TECHNISCHE UNIVERSITÄT MÜNCHEN
TUM SCHOOL OF NATURAL SCIENCES

Reaction Cascades Initiated by Intramolecular *ortho* Photocycloadditions: Studies on Totalsynthetic Applications and Catalysis

Johanna Prößdorf

Vollständiger Abdruck der von der TUM School of Natural Sciences der Technischen Universität München zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigten Dissertation.

Vorsitzender:		Prof. Dr. Klaus Köhler
Prüfer der Dissertation:	1.	Prof. Dr. Thorsten Bach
	2.	apl. Prof. Dr. Wolfgang Eisenreich

Die Dissertation wurde am 03.01.2023 bei der Technischen Universität München eingereicht und durch die TUM School of Natural Sciences am 16.01.2023 angenommen.

The presented PhD work was carried out at the Lehrstuhl für Organische Chemie I at Technische Universität München between Oktober 2019 and November 2022. The thesis was supervised by Prof. Dr. Thorsten Bach.

Publication List:

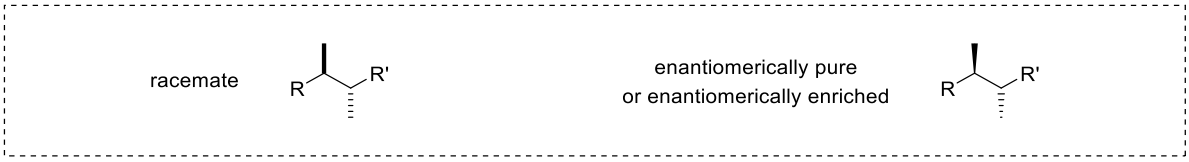
Content of this PhD thesis has been published in the following journals:

- *Concise Total Synthesis of (+)-Atlanticone C;* J. Proessdorf, A. Zech, C. Jandl, T. Bach, *Synlett* **2020**, *31*, 1598–1602.
- *Arene Activation through Iminium Ions: Product Diversity from Intramolecular Photocycloaddition Reactions;* J. Proessdorf, C. Jandl, T. Pickl, T. Bach, *Angew. Chem. Int. Ed.* **2022**, *61*, e202208329.

Conference Contributions:

- 263rd ACS National Meeting & Exposition **2022**, San Diego, USA: *Arene Photoactivation through Iminium Ions: A novel sensitized ortho-Photocycloaddition Cascade* (poster presentation).
- Leopoldina-Symposium „Exploratory Photochemistry: Light Creates Structure“ **2021**, Halle (Saale), Deutschland: *Concise Total Synthesis of (+)-Atlanticone C via a Photochemical Reaction Cascade* (poster presentation).

In this thesis, the relative configuration of racemates is represented by straight lines (bold or hashed). The absolute configuration of enantiomerically pure or enriched compounds is represented by wedge-shaped lines (bold or hashed).



ACKNOWLEDGEMENTS

I especially want to thank

Prof. Dr. Thorsten Bach, not only for mentoring my PhD work but especially for his advice and continuous support throughout my entire studies. His classes during my B.Sc. and M.Sc. studies as well as the research performed in his group strongly encouraged me to major in organic synthesis. Having had the chance to learn from a bright scientist like him was a great honor for me and I enjoyed the free research spirit in his group very much. I also appreciate having had the chance to contribute to the CRC 325 program and the associated financial support.

Dr. Simone Stegbauer and Dr. Stefan Breitenlechner, I gratefully acknowledge their great efforts in all matters concerning lab equipment, safety and management as well as teaching and student lab courses.

Kerstin Voigt, for her help in all matters beyond chemistry and in overcoming bureaucratic burdens.

Dr. Christian Jandl and Thomas Pickl, for a great collaboration regarding single crystal X-ray analysis, as well as *Olaf Ackermann and Jürgen Kudermann*, for their support regarding analytical equipment.

Furthermore, I warmly thank *Simon Maroldt*, *Joseph Yap*, *Andreas Gebendorfer*, *Tim Lenz*, *Sebsatian Lohs*, *Christine Seeleitner*, *Aygün Celic*, *Tessa Trieder*, *Ayla Schüler*, *Maximilian Schmid*, *Ekrem Suylu* and *Marin Smoljo* for synthetic support and their hard work during their preparative internships.

I also want to extend my gratitude to former and current group members for their creative input and encouraging words. Thank you for unforgettable moments in, but also outside lab and for friendships lasting beyond this academic chapter. I will keep our running and triathlon team, Greek nights, California trip and skiing retreat in greatest memory.

Finally, I am forever grateful to my parents *Gabriele* and *Wolfram* for their unconditional support during my studies and beyond. And to my sister *Charlotte* together with my high school friends who are always there for me.

ABSTRACT

Photo-induced dearomatization reactions offer efficient access to complex molecules starting from abundant and inexpensive starting materials. Especially in case of intramolecular addition of an olefin to an aromatic core, three-dimensional polycyclic structures can be constructed within a single step. In contrast to the *meta* photocycloaddition, synthetic applications of the *ortho* and *para* variant remained underexplored. Within the scope of this PhD thesis, reaction cascades initiated by an *ortho* photocycloaddition were investigated regarding synthetic applications and the photocatalytic potential of this method.

The first enantioselctive total synthesis of (+)-atlanticone C was completed. A reaction cascade induced by an intramolecular *ortho* photocycloaddition was employed as the key step in this synthesis and a chiral resolution protocol was developed to access the desired photoproduct in enantiopure form (>98% *ee*). The total synthesis was completed in 10 subsequent steps and with an overall yield of 18%.

To study the potential of these transformations further, the arene photoactivation of benzaldehyde derivatives was investigated. In this context, 2-alk-ω-enyloxy-sustituted benzaldehydes did not display photochemical reactivity at the arene core, whereas the respective iminium ions were found to undergo photo-induced reactions. Three pathways were described and can be performed under visible-light irradiation: a) Most commonly, an *ortho* photocycloaddition led to a yet unprecedented reaction cascade generating benzoxacyclic products (13 examples, 44-99% yield). The reaction cascade proceeded with high diastereoselectivity and was found to be stereoconvergent. b) If the benzene ring was substituted in 3-position, a *meta* photocycloaddition occured furnishing tetracyclic skeletons in excellent regio- and diastereoselectivity (2 examples, 58-79% yield). c) If the tethered olefin was internally substituted, an aza *Paternò-Büchi* reaction was preferred (2 examples, 95-98 % yield).

KURZZUSAMMENFASSUNG

Lichtinduzierte Desaromatisierungsreaktionen bieten einen effizienten Zugang zu komplexen Molekülen ausgehend von leicht verfügbaren, kostengünstigen Ausgangsmaterialien. Insbesondere im Fall der intramolekularen Addition eines Olefins an einen Aromaten, können dreidimensionale polycyclische Strukturen in einem einzigen Schritt aufgebaut werden. Im Gegensatz zur *meta*-Photocycloaddition sind synthetische Anwendungen der *ortho*- und *para*-Variante wenig erforscht. Im Rahmen dieser Doktorarbeit wurden Reaktionskaskaden, initiiert durch eine *ortho*-Photocycloaddition, hinsichtlich ihrer synthetischen Anwendungen und des photokatalytischen Potenzials dieser Methode untersucht.

Dabei wurde die erste enantioselektive Totalsynthese von (+)-Atlanticon C beschrieben. Als Schlüsselschritt dieser Synthese wurde eine Reaktionskaskade durchlaufen, die durch eine intramolekulare *ortho*-Photocycloaddition induziert wurde, und es wurde ein Protokoll zur Racematspaltung entwickelt, um das gewünschte Photoprodukt in enantiomerenreiner Form (>98 % *ee*) zu erhalten. Die Totalsynthese wurde anschließend in 10 Folgeschritten und mit einer Gesamtausbeute von 18% abgeschlossen.

Um das Potenzial dieser Transformation weiter zu untersuchen, wurde die Aren-Photoaktivierung von Benzaldehydderivaten untersucht. In diesem Zusammenhang zeigten 2-Alk-ω-enyloxy-substituierte Benzaldehyde keine photochemische Reaktivität am Aromaten, wohingegen die entsprechenden Iminiumionen photoinduzierte Reaktionen eingingen. Drei Reaktionsmuster wurden beschrieben und können unter Bestrahlung mit sichtbarem Licht durchgeführt werden: a) Am häufigsten beobachtet wurde eine *ortho*-Photocycloaddition die zu einer bis dahin unbekannten Reaktionskaskade führte und benzoxacyclische Produkte lieferte (13 Beispiele, 44–99 % Ausbeute). Die Reaktionskaskade verläuft mit hoher Diastereoselektivität und ist stereokonvergent. b) War der Benzolring in 3-Position substituiert, fand eine *meta*-Photocycloaddition statt, die tetracyclische Gerüste mit ausgezeichneter Regio- und Diastereoselektivität lieferte (2 Beispiele, 58–79 % Ausbeute). c) Wenn das verknüpfte Olefin intern substituiert war, trat bevorzugt eine Aza-*Paternò-Büchi*-Reaktion auf (2 Beispiele, 95–98 % Ausbeute).

CONTENTS

1. INTRODUCTION 1

1.1 Relevance of Small Molecule Synthesis 1

1.2 Photochemistry: Access to Complex Small Molecules 3

2. PHOTOCYCLOADDITION REACTIONS 5

2.1 Intramolecular Arene Photocycloadditions and Synthetic Applications 6

2.2 Recent Advances in Ortho Photocycloaddition Chemistry 9

3. PROJECT AIM 12

3.1 oPCA Reaction Cascade as Key Step in Total Synthesis 12

3.2 Arene Photoactivation of Benzaldehyde Substrates 13

4. ENANTIOSELECTIVE TOTAL SYNTHESIS OF ATLANTICONE C 15

5. ARENE PHOTOACTIVATION TROUGH IMINIUM IONS 21

6. SUMMARY 30

7. LICENSES 35

8. REFERENCES 36

1. INTRODUCTION

1.1 RELEVANCE OF SMALL MOLECULE SYNTHESIS

Pharmacological agents and their development are of great social and economic importance. Whether it is anti-cancer drugs, substances with an antiviral effect, such as drugs against Covid-19 or HIV, or antibiotics, life without them is hard to imagine. From a molecular point of view, these pharmacological substances of organic origin can be divided into two main groups: On the one hand small molecules which are based on a carbon skeleton consisting of about 20-80 carbon atoms with a molecular weight below 1000 g/mol (<1 kDa), and on the other hand so called biologics. These are larger organic molecules, such as polynucleotides, peptides or antibodies with a molecular weight larger than 1000 g/mol (>1 kDa). Small molecules are manufactured by chemical synthesis. They are generally thermally and chemically more stable, whereas biologics tend to be very target-specific, thereby reducing risks of side-effects, but they typically require more complex and costly development processes.[1] Today both drug types play important roles in the global drug market, naming Bristol Myers Squibb's small molecule drug lenalidomid (Revlimid®) (**1**) or AbbVie's antibody adalimumab (Humira®) (**2**) with $ 12.8 bn and $ 20.7 bn blockbuster sales in 2021, respectively (Figure 1a).[2]

With important advances in biotechnology over the last three decades, biologic drugs have become increasingly important. However, due to them being more accessible to patients, small molecules still make up the majority of overall global drug sales (90%)[1c] as well as of newly approved active ingredients. For example, in 2021 the FDA approved 50 new active ingredients in the USA, of which 32 were small molecules including e.g. maralixibat (Livmarli™) (**3**) against cholestatic pruritus and samidorphan (with olanzapine Lybalvi®) (**4**) for the treatment of schizophrenia (Figure 1b).[3]

Those active ingredients often feature complex, three-dimensional structures with e.g. annulated arene cores and multiple stereogenic centers (highlighted in grey). Synthesizing such scaffolds from simple and commercially available starting materials is the key challenge in organic synthesis. This process usually involves the breaking of existing and the formation of new bonds, which may require several individual reactions. Each step usually involves a reaction at only one chemical bond in the molecule but can also lead to undesired side reactions. Therefore, organic chemists

aim at finding methods that enable the formation of new chemical bonds selectively and concisely.

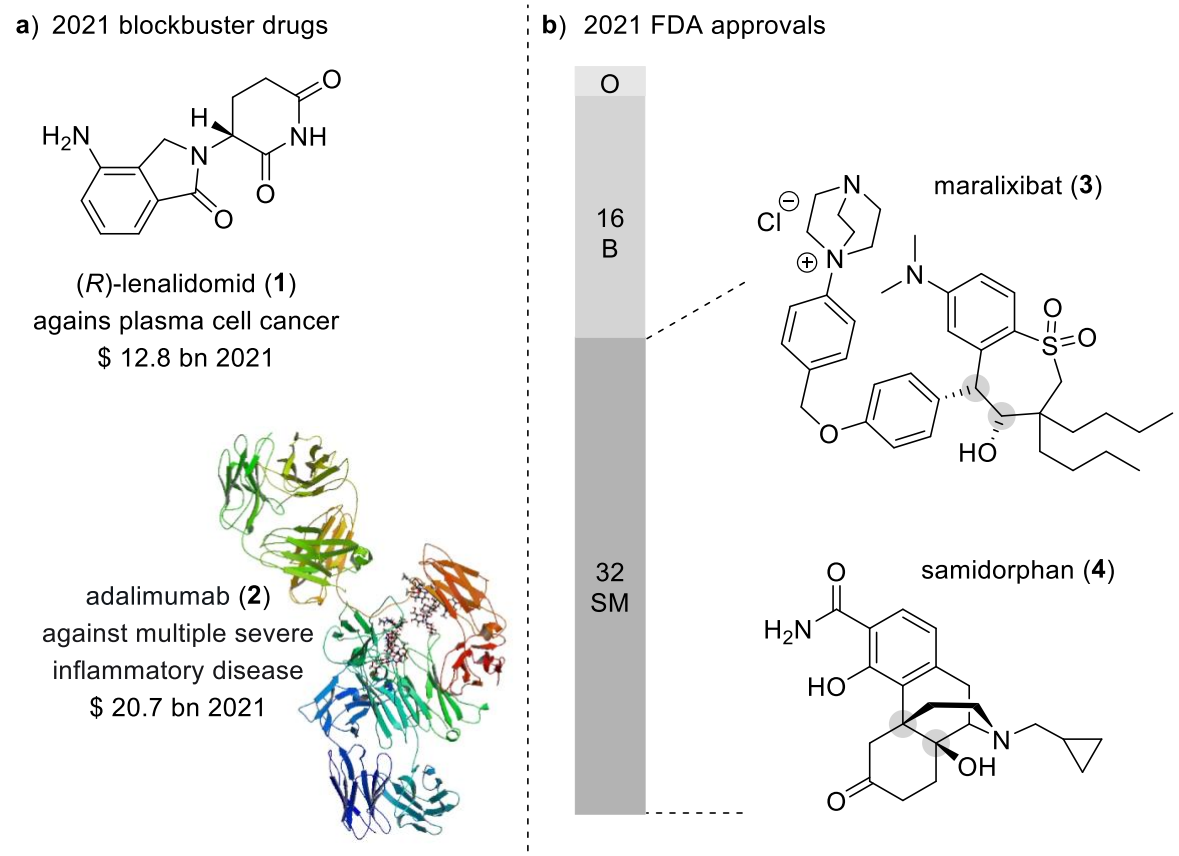
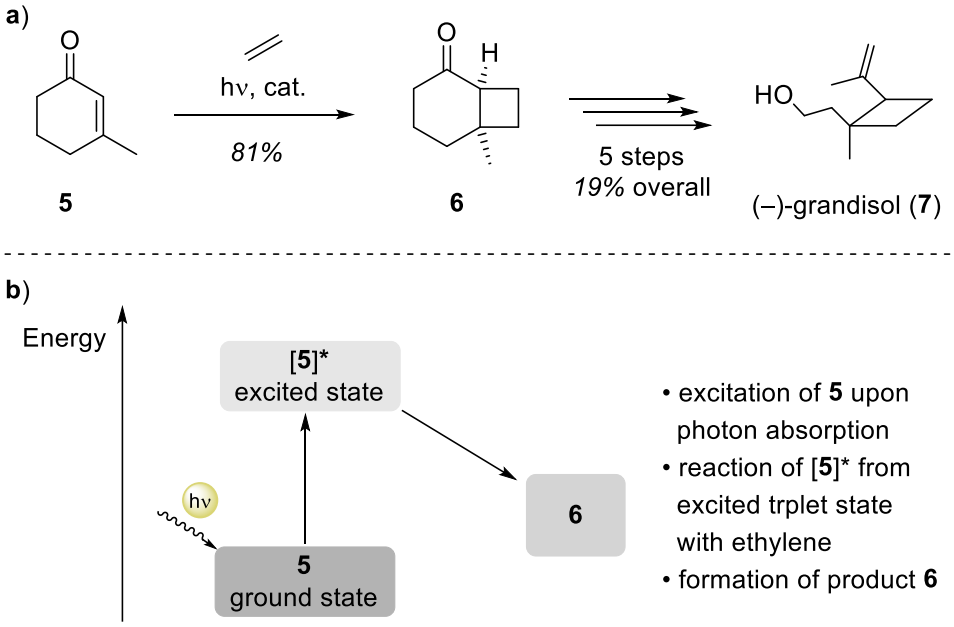


Figure 1: a) Two selected blockbuster drugs, the small molecule Revlimid® (**1**, $C_{13}H_{13}N_3O_3$, 259.3 g/mol) and the antibody Humira®[2] (**2**, $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$, 144190.3 g/mol) belonging to the class of biologic drugs; **b**) split of FDA newly approved drugs in USA 2021, and two selected SM examples.[3] SM = small molecules, B = biologics, O = other (2), stereogenic centers are marked in grey.

Although the research field of organic synthesis is not directly focused on developing new drugs, fundamental findings can later be beneficial for the development of new pharmaceuticals. The key challenge in organic synthesis, and the basis of this PhD work remains developing and understanding new reactions that enable the concise assembly of small molecules and natural products with complex structures from simple and easily accessible building blocks.

1.2 Photochemistry: Access to Complex Small Molecules

In this context, organic synthesis can be divided into several research fields, naming for example: bioorganic chemistry, where enzymes can be applied to construct complex molecules,[4] or organometallic catalysis, where (transition-) metal catalysts enable access to useful scaffolds.[5] However, with respect to this PhD work, special focus is put on the research area of organic photochemistry, where light is employed to excite certain parts of a molecule (chromophores) selectively and to thereby induce chemical reactions. Often this approach enables new chemical routes that would not be accessible using thermal protocols.[6] An example is the total synthesis of the natural product (–)-grandisol by *Bach* and coworkers (Scheme 1a).[7] Here, simple ethylene gas was reacted with cyclohexanone **5** under light irradiation. Cyclobutene product **6** was formed which could be transformed into (–)-grandisol in five consecutive steps.



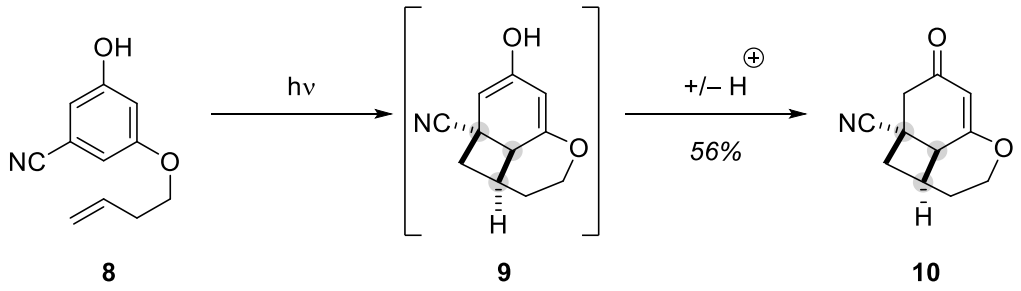
Scheme 1: a) [2+2] Photocycloaddition[9] of ethylene to ketone **5** as key step in the total synthesis of **7**. Conditions for **5**→**6**: λ = 366 nm, 50 mol% chiral *Lewis* acid catalyst, (CH_2Cl_2), –75 °C, 24 h;[7] **b**) general energy scheme for photochemical reactions.[8-10]

A central feature of this light-promoted transformations is the electronically excited state [**5**]*, formed upon irradiation.[8] This excitation significantly alters the reactivity of cyclohexenone **5** and subsequently allows the addition of simple ethylene by [2+2]

photocycloaddition to give product **6**.[9] The observed reactivity cannot be achieved using thermal energy sources as the highly reactive excited species [**5**]* can only be accessed upon the absorption of photons.[8-10] In this sense photo-induced reactions offer powerful and efficient strategies for designing diverse organic frameworks starting from material as simple as ethylene gas.[9-11] Among various photochemical transformations,[6] photocycloadditions (PCA) and their synthetic potential are of particular interest for this work.

2. PHOTOCYCLOADDITION REACTIONS

Photocycloadditions (PCA) are reactions in which upon light-induced addition of another molecule a new molecular cycle is generated.[12] As shown in the previous chapter, PCA reactions between two olefins give a cyclobutane product via a [2+2] mechanism.[9] However, these transformations are not limited to four-membered carbon-based ring products only, but can be extended to diverse molecular scaffolds. Those include heteroatoms and other ring sizes depending on starting materials and reaction conditions.[12] However, in all cases flat double or triple bonds (sp^2 or sp carbon atoms) are transformed into three-dimensional sp^3 centers enabling rapid access to high structural complexity in a single step. Especially in cases of intramolecular reactions, strained polycyclic scaffolds are rapidly constructed, as e.g. *Hoffmann* and *Pete* demonstrated (Scheme 2).[13] Upon irradiation, flat arene **8** reacts intramolecularly with the olefin moiety to polycyclic diene **9** generating three new stereogenic centers in a single step (marked in grey).

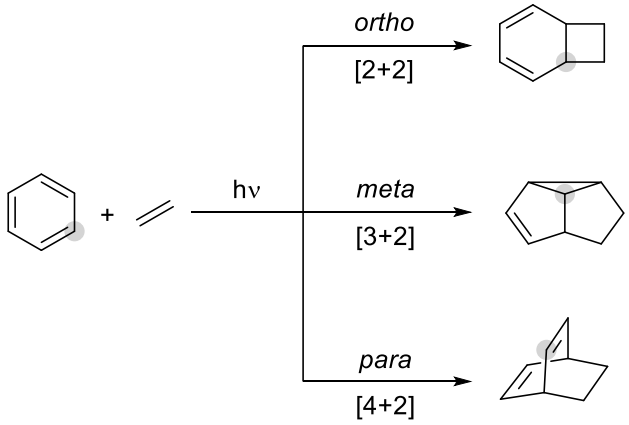


Scheme 2: Accessing polycyclic ring structures by an intramolecular photocycloaddition.[13]

The depicted example also displays a special type of PCA: An arene core is photochemically excited and reacts with the olefin moiety in a formal [2+2]-addition mechanism.[14] Aromaticity is broken up and the generated strained carbon scaffold of **9** is secured by tautomerization to ketone **10**, preventing the reverse reaction.[13] With respect to the natural abundance of aromatic building blocks and the synthetic potential offered by dearomatization reactions, arene photocycloaddtion reactions[14,15] are of particular interest in the context of this PhD research.

2.1 Intramolecular Arene Photocycloadditions and Synthetic Applications

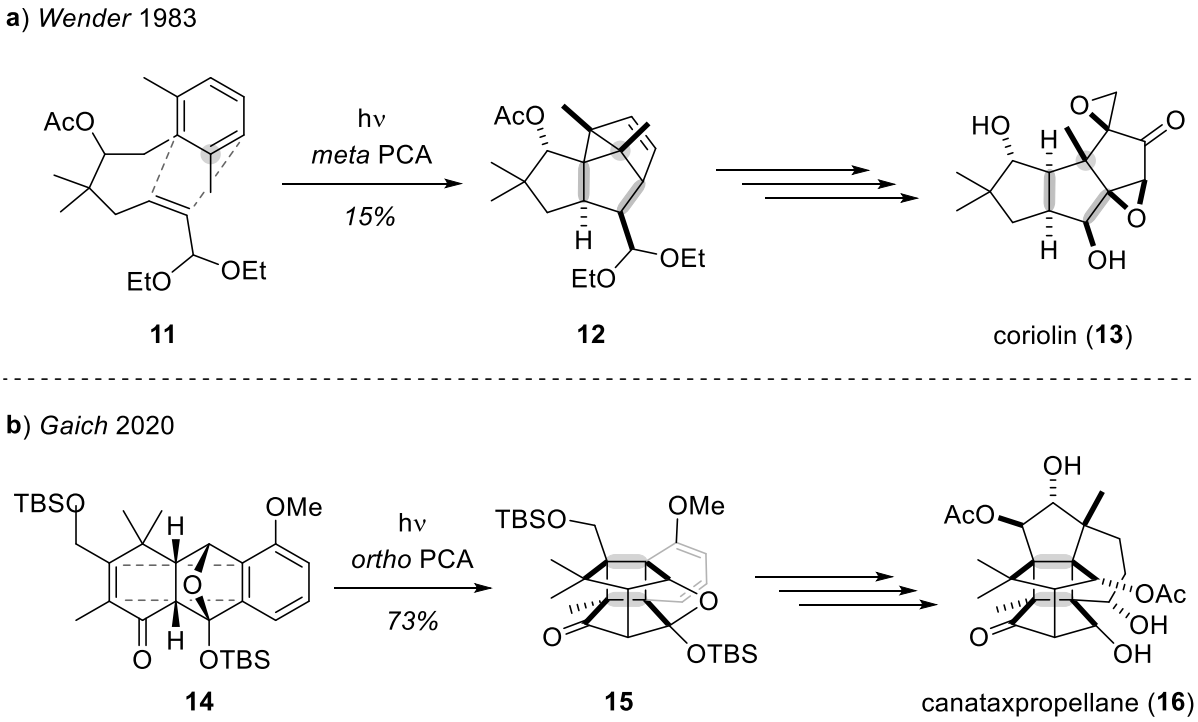
Generally, one can imagine three ways of adding an olefine to an aromatic ring: In *ortho*, *meta* or *para* position, which are formal [2+2], [3+2], [4+2] photocycloadditions, respectively (Scheme 3).[16] As the addition is strongly dependent on electronic properties as well as the geometry of the reaction partners, the reaction outcome often remains unpredictable. However, as a rule of thumb, one can expect an electron-deficient arene and an electron-rich olefin – or *vice versa* – to react in *ortho* position, whereas a small difference in electronic properties favors the *meta* addition mode.[17] The *para*-PCA is the least frequently observed reaction type, but may for example occur when electron-poor arenes are reacted with allene building blocks.[15d]



Scheme 3: Three potential photocycloaddition modes of ethylene to benzene.[16]

In all cases, three-dimensional structures are obtained and the level of molecular complexity even increases when the olefin moiety is directly linked to the arene core. Such intramolecular PCA reactions lead to polycyclic ring structures (see Scheme 2), destined to be applied in total synthesis.[10,11] In the past decades, the *meta* photocycloaddition (mainly as its intramolecular version) has been elegantly applied to the total synthesis of multiple natural products,[18] naming ***Wender's*** synthesis towards coreolin (**13**) as an early example (Scheme 4a).[19] Here, the photochemical transformation (**11**→**12**) represents the key step in constructing the tricyclic carbon skeleton of natural product **13**.[19,20]

In contrast to the *meta* PCA, applications of *ortho* and *para*[21] photocycloaddition reactions have remained underexplored. One of the few, yet recent applications of the former addition mode was demonstrated by *Gaich* and co-workers, who elegantly employed an intramolecular *ortho* PCA to access the carbon-core of tetracyclic substrate **15** (Scheme 4b).[22] With respect to early reports on reaction cascades initiated by intramolecular *ortho* PCAs,[23] it is remarkable that in this case no consecutive thermal reaction of the 1,3-cyclohexadiene moiety of **15** (marked in light grey) was observed. Instead, the material could be isolated and transformed into canataxpropellane (**16**) within further synthetic steps.[22]



Scheme 4: Intramolecular arene photocycloadditions as key steps in total synthesis: **a**) *meta* PCA (newly formed bonds and the central C highlighted in grey) in the total synthesis of **13**;[19,20] **b**) *ortho* PCA to furnish the carbon skeleton of **16**.[22] (1,3-cyclohexadiene moiety marked in grey, TBS = *tert*-butyldimethylsilyl).

As mentioned above, strained 1,3-cyclohexadiene intermediates formed upon *ortho* PCA are prone to undergo further reactions. It became apparent that releasing molecular strain through thermal ring expansions of the adjacent cyclobutane is the preferred pathway and may lead to new intermediates continuing this cascade of reactions.[23-25] In some cases, decomposition might be observed eventually, while in other cases, unexpected products might be obtained.[25] The unpredictability of such

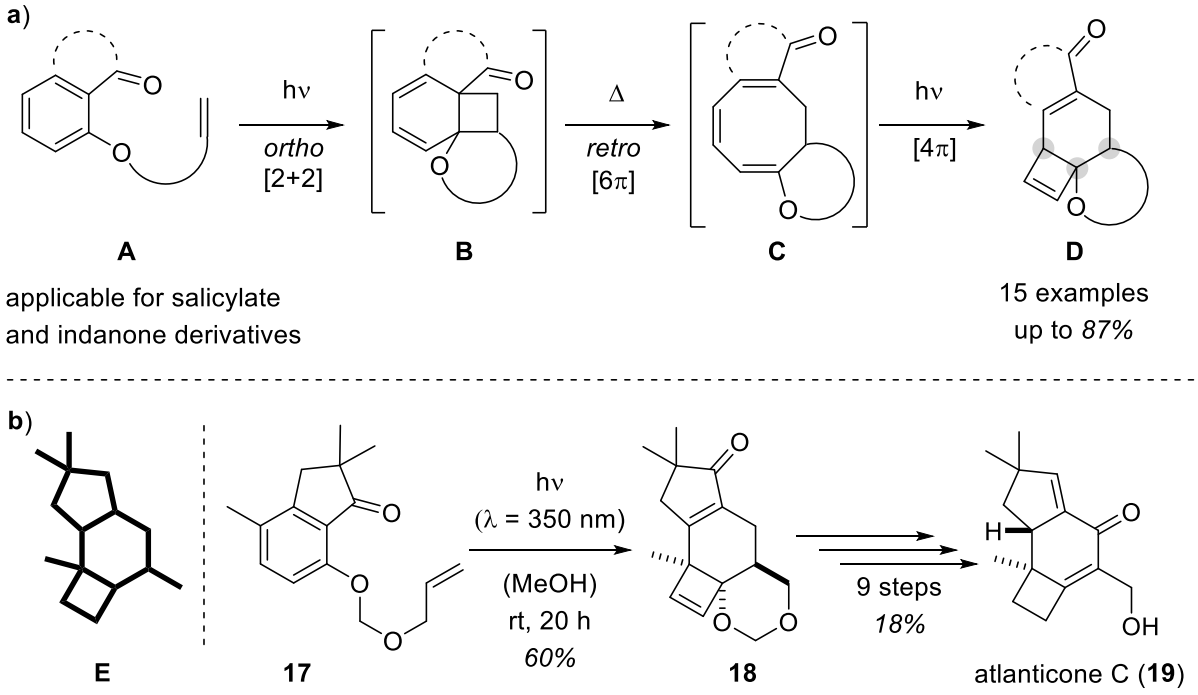
ortho PCA induced reaction cascades might be a reason why chemists have avoided their applications in synthesis. However, looking at it from a different perspective, an array of intramolecular reactions induced only by light irradiation can offer concise and innovative routes to complex molecules. Only in recent years, the synthetic and catalytic potential of (intramolecular) *ortho* photocycloadditions have been further investigated and formed the basis for this work.

2.2 Recent Advances in Ortho Photocycloaddition Chemistry

The following chapter is divided into two sections: a) recent advances in the synthetic application of intramolecular *ortho* photocycloadditions and b) further development of this method with respect to photocatalysis and enantioselective approaches.

a) Synthetic Applications

Inspired by early work,[23] in 2016 our group became interested in photo-induced reaction cascades on salicylic acid derivatives.[26] In particular, esters[26] and indanone[27] substrates **A** were prepared and indeed they were found to undergo an intramolecular photochemical reaction cascade, concisely leading to complex molecules **D** (Scheme 5a).[23,26,27] This sequence of reactions is initiated by an *ortho* photocycloaddition leading to the strained 1,3-diene intermediate **B**. In contrast to *Gaich's* synthesis (see chapter 2.1),[22] a consecutive thermal disrotatory ring opening furnishes triene **C**, which upon further irradiation generates cyclobutene product **D** by [4π] photocyclization. It is worth noting that three stereogenic centers are created within this single operation (Scheme 5a, highlighted in grey). Initially, the developed method was applied to salicylate derivatives,[26] and was later expanded to indanone substrates.[26,27]



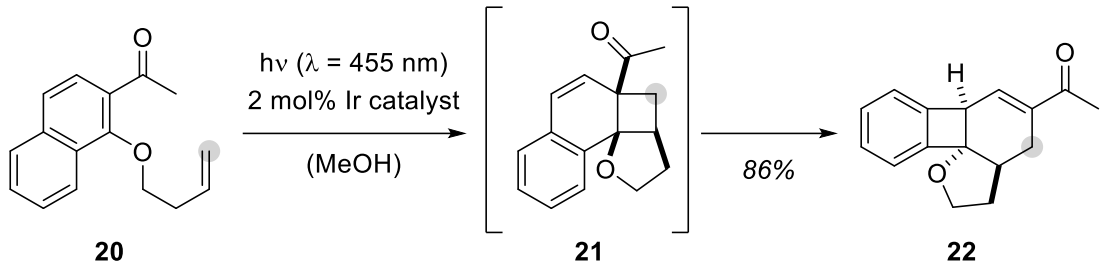
Scheme 5: a) *ortho* PCA initiated intramolecular reaction cascade developed in the group of *Bach*;[26,27] **b**) protoilludane core **E** and the key step in the total synthesis of atlanticone C.[27,29,30]

If indanone substrates were irradiated, a further photoreactivity was observed[27] and synthetically useful structures were obtained. In the particular case, indanone **17** was employed to furnish product **18**, featuring the carbon core **E** of protoilludane natural products (Scheme 5b).[28,30] With this finding, *Bach* and coworkers were able to synthesize racemic atlanticone C (**19**), a member of the protoilludane family in nine steps and 18% yield.[28]

b) Photocatalytic and Asymmetric Approaches

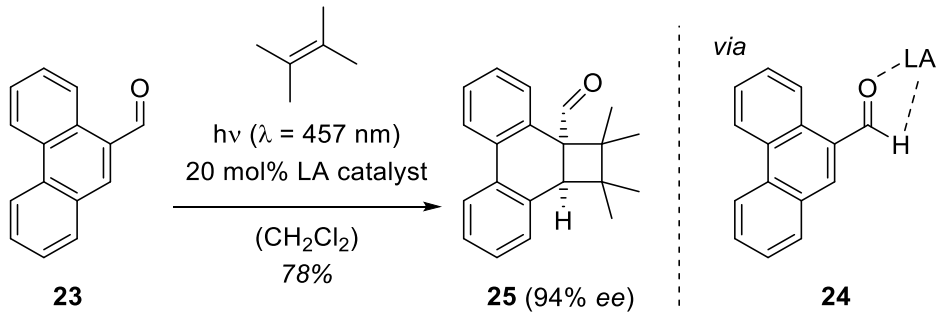
The previously discussed total syntheses demonstrate how photo-induced dearomatization reactions offer an efficient strategy to access complex molecules starting from abundant and inexpensive starting materials. However, in all cases breaking up aromaticity and constructing chiral molecules requires highly energetic UV-light and proceeds racemically. Strategies utilizing visible light (λ >400 nm), another abundant natural resource,[31] have yet not been fully investigated and developing asymmetric variants of such powerful transformations is of high interest in the synthetic community.[32] So far, few catalytic protocols for *ortho* photocycloaddition reaction have been developed, but their applicability is limited to naphthalene and phenanthrene building blocks.

One example is the *ortho* PCA-induced reaction cascade of naphthol derivatives **20** under visible-light photocatalytic conditions published by the group of *Glorius* in 2018 (Scheme 6).[33] Here, an iridium-based photocatalyst (photosensitizer) facilitates the initial *ortho* photocycloaddition (**20**→**21**). The respective catalyst gets excited upon irradiation at $\lambda = 455$ nm and subsequent triplet energy transfer to ketone **20** populates the reactive excited state **20*** (sensitization).[34] This photocatalytic process allows the initial *ortho* PCA and consecutive reactions to proceed under visible-light irradiation.



Scheme 6: An *ortho* PCA-induced reaction cascade of naphthol derivatives under sensitizing conditions.[33]

Simultaneously, our group described an enantioselective intermolecular *ortho* photocycloaddition of phenanthrene aldehydes **23** (Scheme 7).[35] In this case, coordination of a chiral *Lewis* acid catalyst (LA) to the carbonyl moiety introduces chirality and leads to a bathochromic shift of the chiral complex **24**.[36] This concept allows for the irradiation with visible light and the formation of enantiomerically enriched cyclobutane **25**.[35]



Scheme 7: *Lewis* acid (LA) catalyzed enantioselective intermolecular *ortho* photocycloaddition of phenanthrene aldehydes. Coordination to the chiral *Lewis* acid catalyst via **24** enables utilizing visible light irradiation conditions.[35]

The selected examples showcase how *ortho* photocycloadditions can be photochemically catalyzed through energy transfer or *Lewis* acid catalysis. Yet, attempts to apply the same principles to synthetically valuable intramolecular reaction cascades of benzene derivatives (e.g. **A**→**D**, Scheme 5a) remained unsuccessful in our group so far.

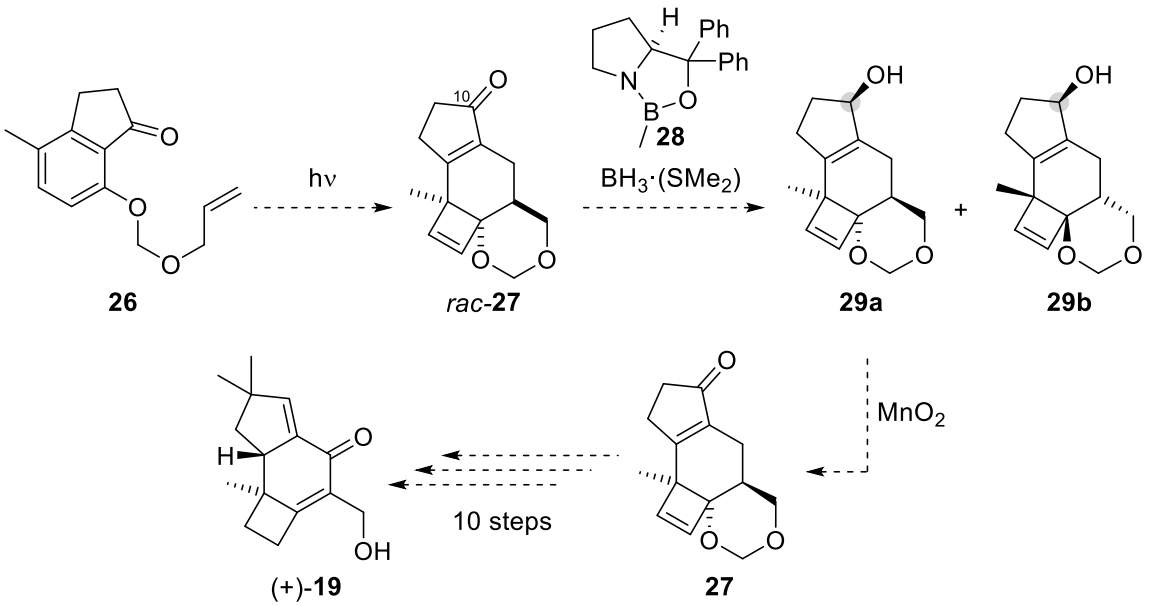
3. PROJECT AIM

Within the scope of this PhD thesis, two sub projects were defined: a) developing enantioselective synthetic applications of the observed intramolecular *ortho* photocycloaddition and b) further investigating this method with respect to photocatalysis and enantioselective approaches.

3.1 OPCA REACTION CASCADE AS KEY STEP IN TOTAL SYNTHESIS

While the racemic total synthesis of atlanticone C was successfully achieved by using the photo-induced reaction cascade as key step in 2019 (see chapter 2.2),[28] the aim of this work was to develop an enantioselective version of this synthetic route. By comparing analytical data of the enantiopure synthetic molecule and the natural atlanticone C (**19**),[30] the absolute configuration of the natural product was to be determined.

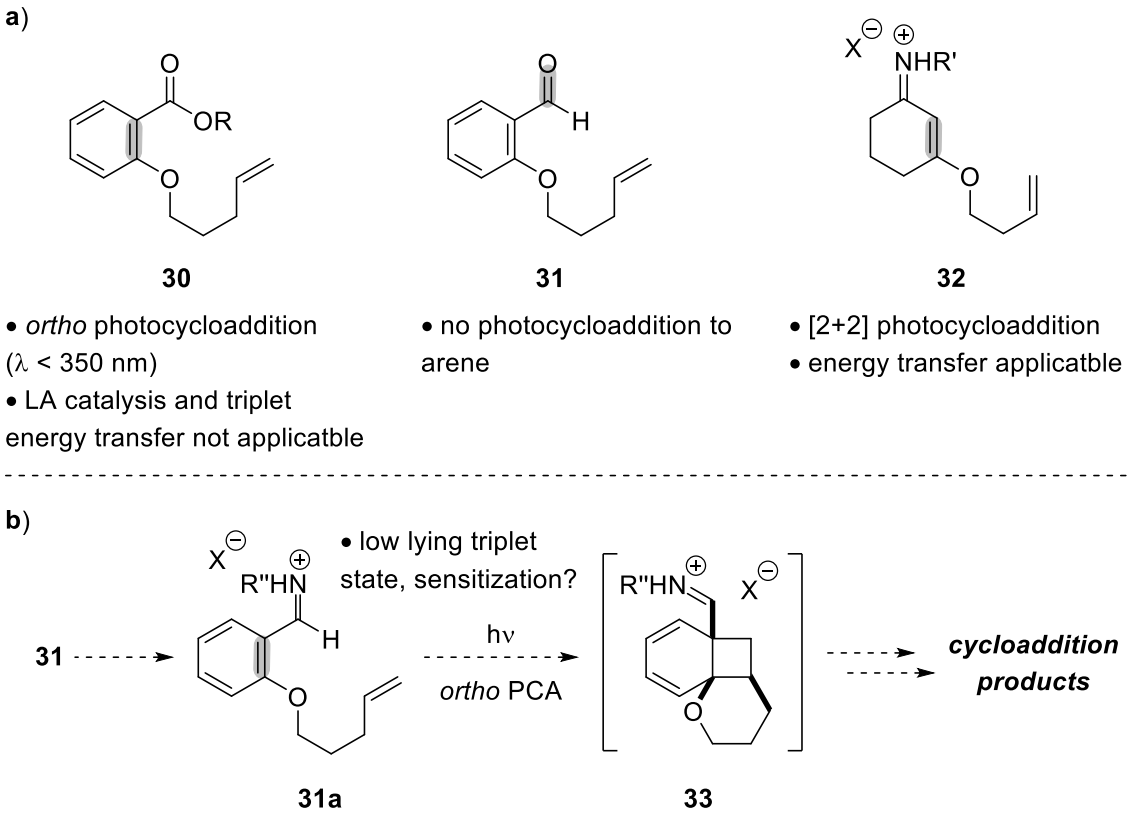
For this purpose, we envisioned a slightly modified indanone substrate **26** as compared to the racemic version, lacking the *gem*-dimethyl group to undergo the reaction cascade furnishing *rac*-**27** (Scheme 8). The sterically approachable carbonyl group at C-10 should then be employed as a handle for chiral resolution. Utilizing catalyst **28**, an enantioselective *Corey-Bakshi-Shibata* (CBS) reduction[37] would generate diastereomers **29a** and **29b**. Chromatographic separation of the two alcohols followed by re-oxidation would give access to enantioenriched photoproduct **27**. Within ten subsequent steps this material could then be transformed to (+)-atlanticone C (**19**). In addition, this approach should give us the opportunity to improve some of the low-yielding synthetic steps previously reported in the racemic version.[28]



Scheme 8: Envisioned approach for the enantioselective total synthesis of (+)-atlanticone C (**19**). Access to enantioenriched photoproduct **27** via chiral resolution: enantioselective CBS reduction[37] of *rac*-**27** followed by separation and re-oxdation of **29a**.

3.2 Arene Photoactivation of Benzaldehyde Substrates

Previous studies in our group on *Lewis* acid catalysis or the use of energy transfer photocatalysts for *ortho* photocycloadditions of benzene-derived ester and indanone substrates **30** remained unsuccessful (Scheme 9a). Seeking to further explore the potential of intramolecular *ortho* photocycloadditions, we turned our attention to benzaldehyde derivatives **31**. However, early on it became apparent that for such substrates reaction at the carbonyl moiety is preferred,[38] which often leads to decomposition of starting material and leaves the arene core untouched. However, inspired by work on [2+2] photocycloadditions of iminium ions,[39] derived from α,β-unsaturated carbonyl compounds **32**,[39a] we planned to investigate this approach further. When carbonyl compounds are transformed into iminium ions, they exhibit a bathochromic shift of the $\pi\pi^*$ absorption and a decrease in triplet energy compared to the respective aldehyde and imines.[40] Applying this principle to arene substrates would potentially increase population of the reactive triplet state and induce the desired reactivity at the aromatic ring (Scheme 9b). We therefore envisioned benzaldehyde-derived iminium ions **31a** to be an alternative substrate class that could undergo *ortho* photocycloaddition reactions and be activated towards energy transfer.



Scheme 9: a) Aromatic photosubstrates **30** and **31** with respective photoactivity and the cyclohexene-derived iminium ion **32** showcasing activation towards energy transfer,[39] LA = *Lewis* acid; **b**) envisioned approach for arene photoactivation through iminium ions. Photoreactivity marked in grey.

To verify this approach, in a first step we would synthesize iminium ions **31a** from salicyclic aldehyde derivatives **31** and investigate their photophysical properties. Because of the expected bathochromic shift and lower lying triplet state of such compounds compared to the respective aldehydes,[40] we expected an intramolecular *ortho* photocycloaddition to occur upon irradiation (**31a**→**33**, Scheme 9b). Within consecutive reactions, as observed previously (see chapter 2.2), highly reactive 1,3-cyclohexadiene intermediates **33** could be transformed into complex molecular scaffolds. With an appropriate photocatalyst for triplet sensitization,[34] those reactions could be carried out with visible-light irradiation. In the long term, developing such a method would offer new opportunities for enantioselective *ortho* photocycloadditions, e.g. by using chiral amines,[39a,c] counter ions[32] or a chiral catalyst[41] in this sense. Against this background, we defined photochemical arene activation through iminium ions as central research in this work.

4. Enantioselective Total Synthesis of Atlanticone C

Title: “Concise Total Synthesis of (+)-Atlanticone C”

Status: Letter, published online July 31, 2020

Journal: *Synlett* **2020**, *31*, 1598-1602

Publisher: Georg Thieme Verlag KG

DOI: 10.1055/s-0040-1707215

Authors: Johanna Proessdorf, Andreas Zech, Christian Jandl, Thorsten Bach

Content: While the racemic total synthesis of atlanticone C had successfully been achieved previously, this manuscript reports the first enantioselective route towards (+)-atlanticone C. The complex protoilludane core was rapidly constructed by the known photochemical reaction cascade starting from an easily accessible indanone precursor (3 steps). An enantioselective *Corey–Bakshi–Shibata* reduction allowed for catalytic chiral resolution of the racemic photoproduct (45% over two steps; up to 98% *ee*) and gave access to enantiomerically enriched photoproduct. This material was efficiently transformed into the (+)-enantiomer of atlanticone C (10 steps; 18% yield), and the absolute configuration of naturally occurring (–)-atlanticone C was thereby determined.

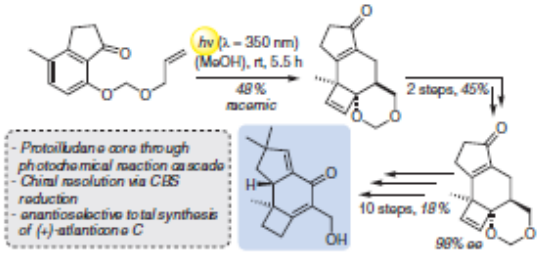
Author contributions: The conceptual contribution was made by T. Bach and A. Zech. Initial test reactions were executed by A. Zech. J. Proessdorf planned, performed, and analyzed the synthetic steps in this total synthesis. For determination of the absolute configuration J. Proessdorf planned and performed the Mosher ester analysis and prepared crystalline material. C. Jandl conducted the X-ray crystallographic analysis. J. Proessdorf and T. Bach wrote the manuscript.

Synlett J. Proessdorf et al. Letter

Concise Total Synthesis of (+)-Atlanticone C

Johanna Proessdorf
Andreas Zech
Christian Jandl
Thorsten Bach*

Department Chemie and Catalysis Research Center (CRC), Technische Universität München, 85747 Garching, Germany
thorsten.bach@ch.tum.de



Received: 27.05.2020
Accepted after revision: 24.06.2020
Published online: 31.07.2020
DOI: 10.1055/s-0040-1707215; Art ID: st-2020-r0313-l

Abstract The first enantioselective total synthesis of (+)-atlanticone C is described. The complex tricyclic protoilludane core was rapidly assembled by a photochemical reaction cascade starting from an easily accessible indanone precursor (3 steps). Optimization of an enantioselective Corey–Bakshi–Shibata reduction permitted a catalytic chiral resolution of the racemic photoproduct (45% over two steps; up to 98% ee). The enantiomerically enriched photoproduct was efficiently transformed into the (+)-enantiomer of atlanticone C (10 steps; 18% yield), and the absolute configuration of naturally occurring (–)-atlanticone C was thereby determined.

Key words asymmetric synthesis, total synthesis, photocycloaddition, chiral resolution, protoilludanes, atlanticone C

Protoilludanes are sesquiterpene natural products with a characteristic tricyclic [5.6.4]-skeleton **A** (Figure 1).[1] Although they share this tricyclic core structure, protoilludanes differ in the oxidation states of their carbon atoms in the three rings. Atlanticone C (**1**),[2] for example, contains a carbonyl oxygen at the C-8 position of the six-membered ring, whereas illudol (**2**)[3] and pasteurestin B (**3**)[4] feature hydroxy groups on the cyclobutane moiety (C-4) or on the five-membered ring (C-10), respectively (Figure 1). For almost 50 years, the unique molecular architecture of protoilludanes and their promising biological activities[4,5] have motivated organic chemists to target this class of natural products for total synthesis.[6]

In all synthetic approaches to these compounds, the key challenge remains to construct the characteristic tricyclic protoilludane core.[6] In several reported syntheses, the rings were built consecutively, frequently employing intermolecular [2+2]-photocycloaddition reactions to access the cyclobutane moiety.[7,8] In other cases, the tricyclic skeleton was obtained through an intramolecular tandem reaction.[5a,9] In their pioneering work, Johnson and Vollhardt accomplished a total synthesis of illudol (**2**) through [2+2+2]-cycloaddition of an enediyne precursor.[10] Our synthetic approach was based on our recently reported work,[11,12] in the course of which we had found that certain indanone substrates **B** undergo an unprecedented **B** → **E** → **F** intramolecular photochemical transformation (Scheme 1). This key step allowed us to access the protoilludane core **E** in a single operation.

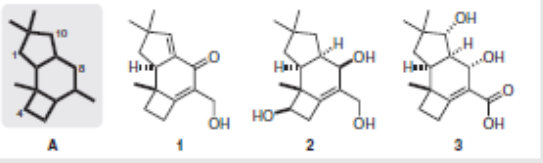
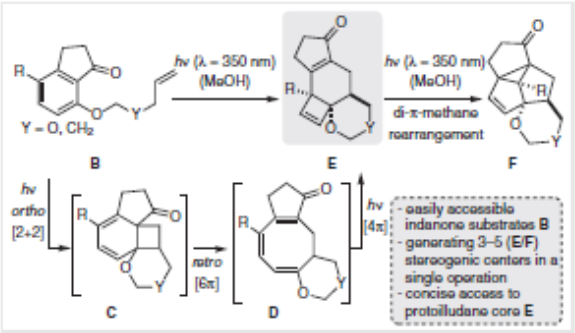


Figure 1 The protoilludane skeleton **A** and representative sesquiterpene natural products: atlanticone C (**1**), illudol (**2**), pasteurestin B (**3**)

The photochemical reaction cascade is initiated by an *ortho*-photocycloaddition[13] of the indanone substrate **B**. The resulting strained diene intermediate **C** undergoes a thermal disrotatory ring opening, forming triene **D**. Upon further irradiation, a [4π]-photocyclization occurs that converts **D** into the desired cyclobutene product **E** featuring three stereogenic centers.[11,12] We also observed that under certain conditions, the product can undergo a third photochemical step, a di-π-methane rearrangement leading to the cyclopropane product **F**.[14] Whereas the above-mentioned approach led to a synthesis of racemic atlanticone C, we have now attempted to synthesize the compound in an enantiopure form. Apart from obtaining proof of the absolute configuration of the product, we also expected to improve some of the consecutive steps, and we wanted to showcase the utility of the photochemical reaction cascade.

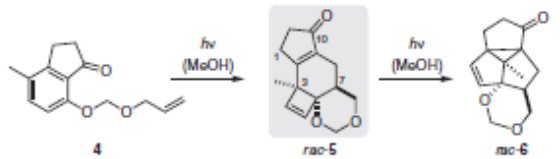
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 Mechanism of the photochemical reaction cascade furnishing the protoilludane core **E**[10–14]

Our modified approach commenced with the synthesis of photosubstrate **4**, which was easily accessible in three steps starting from *p*-methylanisole (see Supporting Information).[11,14] The idea was to resolve the putative reaction product by a subsequent enantioselective reduction, which required a steric distinction of the substituents at the carbonyl carbon atom. The introduction of the *gem*-dimethyl substitution at C-11 was therefore postponed to a later stage after the resolution had been performed. With **4** in hand, we focused on the key step of our synthetic strategy, the photochemical reaction cascade furnishing the protoilludane core. Previous experiments[11,12,14] had shown that the desired photochemical transformation proceeds efficiently in freshly distilled dry methanol as the solvent (0.1 mM) and with irradiation at λ = 300 or 350 nm. We were pleased to detect reasonably good conversions of **4** after irradiation at λ = 300 and 350 nm for two hours (Table 1, entries 1 and 2, respectively). In both cases, formation of the desired photoproduct *rac*-**5**, together with the undesired di-π-methane rearrangement product *rac*-**6**, was observed. Although the conversion of the starting material was similar regardless of the chosen wavelength, we observed a better *rac*-**5**/*rac*-**6** ratio upon irradiation at the longer wavelength (entry 2). However, due to the low conversion, only 27% of the desired product *rac*-**5** was isolated after two hours (entry 2), so longer irradiation times were investigated. A reaction time of 14 hours led to full conversion of **4**, but to an unfavorable product ratio (entry 4). After 5.5 hours, starting material **4** was almost fully consumed, and the desired product *rac*-**5** was isolated in a moderate yet acceptable yield of 48% (entry 3). These latter conditions seemed most appropriate for the further course of the total synthesis of atlanticone C (**1**) and permitted the preparation of *rac*-**5** on a scale of up to 0.75 g.[15]

Table 1 Conversion of Starting Material **4** and Comparison of the Ratio *rac*-**5**/*rac*-**6** upon Variation of the Irradiation Time and Wavelength

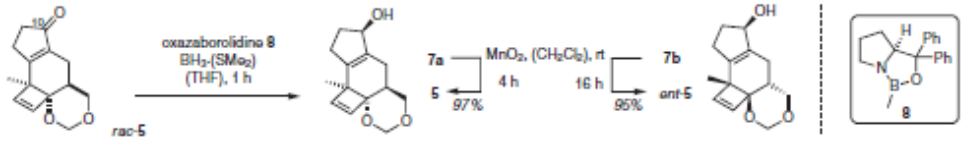


Entry	λ (nm)	Time (h)	**4**/*rac*-**5**/*rac*-**6**[a]	Yield[b] (%) of *rac*-**5**
1	300	2.0	64:26:10	25
2	350	2.0	59:34:7	27
3	350	5.5	6:56:38	48
4	350	14	0:27:73	26

[a] Determined by integration of the appropriate ^{1}H NMR signals.
[b] Yield of isolated product.

Before further conversion of the photoproduct *rac*-**5**, the carbonyl group at C-10 was employed as a handle for a chiral resolution by an enantioselective Corey–Bakshi–Shibata (CBS) reduction.[16] Subsequent reoxidation[17] of the separated diastereoisomers **7a** and **7b** was expected to provide access to the enantiomerically enriched products **5** and *ent*-**5** (Table 2). We were pleased to detect a stereodivergent reduction upon exposure of *rac*-**5** to CBS reduction conditions [(*S*)-2-methyl-CBS-oxazaborolidine **8**, BH_3·(SMe_2), THF].[18] Ketone *rac*-**5** was converted into a separable mixture of alcohols **7a** and **7b** (dr = 46:54; ^{1}H NMR) in 96 and 93% ee, respectively and an overall yield of 85% (entry 1). Interestingly, we observed improved yields and enantioselectivities with substoichiometric amounts of BH_3·(SMe_2). Full conversion of *rac*-**5** was achieved with just 0.6 equivalents of BH_3·(SMe_2), resulting in an improved combined yield of 97% and excellent enantioselectivities of 98 and 94% ee (entry 2). This result indicates that BH_3·(SMe_2) transfers more than one hydride atom under the chosen conditions.[19] Furthermore, the stability of **7a** and **7b** in the presence of an excess of the borane is questionable. Although no significant byproducts were detected by ^{1}H NMR analysis of the crude material or could be isolated from the reaction mixture, it is reasonable to assume that hydroboration of the cyclobutene moiety by excess borane occurs and could result in byproducts, leading to decreased yields of **7a** and **7b**.[20] We attempted to improve the enantiomeric excess of product **7b** by repeating the experiment at a lower temperature (entry 3) or at room temperature (entry 4).[21] Although the enantioselectivity of the reduction at –40 °C remained high (entry 3), a decrease in selectivity for both diastereomers occurred at room temperature (entry 4). In a final set of experiments, we investigated the influence of the loading of catalytic (*S*)-2-methyl-CBS-oxazaborolidine **8** (entries 5–7). Although excellent yields and enantiomeric excesses of >90% were maintained for **7a** at a loading as low as 10 mol% (entry 7), the enantioselectivity toward diastereomer **7b** decreased. Because of the overall better enantioselectivity toward alcohol **7a**, we decided to pursue our total synthesis with this diastereoisomer. The absolute configuration of alcohol **7a** was confirmed by Mosher analysis[22,23] of the two epimeric esters **9a** and **9b**, obtained by esterification[24] with the ap-

Table 2 Chiral Resolution of Racemic Photoproduct *rac*-**5** and Optimization of the Enantioselective CBS Reduction



entry	BH_3-(SMe_2) (equiv)	Temp (°C)	**8** (mol%)	Yield[a] (%) of **7a**	ee[b] (%) of **7a**	Yield[a] (%) of **7b**	ee[b] (%) of **7b**
1	1.0	0	105	42	96	43	93
2	0.6	0	105	44	98	53	94
3	0.6	–40	105	45	98	49	94
4	0.6	rt	105	45	95	52	90
5	0.6	0	50	46	96	52	87
6	0.6	0	25	46	95	49	86
7	0.6	0	10	46	91	50	85

[a] Yield of isolated product.
[b] Determined by chiral HPLC.

propriate chiral acids (see Supporting Information). Because the stability of the esters was low and their purity not completely satisfactory, the chiral alcohol **7a** was crystallized and its configuration was confirmed by anomalous X-ray diffraction (Figure 2).[25]

With almost enantiopure (98% ee) alcohol **7a** in hand, the compound was oxidized to ketone **5**. Interestingly, the two diastereoisomers **7a** and **7b** reacted at different rates in the oxidation step, with the latter being less reactive (Table 2). A *gem*-dimethyl substitution at C-11 was introduced by α-alkylation of ketone **5** with iodomethane, giving ketone **10** in 97% yield (Scheme 2).[26] Completion of the total synthesis starting from ketone **10** followed our previously described sequence,[11] but gave us the chance to improve some of the individual steps. Hydrogenation of the cyclobutene ring to cyclobutane **11**, followed by condensation with *N*-tosylhydrazine, gave hydrazone **12** in 54% yield (44% recovered **11**). With the directing group at C-10 in place, we conducted a reductive transposition, as described by Kabalka et al.[27] Here, an initial hydride attack at C-10 from the desired diastereotopic face and subsequent formation of the double bond at the C-9/C-10 position with release of nitrogen furnished alkene **13**. At this point in the synthesis, all the stereogenic centers present in atlanticone C (**1**) had been established, so we turned our focus on the adjustment of the oxidation states at C-6/C-7 and C-8.

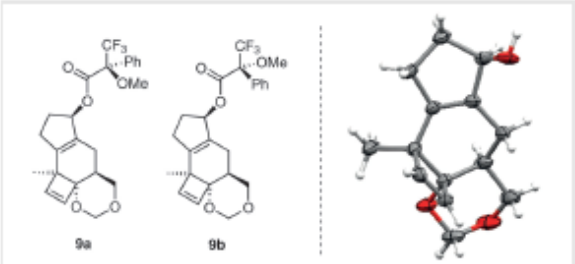
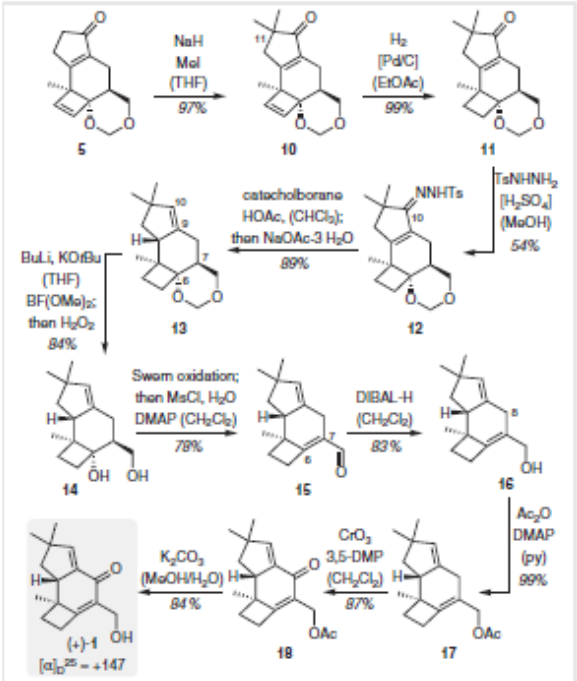


Figure 2 The structure of Mosher esters **9a** and **9b** obtained by esterification of alcohol **7a** and the absolute configuration of alcohol **7a** as determined by anomalous X-ray diffraction[25]



Scheme 2 Completion of the total synthesis of (+)-atlanticone C (**1**) (10 steps, 18% overall yield) from enantiomerically enriched ketone **5**

Because of the instability of **13** under acidic conditions,[11] we continued with a basic acetal cleavage. Treatment of acetal **13** with the Schlosser–Lochmann base (Bu-Li/*t*-BuOK) followed by a quench with $BF(OMe)_2$-OEt_2[28] and an oxidative workup afforded diol **14**. Adjustment of the oxidation state at positions C-6/C-7 was achieved by an initial Swern oxidation to an aldehyde intermediate and subsequent treatment with the Furukawa reagent,[7d] furnishing **15** in 78% yield. In this step, optimization of the substrate concentration for the initial Swern oxidation and a shorter reaction time for the dehydration step led to a 10% improvement in the yield compared with that of the previously reported procedure.[11] DIBAL-H reduction of the resulting aldehyde gave allylic alcohol **16**, which differed from the target atlanticone C (**1**) only in the oxidation state at C-8. With **16** in hand, we proceeded with an acetylation of the hydroxy group. We were able to optimize the acetylation conditions to provide efficient access to the relatively unstable acetate **17** in 99% yield. Key to the high yield was a decrease in temperature from room temperature[11] to 0 °C and a shorter reaction time (10 min). The required allylic oxidation at the C-8 methylene group (**17** → **18**) had been previously performed[11] with pyridine/CrO_3, which gave an unsatisfactory yield of only 44%. A more extensive screen of conditions was now performed, from which 3,5-dimethylpyrazole (3,5-DMP) and CrO_3 emerged as the best reagent combination for conducting the desired oxygenation,[29] giving ketone **18** in 87% yield. Saponification of the ester group proceeded with another yield improvement (84% versus 68% previously), and resulted in the formation of the desired alcohol (+)-**1**. The spectroscopic data of the synthetic product (+)-**1** perfectly matched the data reported for atlanticone C.[2] Furthermore, the specific rotation for (+)-**1** allowed us to determine the absolute configuration of natural (–)-atlanticone C (see Supporting Information). The natural product was levorotary ($[\alpha]_D^{20}$ –224), whereas our compound showed a strongly positive specific rotation. The reason for the discrepancy between the absolute values (–224 vs. +147) is unclear, however. We validated the enantiopurity (>98% ee) of compound **10** by chiral HPLC analysis (see Supporting Information). Compound **10** and all successive products contain at least two stereogenic centers, one of which is quaternary. Any loss of enantiopurity would require simultaneous racemization at all stereogenic centers, which appears unlikely. Although it is not possible to separate racemic atlanticone C into its enantiomers by chiral GLC and HPLC methods, we are nevertheless confident that our final product is enantiopure (>98% ee).

In summary, we have successfully applied a recently described photochemical reaction cascade to a yet-unexplored indanone substrate (Table 1). Efficient CBS reduction of the resulting photoproduct furnished separable diastereoisomers with an excellent enantiomeric excess (97% yield; up to 98% ee), and subsequent reoxidation provided access to the enantiomerically enriched photoproduct **5** (Table 2). With this material in hand, we were able to complete the first enantioselective total synthesis of (+)-atlanticone C in ten steps and 18% yield. The absolute configuration of natural (–)-atlanticone C (**1**) could thus be determined.[2] The reported photochemical reaction cascade seems to be applicable to a variety of structurally diverse substrates, leading to complex and easily convertible products. Accessing high structural complexity in a single operation proves to be a powerful method, and should be applicable in total syntheses of more natural products.[6] Work in this direction is currently underway in our laboratories.

Funding Information

This project was supported by the DeutscheForschungsgemeinschaft (Ba 1372/22-1) and by the TUM Graduate School.

Acknowledgment

We thank O. Ackermann for his help with the chiral HPLC and specific rotation. We also acknowledge the support of L. Meier and J. Kudermann with MS and IR data.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707215.

Primary Data

for this article are available online at https://doi.org/10.1055/s-0040-1707215 and can be cited using the following DOI: 10.4125/pd0121th.

References and Notes

(1) (a) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199. (b) Abraham, W. R. *Curr. Med. Chem.* **2001**, *8*, 583.
(2) Clericuzio, M.; Mella, M.; Toma, L.; Finzi, P. V.; Vidari, G. *Eur. J. Org. Chem.* **2002**, 988.
(3) McMorris, T. C.; Nair, M. S. R.; Anchel, M. *J. Am. Chem. Soc.* **1967**, *89*, 4562.
(4) Takeuchi, T.; Iinuma, H.; Momose, I.; Matsui, S. Jpn. Kokai Tokkyo Koho JP 2001-9452 20010117, **2002**.
(5) For synthetic approaches to pasteurestins, see: (a) Kögl, M.; Brecker, L.; Warrass, R.; Mulzer, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 9320. (b) Kögl, M.; Brecker, L.; Warrass, R.; Mulzer, J. *Eur. J. Org. Chem.* **2008**, 2714. (c) Assante, G.; Dallavalle, S.; Martino, P. A. *J. Antibiot.* **2013**, *66*, 43.
(6) For a review, see: Siengalewicz, P.; Mulzer, J.; Rinner, U. *Eur. J. Org. Chem.* **2011**, 7041.
(7) For examples, see: (a) Matsumoto, T.; Miyano, K.; Kagawa, S.; Yu, S.; Ogawa, J.; Ichihara, A. *Tetrahedron Lett.* **1971**, *12*, 3521. (b) Takeshita, H.; Iwabuchi, H.; Kouno, I.; Iino, M.; Nomura, D. *Chem. Lett.* **1979**, 649. (c) de Mayo, P.; Takeshita, H. *Can. J. Chem.* **1963**, *41*, 440. (d) Furukawa, J.; Morisaki, N.; Kobayashi, H.;

Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 440. (e) Hansen, T. V.; Skattebøl, L.; Stenstrom, Y. *Tetrahedron* **2003**, *59*, 3461.

(8) For reviews on the use of photochemical key steps in natural-product synthesis, see: (a) Kärkäs, M. D.; Porco, J. A. Jr.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683. (b) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000. (c) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (d) Iriondo-Alberdi, J.; Greaney, M. F. *Eur. J. Org. Chem.* **2007**, 4801.

(9) Pitaval, A.; Leboeuf, D.; Ceccon, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 4580; corrigendum: Org. Lett. 2013, 15, 5146.

(10) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381.

(11) Zech, A.; Jandl, C.; Bach, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 14629.

(12) Zech, A.; Bach, T. *J. Org. Chem.* **2018**, *83*, 3069.

(13) For reviews, see: (a) Remy, R.; Bochet, C. G. *Chem. Rev.* **2016**, *116*, 9816. (b) Hoffmann, N. *Photochem. Photobiol. Sci.* **2012**, *11*, 1613. (c) Streit, U.; Bochet, C. G. *Beilstein J. Org. Chem.* **2011**, *7*, 525. (d) Streit, U.; Bochet, C. G. *Chimia* **2008**, *62*, 962. (e) Hoffmann, N. *Synthesis* **2004**, 481. (f) Cornelisse, J.; de Haan, R. In *Molecular and Supramolecular Photochemistry, Vol. 8: Ramamurthy V., Schanze K. S*; Dekker: New York, **2001**, 1. (g) Wagner, P. J. *Acc. Chem. Res.* **2001**, *34*, 1.

(14) Næsborg, L.; Jandl, C.; Zech, A.; Bach, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 5656.

(15) ***rac*-5; Typical Procedure (1.5 mmol Scale)**
Photosubstrate **4** (345 mg, 1.50 mmol, 1.00 equiv) was dissolved in distilled anhyd MeOH (150 mL), and O_2 was removed from the solution by purging with argon with sonication for 15 min. The solution was cannulated into three flame-dried 50–60 mL phototubes and irradiated at λ = 350 nm for 5.5 h under argon. The solvent was removed under reduced pressure, and the residue was purified by automated flash chromatography [silica gel (12 g), hexane–EtOAc (10–45%) (24 CV); UV detection] to give a colorless crystalline solid; yield: 166 mg (715 μmol, 48%); mp 114 °C.
^{1}H NMR (400 MHz, C_6D_6): δ = 6.17 (d, ^3J = 3.0 Hz, 1 H, H-2), 5.76 (d, ^3J = 3.0 Hz, 1 H, H-1), 4.98 (d, ^2J = 6.3 Hz, 1 H, H-4^a), 4.57 (d, ^2J = 6.3 Hz, 1 H, H-4^b), 3.67 (dd, ^2J = 11.0 Hz, ^3J = 4.1 Hz, 1 H, H-6^a), 3.15 (virtual t, $^2J \approx {}^3J$ = 11.0 Hz, 1 H, H-6^b), 2.31–2.26 (m, 1 H, H-7^a), 2.04–1.92 (m, 2 H, H-9), 1.89–1.81 (m, 1 H, H-10^a), 1.77–1.69 (m, 1 H, H-10^b), 1.68–1.63 (m, 1 H, H-6a), 1.19 (s, 3 H, H-11), 1.09 (virtual ddt, ^2J = 16.5 Hz, ^3J = 13.1 Hz, $^4J \approx {}^4J$ = 3.6 Hz, 1 H, H-7^b). ^{13}C NMR (101 MHz, C_6D_6): δ = 205.2 (s, C-8), 173.0 (s, C-10a), 144.5 (d, C-1), 137.2 (s, C-7a), 133.2 (d, C-2), 90.7 (t, C-4), 85.6 (s, C-2a), 68.1 (t, C-6), 53.6 (s, C-10b), 38.2 (d, C-6a), 34.5 (t, C-9), 25.9 (t, C-10), 19.5 (t, C-7), 14.3 (q, C-11).
Please note that the IUPAC compound numbering for *rac*-**5** (Figure 3) differs from the illudane numbering used in this letter.

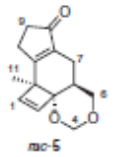


Figure 3 IUPAC compound numbering for *rac*-**5**

(16) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

(17) (a) Gritter, R. J.; Wallace, T. J. *J. Org. Chem.* **1959**, *24*, 1051. (b) Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421.

(18) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214.

(19) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 3147.

(20) Knapp, K. M.; Goldfuss, B.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 5259.

(21) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146.

(22) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dull, D. L.; Mosher, H. S. *J. Am. Chem. Soc.* **1967**, *89*, 4230. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(23) Hoye, T.; Jeffrey, C.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.

(24) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522.

(25) CCDC 2004640 contains the supplementary crystallographic data for compound **7a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(26) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2003**, *5*, 2295.

(27) (a) Kabalka, G. W.; Hutchins, R.; Natale, N. R.; Yang, D. T. C.; Broach, V. *Org. Synth. Coll. Vol. VI*; Wiley: London, **1988**, 293. (b) Shreshta, M. L.; Qi, W.; McIntosh, C. *J. Org. Chem.* **2017**, *82*, 8359.

(28) (a) Fujita, K.; Schloser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (b) Hoffmann, R. W.; Feussner, G.; Zeiss, H.-J.; Schulz, S. *J. Organomet. Chem.* **1980**, *187*, 321.

(29) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

5. ARENE PHOTOACTIVATION TROUGH IMINIUM IONS

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

Status: Research Article, published online August 03, 2022

Journal: *Angewandte Chemie International Edition* **2022**, *61*, e2022083

Publisher: Wiley-VCH Verlag GmbH & Co. KGaA

DOI: 10.1002/anie.202208329

Authors: Johanna Proessdorf, Christian Jandl, Thomas Pickl, Thorsten Bach

Content: Here we report on the photoactivation of benzene-derived substrates through iminium ions. In particular, benzaldehyde-derived iminium perchlorates were found to undergo efficient intramolecular reactions either upon direct irradiation (λ = 366 nm) or under sensitizing conditions (λ = 420 nm) employing a thioxanthone photocatalyst. Three pathways were found: a) Most commonly, an *ortho* photocycloaddition led to a yet unprecedented reaction cascade generating benzoxacyclic products (13 examples, 44-99% yield). The cascade process occurred with high diastereoselectivity and was found to be stereoconvergent. b) If the benzene ring was substituted in the 3-position, a *meta* photocycloaddition was observed. Tetracyclic skeletons were obtained in excellent regio- and diastereoselectivity and feature five stereogenic centers (2 examples, 58-79% yield). c) If the tethered olefin was internally substituted, an aza *Paternò-Büchi* reaction was preferred (2 examples, 95-98 % yield).

Author contributions: The conceptual contribution was made by J. Proessdorf and T. Bach. J. Proessdorf planned, performed, and analyzed the substrate synthesis and photoreactions. Product structures and relative configurations of those were confirmed by NMR studies performed by J. Proessdorf. C. Jandl and T. Pickl conducted the X-ray crystallographic analysis. T. Bach and J. Proessdorf wrote the manuscript.

GDCh Research Articles Angewandte International Edition Chemie www.angewandte.org

Cycloaddition

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

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

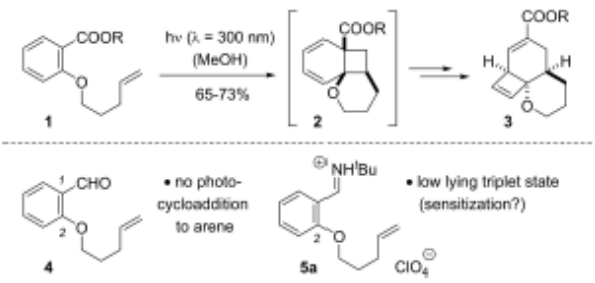
*Johanna Proessdorf, Christian Jandl, Thomas Pickl, and Thorsten Bach**

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).

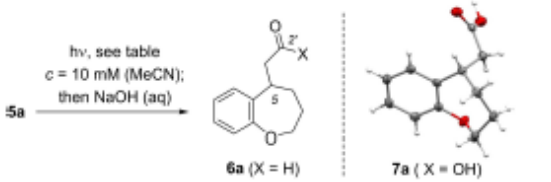
[a] M.Sc. J. Proessdorf, Dr. C. Jandl, M.Sc. T. Pickl, Prof. Dr. T. Bach
Department Chemie and Catalysis Research Center (CRC)
School of Natural Sciences, Technische Universität München
Lichtenbergstraße 4, 85747 Garching (Germany)
E-mail: thorsten.bach@ch.tum.de
Homepage: http://www.oc1.ch.tum.de/home_en/

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

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.

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

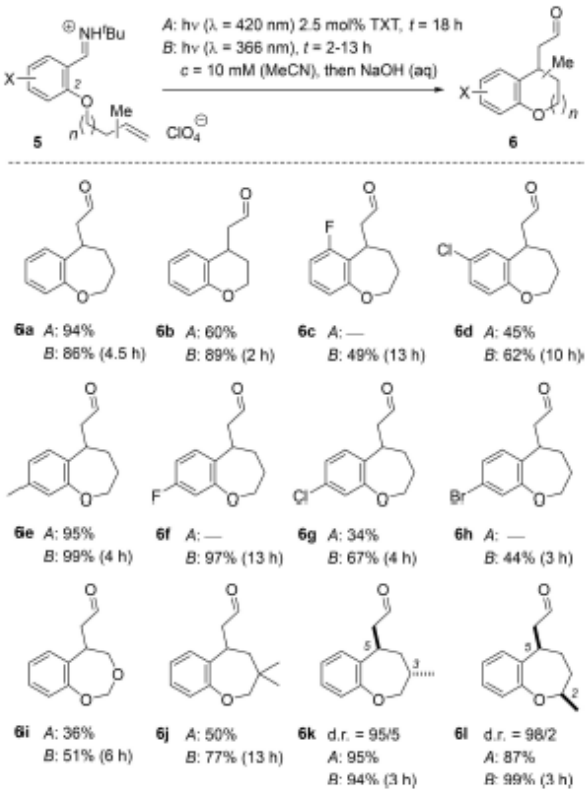
after eight hours. However, the outcome of the reaction remained essentially unchanged (entry 7) as compared to the reaction conducted with 2.5 mol% of catalyst only. The same holds true for an attempted reaction at longer wavelength ($\lambda = 470$ nm) which did not go to completion after 27 hours 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 *Heltanthus 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 *cts* 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.

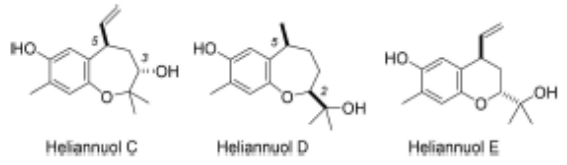
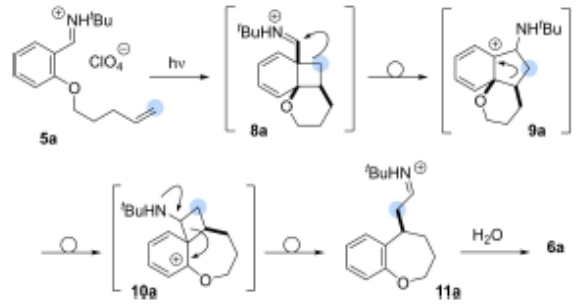
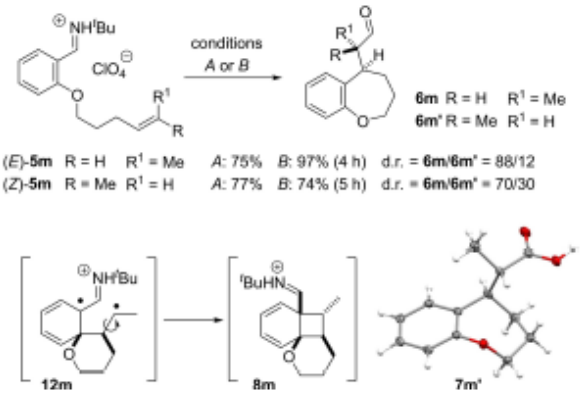


Figure 1. Structures of naturally occurring Heliannuols, which are benzoxacyclic sesquiterpenes isolated from sunflowers.



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.

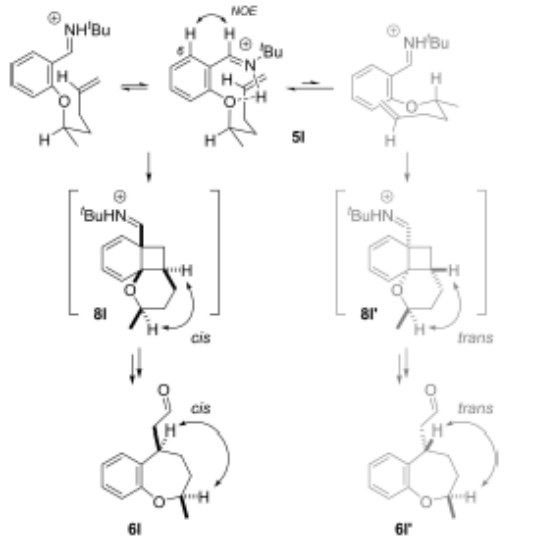
final product thus relates to the formation of iminium ion **11a**.

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

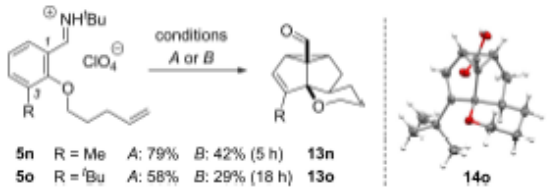


Scheme 5. The facial diastereoselectivity observed in the reaction of substrates **5k** and **5l** can be explained by a six-membered chair conformation of the side chain, in which the methyl group resides in an equatorial position. For compound **5l** the preferred chair conformation is depicted on 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-

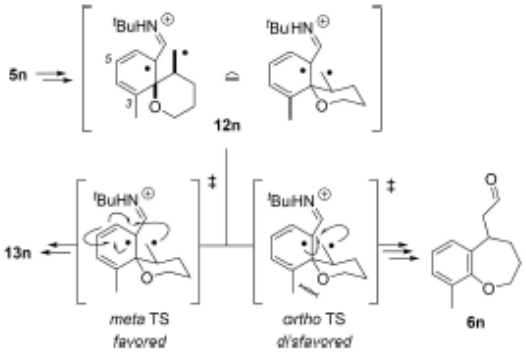


Scheme 6. Formal *meta*-photocycloaddition observed upon irradiation of 1,2,3-trisubstituted benzene derivatives **5n** and **5o** and the structure of acid **14o** (derived from aldehyde **13o**) in the crystal.

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

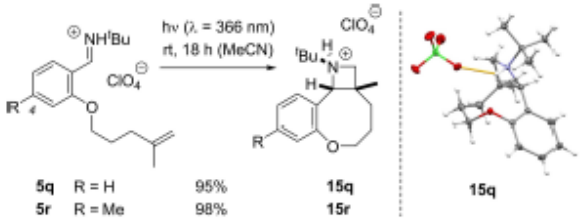


Scheme 7. Tentative explanation for the preferred formation of *meta* photocycloaddition product **13n**, as opposed to the cascade product **6n** derived from an initial *ortho* photocycloaddition (TS = transition state).

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.



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. Macías, 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.

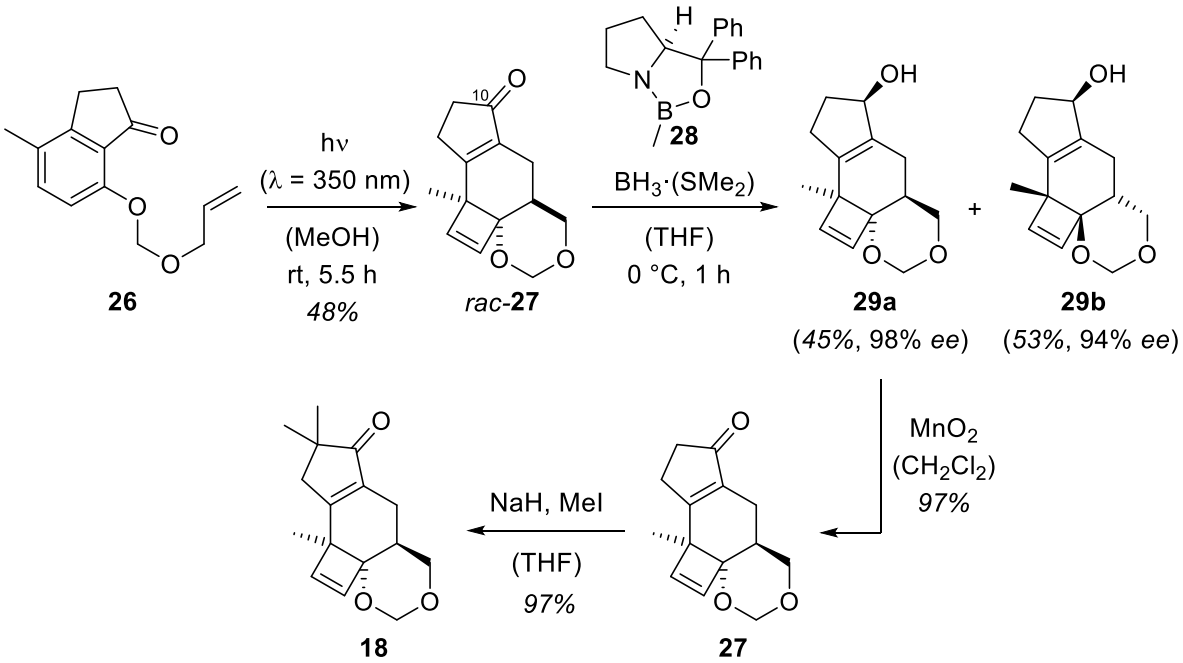
Manuscript received: June 7, 2022
Accepted manuscript online: August 3, 2022
Version of record online: September 2, 2022

6. SUMMARY

Within this PhD work, two main projects were completed. a) The total synthesis of atlanticone C was performed enantioselectively, highlighting the synthetic applicability of the employed *ortho* PCA-induced reaction cascade. And b) benzaldehyde-derived iminium ions were found to undergo efficient, yet unprecedented intramolecular photoreactions resulting in a diverse range of carbon skeletons. These transformations can be performed under direct irradiation or under sensitized conditions utilizing visible light.

a) ENANTIOSELECTIVE TOTAL SYNTHESIS OF ATLANTICONE C

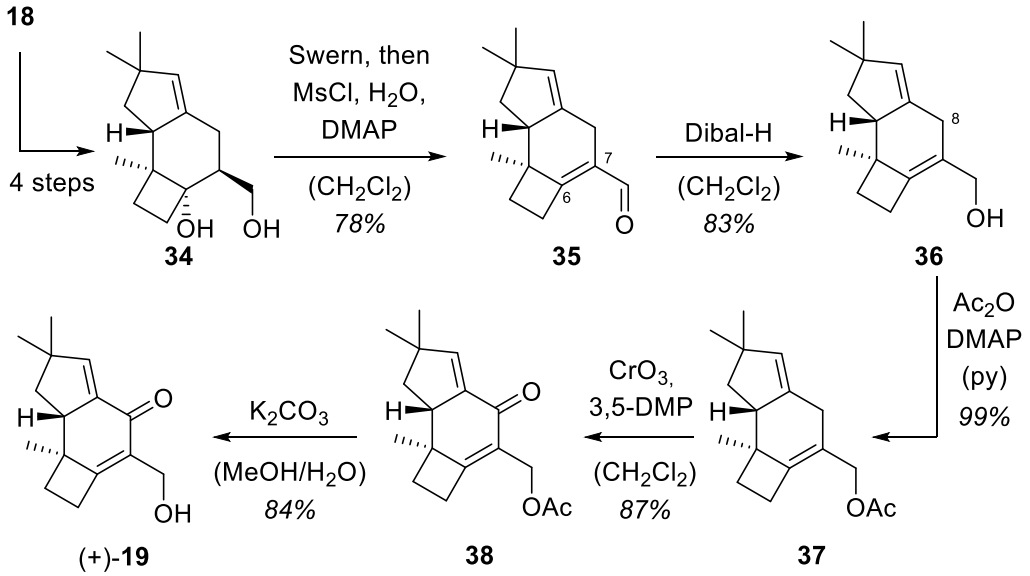
The synthetic route started similarly to the racemic version[28] with the synthesis of photo substrate **26** (Scheme 10).[42,43] Subsequently, the photo-induced reaction cascade was optimized, and the best result was obtained at λ = 350 nm, in MeOH, with a reaction time of 5.5 hours yielding 48% of *rac*-**27** (Scheme 10). In this case, it was particularly challenging to suppress the consecutive photoreactivity of ketone *rac*-**27**[27]. The obtained racemic photoproduct lacked the *gem*-dimethyl group at the α-position and thus enabled a steric distinction of the substituents at C-10.



Scheme 10: Access to enantioenriched photoproduct **27** *via* chiral resolution: Enantioselective CBS reduction[37] of *rac*-**27** followed by separation, re-oxdation of **29a** and *gem*-dimethylation.

Because of the higher enantiomeric purity of **29a**, we continued our studies with this enantiomer. Thus, we first confirmed the absolute configuration of alcohol **29a** both by *Mosher* analysis[44] and anomalous X-ray diffraction and subsequently continued with synthetic steps. Upon re-oxidation of the alcohol to ketone **27**, followed by a *gem*-dimethylation, the desired compound **18** was obtained in enantiopure form (Scheme 10).

The completion of the synthetic route remained unchanged compared to the racemic version,[28] but allowed the improvement of individual transformations, especially within the final steps (Scheme 11). In particular, for the oxidation/dehydration sequence of **34**→**35** a 10% increase in yield was achieved by varying substrate concentration in the *Swern* oxidation[45] step, as well as by a reduced reaction time for the dehydration step. Next, the obtained aldehyde **35** was reduced to alcohol **36** and acetyl protected. For the latter step, we were able to optimize conditions reducing reaction temperature to 0 °C and reaction time to 10 minutes. This provided efficient access to the relatively unstable acetate **37** in 99% yield and we could continue screening various reaction conditions for the subsequent allylic oxidation. While 44% yield were reported for this step in the racemic synthetic route,[28] we found the combined use of CrO_3 and 3,5-dimethylpyrazole (3,5-DMP)[46] to perform best, furnishing ketone **38** in 87% yield now. Finally, saponification of the acetate delivered 84% of the desired enantiopure (+)-atlanticone C (**19** >98% *ee*).

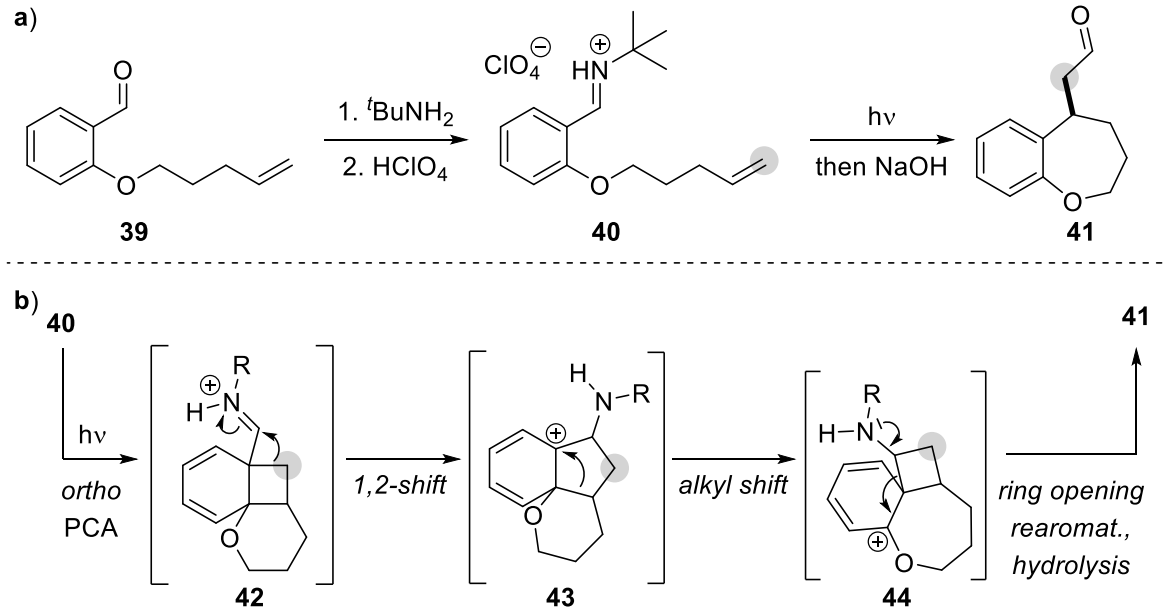


Scheme 11: From diol **34**, the total synthesis of enantiopure (>98% *ee*) atlanticone C (**19**) was completed in five steps and an overall yield of 47%.

Spectroscopic data matched those reported for natural atlanticone C, while the specific rotation indicated the absolute configuration to be opposite to the configuration of naturally occurring (–)-atlanticone C.[30] The natural product was levorotary ($[\alpha]_D^{20} = -224$), [30] whereas our compound showed a strongly positive specific rotation of $[\alpha]_D^{20} = +147$. In summary, starting from enantioenriched photoproduct **27**, the first enantioselective total synthesis of (+)-altlanticone C was completed in 10 steps and with an overall yield of 18%, emphasizing the synthetic utility of this photo-induced reaction cascade.

b) Arene Photoactivation through Iminium Ions

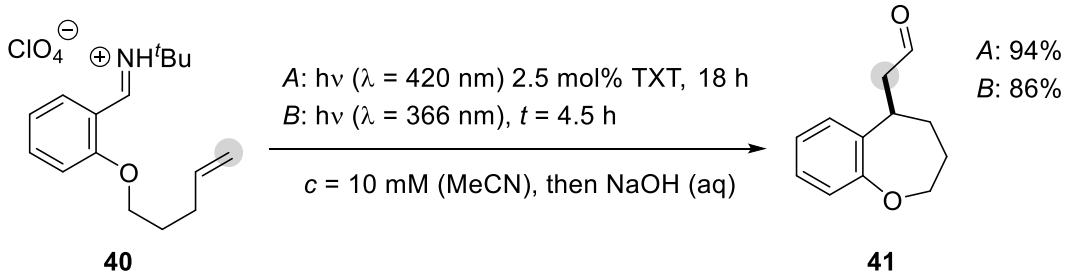
Within this work, we investigated the arene photoactivation through iminium ions of benzaldehyde derivatives. We hypothesized that the respective iminium ions display a lower triplet state as compared to the benzaldehyde moiety, which might be accessible by triplet energy transfer (sensitization).[34] To test this hypothesis, we performed a simple condensation/precipitation sequence[47,48] to obtain iminium perchlorate **40** from aldehyde **39** (Scheme 12a). To our delight, this material indeed showed a bathochromic shift[50] compared to the respective aldehyde and initial irradiation experiments led to clean conversion and formation of unexpected photoproduct **41** (Scheme 12a).



Scheme 12: a) Two step sequence to perchlorate substrate **40**[48,49] and the isolated product **41** obtained upon initial irradiation experiments; **b**) proposed mechanism for the formation of **41**.

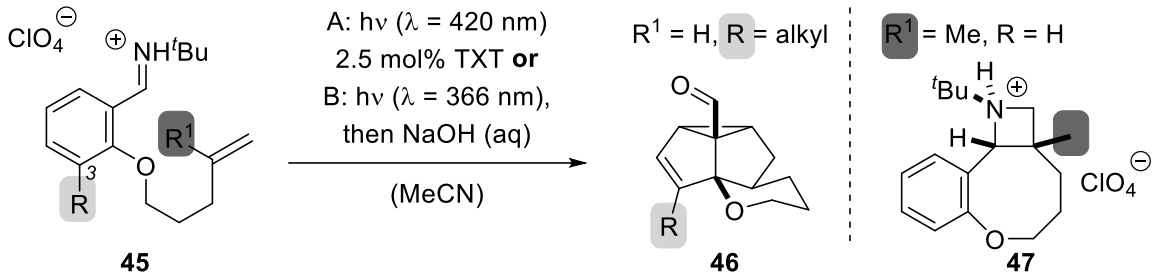
We propose the observed reaction pathway to be initiated by an *ortho* photocycloaddition forming 1,3-cyclohexadiene **42** (Scheme 12b). Instead of a previously observed disrotatory ring opening (see chapter 2.2), 1,2-migration to intermediate **43** releases molecular strain.[48] Next, we propose a ring contraction where the increase in ring strain is compensated by additional stabilization of cation **44** via the adjacent oxygen atom.[49] Finally fragmentation of cyclobutane **44** and subsequent hydrolysis furnishes aldehyde **41**.

With this finding, we continued screening irradiation conditions and found **40** to undergo the photochemical transformation most efficiently under sensitizing conditions (*A*) or upon direct irradiation (*B*) (Scheme 13).



Scheme 13: Efficient transformation of perchlorate **40** to **41** under sensitizing conditions *A* (TXT = thioxanthen-9-one) or upon direct irradiation *B*.

We then turned our attention to the scope of this reaction and found 13 substrates (44-99% yield) to undergo this yet unprecedented formal carboformylation. The cascade process occurred with high diastereoselectivity and was found to be stereoconvergent. In addition, we noticed two other reaction pathways to occur under the selected conditions (Scheme 14). Firstly, if the benzene ring was substituted in 3-position, a *meta* photocycloaddition was observed, generating tetracyclic skeletons with five stereogenic centers in excellent regio- and diastereoselectivity (**46**, 2 examples, 58–79 % yield). Secondly, when the tether was internally substituted at the alkene, an aza *Paternò–Büchi* reaction was preferred and the arene core remained untouched (**47**, 2 examples, 95–98 % yield).



Scheme 14: Within this study, two alternative reaction pathways were found: Structurally different products **46** (*meta* photocycloaddition) and **47** (aza *Paternò–Büchi* reaction) were observed depending on two key substituents (R, R1).

In summary, within this PhD work, the first enantioselctive total synthesis of atlanticone C was completed. Employing a reaction cascade induced by an intramolecular *ortho* photocycloaddition as the key step in this synthesis highlights once more which enormous synthetic potential dearomatization reactions offer. To investigate this powerful method even further, we have turned our attention towards the arene photactivation of benzaldehyde derivatives through iminium ions and found yet unprecedented photo-induced reaction pathways. Within this work we therefore developed a first protocol for intramolecular *ortho* photocycloadditions of iminium perchlorates, that can be performed under visible-light irradiation by triplet sensitization. In the long term, these findings offer new opportunities for enantioselective approaches, e.g. by using chiral amines,[39a,c] counter ions[32] or a chiral catalyst[41] and research in this direction will be continued in the *Bach* group.

7. LICENSES

Work published in the course of this thesis is licensed by the Georg Thieme Verlag KG or can be found *open access* (Angewandte Chemie).

- *Concise Total Synthesis of (+)-Atlanticone C;* J. Proessdorf, A. Zech, C. Jandl, T. Bach, *Synlett* **2020**, *31*, 1598–1602. https://doi.org/10.1055/s-0040-1707215

GEORG THIEME VERLAG KG LICENSE TERMS AND CONDITIONS

Dec 20, 2022

This Agreement between TU Munich -- Johanna Proessdorf ("You") and Georg Thieme Verlag KG ("Georg Thieme Verlag KG") consists of your license details and the terms and conditions provided by Georg Thieme Verlag KG and Copyright Clearance Center.

License Number	5453091241833
License date	Dec 20, 2022
Licensed Content Publisher	Georg Thieme Verlag KG
Licensed Content Publication	Synlett
Licensed Content Title	Concise Total Synthesis of ( )-Atlanticone C
Licensed Content Author	Johanna Proessdorf, Andreas Zech, Christian Jandl, Thorsten Bach
Licensed Content Date	Jan 1, 2020
Licensed Content Volume	31
Licensed Content Issue	16
Type of Use	Dissertation/Thesis
Requestor type	author of the original Thieme publication
Format	print and electronic
Portion	full article/document
Will you be translating?	no
Distribution quantity	50
Title	Reaction Cascades Initiated by Intramolecular ortho Photocycloadditions: Studies on Totalsynthetic Applications & Catalysis
Institution name	Technical University Munich
Expected presentation date	Jan 2023

- *Arene Activation through Iminium Ions: Product Diversity from Intramolecular Photocycloaddition Reactions;* J. Proessdorf, C. Jandl, T. Pickl, T. Bach, *Angew. Chem. Int. Ed.* **2022**, *61*, e202208329. https://doi.org/10.1002/anie.202208329

8. REFERENCES

[1] Overview of drug development and market: a) F. D. Makurvet, *J. Med. Drug Discov.* **2021**, *9*, 100075; b) D. Newman, G. Cragg, *J. Nat. Prod.* **2020**, *83*, 770–803; c) H. BeckMichael, H. B. Haß, C. Schmeck, L. Baerfacker, *J. Med. Drug Discov.* **2022**, *27*, 1560-1574; d) *Points to Consider in Drug Development of Biologics and Small Molecules,* **2020**, nuventra.com (accessed 2022/12).

[2] K. Dunleavy, *The top 20 drugs by worldwide sales in 2021*, **2022**, fiercepharma.com (accessed 2022/12); *Adalimumab*, go.drugbank.com (accessed 2022/12).

[3] U.S. Food and Drug Administration, *Advancing Health through Innovation: New Drug Approvals 2021,* **2021,** fda.gov (accessed 2022/12).

[4] S. Wu, R. Snajdrova, J. C. Moore, K. Baldenius, U. Bornscheuer, *Angew. Chem. Int. Ed.* **2021**, *60*, 88–119.

[5] B. Trost, M. Crawley, *Chem. Rev.* **2003**, *103*, 2921-2944; J. Zweig, D. E. Kim, T. R. Newhouse, *Chem. Rev.* **2017**, *117*, 11680-11752; C. Yuan, B. Liu**,** *Org. Chem. Front.* **2018**, *5*, 106-131.

[6] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**.

[7] S. Poplata, T. Bach, *J. Am. Chem. Soc.* **2018**, *140*, 3228–3231.

[8] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**, pp. 25-72.

[9] S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, 9748-9815

[10] M. Kärkäs, J. Porco, C. Stephenson, *Chem. Rev.* **2016**, *116*, 9683-9747.

[11] T. Bach, J. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000-1045; N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052-1103.

[12] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**, pp. 256-273.

[13] N. Hoffmann, J. Pete, *Tetrahedron Lett.* **1998**, *39*, 5027-5030.

[14] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**, pp. 275-292.

[15] Reviews covering arene-alkene photocycloadditions in general: a) R. Remy, C. G. Bochet, *Chem. Rev.* **2016**, *116*, 9816-9849; b) Z. Zhang, Y. Zhou, X.-W. Liang, *Org. Biomol. Chem.* **2020**, *18*, 5558-5566; 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.* **2007**, *119*, 674-677; *Angew. Chem. Int. Ed.* **2007**, *46*, 663-665; g) N. Hoffmann, *Synthesis* **2004**, 481-495; h) J. J. McCullough, *Chem. Rev.* **1987**, *87*, 811-860.

[16] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**, p. 280.

[17] F. Mueller, J. Mattay*, Chem. Rev.* **1993**, *93*, 99-117.
D. Chappell, A. Russel, *Org. Biomol. Chem.* **2006**, *4*, 4409-4430.

[18] Reviews on *meta* photocycloaddition reactions: 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, *Org. Photochem.* **1989**, *10*, 357-473.

[19] P. Wender, J. Howbert, *Tetrahedron Lett.* **1983**, *24*, 5325-5328.

[20] S. Danishefsky, R. Zamboni, M. Kahn, S. Etheredge, *J. Am. Chem. Soc.* **1980**,*102*, 2097-2098.

[21] Recent examples for the diaza variant of the *para* photocycloaddition has been elegantly employed by the group of Sarlah a) E. 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.

[22] F. Schneider, K. Samarin, S. Zanella, T. Gaich, *Science* **2020**, *367*, 676-681.

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

[24] Reviews on *ortho* photocycloaddition reactions: a) J. Cornelisse, R. de Haan in *Molecular and Supramolecular Photochemistry*, Vol. 8, Dekker, New York, **2001**, pp. 1-126; b) P. J. Wagner, *Acc. Chem. Res.* **2001**, *34*, 1-8.

[25] S. Stegbauer, N. Jeremias, C. Jandl, T. Bach, *Chem. Sci.* **2019**, *10*, 8566-8570.

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

[27] L. Næsborg, C. Jandl, A. Zech, T. Bach, *Angew. Chem. Int. Ed.* **2020**, *59*, 5656-5659.

[28] A. Zech, C. Jandl, T. Bach, *Angew. Chem. Int. Ed.* **2019**, *58*, 14629-14632.

[29] A. G. Gilbert, T. Bach, *Synlett* **2022**, *33*, 10.1055/a-1777-2477.

[30] M. Clericuzio, M. Mella, L. Toma, P. Finzi, G. Vidari, *Eur. J. Org. Chem.* **2002**, 988-994.

[31] a) D. Ravelli, D. Dondi, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2009**, *38*, 1999-2011; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.

[32] M. J. Genzink, J. B. Kidd, W. B. Swords, T. P. Yoon, *Chem. Rev.* **2022**, *122*, 1654–1716.

[33] M. James, J. L. Schwarz, F. Strieth-Kalthoff, B. Wibbeling, F. Glorius, J*. Am. Chem. Soc.* **2018**, *140* , 8624-8628

[34] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**, pp. 47-59 and 423-451.

[35] S. Stegbauer, C. Jandl, T. Bach, *Angew. Chem., Int. Ed.* **2018**, *57*, 14593-14596.

[36] C. Brenninger, J. D. Jolliffe, T. Bach , *Angew. Chem., Int. Ed.* **2018**, *57*, 14338-14349.

[37] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553; b) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

[38] P. Klán, J. Wirz, *Photochemistry of organic compounds*. *From concepts to practice*, Wiley, Chichester, **2009**, pp. 47-59 and 296-326; reviews on the *Paternò–Büchi* reaction: a) M. D'Auria *Photochem. Photobiol. Sci.*, **2019**, *18*, 2297-2362; b) M. Abe *Handbook of Synthetic Photochemistry* , A. Albini, M. Fagnoni, Wiley-VCH, Weinheim, **2009**, p. 217; c) T. Bach, *Synthesis*, **1998**, 683-703.

[39] [2+2] photocycloadditions of iminium ions: a) C. Chen, V. Chang, X. Cai, E. Duesler, P. S. Mariano, *J. Am. Chem. Soc.* **2001**, *123*, 6433-6434; b) F. M. Hörmann, T. S. Chung, E. Rodriguez, M. Jakob, T. Bach, *Angew. Chem. Int. Ed.* **2018**, *57*, 827-831; c) F. Hörmann, C. Kerzig, T. Chung, A. Bauer, O. Wenger, T. Bach, *Angew. Chem. Int. Ed.* **2020**, *59*, 9659-9668; d) Y.-Q. Zou, F. M. Hörmann, T. Bach, *Chem. Soc. Rev.* **2018**, *47*, 278-290.

[40] R. F. Childs, B. D. Dickie, *J. Am. Chem. Soc.* **1983**, *105*, 5041-5046.

[41] F. Pecho, Y. Sempere, J. Gramüller, F. M. Hörmann, R. M. Gschwind, T.

Bach, *J. Am. Chem. Soc.* **2021**, *143*, 9350–9354.

[42] W. D. Crow, U. Engkaninan-Low, Y. Pang, *Austr. J. Chem.* **1984**, *37*, 1915-1924.

[43] D. S.Connor, G. Klein, G. Taylor, R. Boeckman, J. B. Medwid, *Org. Synth.* **1972**, *52*, 16.

[44] a) J. Dale, D. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543-2549; b) D. Dull, H. S. Mosher, *J. Am. Chem. Soc.* **1967**, *89*, 4230-4231; c) J. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

[45] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651-1660.

[46] W. G. Salmond, M. A. Barta, J. L. Havens, *J. Org. Chem.* **1978**, *43*, 2057-2059.

[47] Imine condensation: R. Bisht, B. Chattopadhyay, *J. Am. Chem. Soc.* **2016**, *138*, 84-87.

[48] Perchlorate precipitation: J. Stavinoha, P. S. Mariano, *J. Am. Chem. Soc.* **1981**, *103*, 3136-3148.

[49] Related 1,2-migration: X.-Z. Shu, X.-Y. Liu, K.-G. Ji, H.-Q. Xiao, Y.-M. Liang, *Chem. Eur. J.* **2008**, *14*, 5282–5289.