linear triquinanes like hirsutene. On the other hand, cleavage of



Scheme 2. Intramolecular meta photocycloaddition.



Scheme 3. Natural products synthesis by different cyclopropane openings. A topological analysis.

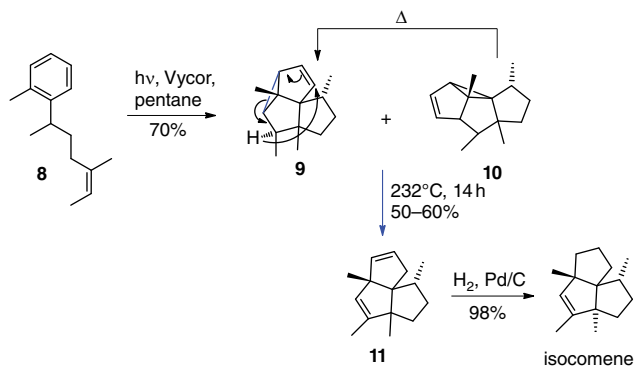
the internal allylic σ -bond (red) gives sesquiterpenoids like α -cedrene. From this type of product, another internal σ -bond (green) can be cleaved leading to other polycyclic structures like rudmollin.

The pioneer work of Wender and Howbert displayed many applications of the meta photocycloaddition in total syntheses of natural products.^[37] In this first of a large series of articles, in 1981, they described their strategy considering the mode of addition (ortho, meta, para), regioselectivity, *endo/exo* selectivity and stereochemistry. First, they pointed out that the intramolecular reaction drastically reduces the

number of possible cycloadducts compared to the intermolecular version. Then they adjusted the substituents and their electronic properties to favour the meta mode and to direct the regioselectivity. Finally, the *endo/exo* selectivity and stereochemistry were explained by looking at the conformations of the exciplexes. Some of these syntheses will now be briefly discussed focusing on the crucial steps of meta photocycloaddition and cyclopropane opening.

In the total synthesis of isocomene, the meta photocycloaddition of the aromatic compound **8** gives both the linear and angular cycloadducts **9** and **10** (Scheme 4).^[38]

It should be pointed out that the reaction was stereospecific with respect to the chiral centre in **8** which is explained by an allylic 1,3-strain effect.^[39] This was observed in many similar reactions. The linear adduct **10** was transformed into the angular one (**9**) by a thermal vinyl cyclopropane

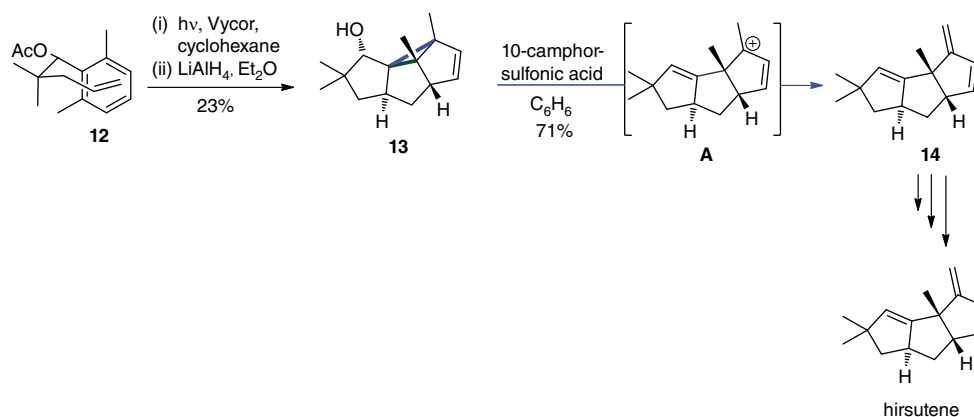


Scheme 4. Total synthesis of isocomene.

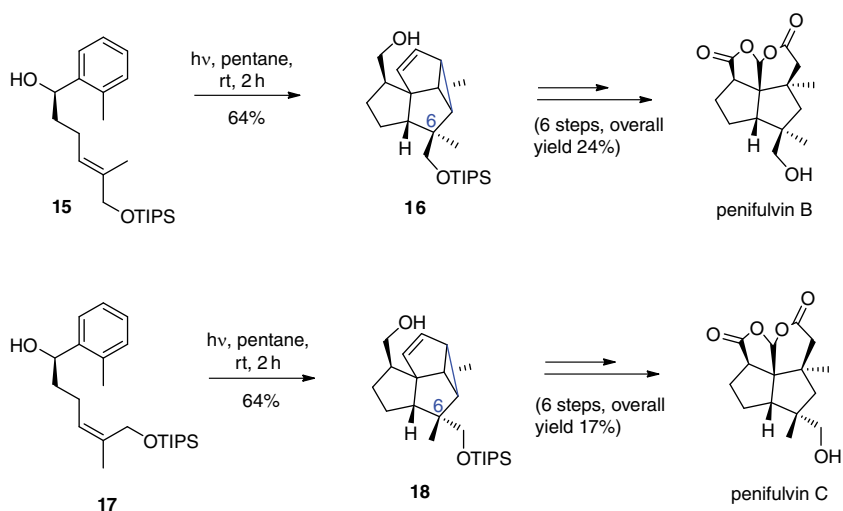
rearrangement. Conveniently, this process also leads to the opening of the cyclopropane by a 1,5-hydrogen transfer to yield product **11**. Isocomene was then obtained by a regio-selective catalytic hydrogenation.

In the synthesis of hirsutene, the meta photocycloaddition was less efficient (**Scheme 5**).^[40] It was improved by adding an acetyl function on the lateral chain of substrate **12**. Treating the meta adduct **13** with 10-camphor-sulfonic acid then led to intermediate **A** with a tertiary allylic positive charge that was neutralised by an E₁ elimination to yield product **14**. Hirsutene was then obtained after four additional steps.

The enantioselective total syntheses of penifulvins A, B and C were developed more recently by Gaich and Mulzer using a similar methodology (**Scheme 6**).^[41,42] The stereogenic quaternary carbon centres in position 6 of adducts **16** and **18** were set by the trisubstituted E/Z double bonds of substrates **15** and **17** respectively. Due to the fact that the photocycloadditions occur at the singlet excited state, no long living radical intermediates are generated enabling E/Z



Scheme 5. Total synthesis of hirsutene.



Scheme 6. Total syntheses of penifulvins B and C in analogy to the synthesis of penifulvin A.

isomerisation. It should be pointed out that such reactions can be carried out with compounds possessing non-protected hydroxy functions.

In the synthesis of α -cedrene, the meta photocycloaddition of compound **19** led to a mixture of products **20** and **21** (Scheme 7). These two adducts converged into product **22** when the internal allylic σ -bond was cleaved by an addition of Br_2 followed by radical debromination using tributyltin hydride. α -Cedrene was finally obtained with 58% yield by a Wolff–Kishner reduction of product **22**.

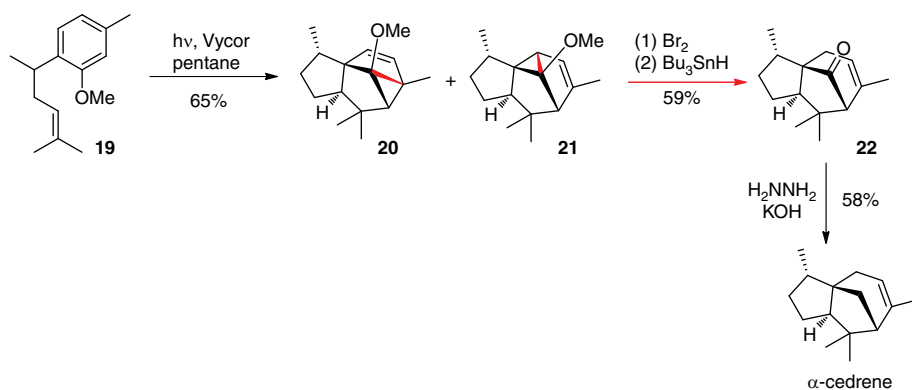
A similar strategy was applied to the synthesis of rudmollin. This synthesis required the cleavage of two σ -bonds of the cyclopropane (Scheme 8).^[43] Irradiation of substrate **23** yielded a mixture of meta adducts **24** and **25**. As for α -cedrene, the cleavage by electrophilic activation of the internal allylic σ -bond of the two products **24** and **25** led to a unique product **26**. Compound **27** was obtained after eight additional steps; its geometry allowed the cleavage of

another σ -bond originating from the initial cyclopropane. Mesylation of the alcohol, followed by addition of lithium aluminium hydride, induced fragmentation to give product **28**. Rudmollin was then obtained after six additional steps.

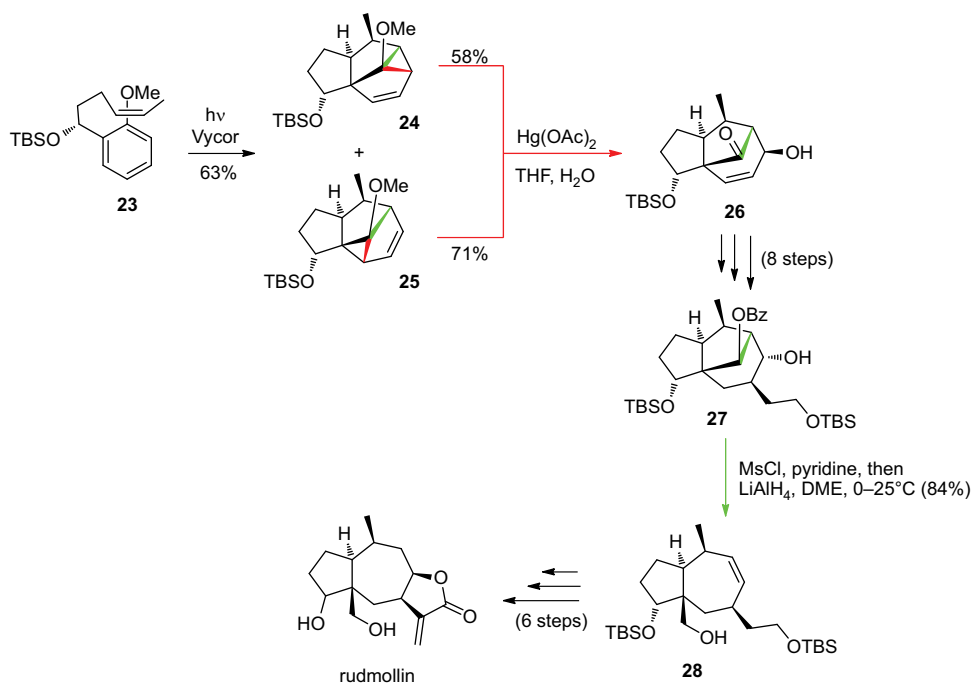
Asymmetric induction of meta photocycloadditions

High diastereoselectivities were observed by Sugimura and co-workers by introducing a chiral tether (Scheme 9). Irradiation of substrate **29** yielded predominantly adduct **31** (70%) and traces of product **30** (<2%).^[44,45]

Several photochemical reactions have been carried out with cyclodextrin (CD) inclusion complexes in order to induce chirality by the host structure.^[46,47] Moderate enantioselectivities were obtained by Vízvárdi and co-workers by complexation of the substrates in CDs (Scheme 10).^[48]

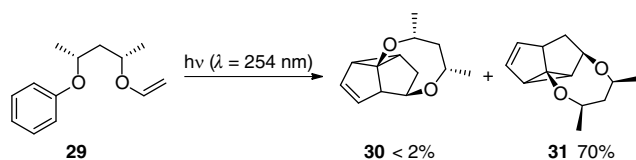


Scheme 7. Total synthesis of α -cedrene.

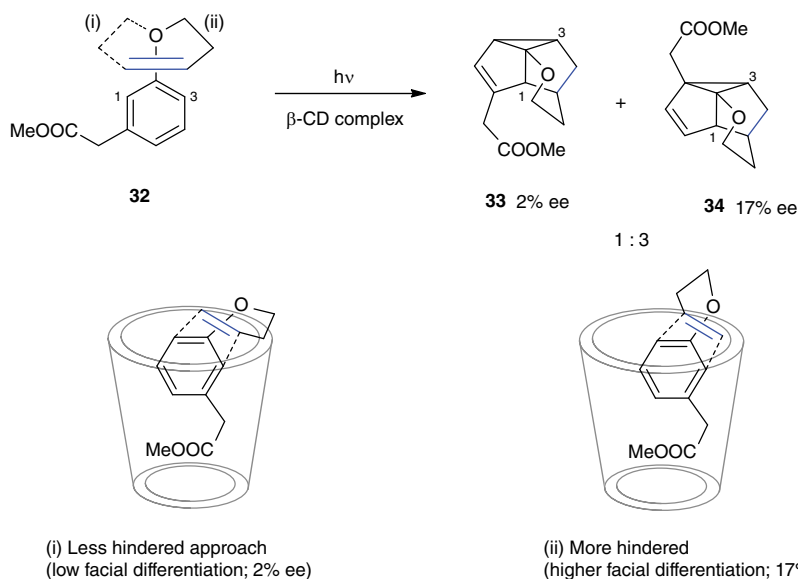


Scheme 8. Total synthesis of rudmollin.

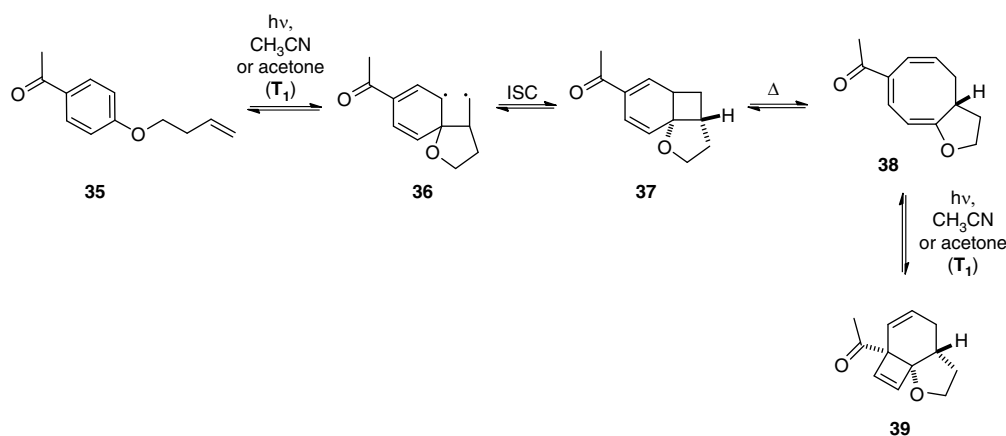
The irradiation of a β -CD complex of substrate **32** yields products **33** and **34** in a 1:3 ratio with an enantiomeric excess (ee) of 2 and 17% respectively. The difference of ee was explained by comparing the approaches leading to each product in the CD cavity. The stereodifferentiation in approach (ii) is more expressed than in approach (i), the facial enantioselectivity is thus higher for product **34** than for product **33**.



Scheme 9. Diastereoselective meta photocycloaddition using a chiral tether.



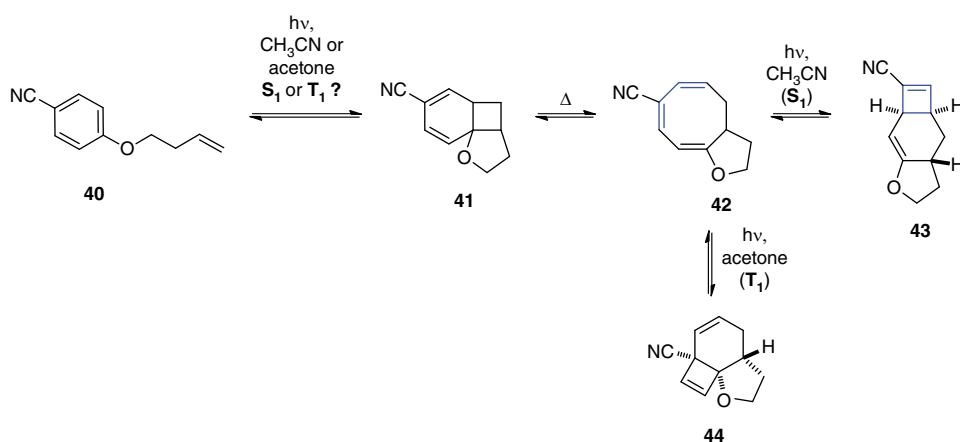
Scheme 10. Enantioselective meta photocycloaddition by irradiating a β -CD complex.



Scheme 11. Ortho photocycloaddition of acetophenone derivative **35**.

Competition between [2 + 2] and [2 + 3] photocycloadditions at the singlet and triplet excited state

The intramolecular ortho photocycloaddition gives access to interesting tricyclic structures that often rearrange into more stable products. Selective ortho photocycloaddition is usually induced by placing an electron-withdrawing substituent on the aromatic ring. Furthermore, acetophenone derivatives give exclusively ortho photocycloadditions since they react at the triplet excited state. In accordance with the El Sayed rules,^[2,49] this is due to the facile intersystem crossing from the $n-\pi^*$ singlet excited state to $\pi-\pi^*$ triplet excited state of the aromatic ketones.^[50] In this case, the primary adduct **37** of ortho photocycloaddition is formed via a biradical intermediate^[51] **36** that combines after intersystem crossing (Scheme 11). The initial ortho photocycloaddition adducts **37** then undergo a spontaneous thermal disrotatory ring



Scheme 12. Ortho photocycloaddition of benzonitrile derivative 40.

opening. Finally, a photochemical disrotatory cyclisation of cyclooctatriene **38** leads to the stable product **39**.^[52]

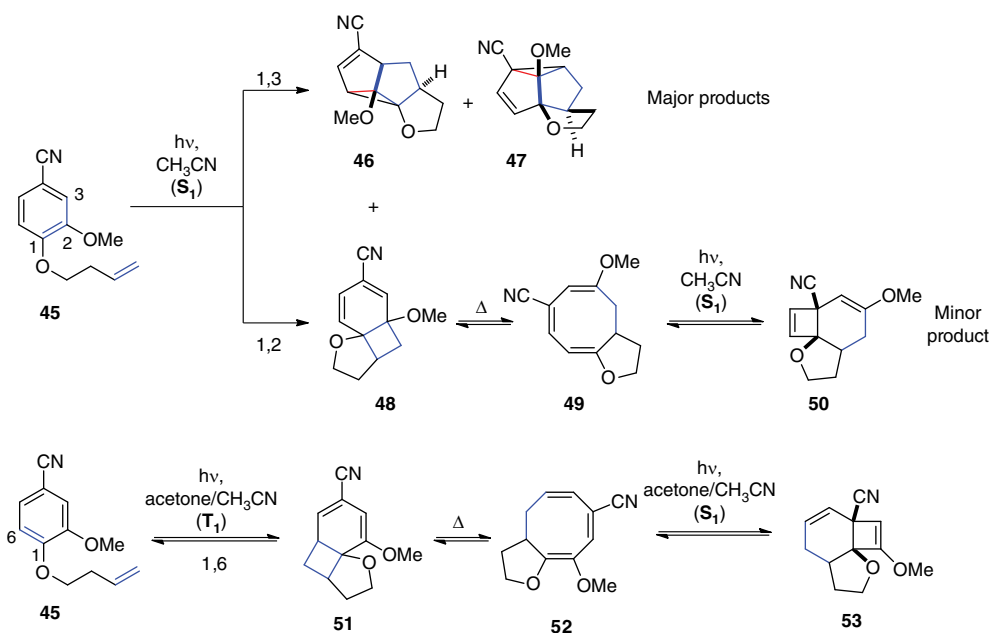
Cosstick *et al.* observed the same consecutive rearrangements of the primary ortho adduct **41** when irradiating benzonitrile derivative **40** in acetonitrile (Scheme 12).^[53] This study opened the question of singlet or triplet intermediates for these derivatives because they noticed that the reaction rate was not affected when irradiating solutions saturated by xenon.^[54] In such conditions, xenon induces an increased spin-orbit coupling by a heavy atom effect. Later, the authors performed more quenching experiments.^[55] First, they compared the intensity of fluorescence of compounds bearing an alkene on the side chain with the saturated analogues. The fluorescence was quenched by 50% for the derivatives with alkenes, proving that there is an interaction between the singlet excited state aromatic and ground state alkene. However, they noted that the quenching was less pronounced compared to aromatic compounds known to react at the singlet excited state. Then they observed that the formation of the cyclooctatriene **42** was quenched by 50% in the presence of a low concentration of 2,5-dimethylhexa-2,4-diene or 2,3-dimethylbuta-1,3-diene. As these dienes are triplet quenchers, the result may indicate that the first step of the ortho photocycloaddition occurs at the triplet state, but the possibility of side reactions with the dienes was not ruled out. Nevertheless, in this experiment the photocyclisation to form final product **43** was not affected, they thus concluded that the last step of photocyclisation of the cyclooctatriene takes place at the singlet excited state in acetonitrile as solvent.

Following this work, Wagner *et al.* performed the irradiation of the same compound in acetone in a larger study investigating the effect of triplet sensitisation.^[56] The triplet reaction in acetone yielded a different product **44**. Triplet sensitisation did not impact the first step of the ortho photocycloaddition. However, it caused a different electrocycloaddition of the cyclooctatriene **42**, confirming that the product **43** is obtained from a photocyclisation at the singlet excited state.

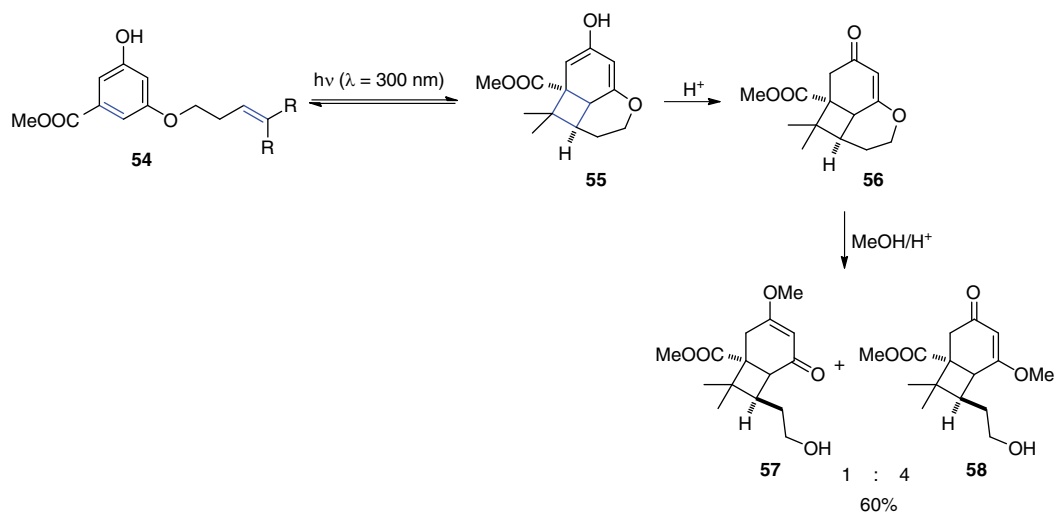
Our recent results give new insights on the nature of the excited state involved in the first step of ortho photocycloaddition of benzonitrile derivatives (Scheme 13).^[57] The irradiation of benzonitrile derivative **45** bearing a methoxy substituent revealed that the singlet excited state prevails by direct absorption in acetonitrile. On the one hand, the major products **46** and **47** are the result of a singlet state meta photocycloaddition. Their formation is favoured by the methoxy substituent that stabilises the zwitterionic intermediate (see meta photocycloadditions section). Compound **46** was completely transformed into **47** by prolonged irradiation. On the other hand, the regioselectivity of the [2 + 2] addition served as a support that the ortho adduct **50** is formed at the singlet excited state. The irradiation in acetonitrile yielded product **50** resulting from the known rearrangements of adduct **48** which is formed by an ortho photocycloaddition on positions 1,2. After complete conversion of **45** and prolonged irradiation, its 15% portion of the product mixture didn't change. In contrast, triplet sensitisation by irradiation in an acetonitrile/acetone mixture yielded product **53** resulting from an ortho photocycloaddition on positions 1,6. No product was isolated when irradiations were carried out in pure acetone, indicating that the photocyclisation of cyclooctatrienes **52** is not effective at the triplet state. The reaction is only possible in an acetonitrile/acetone mixture that permits the triplet ortho photocycloaddition by sensitisation of substrate **45** as well as the singlet photocyclisation by direct absorption of cyclooctatriene **52**. A typical triplet-excited state reaction of a cyclooctatriene intermediate is reported in Ref. [58].

Applications of ortho photocycloaddition in total syntheses

An early example of application of ortho photocycloadditions was the synthesis of compounds **57** and **58** (Scheme 14)^[59,60] that are 5,5-dialkylcyclohexane-1,3-dione analogues of known herbicides.^[61–64] The irradiation of the 3,5-dihydroxy



Scheme 13. Meta and ortho photocycloadditions of benzotrile derivative **45** bearing a methoxy substituent. Singlet and triplet excited state reactivity.



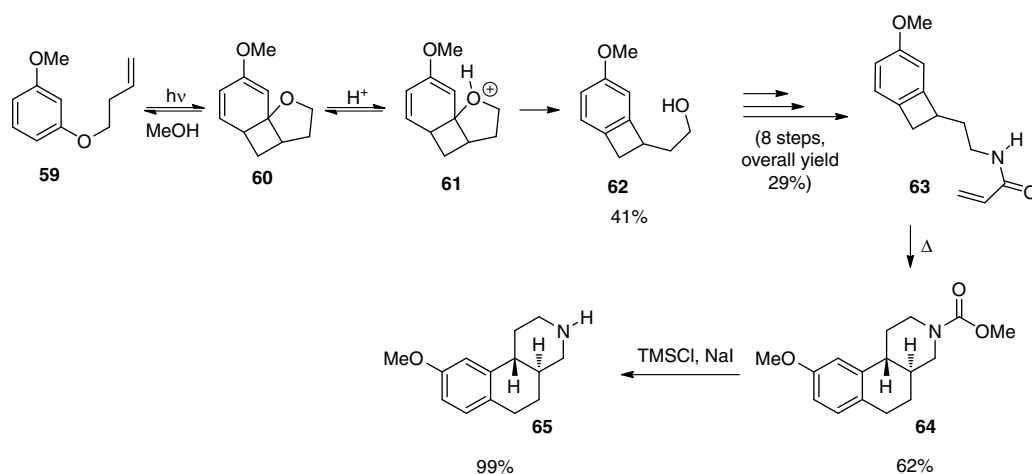
Scheme 14. Synthesis of compounds **57** and **58** analogues of known herbicides.

derivative **54** gave product **56** via a tautomerisation of the primary ortho adduct **55**. The final products **57** and **58** were obtained after a ring opening induced by methanol addition under acidic conditions.

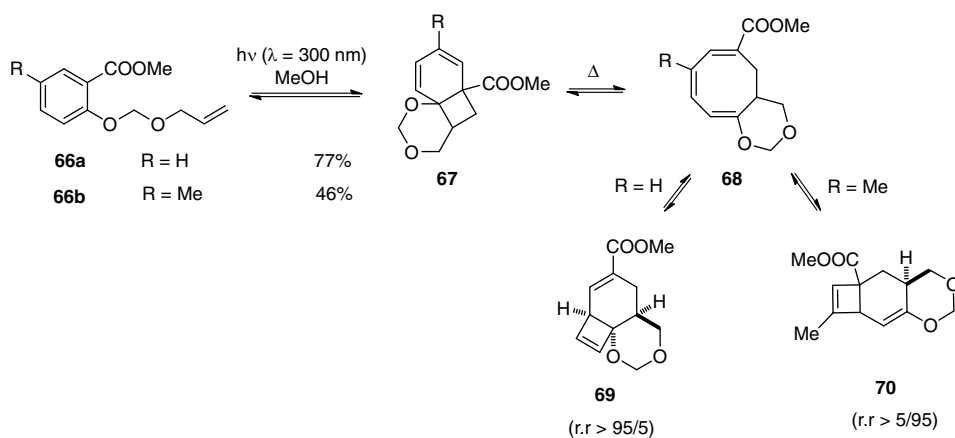
Resorcinol derivatives such as **59** possess low photo-reactivity when irradiated under standard conditions due to the reversibility of the reaction (Scheme 15). When irradiated in an acidic medium, product **62** was isolated.^[65,66] Under these acidic conditions, the tetrahydrofuran moiety of the primary ortho adduct **60** is protonated. Subsequent opening of the tetrahydrofuran ring then leads to product **62**. This type of benzocyclobutenes are valuable synthesis

intermediates.^[67] Product **63** was obtained after eight steps, and it was efficiently transformed into product **64** via a thermal rearrangement. Removal of the methyl carbamate protecting group finally gave benzoctahydroisoquinoline **65**.^[68,69] This compound is a rigidified structural analogue of dopamine and has a selective affinity to certain dopamine receptors.

More recently, Zech and Bach have revisited the ortho photocycloadditions on salicylic acid derivatives.^[70] In prevision of total syntheses,^[71] gradual changes to the substrate structures were performed in order to study the selectivity of the reaction (Scheme 16).^[72] For example, an additional



Scheme 15. Synthesis of benzoctahydroisoquinoline **65** as a dopamine analogue.



Scheme 16. Regioselectivity depending on the substitution pattern on the aromatic compound.

oxygen atom in the side chain (**66a**) gave product **69** as expected, after the known rearrangements of primary adduct **67** and cyclooctatriene **68**. However, a methyl substituent (**66b**, R=Me) yielded a different regioisomer (**70**) after photocyclisation of the cyclooctatriene **68**.

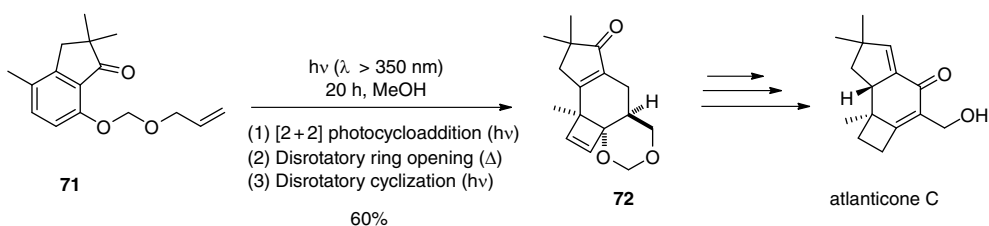
In their strategy for the total synthesis of atlanticone C, this methyl group had to be introduced before the photochemical step so they replaced the ester function with a cyclic ketone (**71**) to force the formation of the desired regioisomer **72** (Scheme 17).^[72] To prevent undesired photochemical reactivity of the α,β -unsaturated carbonyl function, an aqueous solution of $\text{Fe}_2(\text{SO}_4)_3$ was used to absorb light below $\lambda = 350$ nm. Synthesis of atlanticone C from product **72** was completed by modifications of the oxidation state of several carbon atoms and introduction of a stereogenic centre. It was performed in nine steps with an overall yield of 6%.

The research group later described the first enantioselective total synthesis of (+)-atlanticone C using a similar photochemical reaction cascade.^[73] A catalytic chiral resolution of the racemic photoproduct was enabled by an enantioselective Corey–Bakshi–Shibata reduction. This time, (+)-atlanticone C

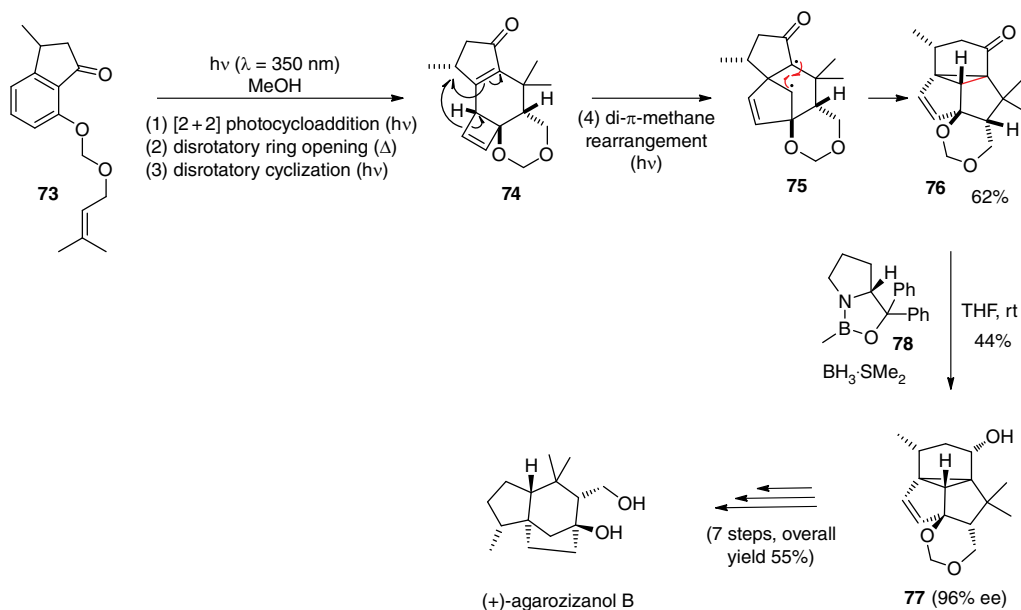
was prepared in 10 steps with 18% yield from the enantiomerically pure photoproduct.

When similar compounds to **71** were irradiated at $\lambda = 350$ nm, a new reactivity was observed.^[74] Rauscher and co-workers used this photochemical reaction cascade for the total synthesis of (+)-agarozizanol B (Scheme 18).^[75] In this reaction, irradiation of substrate **73** yields product **74** after the classical sequence of ortho photocycloaddition, ring opening and photocyclisation. Compound **74** absorbs light under these conditions and undergoes a di- π -methane rearrangement to give product **76** via the biradical intermediate **75**. The overall yield for these four successive reactions is 62%. Product **77** was then obtained with an ee of 96% with the same process used in the (+)-atlanticone C synthesis.^[73] The oxazaborolidine **78** was used for a catalytic chiral resolution of the photoproduct **76** by a Corey–Bakshi–Shibata reduction.^[76] Finally, (+)-agarozizanol B was obtained from compound **77** after seven steps with an overall yield of 55%.

The synthetic value of the ortho photocycloaddition is considerably increased when applied to hetero-aromatic substrates such as a pentafluoropyridine,^[77] oxazolopyridine,^[78]



Scheme 17. Total synthesis of atlanticonone C.



Scheme 18. Total synthesis of (+)-agarozizanol B.

benzotriazole,^[79] or even polycyclic aromatics like cyanonaphthalene.^[80] More complex alkene partners can also be considered like naphthalene^[81,82] or 1-cyanonaphthalene.^[83]

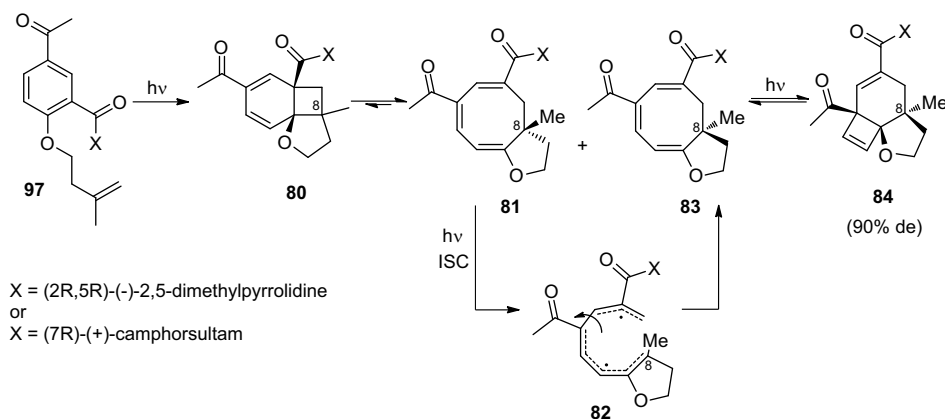
Chiral induction of ortho photocycloadditions

Wagner and McMahon performed diastereoselective ortho photocycloadditions by irradiating compounds bearing a chiral auxiliary (Scheme 19).^[58] Using (2*R*,5*R*)-(-)-2,5-dimethylpyrrolidine or (7*R*)-(-)-camphorsultam attached to substrate **79**, the final product **84** was isolated with a diastereoisomeric excess of 90%. The only permanent stereogenic centre C8 is created during the first step of the ortho photocycloaddition. Compound **80** is formed with a low diastereoselectivity. It is then increased by a photoepimerisation of cyclooctatriene **81**. The authors suggested that this kinetic resolution is due to the intersystem crossing to the triplet state facilitated by the acetyl substituent. It leads to ring opening of cyclooctatriene **81** to the tetraene biradical **82** where the rotation of the σ -bond between the

allyl and pentadienyl moieties leads to an epimerisation during ring closing to cyclooctatriene **83**.

Conclusion

Starting from relatively simple products, photocycloadditions of benzene derivatives with alkenes provide efficient access to compounds with a high degree of molecular complexity. Mainly [2 + 3] (meta) or [2 + 2] (ortho) photocycloaddition take place. In the latter case, photochemical and thermal rearrangements of the primary adducts are generally observed. The meta photocycloaddition occurs at the singlet excited state. The ortho addition, however, can take place either at the singlet or the triplet excited state. In this case, the spin multiplicity may have an influence on the regioselectivity of cycloaddition. In this context, more systematic and detailed studies of the influence of the substitution pattern on the regioselectivity and the cycloaddition mode is necessary. For example, recent findings suggest that the role of the singlet excited state in ortho photocycloadditions of nitrile and ester substituted aromatic compounds may have been overlooked.



Scheme 19. Diastereoselective ortho photocycloaddition with chiral auxiliary.

The meta photocycloaddition has already proven to be a key step in many syntheses of natural products. A topological analysis is helpful in this regard. In this context, the ortho photocycloaddition was neglected in the past. However, recently, impressive syntheses have been published using this photocycloaddition as a key step. The application of photocycloadditions of benzene derivatives to organic synthesis can further be strengthened if challenges such as chiral induction or para photocycloadditions continue to be addressed.

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Data availability. Data sharing is not applicable as no new data were generated or analysed during this study.

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