Direct excitation of carbonyl cyclopropanes: From divergent photo-isomerization and annulation to unified reductive C-C cleavage.

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ABSTRACT: We report herein our studies on the direct photoactivation of carbonyl cyclopropanes to give biradical intermediates, leading to selective cleavage of the more substituted carbon-carbon bond. Depending on the substrate structure, extended alkenes were isolated or directly reacted in a photo-Nazarov process to give bicyclic products. Based on these results, a unified reductive ring-opening reaction was developed by using diphenyl disulfide as a HAT reagent. By performing a sequential cyclopropanation/selective ring opening reaction, we achieved a CH_2 insertion into the α,β bond of both acyclic and cyclic unsaturated carbonyl compounds. Our protocol therefore provides a further tool for framework-editing of carbocycles, complementing the recent progress in "skeletal editing" strategies.

Photochemistry has enabled numerous unique transformations using light as a green energy source.[1] Carbonyl compounds have been known since a long time as one of the most important photoactive species in both synthetic and biological applications.[2] They can be used as either photoactive substrates[2] or as photocatalysts as exemplified by thioxanthone[3a] or benzophenone.[3b,c] The excitation of carbonyl compounds can be achieved via either energy transfer catalysis[4-8] or direct excitation (Scheme 1A).[2] Although energy transfer catalysis provides milder conditions to activate molecules with a low-energy light source, extensive optimization of the photocatalyst is usually required.[4] Furthermore, electron transfer pathways are usually a competitive mechanism, leading to the formation of by-products.[4,8] Alternatively, the direct excitation of carbonyl compounds enables several well-known transformations, such as the Paternò–Büchi[9] or Norrish-type reactions.[10] However, most studies focused on alkene-conjugated carbonyl compounds since the extended conjugated system makes them highly photoreactive.[11] Excitation of the π system of either the C=O or the C=C bond can occur, leading to Paternò–Büchi reactions[9] or [2+n] annulations.[11] These transformations have been studied intensively since the start of photochemistry and have seen renewed interest in the past few decades. In contrast, the homolytic fission of α C-C σ bonds in carbonyl compounds is underdeveloped due to two main reasons: i. The excitation of σ-carbonyl compounds requires higher energy than π-conjugated systems,[2a,b] ii. The bond dissociation energy of σ bonds is much larger than the one of π bonds, making the process thermodynamically challenging.

To promote such transformations, the first strategy was reported by Suarez[12] and Sarpong[13] (Scheme 1B) by introducing a heteroatom at β position of the carbonyl group.

The heteroatom is stabilizing radical intermediates generated from a hydrogen atom transfer (HAT) process. As a result, the Norrish type II C-C bond cleavage, which involves a HAT process, became more favorable than the Norrish type I direct fragmentation.[10,13b] After C-C cleavage, an aldol-type reaction led then to formation of the ring-contracted product **I**. In addition, the competitive Norrish-Yang pathway to give strained ring **II** is also less favorable than in the case of acyl-substituted carbocycles.[10a,13a-c]

To achieve selective C-C bond cleavage on carbocycles, we envisioned the use of strained rings to lower the bond dissociation energy of the C-C σ bond (Scheme 1B). In the case of cyclic substrates, a ring expansion to give products **III** or **IV** could be achieved from the direct excitation of carbonyl compounds, complementing the ring-contraction strategy of Suarez and Sarpong. When considering that bicyclic structures containing carbonyl cyclopropanes are usually synthesized from the corresponding olefins, a sequential cyclopropanation/selective ring-opening reaction would provide a direct strategy for CH_2 homologation of α,β unsaturated carbonyl compounds (Scheme 1C). The insertion would happen on the α,β bond of the carbonyl group, in contrast to most existing homologation reactions proceeding via insertion into the carbonyl – carbon bond.[14] The key for success of this approach would rely on selective cleavage of the endocyclic C-C bond. Interestingly, most methods for reductive cyclopropane ring-opening are based on transition metals and favor cleavage of the exocyclic C-C bond.[15] We envisioned however that selective endocyclic C-C bond cleavage could be achieved through formation of the most stable 1,3 biradical intermediate.

Scheme 1. Photo-excitation of carbonyl compounds: Towards the selective cleavage of σ C-C bonds.
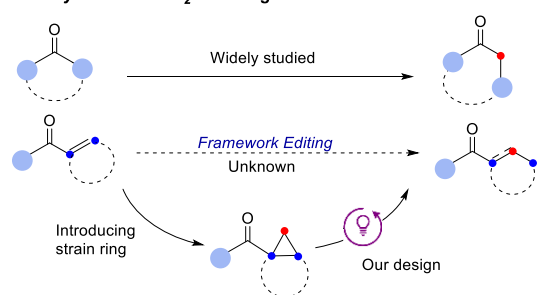

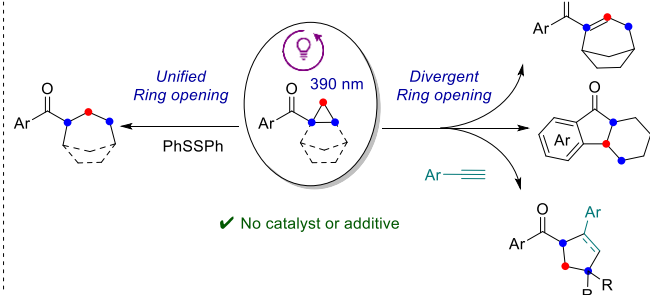*A. Photo-excitation of carbonyl compounds*
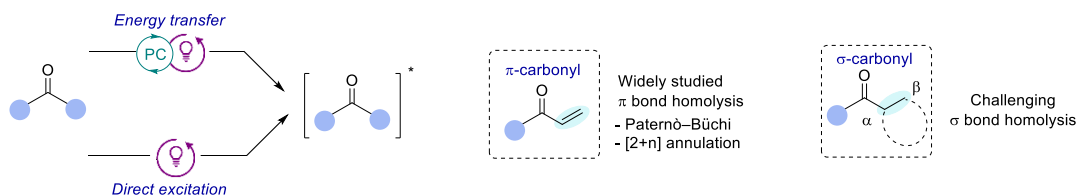
B. Photo-homolysis of σ bonds in carbonyl compounds
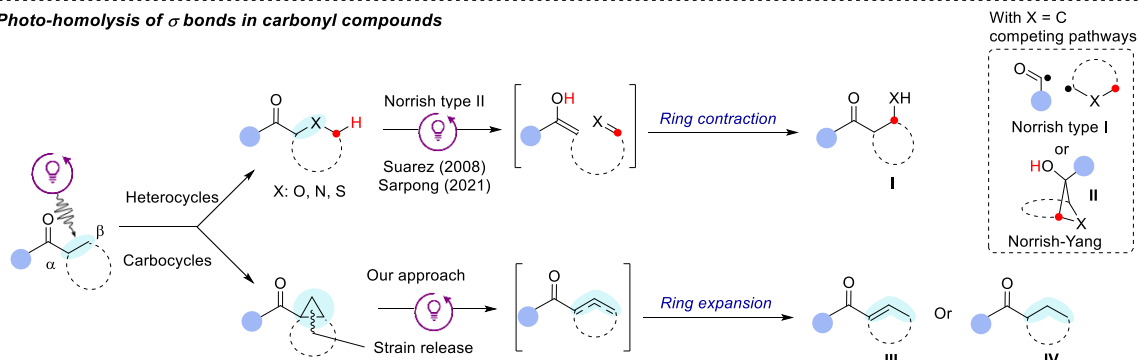
C. Carbonyl directed CH₂ homologation
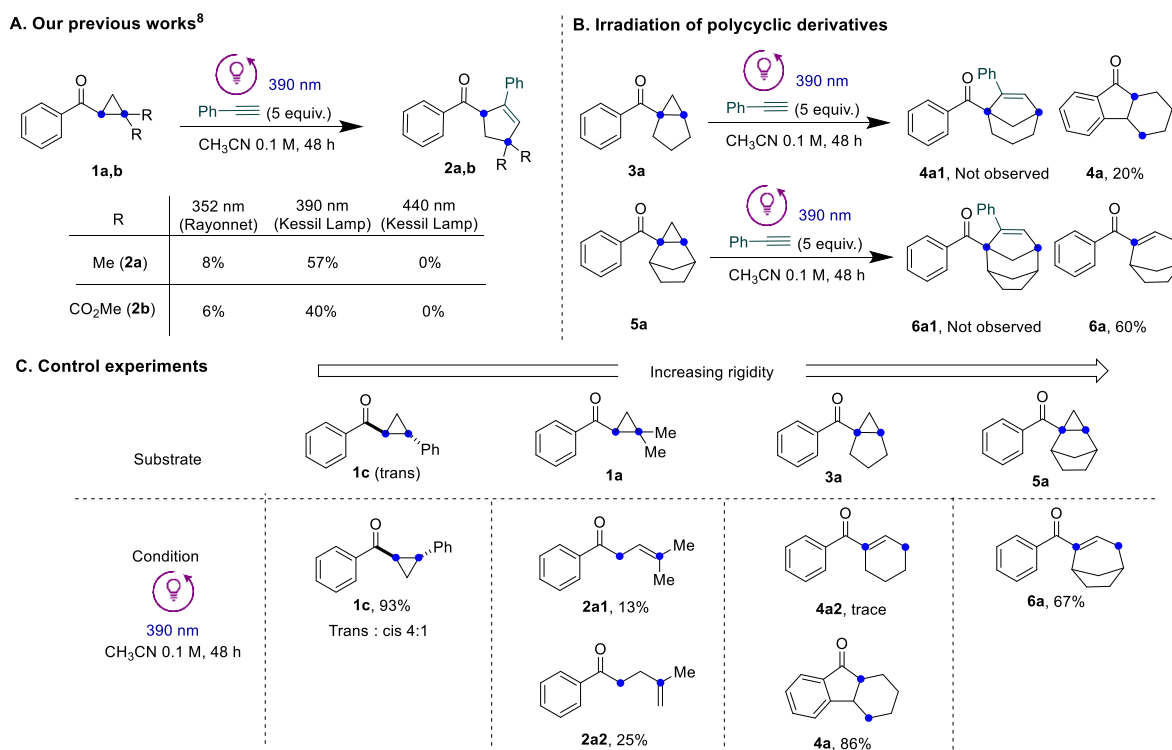
D. This work

In this work, we report first our mechanistic studies on the direct photoexcitation of cyclopropyl carbonyl compounds by experiments and quantum chemical computation. Our investigations resulted in the discovery of efficient photoisomerization processes in case of polycyclic substrates, as well as a cascade photoisomerization- photo Nazarov reaction for bicyclic compounds (Scheme 1D). By adding diphenyl disulfide as a hydrogen atom transfer (HAT) reagent, we were then able to achieve a unified ring opening reaction applicable to both linear and cyclic biradicals, paving the way for the development of a novel homologation methodology for α,β unsaturated ketones

In our previous work,[8] we reported preliminary results on the [3+2] annulation of cyclopropanes **1a** and **1b** with phenylacetylene to give products **2a** and **2b** (57% and 40% yield, Scheme 2A) in the absence of a photocatalyst. The reaction was successful for geminally disubstituted carbonyl cyclopropanes under irradiation at 390 nm with a UV Kessil lamp. A lower yield was obtained at 352 nm and no conversion was observed at 440 nm. In addition, Brown and coworkers reported the formation of biradicals from bicyclo[1,1,0] butane (BCB)[5] and housane derivatives,[7] which are more strained ring systems. We wondered if it would be possible to extend the annulation reaction to larger bicyclic

ring systems such as bicyclo[3,1,0]hexane **3a** or norbornene derivative **5a** (Scheme 2B). Under our conditions, we however observed rearrangements leading to products **4a** and **6a** instead of the expected [3+2] annulations to give **4a1** and **6a1**.

While the mechanism of the [3+2] annulation has been investigated by our group[8] and others,[5,7,15e] the behavior of 1,3 biradicals in transformations beyond annulation has not been described thoroughly in the literature.[15e] Therefore, we decided to initiate more systematic studies in the absence of alkynes as biradical trap (Scheme 2C). We first performed the irradiation of *trans*-cyclopropane **1c**. After 48 hours of irradiation, epimerization was observed and **1c** was recovered in 93% yield as a 4:1 mixture of *trans* and *cis* isomers, suggesting that homolysis of the C-C bond was occurring and was reversible, as had been observed previously.[16] Performing the same control experiment with **1a** resulted in a mixture of isomerization products **2a1** and **2a2** with 40% of **1a** recovered. These products might arise from a Norrish type II reaction. The different reaction outcome between **1a** and **1c** suggested that there may be a competition between Norrish type II reaction and reversible C-C bond cleavage depending on the substrate.

Scheme 2. Divergent reaction outcome after photo-excitation of cyclopropane carbonyl compounds.

A. Our previous works[8]

R	352 nm (Rayonnet)	390 nm (Kessil Lamp)	440 nm (Kessil Lamp)
Me (**2a**)	8%	57%	0%
CO₂Me (**2b**)	6%	40%	0%

B. Irradiation of polycyclic derivatives

C. Control experiments

We then conducted the same experiments on more rigid polycyclic structures **3a** and **5a**. To our delight, products **4a** and **6a** were obtained in good yields (86% and 67% respectively). A trace amount of photoisomerization product **4a2** was also observed. This could indicate that both reactions proceeded via formation of the ring-opened alkene products, but in the case of **4a2** a fast photo-Nazarov reaction led to **4a**.[17] Based on these observations, two different mechanisms could be considered starting from the excited triplet states **1a_T** and **3a_T** (Scheme 3A). **A**: Norrish type II reaction via either 1,4- or 1,5-HAT to give biradicals **I_A1-1a_T/3a_T** and **I_A2-1a_T/3a_T**, respectively, followed by C-C bond cleavage. **B**: direct homolysis to generate 1,3 biradicals **I_B1-1a_T/3a_T**, which then undergo the HAT process. As both pathways could ultimately lead to the observed products, we further conducted quantum chemical computations at DLPNO-CCSD(T)/def2-TZVPP//M06/def2-SVP level (see Computational Details in SI for further details). to gain further insight on the reaction mechanism. We first performed a computational study on monocyclic cyclopropane **1a**. The excitation of **1a** lead to a triplet state **1a_T** with an energy of 75.1 Kcal/mol. 1,4 HAT from **1a_T** was computed to be unfavorable with a high energy for transition state **TS_A'-1a_T** (93.3 Kcal/mol). Both 1,5 HAT and direct C-C bond homolysis are potentially feasible, with very similar energy barriers of 7.4 and 8.1 Kcal/mol respectively. 1,5 HAT delivers intermediates **I_A1-1a_T**, which is 9.6 Kcal/mol more stable than **1a_T**. Intermediate **I_B1-1a_T** is even more stable, with a free energy of 23.6 Kcal/mol lower than **1a_T**. Although both **I_A1-1a_T** and **I_B1-1a_T** can lead to **1a1_T** –the triplet excited state of the major product **2a1**, the energy barrier of C-C bond cleavage from **I_A1-1a_T** is lower than the one for 1,6 HAT from **I_B1-1a_T**, suggesting Path A is potentially more favorable than Path B. **2a2** could be formed from intermediate **I_B1-1a_T** by a 1,4

HAT process. However, this pathway is unlikely as the computed activation energy was 35.3 Kcal/mol. We hypothesize that **1a** can undergo Norrish type I fragmentation, leading to generation of the allyl radical. It was reported that the radical-radical coupling can happen at a least steric hindered center between allyl radical and acyl radical, leading to olefin **7a2** (see SI for detail mechanism).[18a]

We then performed similar computations on bicyclic cyclopropane **3a**. In this case, the Norrish type II pathway A is energetically unfavorable for both 1,4 and 1,5 HAT with energy barriers of more than 20 Kcal/mol, while only 6.1 Kcal/mol is required for C-C bond cleavage. The reason might be due to the rigidity of structure **3a**, making the HAT process geometrically less favored. Intermediate **4a1** could be obtained via 1,4 HAT from **I_B1-3a_T** to **I_B2-3a_T** then ISC and relaxation the singlet ground state **I_B2-3a_s**. However, transition state **TS_B2-3a_T** was around 33 Kcal/mol higher in energy than **I_B1-3a_T**, which is challenging to reach under our conditions. When looking at the singlet state energy surface of intermediate **I_B1-3a_T**, we realized that after ISC, **I_B1-3a_T** would spontaneously transform to **4a2** via a 1,2 hydrogen shifts. In fact, it was demonstrated that the generation of 1,3 biradical often result in 1,2 hydrogen shifts in competition with radical-radical coupling to give cyclopropanes.[18b-f]

As described in literature, the photo-Nazarov reaction only happens if sufficient twisting of the double bond is possible (see SI).[17] This process is well established with cyclohexenyl phenyl ketones such as **4a2**, furnishing product **4a** under UV irradiation. In contrast, more rigid structures such as present in **5a** disfavor double bond twisting, hence the intermediate olefin **6a** can be isolated.

Scheme 3. A. Proposed mechanism. B. Free energy profile for the photo-reaction of 1a. C. Free energy profile for the photo-reaction of 3a.

A. Proposed mechanism

B. Free energy profile for the photo-reaction of 1a

DLPNO-CCSD(T)/def2-TZVPP//M06/def2-SVP

C. Free energy profile for the photo-reaction of 3a

DLPNO-CCSD(T)/def2-TZVPP//M06/def2-SVP
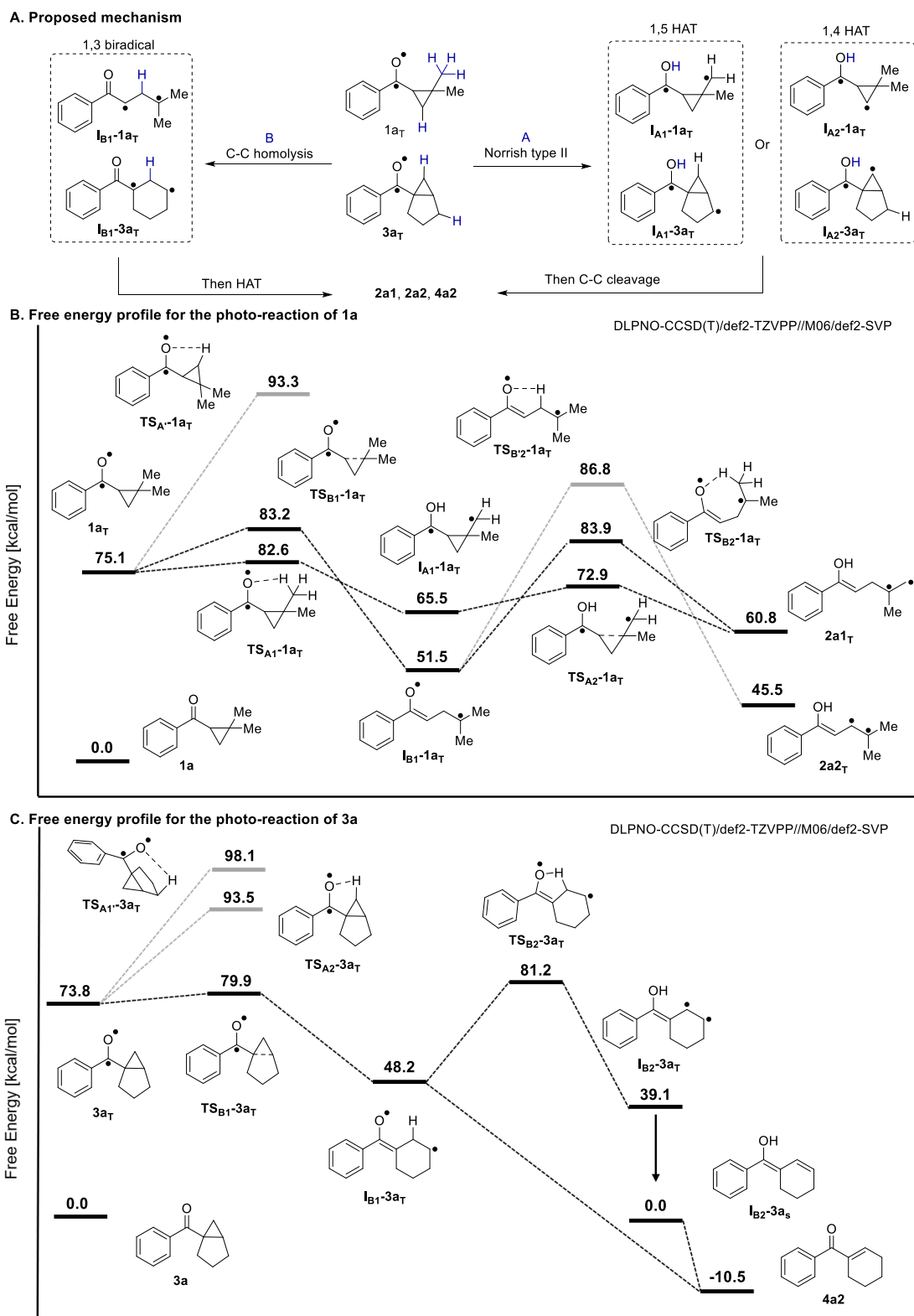
Annotation: TS: Transition state, I: intermediate, T: triplet state, S: singlet state

We then explored synthetic applications of the photo-rearrangement of polycyclic cyclopropanes **3a-k** and **5a-c** (Scheme 4A). Starting from bicyclohexanes **3a-d**, hydrofluorenones **4a-d** bearing alkyl and fluoro substituents were formed in 71 – 86% yield via the photo-isomerization-Nazarov cascade. Tetrahydropyran and thiophene derivatives **4e** and **4f** were also successfully obtained. Bicyclo[3,2,1]octene products **6a–c** were obtained in 54 – 67% yield via the photo-induced isomerization starting from norbornene derived cyclopropanes **5a-c**.

During the investigation of the scope, we often observed a trace amount of reductive ring opening product **7**. We speculated that **7** may be formed via a hydrogen atom transfer on the speculative biradical intermediate. As described in the quantum chemical computations (Scheme 3), a 1,3 biradical is always the most stable first intermediate generated from both bicyclic and linear cyclopropanes. We therefore speculated that a suitable HAT transfer reagent would allow to intercept the biradical intermediate in all cases, leading to a general homologation protocol.

Scheme 4. Synthetic applications of the photomediated ring-opening of carbonyl cyclopropanes.
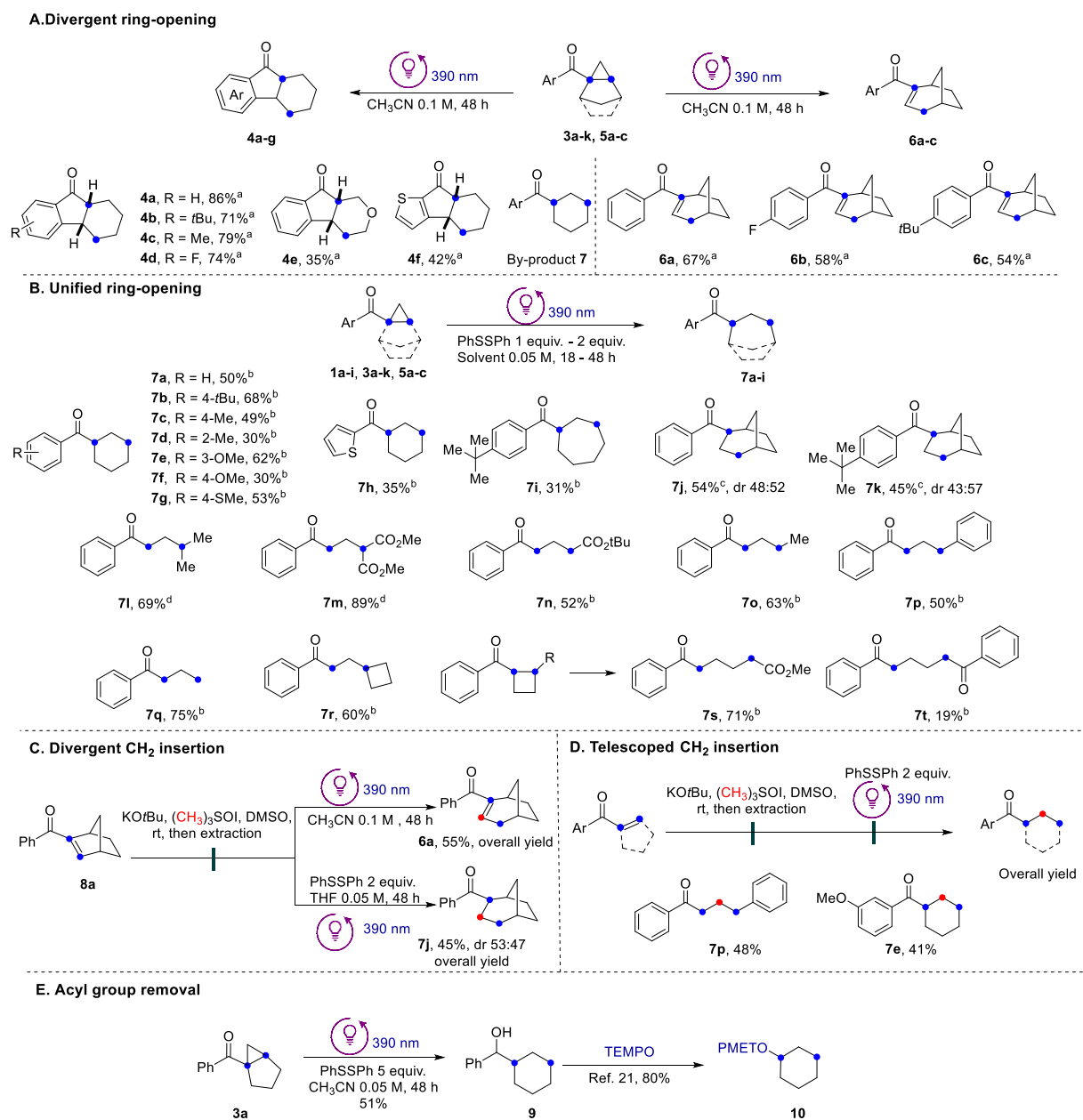
Reaction conditions: [a]**3** or **5** (1 equiv.), CH$_3$CN (0.1 M), Kessil lamp (390 nm, 40 W), 48 h. [b]**1**, **3** or **5** (1 equiv.), PhSSPh (1.7 – 2 equiv) DMSO (0.05 M), Kessil lamp (390 nm, 40 W), 48 h. [c]**5** (1 equiv.), PhSSPh (2 equiv) THF (0.05 M), Kessil lamp (390 nm, 40 W), 48 h. [d]**1** (1 equiv.), PhSSPh (1.2 equiv) CH$_3$CN (0.05 M), Kessil lamp (390 nm, 40 W), 18 h.

After optimization with several types of HAT reagents (See SI for detail), we were please to obtain reductive ring opening of product **7a** starting from bicyclo [3,1,0] hexane derivative in 50% yield (Scheme 4B). The protocol only required the addition of 2 equivalents of diphenyl disulfide as a HAT reagent.[19] Compared with previous studies on light-mediated ring-opening reduction of cyclopropanes, strongly reductive conditions were required, and the scope was limited to spiro cyclopropyl oxindoles[20a] or aryl substituted cyclopropanes,[20b] making these approaches not suitable for the development of a general homologation protocol. Several differently substituted-aryl cyclohexyl ketones **7b-h** were obtained in yield ranging from 30 to 68%. The reaction is also possible for the formation of medium sized ring **7i** in moderate yield. Starting from cyclopropanes **5a** and **5c** derived from the norbornene skeleton, products **7j** and **7k** were obtained in 54% and 45% yield respectively.

For linear di-substituted carbonyl cyclopropanes **1a** and **1b**, only 1.2 equivalents of diphenyl disulfide are sufficient to furnish products **7l** and **7m** in good yields (69 and 89%). In contrast, 1.7 equivalents of diphenyl disulfide were required to reduce mono substituted or non-substituted carbonyl cyclopropanes, giving products **7n-q** in 50 to 75% isolated yield. It is worth mentioning that a non-substituted cyclopropane can be used in this protocol, while no conversion was observed with the same substrate in the [3+2] annulation with alkynes. Starting from spirocyclic cyclopropane **1i**, 60% of product **7r** was obtained and the cyclobutane ring remained untouched, demonstrating the chemoselectivity of the reaction. Carbonyl cyclobutanes delivered products **7s** and **7t**. This strategy can therefore potentially be used as an alternative of the DeMayo reaction for the insertion of two carbon atoms.

Taking advantage of the simplicity of the reaction protocol, we performed a sequence of cyclopropanation/ring-expansion directly from norbornene derivative **8a** (Scheme 4C). Without the need to purify the cyclopropane intermediate, we were delighted to observe the formation of product **6a** in 55% and **7j** in 45% overall yield. Overall, through only small changes in reaction conditions, we could access both saturated and unsaturated products resulting from a one carbon insertion. The same reductive telescoped process was also successful for both linear and bicyclic cyclopropanes, resulting in ring opening products **7p** and **7e** in 48% and 41% overall yield respectively (Scheme 4D).

In some cases, we observed an over reduction of the carbonyl group to give the corresponding alcohol. Considering that the alcohol could be a suitable precursor for the removal of the acyl group via a further C-C bond cleavage step, we performed the reaction from cyclopropane **3a** with 5 equivalents of phenyl disulfide (Scheme 4E). In this case, 51% of alcohol **9** was isolated. The conversion of **9** into ether **10** in 80% yield has been reported,[21] demonstrating the possibility for acyl group removal, which can therefore be considered as a transient activating group for the cyclopropane.

Based on our reported preliminary results on the [3+2] annulation under photocatalyst free conditions (Scheme 2A),[8] we then further explored the scope of disubstituted cyclopropane substrates (Scheme 5). This protocol is especially attractive due to its simplicity, as no catalyst, Lewis or Brønsted acid or other additive is required, in contrast to other reported methods.[22] The best yields were obtained with 5 equivalents of alkynes as trapping reagents under irradiation for 48 hours (see SI for optimization).

Scheme 5. Scope of the photocatalyst free [3+2] annulation.
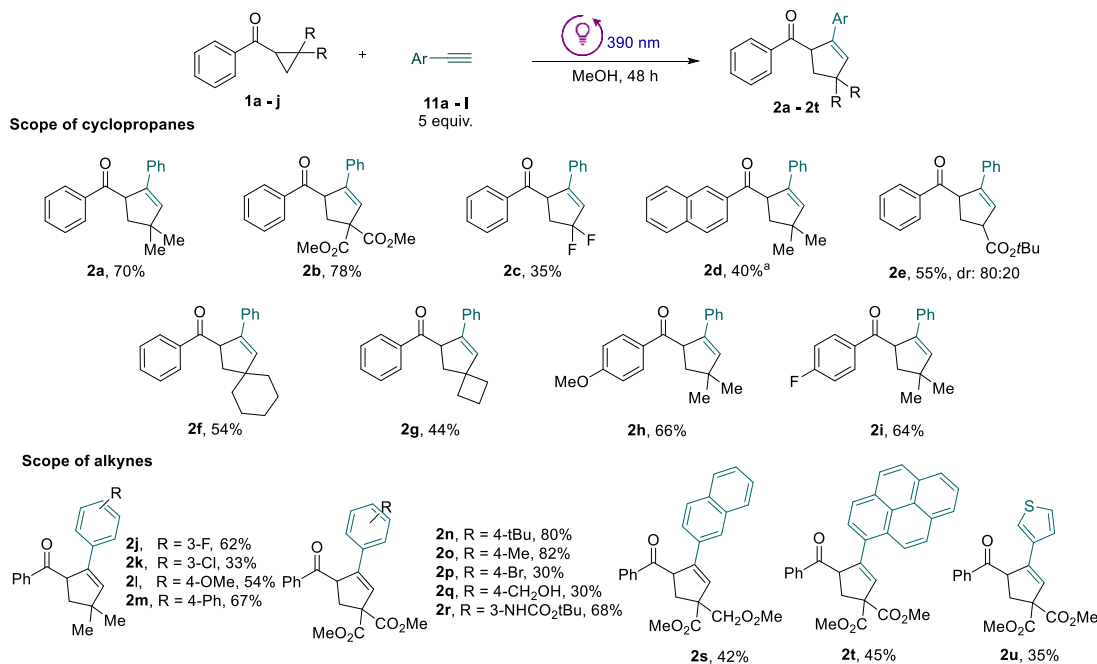
Reaction conditions: [a] 1 (1 equiv.), 11 (5 equiv.) MeOH (0.2 – 0.25 M), Kessil lamp (390 nm, 40 W), 48 h.

Cyclopropanes having vicinal di-substituents such as dimethyl, difluoro or diester gave the best results (products **2a-d** with 50-78% yield). Both naphthyl and mono substituted cyclopropanes can be used in this transformation, albeit moderate yields were obtained (**2d** - 40% and **2e** - 55%). Spiro[4.5]decene **2f** (54%) and spiro[4.3]octene **2g** (44%) could be synthesized from the corresponding spirocyclopropanes. Substrates bearing methoxy or fluorine groups on the benzene ring of the carbonyl group gave similar yields (**2h** – 66% and **2i** – 64%).

We then studied the scope of alkyne partners. In general, electron rich aromatic alkynes gave better results than the electron poor counterparts (see SI for scope limitation). Apart from 3-fluoro and 3-chloro phenyl acetylene, there was no product observed from other electron poor aromatic alkynes. In contrast, [3+2] products were obtained for a wide range of electron donating groups on the benzene ring, such as alkyl, amide, methoxy, phenyl and alkylalcohol (**2j** – **2r**, 30 – 82% yield). Unfortunately, aliphatic alkynes were not suitable for the reaction, which constituted a limitation when compared to our previous study on energy transfer catalysis.[8] Alkynes bearing extended aromatic systems or heterocycles delivered products **2s-u** in moderate yields (35 – 45%). During completion of this manuscript, Zhang and co-workers reported the same [3+2] annulation with ethanol as a solvent.[23] Nevertheless, our study presents a broader range of alkyne coupling partners. In fact, there are only two identical substrates present in both works. Therefore, we believe that adding our own results on this transformation will be still useful for the synthetic community.

In conclusion, we have presented in this work a detailed study of the reactivity of biradicals generated from the direct photoexcitation of carbonyl cyclopropanes. Depending on the substrate structure, intramolecular photoisomerization processes were favored or [3+2] annulations could be developed. Quantum chemical computations confirmed that 1,3 biradicals are viable key intermediates. By taking advantage of this common intermediate, a unified reductive strategy for the ring-opening of carbonyl cyclopropanes was achieved using diphenyl disulfide as a HAT reagent. These transformations pave the way for the development of new homologation strategies resulting in formal CH_2 insertion onto the α,β c-C bond of unsaturated carbonyl compounds, extending the current toolbox[24] for the "skeletal editing" of organic compounds.

ASSOCIATED CONTENT

Supporting information: General methods, experimental procedures, characterization data, computational details and copy of NMR spectra for new compounds (.pdf). Cartesian coordinates of optimized structures (.xyz). Raw data for NMR, IR and MS will be provided upon final publication of the work.

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Author Contributions

T. V. T. N. planned the research and performed the experiments, prepared the material for the redaction of the manuscript and the supporting information. A. B. performed studies on the [3+2] annulation. D. B. contributed to investigations of the scope of the photoisomerization and reductive ring-opening of polycyclic compounds. M. D. W performed the DFT computations and prepared the supporting material for computation. J. W. supervised the research, participated to the redaction and edition of the manuscript, as well as proof-read the supporting information. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no conflict of interest.

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