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A Photochemical Macrocyclization Route to Asymmetric Strained [3.2] Paracyclophanes

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Abstract: The intricate frameworks of paracyclophanes are an important target for synthesis since they are found in various chiral auxiliaries, solar cells, high-performance plastics, pharmaceuticals, and molecular machines. Whereas numerous methods exist for the preparation of symmetric paracyclophanes, protocols for the efficient synthesis of strained asymmetric scaffolds are limited. Here we report a remarkably simple photochemical route to strained [3.2]paracyclophanes starting from readily available educts. By way of NMR and X-ray analyses, we discovered that UV-irradiation of an aromatic carboxylic ester tethered to a toluene moiety leads to the intramolecular formation of a new C–C bond, with loss of an alcohol. A systematic evaluation of the reaction conditions and substituents, as well as radical starter and triplet quenching experiments, point to a reaction mechanism involving an excited triplet state and hydrogen atom transfer. The new method proved to be robust and versatile enabling the synthesis of a range of cyclophanes with different substitutions, including an unusual diastereoisomer with two planar chiral centers, and thus proved to be a valuable addition to the synthetic toolbox.

Introduction

Paracyclophanes are an important class of structurally unique aromatic compounds that are characterized by two stacked phenyl rings bridged by aliphatic chains (**1**, Figure 1A).[1] Owing to their unusual architectures, paracyclophanes often exhibit high ring tension with bent phenyl rings that have atypical reactivities.[2] Furthermore, the stacked aromatic rings can interact with each other through their ring currents,[3] and planar chirality can result from restricted rotation of the aryl moieties.[4] As a result of these properties, cyclophanes lend themselves to broad application in molecular machines,[5] polymers,[6] chiral ligands (such as **2**),[7] catalysts,[8] solar cells,[9] molecular scaffolds (such as **3**),[10] and as hosts in molecular recognition processes.[11] The cavity between the phenyl rings can incorporate atoms or small molecules for drug delivery and thus serve as a transporter (e.g., **4**).[12] In addition, naturally occurring cyclophanes (e.g., **5**) have attracted great attention because they are endowed with biological activities.[13] These manifold purposes have propelled the development of synthetic routes to paracyclophanes, which can be divided into two general strategies, macrocyclizations and ring contractions (Figure 1B).[14] In a controlled approach, a bridge is pre-formed in the *para* position between the two phenyl rings, thus preventing homocouplings. However, in some cases, dimerization of two starter units into larger and less strained cyclophanes may occur. Examples of controlled macrocyclization are ring-closing metathesis (RCM),[15] Wurtz coupling with elemental sodium,[16] or photochemical H-abstractions by ketones.[17] Alternatively, the macrocycle may be generated by forming two new bonds concomitantly with little or no reaction control. Examples are the 1,6-Hofmann elimination,[14] low-pressure pyrolysis of *para*-xylene,[18] and photochemical [2+2]-cycloadditions of styrenes.[19] To generate increased ring strain, larger rings may be contracted (Figure 1B). A number of ring contraction reactions have been established in which components of the bridges (such as S, Se, SO_2 or CO_2 groups) are eliminated by flash vacuum pyrolysis[20] or by UV light irradiation.[21] On the other hand, ring expansion reactions (Figure 1B) allow the synthesis of some asymmetric cyclophanes, but these transformations require several steps.[22] Small cyclophanes, especially with unsymmetrical bridges, are particularly difficult to synthesize with existing methods, and there is a lack of general, direct, and simple synthetic methods for [3.2]-cyclophanes.[23] The few existing methods are limited by their low functional group tolerance, laborious synthesis of starting materials, low yields, or toxicity.[24]

Here, we report a new principal route to strained cyclophanes, in particular 13-membered [3.2]paracyclophanes,

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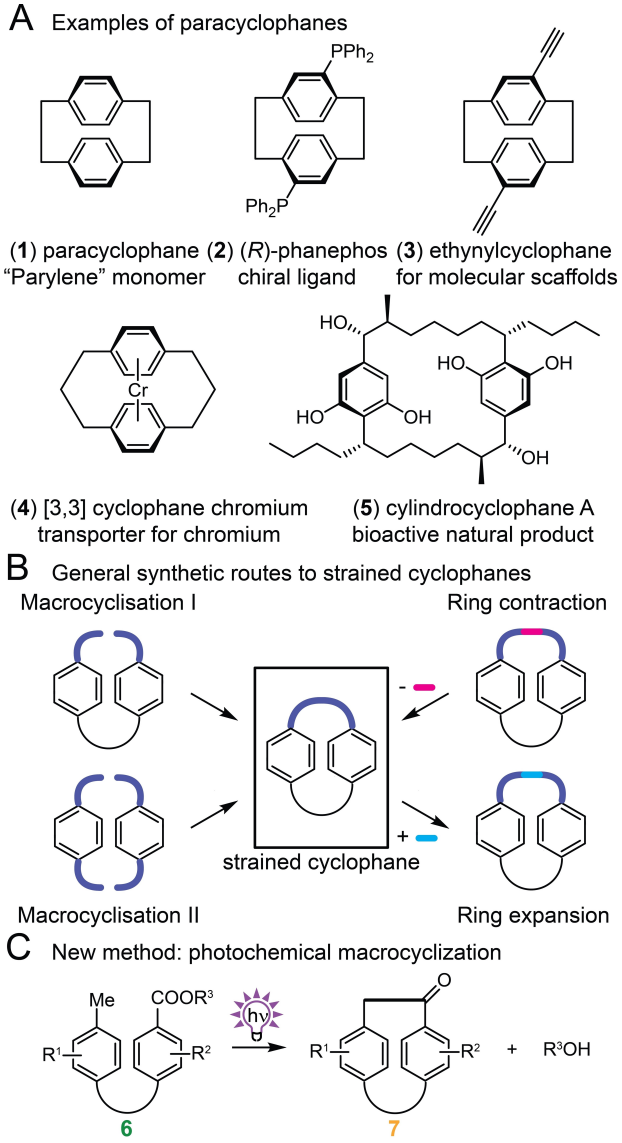

Figure 1. Examples of paracyclophanes, general synthetic strategies, and new macrocyclization route to paracyclophanes. A) Structures of paracyclophane (**1**), a chiral paracyclophane phosphine ligand (**2**), a bis ethynyl[2.2]paracyclophane (**3**), a (η^{12}-[3.3]paracyclophane)chromium(0) complex (**4**), and the natural product cylindrocyclophane A (**5**). B) Synthetic routes to cyclophanes via two types of macrocyclization, ring contraction to more strained cyclophanes, and ring expansion to less strained cyclophanes. C) New pathway to ketocyclophanes (**7**) from aromatic ester (**6**).

through photochemical macrocyclization with high reaction control (Figure 1C). We show that this protocol involves an underappreciated photoinduced C–C bond formation between an ester and a methyl group. In addition to providing the first insight into this remarkable transformation, we explore the scope of the method, which proved to be robust and tolerates several functional groups.

Results and Discussion

While investigating the suitability of various linker systems for a directed photochemical aryl coupling,[25] we noted an irregular behavior of an ether-linked bis-aryl substrate. Although methyl 4-(4-methylphenethoxy)benzoate (**6a**) quickly lost its fluorescence on a thin-layer chromatography (TLC) plate upon irradiation ($\lambda = 254$ nm), a change that is indicative of a light-induced conversion,[25c] high-resolution mass spectrometry (HRMS) revealed that the new compound differs from the expected biphenyl. The deduced molecular formula ($C_{16}H_{14}O_2$) of the photoproduct indicates a loss of "CH_4O" compared to **6a** (Figure 2B). This conversion is startling since ester hydrolysis would result in the loss of a methylene group (CH_2), and the extrusion of the linker would result in the loss of acetaldehyde (C_2H_4O).[26] Moreover, MSMS experiments indicated that the resulting photoproduct has an unusually high stability, fragmenting only at very high energies (see Supporting Information). To gain more insight into the structure of the photoproduct, we scaled up the photoreaction in a flow reactor (Figure 2A).[25a] Compared to the ^{1}H NMR spectrum of the educt (**6a**), the spectrum of the purified photoproduct lacks the signals of both methyl groups. Instead, a signal at $\delta = 3.75$ ppm indicates the presence of a new methylene group (Figure 2B). Thus, we concluded that the irradiation of **6a** promoted an intramolecular C–C bond formation to yield a cyclophane (**7a**). HMBC cross-peaks of the signal at $\delta = 3.75$ ppm to both aromatics (see Supporting Information) support the new linkage.

To unequivocally confirm the deduced cyclophane structure, we turned towards X-ray crystallography. We succeeded in growing single crystals of **7a** (DCM, −20 °C) that were sufficiently large for diffraction experiments. The crystal structure shows that both phenyl rings are superimposed and bridged by their 1,4-substituents (Figure 2C). The ring tension in **7a** becomes apparent when comparing the bond angles with non-tensioned rings like benzene; the carbons of the aromatic ring are up to 17.3 pm out of plane, which is a stronger bending than in [2.2] paracyclophane,[27] meaning that **7a** adopts a boat-like configuration.

It is surprising that a strained paracyclophane emerges from irradiation of an aromatic carboxylic acid ester. Recently, it has been reported that a phenol-linked phenacyl benzoate can be cyclized into a cyclophane through the well-understood cleavage of benzoate as a photoremovable protecting group.[28] While the linker is similar in both studies, the macrocyclization to the [3.3]cyclophane through the reaction of an α-acyl radical with a phenol[29] is markedly different to the route to the [3.2]cyclophane reported herein, which employs an ester group. In contrast to the well-studied photochemistry of ketones and aldehydes (such as Norrish reactions, Paternò–Büchi reactions, electron transfer reactions and intermolecular hydrogen abstractions),[30] photochemical reactions with esters are rare.[31] Among the few known examples are the reaction of excited methyl benzoate with alkenes to form oxetanes,[32] and the photoreduction of aromatic esters with electron-withdrawing substituents to form pinacols or carbinols.[33] A photoreduction

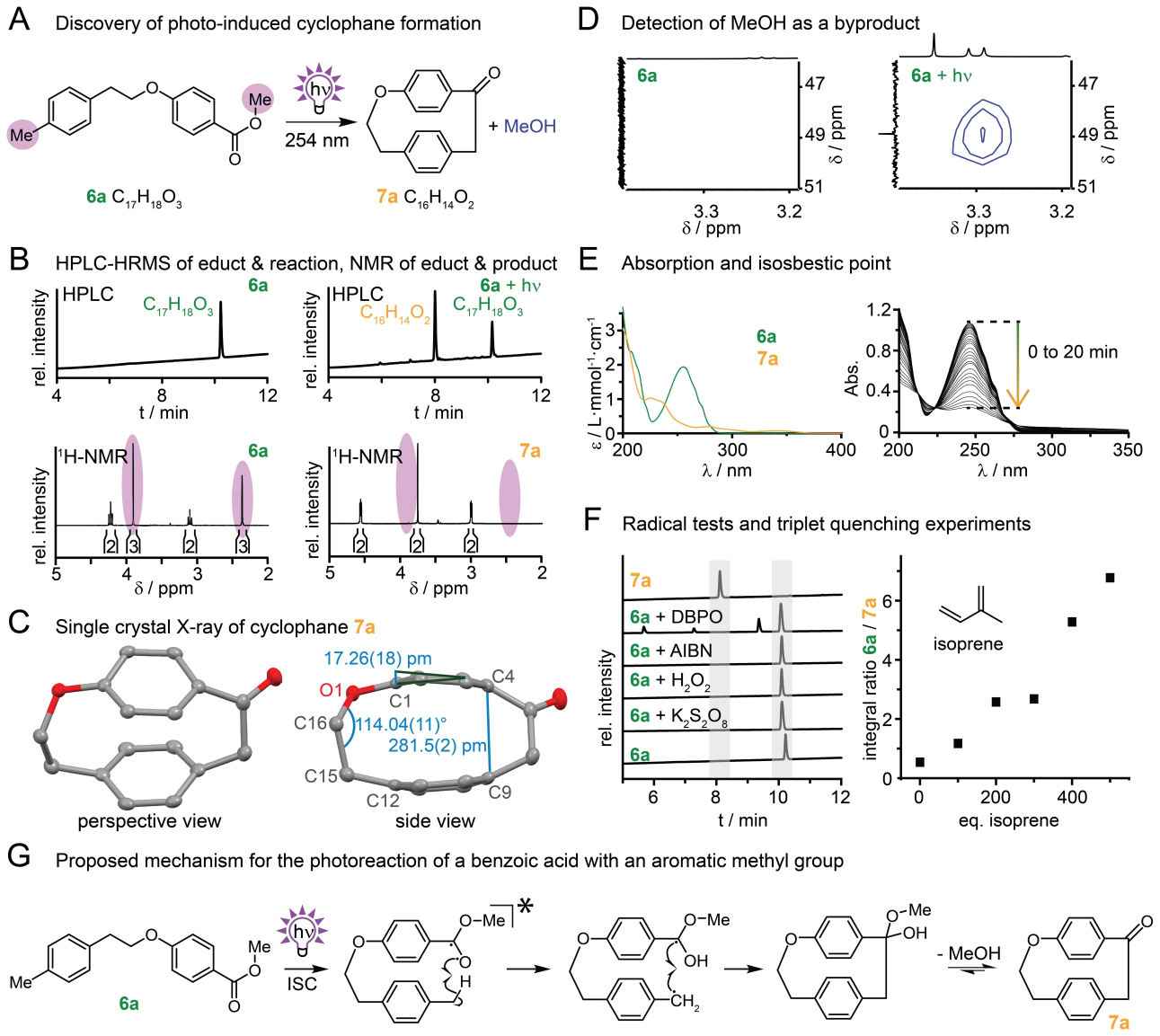

Figure 2. Discovery, structure elucidation, and mechanistic analysis of photoinduced paracyclophane formation. A) Serendipitously discovered reaction leading to paracyclophane **7a**. B) HPLC-HRMS profiles showing UV-vis trace of crude photoproducts with assigned sum formula, and ^{1}H NMR showing the loss of methyl groups in the photoproduct. C) Molecular structure and atom numbering scheme of **7a**. The ellipsoids represent a probability of 30%. Hydrogen atoms are omitted for clarity. Non-bonding distance of C1–C9: 281.5(2) pm; distance of C1 out of the plane (C2–C3–C5–C6): 17.26(18) pm; bond angle O1-C16-C15: 114.04(11) degree. D) Detection of MeOH as a byproduct (2D HSQC NMR experiments). E) Absorption spectra of **6a** and **7a**, and of **6a** alone after defined light exposure time with isosbestic point. F) Employing chemical probes for mechanistic considerations; using radical starters with **6a** in the absence of UV light, and using different amounts of isoprene as a triplet quencher during the irradiation of **6a**. G) Proposed radical mechanism with benzylic hydrogen abstraction and subsequent release of MeOH.

of aromatic esters to ketones has previously only been observed as a side reaction of excited methyl benzoate and 2,5-dimethylfuran.[34] However, this reaction has not been studied in detail, and its potential synthetic utility has been ignored. Considering that methyl groups and esters represent two of the most common functional groups, it is remarkable that their light-promoted coupling has been overlooked.

The unexpected conversion of **6a** into **7a** suggests that methanol would be formed as a byproduct. To verify the predicted release of MeOH, we irradiated **6a** in a quartz NMR tube. HSQC measurements revealed an emerging signal that was assigned to the CH_3 group of MeOH (Figure 2D). Monitoring of the irradiation of **6a** in a cuvette did not give any indication of a long-lived intermediate (Figure 2E and Supporting Information). To test for the involvement of photochemically excited states during the formation of cyclophane **7a**, we employed radical starters (benzoyl peroxide (DBPO), azobisisobutyronitrile (AIBN), H_2O_2 and $K_2S_2O_8$) that would mimic ground state reactivity. Since cyclophanes were not formed in the dark (Figure 2F), a photochemically activated species is obviously necessary.

In principle, it is conceivable that the reaction mechanism involves carbanions attacking the carbonyl group. We found, however, that photo-induced cyclophane formation does not require the addition of a reductant and even proceeds in the presence of water. Thus, the formation of a benzylic carbanion during the reaction can be excluded.[35] Alternatively, one may consider a pathway related to a type II Norrish reaction, in which a γ-hydrogen is abstracted by way of an activated carbonyl, forming a diradical.[36] By analogy, the excited ester group would abstract a μ-hydrogen, yielding a diradical that would combine to form the cyclophane ring. Since Norrish-type reactions can originate from either singlet or triplet states,[37] we tested the spin multiplicity of the excited state and irradiated compound **6a** in the presence of the triplet quencher isoprene. We observed a marked quenching effect with increasing amounts of isoprene in MeOH, thus indicating a triplet intermediate (Figure 2F). We also determined the quantum yield of the reaction with a chemical actinometer and found that it is $\Phi = 0.08$ at $\lambda = 254$ nm in MeCN.[38] Taken together, these experiments indicate that the benzoic acid is excited by UV light, initially forming an excited singlet state. Intersystem crossing (ISC) would lead to an excited triplet state with radical character. This biradical would abstract a proton from the benzylic methyl group to form a benzyl radical by hydrogen atom transfer (HAT).[39] Recombination of the two carbon-centered radicals would then yield a new carbon-carbon bond and a hemiacetal, which subsequently releases MeOH, as monitored in the NMR tube (Figure 2D).

To optimize the reaction conditions, we altered various reaction parameters such as solvent, light, temperature, and oxygen concentration (Figure 3A,B). We noted that the use of tetrahydrofuran (THF) or 2-PrOH as solvents give only low yields of the paracyclophane, likely because of their interference with HAT processes.[39] Polar solvents with high bond dissociation energies (BDEs) such as MeOH and MeCN give substantially better yields. Best results were obtained using a mixture of MeCN and water (1:1), enabling the complete turnover of **6a**. Using UV–B light leads to reduced product formation, and the temperature has no pronounced effect on conversion and yield.

Argon- or oxygen-saturated MeCN have a minor effect on the rate, but the presence of oxygen leads to side products with unknown structures and promotes educt degradation. Nonetheless, it is remarkable that the photoreaction takes place in oxygen-saturated solvents. By combining the beneficial reaction parameters (MeCN:H_2O, 254 nm with 118 W m^{-2}, 10 °C and argon-saturated solvents) the yield doubled (31% versus 65% isolated yield) compared to the non-optimized reaction conditions, and a scale-up of the reaction provided 66% isolated yield of cyclophane **7a** (Figure 3C). Using these optimized reaction conditions, we next investigated the effect of substituents and linkers of **6a**. We noted that different types of esters (Figure 4A) are also converted into **7a** and the corresponding alcohols, such as isopropanol from isopropyl ester **6c** (see Supporting Information). To our surprise, even the free carboxylic acid **6d** is amenable to the photoreaction. However, the sodium salt of the carboxylic acid **6e** cannot be used for the macrocyclization. In lieu of the carboxy group, we

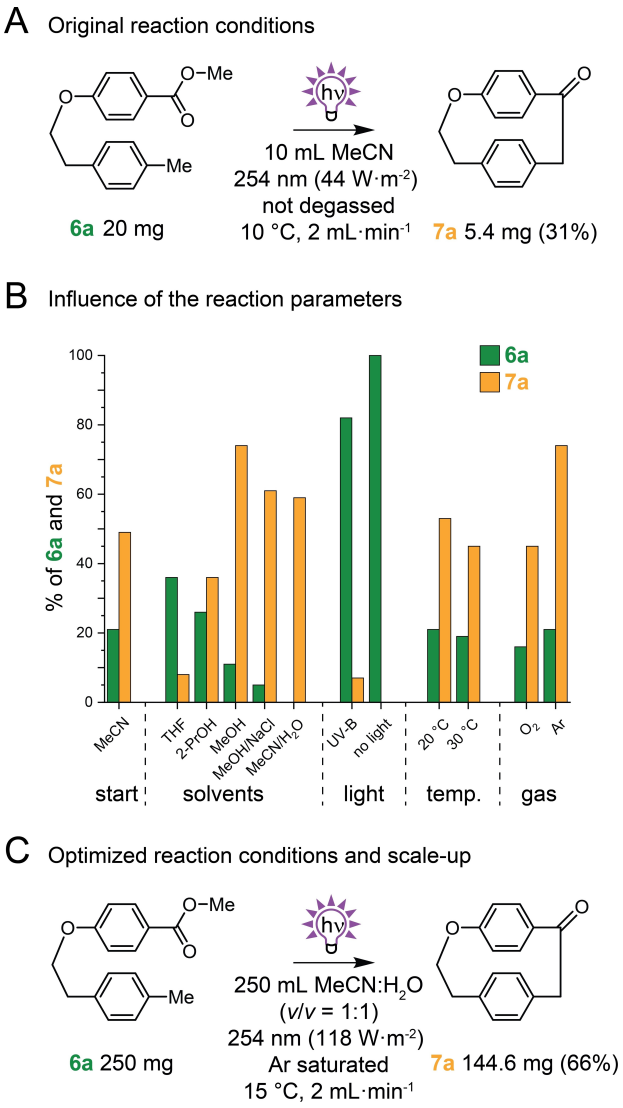

Figure 3. Optimization of the photoreaction to form paracyclophanes. A) Original reaction conditions. B) Parameters were modified by varying the solvent type, light source, temperature, and type of gas saturating the solvent. Starting conditions: 20 mg **6a** is dissolved in 10 mL MeCN and irradiated at 254 nm (no filter was used, resulting in 118 W·m^{-2} light intensity) with a flow of 1 mL min^{-1} at 10 °C. Percentage of **6a** and **7a** were determined by HPLC-MS with an external standard. temp. = temperature. C) Optimized conditions and scale-up of photoreaction.

tested a nitrile (**6f**) and an acetyl group (**6g**) (Figure 4C). Yet, cyclophane formation could not be detected, indicating that this photoreaction works exclusively with carboxylic acid derivatives. When shortening the linker (Figure 4B) by one methylene group (**6h**), we obtained a new photoproduct, but not a cyclophane. NMR analyses revealed that a diphenylmethane has formed, the product of a photo-Claisen reaction (see Supporting Information).[40] When extending the linker, cyclophane **7i** with a larger ring is formed, but only in low yields, suggesting that the distance between the carboxy group and the methyl group is too large. Eventually, we tested different compositions of the linkers and substituted the oxygen for sulfur (**6j**), nitrogen (**6k**) and carbon (**6l**) (Fig-

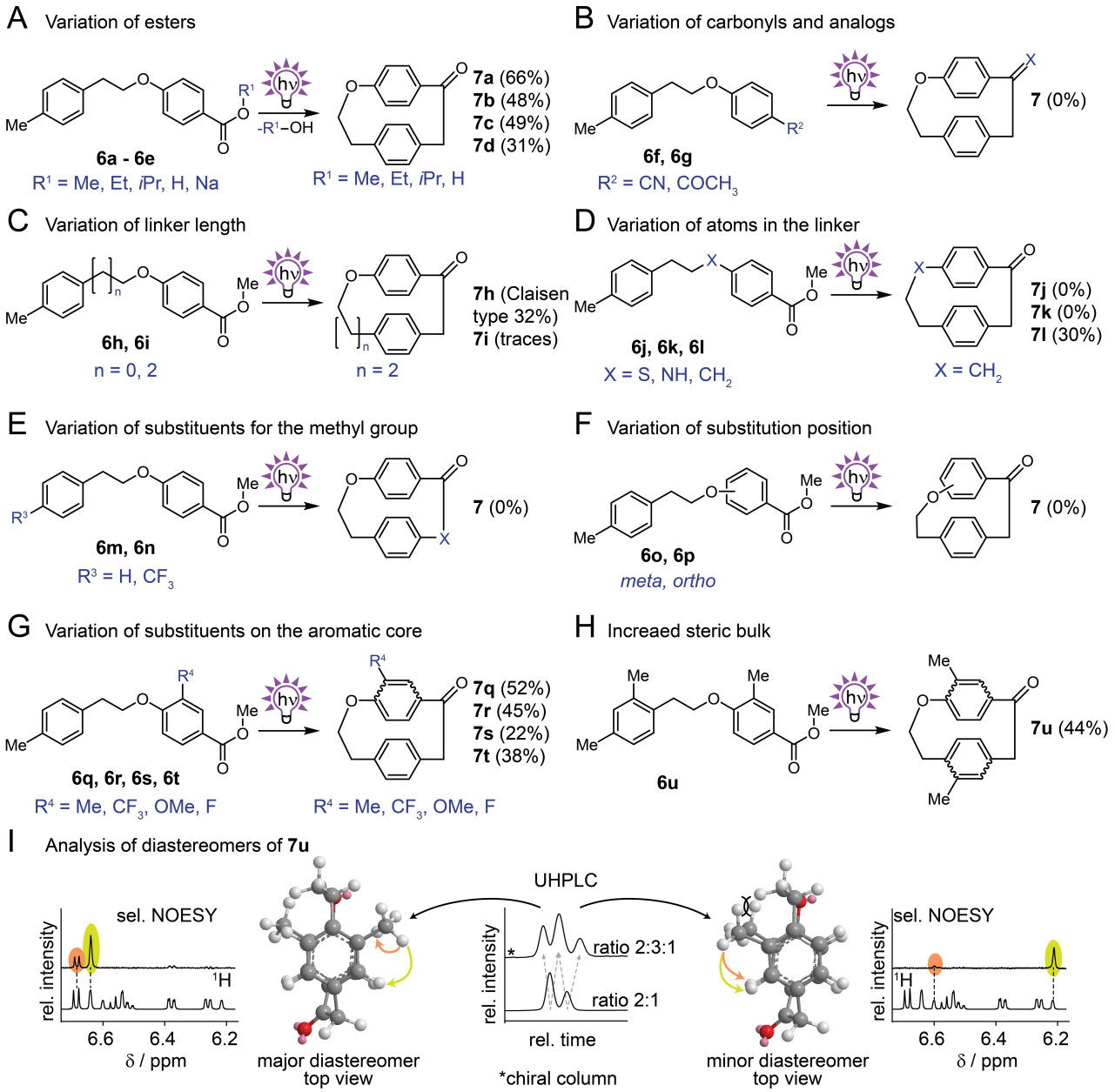

Figure 4. Systematic variation of functional groups and positions to explore the scope of the photochemical reaction. A) Variation of the leaving group of the substrate. B) Replacement of the ester group. C) Variation of the linker size. D) Substitution of the oxygen in the ether linkage. E) Substitution of the aromatic methyl group. F) Variation of the position of the ether linkage. G) Addition of functional groups to the aromatic core. H) Increased steric bulk. I). Separation of diastereomers (by UHPLC) and enantiomers (by chiral UHPLC; ratio 2:3:1, where the integral of 3 is a mixture of two isomers with the integrals of 1 and 2), and determination of methyl group positions by selective NOESY NMR experiments of the diastereomeric mixture.

ure 4D).[25c] We found that only the carbon-substituted linker **6l** is able to form a cyclophane (**7l**), but the ether works substantially better.

According to the postulated reaction mechanism, HAT is an essential part of the transformation. Hence, substitutions of the methyl group with a CF_3 group (**6m**) or a hydrogen (**6n**) would inhibit cyclophane formation (Figure 4E). As expected, no cyclophanes could be detected when irradiating **6m** or **6n**, showing that C–H or C–F abstractions are not viable under these conditions.[41] Different positions of the carboxylic acid (**6o**, **6p**) (Figure 4F) are not tolerated either. Even so, derivatives of **6a** with methyl (**6q**), trifluoromethyl (**6r**), methoxy (**6s**) or fluoro (**6t**) substituents at the aromatic rings were successfully incorporated into the cyclophane (Figure 4G). Methyl (+*I* effect) and trifluoromethyl (-*I* effect) substituents allow the synthesis of the corresponding cyclophanes in good yields (52% and 45%). Incorporation of a methoxy group (+*M* effect), however, slowed down conversion and required increased dwell time to give 22% of **7s**. Notably, the four substituted cyclophanes (**7q**, **7r**, **7s** and **7t**) exhibit planar chirality. The enantiomers (R_p and S_p)

are present in a molar ratio of 1:1, as determined by chiral HPLC (see Supporting Information).

Finally, we investigated whether this method was suitable for the preparation of cyclophane **7u** with two methyl groups (Figure 4H). This compound possesses two chiral centers, resulting in diastereomers with pseudo-*gem* and pseudo-*meta* methyl groups.[27] We separated the diastereomers (integral ratio of 2:1) by UHPLC, and using a chiral column we were also able to separate two of the four enantiomers (Figure 4I). 1D-selective NOESY experiments showed that that the diastereomer with lower steric hindrance is formed twice as frequently (Figure 4I). This experiment shows that even complex and sterically demanding cyclophanes can be synthesized by the new method.

Conclusion

We report herein the serendipitous discovery of a new synthetic route to strained paracyclophanes. Surprisingly, this avenue invokes a new type of photoinduced C–C bond formation involving an aromatic ester and a non-activated methyl group. Intriguingly, our findings suggest that this photoreaction is an overlooked variant of a Norrish type II reaction that proceeds via excited carboxyl states, radical-mediated abstraction of a benzylic hydrogen through HAT, and cyclization of the diradical. The resulting ketone functionality provides a useful handle for further modifications of the paracyclophane, such as reduction, substitution or ring expansion.[22] Moreover, the photoinduced macrocyclization offers a facile alternative to the sparse methods available for the synthesis of asymmetric cyclophanes. In particular, the new synthetic method now allows the targeted synthesis of [3.2]cyclophanes. Such compounds can be valuable because the cavity between the phenyl rings allows the incorporation of metals such as chromium or lithium.[9,12d] On a more general note, this novel photochemical macrocyclization may change our way of thinking when it comes to the synthetic utility of excited benzoic acids and their esters. Since these reactive species are capable of abstracting hydrogen atoms intramolecularly to form strained rings, the reaction likely bears further, untapped potential. Beyond providing swift access to asymmetric functionalized paracyclophanes, we expect that this method will prove to be a useful addition to the synthetic chemistry toolbox.

Experimental Section

General procedure of the photoreaction: a potential cyclophane precursor derivative (prepared by any method available) is dissolved in methanol, acetonitrile or acetonitrile water mixture to give a concentration between 1 and 2 mg mL^{-1}. The solution is loaded on a continuous-flow thin-film photoreactor and irradiated with a 254 nm UV lamp. Average dwell times should be set in the range of 7.5 to 45 min, depending on the individual reaction speed. A typical silica window size of a photoreactor is 17×32 cm and suitable UV sources are six low-pressure metal vapor UV-C (15 W power consumption each). The solvent feed of the photoreactor should be operated using an adjustable pump with appropriate flow rates. Reactor temperatures should be in the range of 10 to 20 °C. Throughout the reaction, proper shielding of the setup must be ensured to protect the user from UV irradiation. The fractions containing the crude photoproducts are collected, the solvents are removed under reduced pressure and the residues are purified by flash chromatography to yield the desired ketocyclophane. Full experimental details, methods, detailed synthetic procedures, and physicochemical characterization of new compounds including NMR spectra are available in the Supporting Information.

Deposition Number (https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202202577) 2189278 (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 (www.ccdc.cam.ac.uk/structures).

Author contributions

V.H. and C.H. conceptualized the project. V.H. performed experiments and compiled data. H.G. performed X-ray analysis. V.H. and C.H. wrote the manuscript. C.H. supervised the project.

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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: C–C coupling · cyclophanes · hydrogen transfer · photochemistry · synthetic methods

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