How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202208329
International Edition: doi.org/10.1002/anie.202208329
German Edition: doi.org/10.1002/ange.202208329

Cycloaddition

Arene Activation through Iminium Ions: Product Diversity from Intramolecular Photocycloaddition Reactions

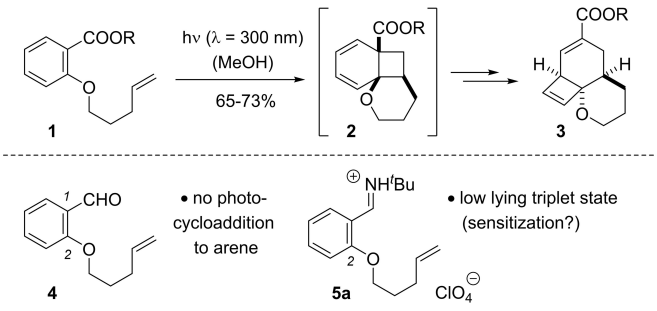
*Johanna Proessdorf, Christian Jandl, Thomas Pickl, and Thorsten Bach**

Abstract: While 2-alk-ω-enyloxy-sustituted benzaldehydes do not display any photochemical reactivity at the arene core, the respective iminium perchlorates were found to undergo efficient reactions either upon direct irradiation (λ = 366 nm) or under sensitizing conditions (λ = 420 nm, 2.5 mol% thioxanthen-9-one). Three pathways were found: (a) Most commonly, the reaction led to benzoxacyclic products in which the olefin in the tether underwent a formal, yet unprecedented carboformylation (13 examples, 44–99 % yield). The cascade process occurred with high diastereoselectivity and was found to be stereoconvergent. (b) If a substituent resides in the 3-position of the benzene ring, a *meta* photocycloaddition was observed which produced tetracyclic skeletons with five stereogenic centers in excellent regio- and diastereoselectivity (2 examples, 58–79 % yield). (c) If the tether was internally substituted at the alkene, an arene photocycloaddition was avoided and an azetidine was formed in an aza Paternò–Büchi reaction (2 examples, 95–98 % yield).

Introduction

Benzene and its derivatives display a rich and diverse photochemical reactivity. With olefins as substrates, three different photocycloaddition pathways are possible which have been classified—depending on the mode of addition—as *ortho* (1,2), *meta* (1,3), or *para* (1,4) photocycloaddition.[1] Benzene photocycloaddition chemistry has been studied since the late 1950s and 1960 s[2] and a wealth of information has been generated regarding the different reaction modes of the benzene core. The *para* photocycloaddition is the least frequently observed reaction among the three arene-alkene photocycloadditions and there is a relatively limited number of reports on its use in synthesis.[3] The *meta* photocycloaddition displays a much broader scope and the reactivity pattern of its components is well understood. Typically, the reaction occurs between electron rich arenes and alkenes, i.e. between compounds with a comparable electron-donating ability, evident by a small difference in their redox potentials. The *meta* photocycloaddition has been—mainly as its intramolecular version—elegantly applied to the total synthesis of natural products.[1,4,5] Less frequently, the *meta* photocycloaddition is observed for a combination of electron deficient arenes and alkenes.[4] In most cases, the reaction occurs on the singlet hypersurface and the formation of exciplexes has been invoked in several examples.[6] The *ortho* photocycloaddition occurs typically between arenes and alkenes with opposite electronic properties, e.g. an electron deficient arene and an electron rich olefin.[1,7] In contrast to the *meta* photocycloaddition, the reaction has seen less synthetic applications,[8] which is largely due to the fact that the primary photocycloaddition products of benzenes are rarely stable. Consecutive reactions are observed due to the lability of the primary cyclohexa-1,3-diene which is formed upon benzene *ortho* photocycloaddition.[1,7] We have recently investigated the intramolecular *ortho* photocycloaddition of salicylic acid-derived compounds **1**[9] and could establish conditions under which a single product **3** was formed from the primary adduct **2** (Scheme 1).[10] The reaction could be extended to indanone derivatives and was successfully implemented in the total synthesis of naturally occurring sesquiterpenes.[11]

Attempts to involve the related 2-pent-4-enyloxy-substituted benzaldehyde (**4**) in an *ortho* photocycloaddition turned out to be futile and we found under various



Scheme 1. The *ortho* photocycloaddition of salicylic acid-derived compounds **1** leads—presumably via intermediates **2**—to products **3** (top). Benzaldehyde **4** shows no photochemical reactivity at the arene ring which triggered the present study on the photochemistry of its iminium ion derivative **5a** (bottom).

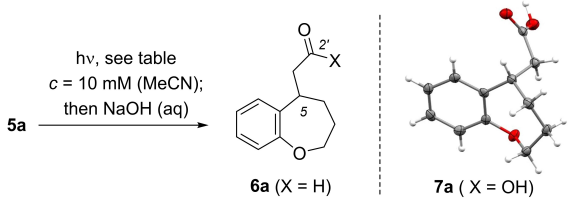
[*] M.Sc. J. Proessdorf, Dr. C. Jandl, M.Sc. T. Pickl, Prof. Dr. T. Bach
Department Chemie and Catalysis Research Center (CRC)
School of Natural Sciences, Technische Universität München
Lichtenbergstraße 4, 85747 Garching (Germany)
E-mail: thorsten.bach@ch.tum.de
Homepage: http://www.oc1.ch.tum.de/home_en/

conditions no indication for a reaction at the benzene core. Since we speculated that the nπ* triplet, which is located essentially at the aldehyde carbonyl group,[12] was responsible for this behavior, we considered iminium ions such as compound **5a** as potential surrogates. In analogy to the iminium ions derived from α,β-unsaturated carbonyl compounds,[13] we hypothesized that the arene iminium ions display a low triplet state which might be accessible by triplet energy transfer (sensitization). Iminium ions like **5a** have not been previously employed[14] in photocycloaddition reactions. Mariano and co-workers studied the reactivity of cyclic 2-phenyl-1-pyrrolinium ions towards different olefins.[15] They found mainly single electron transfer (SET) reactions with typical olefins such as isobutene and cyclohexene. A sensitization with benzophenone was not possible. Only with some electron deficient olefins, e.g. acrylonitrile, products were observed upon direct irradiation (λ = 260 nm; Corex filter) which emanate from an *ortho* photocycloaddition. In the present case, the electronic situation of the substrates was different due to the electron donating alkenyloxy substituent in 2-position. Visible light irradiation could be applied to initiate a reaction if a suitable sensitizer was used. It was found that the reactivity pattern of the iminium ions changed abruptly depending on some key skeletal features. For most substrates, a yet unprecedented reaction cascade was observed which is likely initiated by an intramolecular *ortho* photocycloaddition. Benzoxepanes or chromanes were isolated as products depending on the length of the tether. For substrates with a substituent in 3-positiion, a *meta* photocycloaddition was observed. Substrates with a 4-methylpent-4-enyloxy substituent in 2-position delivered products of an aza Paternò–Büchi reaction. The details of our study are summarized in this account.

Results and Discussion

Our optimization experiments commenced with the iminium salt **5a** which was available from aldehyde **4** by condensation with *tert*-butyl amine in dichloromethane[16] and subsequent crystallization of the respective perchlorate from ether at 0 °C (see the Supporting Information for details). The salt was soluble in acetonitrile and methanol. Preliminary experiments in both solvents revealed that the reactions were cleaner in acetonitrile and this solvent was used for the ensuing optimization. Since we expected the iminium salt of the product to be difficult to isolate by chromatography, the crude material was subjected to base-catalyzed hydrolysis (5 M NaOH in water). Irradiation at λ = 350 nm revealed the formation of a new product (Table 1, entry 1), the spectral data of which did not match the expected values for an immediate *ortho* photocycloaddition product nor for a product of the previously observed cascade reaction[10] (cf. **1**→**3**, Scheme 1). The product was clearly an aldehyde and it slowly oxidized to the respective carboxylic acid upon standing at ambient temperature under air. The latter compound produced crystals suitable for single crystal X-ray analysis.[17] It was found that a benzoxepane had been formed which displayed a 2′-oxoethyl group in 5-position. Except for the carboxyl group, aldehyde **6a** showed the same NMR pattern as carboxylic acid **7a**, which is why the depicted structure (Table 1) was assigned to the former compound. In addition, NMR spectra of the crude product (prior to hydrolysis) revealed that the benzoxepane skeleton was produced during the photochemical reaction but not during the hydrolysis step. Irradiation at λ = 366 nm was even more efficient than at λ = 350 nm and delivered product **6a** in 86 % yield (entry 2). At longer wavelength (λ = 420 nm) the reaction slowed down notably and remained incomplete even after 44 hours of irradiation (entry 3). The addition of thioxanthen-9-one (TXT), which is a known triplet sensitizer (triplet energy $E_T = 268\ kJ\ mol^{-1}$, 77 K, EtOH),[18] accelerated the reaction at λ = 420 nm significantly. With as little as 2.5 mol% of TXT, full conversion was attained after 18 hours and product **6a** was isolated in 94 % yield (entry 4). At λ = 457 nm there was no conversion in the absence of a sensitizer (entry 5). The iridium complex $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (2.5 mol%; $E_T = 252\ kJ\ mol^{-1}$, rt, MeCN)[19] allowed to recover the reactivity of substrate **5a** at λ = 457 nm but the conversion remained incomplete after 27 hours (entry 6). Since we speculated that catalyst degradation might be responsible for the incomplete conversion, another 2.5 mol% of the iridium catalyst was added

Table 1: Optimization of reaction conditions for the intramolecular photocycloaddition/rearrangement cascade of iminium salt **5a** to benzoxepane **6a**. The structure of compound 6a was corroborated by single-crystal X-ray analysis of the respective acid **7a**.



Entry[a]	λ[b] [nm]	t[c] [h]	Sens.[d]	Yield[e] [%]	s.m.[f] [%]
1	350	6.5	–	81	–
2	366	4.5	–	86	–
3	420	44	–	64	8
4	420	18	TXT	94	–
5	457	24	–	–	> 99[g]
6	457	27	Ir complex	70	18
7	457	27	Ir complex[h]	65	24
8	470	27	Ir complex	69	28

[a] Reactions were performed in acetonitrile by irradiation at the indicated wavelength ($c = 10$ mM) at room temperature. The primary photoproduct was subsequently hydrolyzed by addition of aqueous NaOH solution. [b] Emission maximum of the respective irradiation source (for detailed emission spectra, see the Supporting Information). [c] Irradiation time. [d] Sensitizer, TXT = thioxanthen-9-one (2.5 mol%), Ir complex (2.5 mol%): $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$; {dF-$(CF_3)$ppy} = 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl; dttpby = 4,4-di-*tert*-butyl-2,2-bipyridine. [e] Yield of isolated product **6a**. [f] Yield of recovered starting material as the respective aldehyde **4** (Scheme 1). [g] The product was not hydrolyzed but the iminium salt **5a** was re-isolated. [h] After 8 h, another 2.5 mol% of the Ir complex were added.

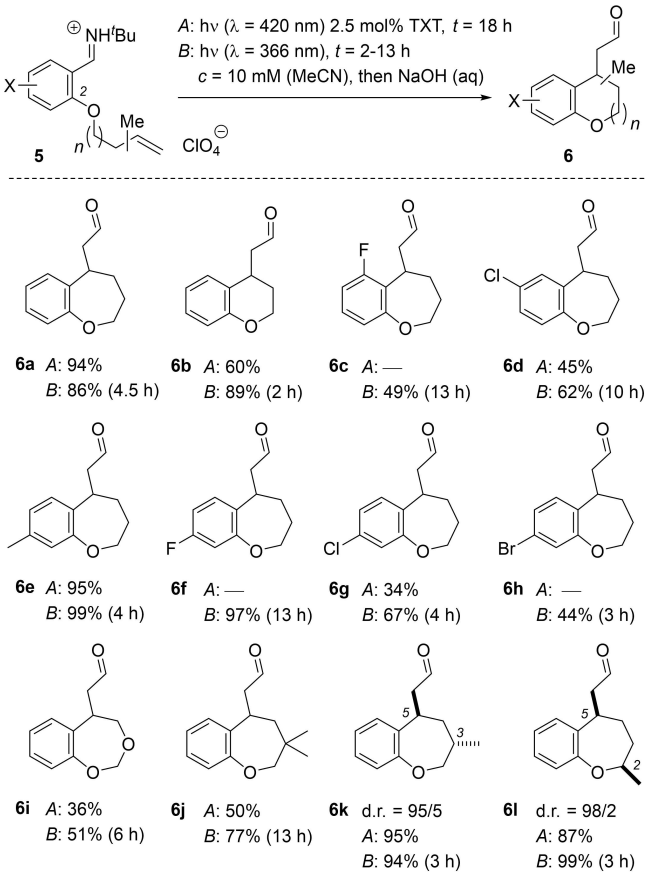
after eight hours. However, the outcome of the reaction remained essentially unchanged (entry 7) as compared to the reaction conducted with 2.5 mol% of catalyst only. The same holds true for an attempted reaction at longer wavelength ($\lambda = 470$ nm) which did not go to completion after 27 hours and gave 69 % yield of product together with 28 % yield of recovered starting material.

Despite the fact that the outcome of the irradiation experiments was unexpected, it was exciting to recognize a product pattern not yet reported for photochemical arene-alkene photocycloaddition reactions. The excitement about this discovery was enhanced once we realized that benzoxacyclic sesquiterpenes represent a biologically relevant compound class.[20] The common sunflower *Helianthus annuus* for example produces compounds named Heliannuols, which have been reported to show allelepathic properties.[21] Several representatives of this class of natural products were found to display either a benzoxepane (e.g. Heliannuol C and D) or a chromane (e.g. Heliannuol E) skeleton (Figure 1).

Against this background, it seemed adequate to systemically study the scope of the newly discovered photochemical transformation. Two different sets of conditions were applied to the respective iminium perchlorates **5** (Scheme 2). Conditions *A* included an irradiation with visible light ($\lambda =$ 420 nm) for 18 hours in the presence of catalytic quantities (2.5 mol%) of TXT. UV irradiation ($\lambda = 366$ nm) was employed within conditions *B* and was applied as long as full conversion was recorded by TLC analysis (2–13 h). Under both conditions, acetonitrile was employed as the solvent with a substrate concentration of $c = 10$ mM and the crude material was hydrolyzed under basic conditions. To our delight, we found that a shorter alkyl chain linking the olefin to the arene was compatible with the reaction and delivered chromane **6b** in high yields.

When varying the substituent X within the arene part, we noted that a sensitized reaction (conditions *A*) was not always successful and that the direct irradiation conditions *B* gave higher yields (products **6c**–**6h**). A modification of the tether by either introducing an oxygen atom (product **6i**) or a *gem*-dimethyl substitution (product **6j**) turned out to be compatible with the reaction conditions. With regard to Heliannuols C and D, the facial diastereoselectivity of the reaction was interrogated. It was found that the outcome matches the relative configuration at positions C3/C5 (Heliannuol C) and at positions C2/C5 (Heliannuol D) of the natural product. Substituents at the respective positions were found to be *trans* for product **6k** and *cis* for product **6l** (d.r. = diastereomeric ratio). In the former case, the assignment of the relative product configuration was based on nuclear Overhauser enhancement spectroscopy (NOESY), in the latter case the assignment rests on the crystal structure of acid **7l** derived from **6l** by oxidation.[22] In further studies regarding the substrate scope (see the Supporting Information for details), it was found that the oxygen substituent in 2-position of substrates **5** is crucial for the success of the reaction. A carbon-tethered olefin was found to be unreactive, neither did a tethered alkyne (pent-4-ynyloxy substituent in 2-position) produce any product. The arene-alkene photocycloaddition reactivity also vanished for methoxy-substituted arenes and for all substrates with a substituent in 5-position (exception **5d**→**6d**). It is likely that the substituents alter the electronic properties of the arene and render the triplet state inaccessible. Since only the standard conditions *A* and *B* were applied it is conceivable that irradiation at shorter wavelength or with a different sensitizer are more successful for these substrates.

As mentioned above, the immediate precursors to aldehyde products **6** are the respective iminium ions and there is no indication that the skeleton of the molecule is altered in the hydrolysis step. For the reaction **5a**→**6a** (Scheme 3), a possible explanation for the formation of the



Scheme 2. Synthesis of various benzoxepanes and of a chromane (**6b**) from iminium salts **5** mediated by visible light and thioxanthen-9-one (TXT) as a sensitizer (conditions *A*) or by UV-A irradiation (conditions *B*). Products **6f**, **6h**, and **6j** could not be obtained completely free from aliphatic impurities.

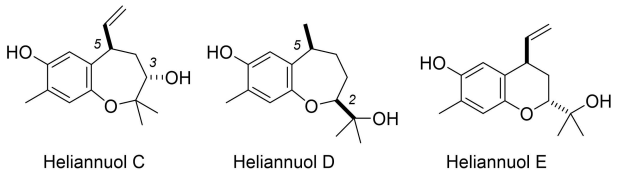
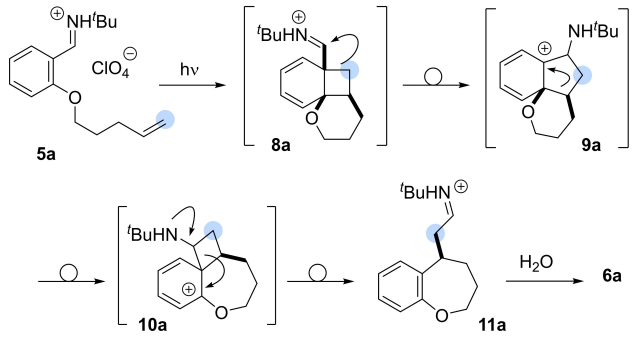
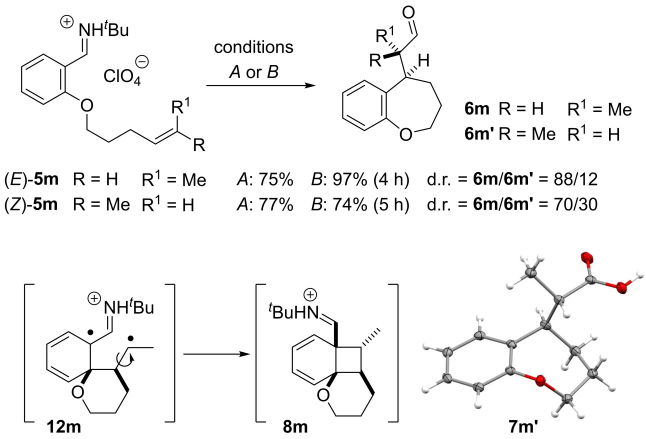


Figure 1. Structures of naturally occurring Heliannuols, which are benzoxacyclic sesquiterpenes isolated from sunflowers.



Scheme 3. Mechanistic proposal for the formation of product **6a** from iminium salt **5a**. An intramolecular *ortho* photocycloaddition to cation **8a** initiates a cascade of 1,2-migrations and a ring fragmentation to iminium ion **11a** which is hydrolyzed to the final product. For a better orientation the terminal olefin carbon atom is highlighted by a blue circle.



Scheme 4. The cascade reaction of the two diastereoisomers (*E*)- and (*Z*)-**5m** to products **6m** and **6m′** proceeded stereoconvergently. The product d.r. was identical before and after hydrolysis suggesting that the stereoconvergence stems from the photocycloaddition step. A putative triplet diradical **12m** allows for free rotation around the indicated single bond leading to the preferential formation of primary photoproduct **8m**. The relative configuration of this intermediate translates into the relative configuration of product **6m**. Acid **7m′** was obtained from the minor diastereoisomer **6m′** upon standing on air and its structure was elucidated by single-crystal X-ray analysis.

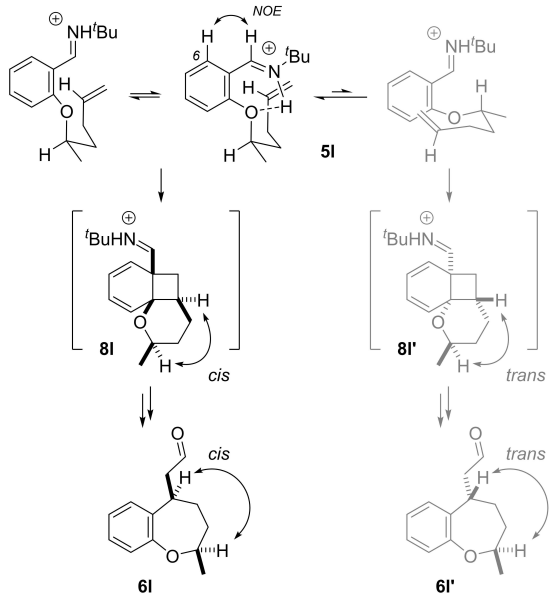
final product thus relates to the formation of iminium ion **11a**.

In this intermediate, the alkene double bond has been inserted into the aryl-CNH^{t}Bu bond, which is not feasible in a single step. Rather, we postulate an *ortho* photocycloaddition as the first step of the reaction forming cyclobutane **8a**. There is precedence for the first migration from previous work[15] but in the present case it is impossible for intermediate **9a** to restore aromaticity by elimination of a proton. We therefore propose that a ring contraction precedes the fragmentation of cyclobutane **10a** to the iminium ion **11a**. The increase in ring strain is compensated by the additional stabilization of cation **10a** via the adjacent oxygen atom.[23] The propensity of intermediate **8a** to undergo a 1,2-migration enables the molecule to escape the disrotatory cyclohexa-1,3-diene ring opening observed for the respective esters and ketones (see above).

There is circumstantial evidence that the photochemical step of the cascade reaction occurs on the triplet hypersurface. Although the lack of phosphorescence for most iminium ions **5** did not allow to assess their triplet energy, we found the bromo compound **5h** to be luminescent. Very likely, the heavy atom effect facilitates intersystem crossing (ISC) and enables to detect triplet emission at 77 K.[13b,24] The energy of the (0,0) transition was calculated from the emission in the short-wavelength regime (point of inflection)[25] and was found to be 257 kJ mol^{-1} (77 K, EtOH). We expect the other iminium ions to display similar triplet energies which renders energy transfer from TXT thermodynamically feasible. A second piece of evidence suggesting triplet reactivity was found when we studied the reaction of the hex-4-enyloxy substituted arenes **5m**. In this case, both diastereoisomers were subjected individually to the reaction conditions and provided products **6m** and **6m′** under either reaction conditions *A* or *B* (Scheme 4).

In both cases, product **6m** prevailed irrespective of the double bond configuration. It was verified by ^{1}H NMR analysis that the d.r. does not change in the hydrolysis step which in turns means that the relative configuration between the stereogenic centers is established en route to the benzoxepane iminium ion. Since the 1,2-migration steps are expected to occur stereospecifically,[26] it is likely that the erosion of the relative configuration occurs in the *ortho* photocycloaddition step. Indeed, a triplet pathway[27] requires formation of cyclobutane **8m** to occur via 1,4-diradical intermediate **12m** in which rotation around the former double bond is feasible. For steric reasons, cyclobutane **8m** should be preferred over its epimer **8m′** (not shown) and delivers in consecutive steps the major product **6m**. The other epimer **6m′** derives from **8m′** and its configuration was established from the crystal structure of carboxylic acid **7m′**.[28]

The *ortho* photocycloaddition step of the putative reaction cascade should also account for the relative configuration of the newly formed stereogenic center(s). The diastereoselective formation of products **6k** and **6l** is suggested to rest on a selective approach of the tethered olefin onto the arene (Scheme 2). The situation for the reaction of chiral substrate **5l** is depicted in Scheme 5. There are two chair conformation conceivable leading to intermediate products **8l** and **8l′** with the tetrahydropyran *cis*-fused to the cyclobutane ring. The former intermediate forms if the oxygen tether shows away from the iminium group and the methyl group at the stereogenic center adapts the equatorial position in a chair-type conformation. The relative configuration of the stereogenic centers will not be altered and the two indicated hydrogen atoms remain *cis*-positioned to each other in product **6l**. In analogy, the alternative cycloaddition mode manifests the opposite relative configuration translating into product structure **6l′** with the substituents being *trans*-positioned. A reason for the preferred conformation of substrates **5** in the *ortho* photocycloaddition could be a hydrogen bond between the

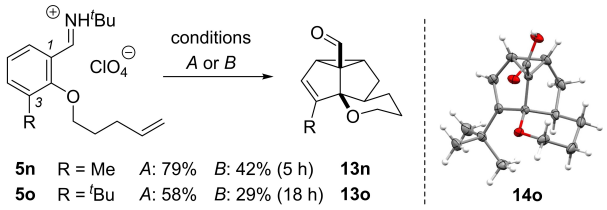


Scheme 5. The facial diastereoselectivity observed in the reaction of substrates **5k** and **5l** can be explained by a six-membered chair conformation of the side chain, in which the methyl group resides in an equatorial position. For compound **5l** the preferred chair conformation is depicted on the left. The preference is potentially due to intramolecular hydrogen bonding and intermediate **8l** is formed with a distinct relative configuration. According to the proposed mechanism for subsequent transformations of intermediates **8** (Scheme 3), the relative configuration at the two stereogenic centers is retained in products **6**.

iminium nitrogen and the oxygen atom. In the crystal structure of compound **5e**,[29] the hydrogen bond is suggested but its existence in polar solvents such as acetonitrile was not experimentally confirmed. NOESY measurements support the proximity of the indicated hydrogen atoms at the imine carbon atom and at carbon atom C6.

The relative configuration of product **6k** can be explained in full analogy to the formation of **6l**. A related chair conformation with the methyl group in an equatorial position leads to an intermediate in which the hydrogen atoms at the stereogenic centers are located *trans* to each other and they remain *trans* in the final product. It should be noted that the arguments provided for the preferred formation of the intermediate *ortho* photocycloaddition product (e.g. **8l**) apply irrespective of whether cyclobutane formation occurs as a triplet or as a singlet process.

As described in the previous chapters, iminium ions derived from various 2-pent-4-enyloxy-benzaldehydes **5c**–**5h** had given consistently benzooxepane products **6** irrespective whether substituents were positioned in 4- (products **6e**–**6h**, Scheme 2), 5- (product **6d**), or 6-position (product **6c**). This outcome changed dramatically when subjecting iminium ions to the reaction conditions that displayed an alkyl substituent in 3-position. Substrates **5n** and **5o** (Scheme 6) delivered under either conditions *A* and *B* structurally different products the constitution of which was again resolved by X-ray analysis. Aldehyde **13o** obtained in 58 % yield upon sensitized irradiation (conditions A) of 1,2,3-

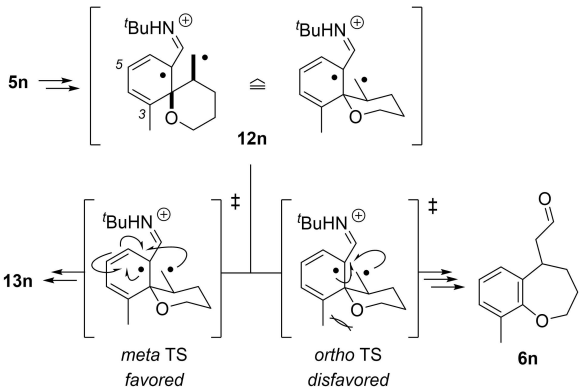


Scheme 6. Formal *meta*-photocycloaddition observed upon irradiation of 1,2,3-trisubstituted benzene derivatives **5n** and **5o** and the structure of acid **14o** (derived from aldehyde **13o**) in the crystal.

trisubstituted benzene **5o** was oxidized upon standing and produced crystals of the respective acid **14o**.[30] The crystal structure revealed the product to contain a tricyclo[5.1.0.0^{4,8}]oct-2-ene core which is the hallmark of a *meta* photocycloaddition. Likewise, the 3-methyl-substituted iminium ion **5n** delivered the tetracyclic product **13n** in 79 % under sensitizing conditions. Both products were also obtained by direct irradiation (conditions B) but the yield was lower. In the case of **5n**, direct irradiation resulted in the formation of the benzooxepane product **6n** as a side product (23 %). In the case of **5o**, the reaction was incomplete and 62 % of starting material was re-isolated.

The significantly higher yields obtained for products **13** under sensitizing conditions suggest that product formation occurs via a triplet reaction pathway, which is a rarely observed reaction pathway for a *meta* photocycloaddition.[1,4] For substrate **5n**, triplet 1,4-diradical **12n** would be a likely intermediate in which the initial bond formation has led to a six-membered tetrahydropyran ring. If ring closure to a cyclobutane occurred (*ortho* transition state) the repulsion between the methyl group and the oxygen atom would be further increased because the tetrahydopyran ring is planarized (Scheme 7). The repulsion should be even stronger if a *tert*-butyl group is present and this pathway is not accessible for substrate **5o**.

If the *meta* photocycloaddition product is formed (*meta* transition state), the tetrahydropyran ring can remain in its chair conformation avoiding torsional strain between the

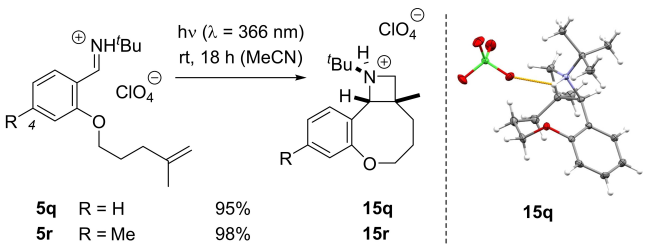


Scheme 7. Tentative explanation for the preferred formation of *meta* photocycloaddition product **13n**, as opposed to the cascade product **6n** derived from an initial *ortho* photocycloaddition (TS = transition state).

methyl group and the oxygen atom. The crystal structure of compound **14o**[30] nicely illustrates the strain release between the substituent at the former carbon atom C3 (*tert*-butyl) and the tetrahydropyran in its chair conformation. An important feature of the substituent R in substrates **5** is associated with the fact that they allow for the formation of the tricyclo[5.1.0.0^{4,8}]oct-2-ene core as a single regioisomer. Cyclopropane formation occurs exclusively at the former carbon atom C5 but not at C3. While many intramolecular *meta* photocycloaddition reaction suffer from a divergent regioselectivity (linear vs. angular product),[1,4] single isomers were isolated in the present case. Five stereogenic centers are established in a dearomatization reaction[31] with perfect control of the relative configuration.

Apart from the two reactivity modes already described, a third photocycloaddition pathway was observed for iminium ion **5q** (Scheme 8). In this instance, the tethered alkenyl group bears a substituent at the internal carbon atom of the double bond. The reaction in the presence of a sensitizer (conditions *A*) turned out to be sluggish and only 50 % conversion was observed after the standard reaction time of 18 hours. Conditions *B* were better suited for the conversion of this substrate and the reaction was complete after 18 hours. It was noted, that the product was not an iminium ion which is why we omitted the hydrolytic work-up. Instead, the product was isolated simply by removal of the solvent and turned out to be the protonated azetidinium salt **15q**. Its structure was secured by single crystal X-ray analysis.[32]

In an analogous fashion, the 4-methylsubstituted derivative **5r** produced under identical conditions product **15r**. Azetidine formation can be accounted for by a photochemical [2+2] photocycloaddition at the iminium double bond (aza Paternò–Büchi reaction).[33] Due to its additional substituent, an arene photocycloaddition would require for substrates **5q** and **5r** the formation of a quaternary carbon atom in the congested environment of a tetrahydropyran (cf. Scheme 7) as the first reaction step. The 1,4-diradical intermediate appears to be not formed but rather an alternative attack of the alkene occurs at the C=N bond.



5q	R = H	95%	**15q**	**15q**
5r	R = Me	98%	**15r**	

Scheme 8. Intramolecular aza Paternò–Büchi reaction of iminium ions **5q** and **5r** to azetidines **15q** and **15r**; the constitution and relative configuration of product **15q** was elucidated by single-crystal X-ray crystallography.

Conclusion

In summary, it was found that iminium ions derived from 2-alk-ω-enyloxy-substituted benzaldehydes show three clearly distinct reaction modes. The reaction pathway observed for most substrates leads to the formation of benzoxacyclic products, which bear—after hydrolysis—a 2-oxoethyl substituent either in 5-position of a benzoxepane or in 4-position of a chromane skeleton. The reaction occurs with excellent facial diastereoselectivity and provides access to 2,5- or 3,5-disubstituted benzoxepanes. The latter observation bears relevance to a potential application for the synthesis of biologically active benzoxepanes. A variation of the typical reaction scheme was observed for two clearly defined scenarios: If the substrate displays an alkyl group in 3-position of the benzene ring, a *meta* photocycloaddition was the preferred reaction mode giving access to tetracyclic products **13n** and **13o**. The remarkable features of this process are the selective formation of a single alicyclic skeleton (high regioselectivity) and the simultaneous generation of five stereogenic centers. Applications of this new *meta* photocycloaddition variant are conceivable in the total synthesis of diquinanes which bear a carbon and an oxygen substituent at the carbon atoms in positions C1 and C5 of the bicyclo[3.3.0]octane ring. Eventually, an additional substituent at the internal alkene double bond within the 2-alk-ω-enyloxy tether avoids any arene photocycloaddition but forces an aza Paternò–Büchi reaction at the iminium C=N bond. The observed product diversity is not random but predictable and the reaction outcome of the arene photocycloaddition reactions can be rationalized by assuming a triplet reaction pathway.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (Ba 1372/22-1) is gratefully acknowledged. JP warmly thanks A. Celic, T. Trieder and A. Schüler for synthetic support. We thank J. Großkopf for recording the fluorescence spectra. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cycloaddition · Oxygen Heterocycles · Photochemistry · Rearrangement · Sensitizers

[1] For reviews covering arene-alkene photocycloadditions in general, see: a) Z. Zhang, Y.-J. Zhou, X.-W. Liang, *Org. Biomol. Chem.* **2020**, *18*, 5558–5566; b) R. Remy, C. G. Bochet, *Chem. Rev.* **2016**, *116*, 9816–9849; c) N. Hoffmann, *Photochem. Photobiol. Sci.* **2012**, *11*, 1613–1641; d) U. Streit, C. G. Bochet, *Beilstein J. Org. Chem.* **2011**, *7*, 525–542; e) U. Streit, C. G. Bochet, *Chimia* **2008**, *62*, 962–966; f) J. Mattay, *Angew. Chem. Int. Ed.* **2007**, *46*, 663–665; *Angew. Chem.* **2007**, *119*, 674–677; g) N. Hoffmann, *Synthesis* **2004**, 481–495; h) J. J. McCullough, *Chem. Rev.* **1987**, *87*, 811–860.

[2] For pioneering studies on benzene-alkene photocycloaddition reactions, see: a) H. J. F. Angus, D. Bryce-Smith, *Proc. Chem. Soc.* **1959**, 326–327; b) G. O. Schenck, R. Steinmetz, *Tetrahedron Lett.* **1960**, *1*, 1–8; c) E. Grovenstein, D. V. Rao, *Tetrahedron Lett.* **1961**, *2*, 148–150; d) C. G. Krespan, B. C. McKusick, T. L. Cairns, *J. Am. Chem. Soc.* **1961**, *83*, 3428–3432; e) D. Bryce-Smith, A. Gilbert, B. H. Orger, *Chem. Commun.* **1966**, 512–514; f) K. E. Wilzbach, L. A. Kaplan, *J. Am. Chem. Soc.* **1966**, *88*, 2066–2067.

[3] In recent years, the diaza variant of the *para* photocycloaddition has been elegantly utilized by Sarlah and co-workers: a) E. H. Southgate, J. Pospech, J. Fu, D. R. Holycross, D. Sarlah, *Nat. Chem.* **2016**, *8*, 922–928; b) M. Okumura, D. Sarlah, *Synlett* **2018**, *29*, 845–855.

[4] For reviews exclusively on *meta* photocycloaddition reactions, see: a) D. Chappell, A. T. Russell, *Org. Biomol. Chem.* **2006**, *4*, 4409–4430; b) J. Cornelisse, *Chem. Rev.* **1993**, *93*, 615–669; c) P. A. Wender, L. Siggel, J. M. Nuss, *Organic Photochemistry, Vol. 10*, Marcel Dekker, New York, **1989**, pp. 357–473.

[5] Examples: a) P. A. Wender, J. J. Howbert, *J. Am. Chem. Soc.* **1981**, *103*, 688–690; b) P. A. Wender, G. B. Dreyer, *J. Am. Chem. Soc.* **1982**, *104*, 5805–5807; c) C. Baralotto, M. Chanon, M. Julliard, *J. Org. Chem.* **1996**, *61*, 3576–3577; d) A. G. Avent, P. W. Byrne, C. S. Penkett, *Org. Lett.* **1999**, *1*, 2073–2075; e) J. W. Boyd, M. Greaves, J. Kettle, A. T. Russell, J. W. Steed, *Angew. Chem. Int. Ed.* **2005**, *44*, 944–946; *Angew. Chem.* **2005**, *117*, 966–968; f) T. Gaich, J. Mulzer, *J. Am. Chem. Soc.* **2009**, *131*, 452–453; g) J. Westphal, C. E. Schumacher, H.-G. Schmalz, *Synthesis* **2017**, *49*, 218–224.

[6] a) R. Srinivasan, J. A. Ors, *Chem. Phys. Lett.* **1976**, *42*, 506–508; b) H. Leismann, J. Mattay, H.-D. Scharf, *J. Am. Chem. Soc.* **1984**, *106*, 3985–3991; c) J. Mattay, *Tetrahedron* **1985**, *41*, 2405–2417; d) D. Bryce-Smith, A. Gilbert, J. Mattay, *Tetrahedron* **1986**, *42*, 6011–6014 and refs. cited therein.

[7] For reviews exclusively on *ortho* photocycloaddition reactions, see: a) J. Cornelisse, R. de Haan, in *Molecular and Supramolecular Photochemistry, Vol. 8* (Eds: V. Ramamurthy, K. Schanze), Dekker, New York, **2001**, pp. 1–126; b) P. J. Wagner, *Acc. Chem. Res.* **2001**, *34*, 1–8.

[8] For recent synthetic work involving a stable cyclohexa-1,3-diene intermediate, see: a) F. Schneider, K. Samarin, S. Zanella, T. Gaich, *Science* **2020**, *367*, 676–681; b) F. Schneider, L. Pan, M. Ottenbruch, T. List, T. Gaich, *Acc. Chem. Res.* **2021**, *54*, 2347–2360.

[9] P. J. Wagner, R. P. Smart, *Tetrahedron Lett.* **1995**, *36*, 5135–5138.

[10] A. Zech, T. Bach, *J. Org. Chem.* **2018**, *83*, 3069–3077.

[11] a) A. Zech, C. Jandl, T. Bach, *Angew. Chem. Int. Ed.* **2019**, *58*, 14629–14632; *Angew. Chem.* **2019**, *131*, 14771–14774; b) J. Proessdorf, A. Zech, C. Jandl, T. Bach, *Synlett* **2020**, *31*, 1598–1602; c) N. Rauscher, L. Næsborg, C. Jandl, T. Bach, *Angew. Chem. Int. Ed.* **2021**, *60*, 24039–24042; *Angew. Chem.* **2021**, *133*, 24241–24244; d) A. G. Gilbert, T. Bach, *Synlett* **2022**, https://doi.org/10.1055/a-1777-2477.

[12] a) M. Koyanagi, L. Goodman, *J. Chem. Phys.* **1971**, *55*, 2959–2976; b) Q. Ou, J. E. Subotnik, *J. Phys. Chem. C* **2013**, *117*, 19839–19849.

[13] a) F. M. Hörmann, T. S. Chung, E. Rodriguez, M. Jakob, T. Bach, *Angew. Chem. Int. Ed.* **2018**, *57*, 827–831; *Angew. Chem.* **2018**, *130*, 835–839; b) F. M. Hörmann, C. Kerzig, T. S. Chung, A. Bauer, O. S. Wenger, T. Bach, *Angew. Chem. Int. Ed.* **2020**, *59*, 9659–9668; *Angew. Chem.* **2020**, *132*, 9746–9755.

[14] For recent work on photoredox reactions involving iminium ions, see: a) M. Silvi, C. Verrier, Y. P. Rey, L. Buzzetti, P. Melchiorre, *Nat. Chem.* **2017**, *9*, 868–873; b) D. Mazzarella, G. E. M. Crisenza, P. Melchiorre, *J. Am. Chem. Soc.* **2018**, *140*, 8439–8443; c) G. Goti, B. Bieszczad, A. Vega-Peñaloza, P. Melchiorre, *Angew. Chem. Int. Ed.* **2019**, *58*, 1213–1217; *Angew. Chem.* **2019**, *131*, 1226–1230; d) M. Berger, D. Carboni, P. Melchiorre, *Angew. Chem. Int. Ed.* **2021**, *60*, 26373–26377; *Angew. Chem.* **2021**, *133*, 26577–26581.

[15] J. L. Stavinoha, P. S. Mariano, *J. Am. Chem. Soc.* **1981**, *103*, 3136–3148.

[16] For the imine condensation: R. Bisht, B. Chattopadhyay, *J. Am. Chem. Soc.* **2016**, *138*, 84–87. Perchlorate precipitation: see ref. [15].

[17] Deposition Number 2175928 (for **7a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[18] A. Iyer, A. Clay, S. Jockusch, J. Sivaguru, *J. Phys. Org. Chem.* **2017**, *30*, e3738.

[19] A. Singh, K. Teegardin, M. Kelly, K. S. Prasad, S. Krishnan, J. D. Weaver, *J. Organomet. Chem.* **2015**, *776*, 51–59.

[20] For general reviews on photochemical key steps in the context of natural product total synthesis, see: a) M. D. Kärkäs, J. A. Porco Jr, C. R. J. Stephenson, *Chem. Rev.* **2016**, *116*, 9683–9747; b) T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045; *Angew. Chem.* **2011**, *123*, 1032–1077; c) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052–1103.

[21] a) F. A. Macias, J. M. G. Molinillo, R. M. Varela, A. Torres, F. R. Fronczek, *J. Org. Chem.* **1994**, *59*, 8261–8266; b) D. Sarkar, M. K. Ghosh, *Curr. Org. Chem.* **2018**, *22*, 18–56.

[22] Deposition Number 2175929 (for **7l**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[23] For a related 1,2-migration, leading to cyclobutane formation, see: X.-Z. Shu, X.-Y. Liu, K.-G. Ji, H.-Q. Xiao, Y.-M. Liang, *Chem. Eur. J.* **2008**, *14*, 5282–5289.

[24] J. C. Koziar, D. O. Cowan, *Acc. Chem. Res.* **1978**, *11*, 334–341.

[25] a) D. Guillaumont, H. Bazin, J.-M. Benech, M. Boyer, G. Mathis, *ChemPhysChem* **2007**, *8*, 480–488; b) M. Bortoluzzi, G. Paolucci, S. Polizzi, L. Bellotto, F. Enrichi, S. Ciorba, B. S. Richards, *Inorg. Chem. Commun.* **2011**, *14*, 1762–1766; c) J. Großkopf, T. Kratz, T. Rigotti, T. Bach, *Chem. Rev.* **2022**, *122*, 1626–1653.

[26] a) X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, Z.-H. Chen, S.-H. Wang, *Chem. Soc. Rev.* **2017**, *46*, 2272–2305; b) *Molecular Rearrangements in Organic Synthesis* (Ed.: C. M. Rojas), Wiley, Hoboken, **2015**; c) J. Kallmerten, in *Methoden der Organischen Chemie (Houben-Weyl) 4te Aufl.*, Band E 21c (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 3810–3832.

[27] Examples for stereoconvergent reactions via triplet intermediates: a) W. L. Dilling, T. E. Tabor, F. P. Boer, P. P. North, *J. Am. Chem. Soc.* **1970**, *92*, 1399–1400; b) N. P. Peet, R. L. Cargill, D. F. Bushey, *J. Org. Chem.* **1973**, *38*, 1218–1221; c) D. Becker, M. Nagler, S. Hirsh, J. Ramun, *Chem. Commun.* **1983**,

371–373; d) J. F. D. Kelly, J. M. Kelly, T. B. H. McMurry, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1933–1941; e) S. Poplata, A. Bauer, G. Storch, T. Bach, *Chem. Eur. J.* **2019**, *25*, 8135–8148; f) T. Rigotti, D. P. Schwinger, R. Graßl, C. Jandl, T. Bach, *Chem. Sci.* **2022**, *13*, 2378–2384.

[28] Deposition Number 2175930 (for **7m′**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[29] Deposition Number 2175927 (for **5e**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[30] Deposition Number 2175931 (for **14o**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[31] Recent reviews: a) Y.-Z. Cheng, Z. Feng, X. Zhang, S.-L. You, *Chem. Soc. Rev.* **2022**, *51*, 2145–2170; b) M. Okumura, D. Sarlah, *Eur. J. Org. Chem.* **2020**, 1259–1273; c) W. C. Wertjes, E. H. Southgate, D. Sarlah, *Chem. Soc. Rev.* **2018**, *47*, 7996–8017.

[32] Deposition Number 2175932 (for **15q**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[33] Reviews: a) A. D. Richardson, M. R. Becker, C. S. Schindler, *Chem. Sci.* **2020**, *11*, 7553–7561; b) S. K. Kandappa, L. K. Valloli, S. Ahuja, J. Parthiban, J. Sivaguru, *Chem. Soc. Rev.* **2021**, *50*, 1617–1641.

Manuscript received: June 7, 2022
Accepted manuscript online: August 3, 2022
Version of record online: September 2, 2022