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Authors: Renè Hommelsheim, Yujing Guo, Zhen Yang, Claire Empel,
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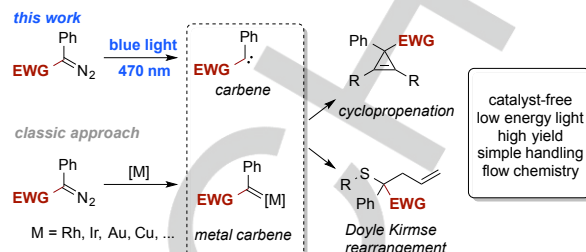
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Blue Light Induced Carbene Transfer Reactions of Diazoalkanes

Renè Hommelsheim,^[a] Yujing Guo,^[a] Zhen Yang,^[a] Claire Empel,^[a] and Rene M. Koenigs^{*,[a]}

Abstract: Carbenes are very important reactive intermediates to access a variety of complex molecules and possess widespread application in organic synthesis or drug discovery. Typically, their chemistry is accessed by the use of transition metal catalysts. Herein, we describe the application of low energy blue light for the photochemical generation of carbenes from donor-acceptor diazoalkanes. This catalyst-free and operationally simple approach enables highly efficient cyclopropenation reactions with alkynes and rearrangement of sulfides under mild reaction conditions, which can be utilized under both batch and continuous-flow conditions.



Scheme 1. Blue light promoted carbene transfer reactions of diazoalkanes.

Carbene transfer reactions are an important synthetic tool for highly efficient cycloaddition and rearrangement reactions or C—H and X—H insertion reactions.^[1–3] Typically, these reactions are conducted in the presence of transition metal catalysts that are required to access a metal carbene intermediate from appropriate precursors.^[1,2] For this purpose, diazoalkanes are ideally suited and, upon liberation of nitrogen, can be applied in a variety of carbene transfer reactions. Modern synthetic organic chemistry mostly relies on the utility of scarce precious metal catalysts, such as rhodium, iridium or gold with remarkable efficiency;^[1] and more recently, earth-abundant non-precious metal catalysts have emerged as a sustainable alternative.^[2,4] In classic organic synthesis, UV light is a common source to liberate carbenes from diazoalkanes,^[3] yet applications are limited due to side-reactions caused by the high-energy UV light. Despite the fact, that most diazoalkanes are intensely colored and absorb visible light, carbene transfer reactions relying on the irradiation with visible light are vastly underexplored. Only recently, Davies *et al.* and Zhou, He and co-workers reported on first applications of carbene transfer reactions mediated by low energy visible light.^[5,6] Moreover, as light-mediated carbene transfer reactions are conducted in the absence of any transition metal catalyst, these processes should allow further insight into the transition state of, e.g. the Doyle-Kirmse reaction, and thus provide a better understanding of the reaction mechanism.^[7] Against the background of the development of environmentally benign transformations and high costs of precious metal catalysts, we became interested in catalyst-free, visible light mediated carbene transfer reactions of diazoalkanes (Scheme 1). A particularly interesting reaction is the cyclopropenation reaction of alkynes,^[8–15] for which a variety of expensive, precious metal catalysts, based on Rh(II),^[9] Au(III),^[10] Ir(I)^[11] or Ag(I)^[12] are reported. Valdés *et al.* reported on a metal-free cyclopropenation reaction using tosylhydrazones, which provide upon heating trifluoromethyl containing cyclopropanes in low to moderate yield and limitations in substrate scope.^[14]

We hypothesized that diazoalkanes, upon irradiation with low-energy visible light, can open up a pathway towards carbenes that, in the presence of an alkyne, should undergo a catalyst-free cyclopropenation reaction. We commenced our investigations by studying the reaction of phenylacetylene (**1**) with diazoester **2** as a model reaction. Further investigations revealed that 10 eq. of phenylacetylene^[16] and the addition of the diazoester (**2**) by syringe pump to a solution of the alkyne (**1**) proved optimal (Table 1, entry 5). Under these conditions, the cyclopropane (**3**) could be isolated in excellent yield (97%). Notably, a broad range of solvents proved compatible and cyclopropane **3** was obtained in moderate yields. Only THF and 1,4-dioxane were incompatible, which might be attributed to ylide formation.^[17] To demonstrate that light is indeed needed, we carried out the reaction in the dark, yet no reaction was observed even after 24 hours. In contrast to many metal catalyzed cyclopropenation reactions, these visible light mediated reactions are operationally simple and can be carried out without exclusion of moisture and oxygen in standard p.A. grade solvents.

Table 1. Optimization of the cyclopropenation reaction.

# ^[a]	Solvent	Concentration	Ratio (1:2)	Yield (3)
1	DCM	0.2 M	4 : 1	57%
2	DCM	0.2 M	1 : 2	12%
3	DCM	0.2 M	10 : 1	67%
4	DCM	0.1 M	10 : 1	77%
5^[b]	DCM	0.1 M	10 : 1	97%
6 ^[c]	DCM	0.1 M	10 : 1	no reaction

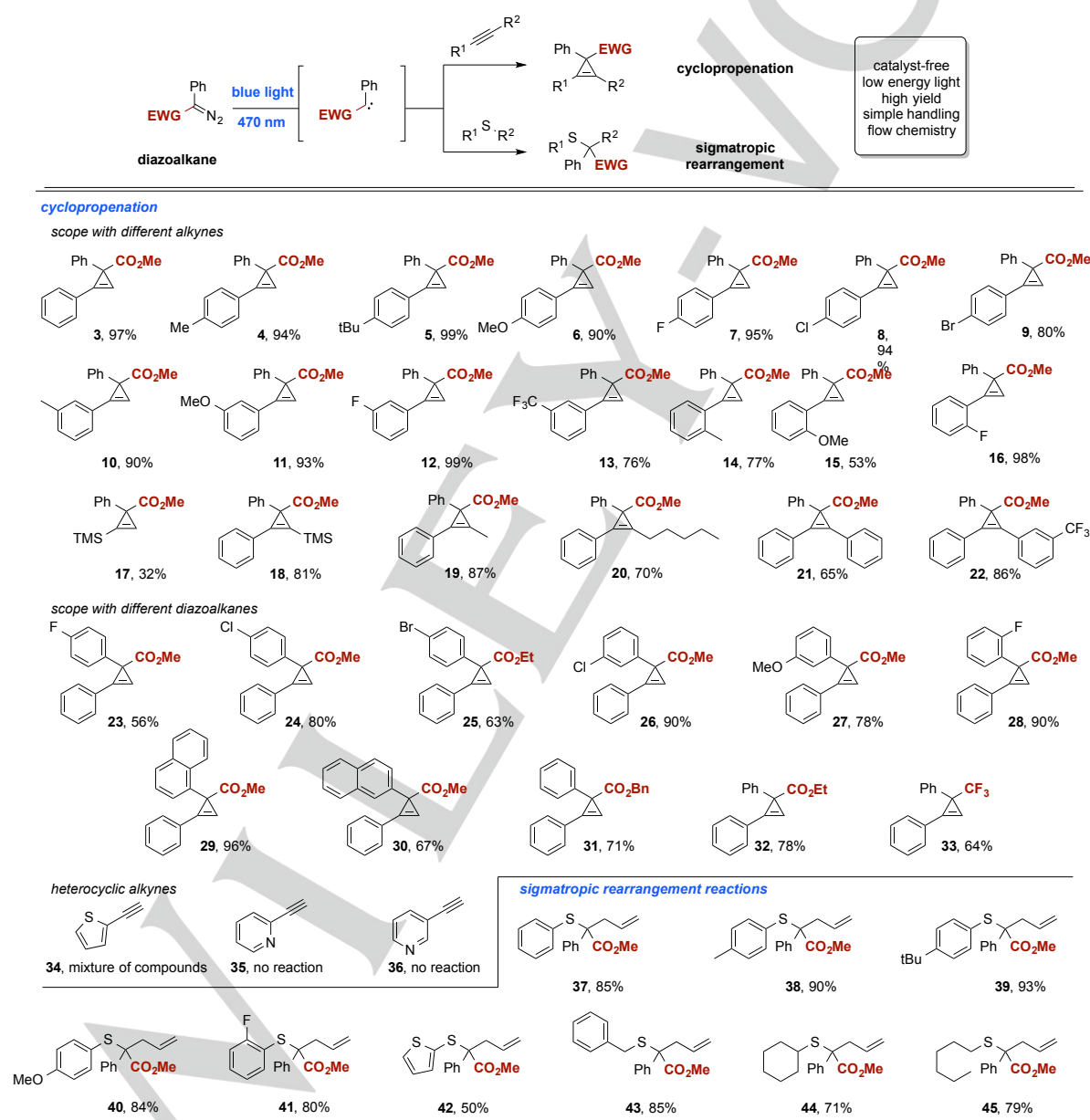
^[a]Reaction conditions: 0.25 mmol **2** and **1** were dissolved in 1.25 mL DCM. The mixture was irradiated with blue LEDs (470 nm) for 16 h. Yields refer to isolated products. ^[b]2.0 mL reaction solution. Then addition of 0.5 mL solution of **1** in DCM over 5 h. ^[c]Reaction in the dark.

[a] Renè Hommelsheim, Yujing Guo, Zhen Yang, Claire Empel, Prof. Dr. Rene M. Koenigs
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, D-52074 Aachen, Germany
E-mail: rene.koenigs@rwth-aachen.de

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With the best conditions in hand, we initially investigated the robustness of this method in cyclopropanation reactions of terminal alkynes. Arylacetylenes readily reacted under catalyst-free conditions and irradiation with blue LEDs to the desired cyclopropene in excellent yield, disregarding of the substitution pattern (**3-17**). Different halogens, electron-withdrawing and donating groups, such as a trifluoromethyl or a methoxy group, proved compatible with the reaction conditions and the corresponding cyclopropenes were isolated in high yield. Heterocyclic substrates such thiophene acetylene (**34**) reacted to a mixture of compounds and pyridyl-acetylenes (**35,36**) did not provide the cyclopropene, which might be attributed to an

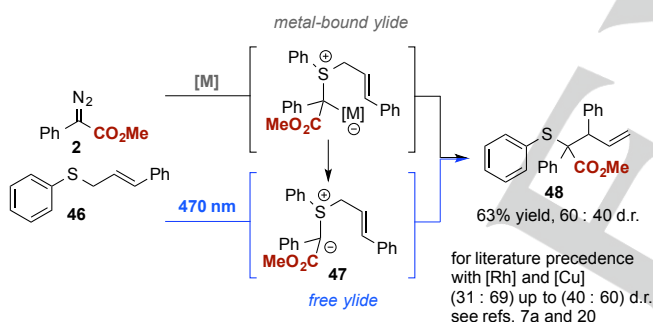
ylide formation of the electrophilic carbene with the nucleophilic sulfur or nitrogen atom, resulting in significant formation of undesired by-products.^[18] With regards to the reactivity of disubstituted alkynes, a variety of disubstituted alkynes reacted in high yield to the desired cyclopropene. Alkyl-aryl substituted alkynes provided the target cyclopropene in very good yield (**19, 20**). 1,2-Diaryl alkynes reacted with high yield to the tetra-substituted cyclopropene (**21, 22**). Notably, even TMS-protected alkynes reacted smoothly under the present reaction conditions to the desired cyclopropene (**17, 18**). Similarly, different donor-acceptor diazoalkanes smoothly reacted to the desired cyclopropene (**23-33**).



Scheme 2. Scope of the photochemical carbene transfer reactions. *Reaction conditions:* substrate (10.0 eq. for cyclopropanation, 5.0 eq. for Doyle-Kirmse rearrangements) was dissolved in 2 mL DCM and a solution of diazoalkane (0.25 mmol, 1.0 eq.) in 0.5 mL DCM was added over a period of 5 h. The reaction mixture was irradiated with blue LEDs (470 nm) for a total of 16 h. Yields refer to isolated products.

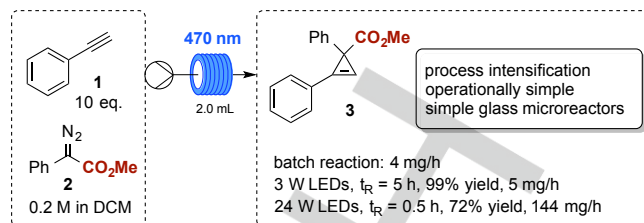
To further demonstrate the applicability of the blue light induced carbene transfer reactions, we next probed this protocol in sigmatropic rearrangement reactions that are a powerful tool to construct densely functionalized small molecules.^[1f,19] In particular, the reaction of sulfides with carbenes provides an access to sulfur ylides that readily, depending on the substitution pattern, undergo [1,2]- or [2,3]-sigmatropic rearrangement. Allylic sulfides smoothly reacted under the photochemical reaction conditions in a Doyle-Kirmse reaction to provide the homoallylic sulfides in very high isolated yield (**37-45**), including aliphatic and heteroaromatic thioethers.

Although the Doyle-Kirmse reaction was initially described 50 years ago,^[19b,c] the exact reaction pathway still remains an unresolved question. In particular, it is still unclear, if Doyle-Kirmse rearrangements occur via a free or a metal-bound ylide intermediate.^[7] Current data from transition metal catalyzed Doyle-Kirmse rearrangements point at a free ylide mechanism, though the role of a metal-bound ylide cannot be finally ruled out (Scheme 3).^[7a] As our photochemical access to carbene transfer reactions is essentially metal-free, we decided to study a substituted allylic sulfide (**46**) under our reaction conditions. We could obtain the desired rearrangement product **48** in good yield with a diastereomeric ratio of 60:40, which compares favorably with data from transition metal catalysis (Scheme 3),^[7a,20] and thus provides further evidence of a free ylide (**47**) mechanism in rearrangement reactions of sulfur ylides.



Scheme 3. Sigmatropic rearrangement under metal-free vs. metal-catalyzed conditions. With metals both ylides are potential intermediates. Under metal-free conditions, only a free ylide intermediate is possible.

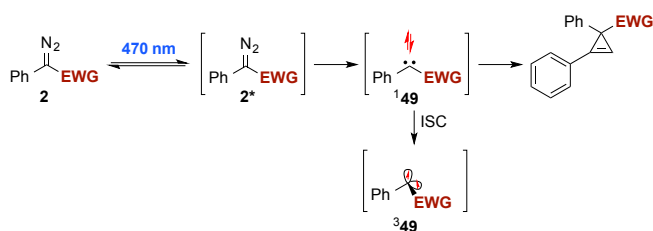
Encouraged by the previous results and building on our experience on continuous processes with diazoalkanes,^[21] we became intrigued in studying the blue light induced carbene formation under continuous-flow conditions.^[22] Flow chemistry is ideally suited to conduct photochemical transformations, as small channel diameters and high reaction surface facilitate the influx of photons into the reaction solution. Consequently, we investigated a flow setup and focused on process intensification of this approach. While in a conventional batch reaction 16 hours of reaction time were required, the same light source could be used with a glass microreactor (little things factory: LTF-VS, volume 1.0 mL) and quantitative conversion of the diazoalkane was observed within a reaction time of 5 hours,



Scheme 4. Visible light mediated cyclopropanation reactions in continuous-flow, t_R = residence time in the microreactor (LTF-VS module).

which is in the same range in terms of productivity (4 vs. 5 mg product/h). To further intensify the flow process, we used two glass microreactors and a total of eight LEDs (24 W, 240 lm).^[17] This modified setup proved highly efficient and the reaction time could be further reduced to 30 min, which now allows a productivity of up to 144 mg of cyclopropene **3** per hour, which is 36 times higher when comparing to the batch data.^[17] This result highlights the potential of continuous processes for reaction intensification as it opens up reaction parameters that are inaccessible in conventional batch chemistry.

Platz *et al.* studied the intramolecular UV light mediated cyclopropanation from a mechanistic perspective by UV/VIS and IR spectroscopy, revealing a free singlet carbene to undergo cyclopropanation reaction. The authors observed that a triplet carbene forms only in minor quantities.^[15] With regards to the mechanism of the blue light induced carbene transfer reactions, we hypothesize that upon photolysis of the diazoalkane an electrophilic singlet carbene^[23] is generated that can react with nucleophiles in downstream transformations, such as cyclopropanation or rearrangement reactions. Intersystem crossing of the singlet carbene **149** provides a triplet carbene **349**, which is an unproductive pathway and is significantly slowed down, which might be a result of conformational changes of the carbon framework upon intersystem crossing.^[24]



Scheme 5. Postulated mechanism of the blue light induced carbene transfer reaction.

In summary, we herein describe a photochemical process that involves the photolysis of donor-acceptor diazoalkanes to enable metal-free carbene transfer reactions. Notably, this operationally simple protocol allows highly efficient cyclopropanation reactions with a broad range of alkynes without the need to exclude moisture and air. It furthermore opens up a catalyst-free approach to Doyle-Kirmse reactions and our investigations suggest a free ylide intermediate being involved in this sigmatropic rearrangement reaction. We evaluated this protocol

in a continuous-flow setup that allows a 36-fold increase in productivity over conventional batch cyclopropanation and rearrangement reactions. The photochemical carbene transfer reaction thus opens up alternative pathways to small molecules with applications ranging in organic synthesis, drug discovery to agrochemistry.

Acknowledgements

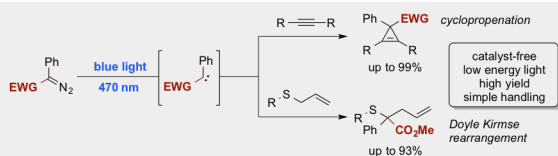
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Keywords: diazoalkane • photochemistry • cyclopropanation • rearrangement • continuous-flow

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R. Hommelsheim, Y. Guo, Z. Yang, C. Empel, and R. M. Koenigs*

Page No. – Page No.

Blue Light Induced Carbene Transfer Reactions of Diazoalkanes

The photolysis of donor-acceptor diazoalkanes with low energy blue light provides an operationally simple access to carbene transfer reactions. Without the need of exclusion of moisture or air, cyclopropanation and rearrangement reactions of sulfur ylides can be performed with high efficiency using both batch and flow chemistry protocols.

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