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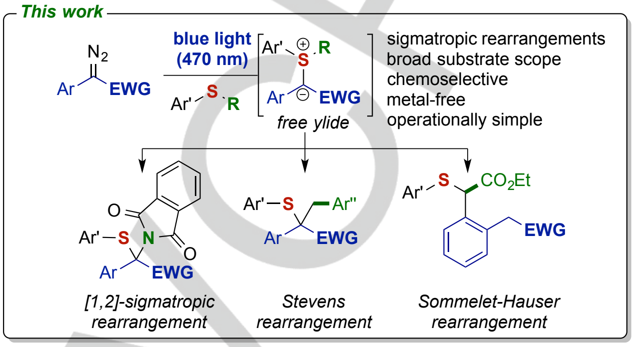
# Photochemical, metal-free sigmatropic rearrangement reactions of sulfur ylides

Zhen Yang,[a] Yujing Guo,[a] and Rene M. Koenigs*[a]

**Abstract:** *Sigmatropic rearrangement reactions constitute one of the most fundamental reactions of carbenes. While state-of-the-art synthetic methods require the use of expensive precious metal catalysts, the application of visible light for the photolysis of α-aryldiazoacetates is much less investigated and provides an operationally simple entry to carbenes under mild reaction conditions. Herein, we report on blue light induced sigmatropic rearrangement reactions of sulfur compounds with α-aryldiazoacetates. This process, depending on the substitution pattern of the sulfide, opens up formal insertion reaction of carbenes into S-N, S-C or C-H bonds.*

The application of visible light in organic synthesis has received tremendous interest in the past decade and has evolved to a powerful tool to conduct a broad variety of photochemical[1] and photocatalytic[2] transformations and enables a rich portfolio of chemical transformations that is primarily based on radical chemistry.[2,3] Although the photochemical transfer of electrophilic, electronically unsaturated carbenes is known since the 1950's using high-energy UV-light,[4] chemical applications remained scarce due to low-yielding transformations and side reactions caused by the strong UV-light.[4,5] Only recently, the application of visible light caught the attention of synthetic organic chemists[6-8] and a few initial applications by the Davies group,[8a] He and-coworkers,[8b] Lu, Xiao *et al.*[8c] and our group[8d] reported on the use of blue light in carbene transfer reactions to conduct cyclopropa(e)nation, X-H insertion, olefination or Doyle-Kirmse rearrangement reactions.[8,9]

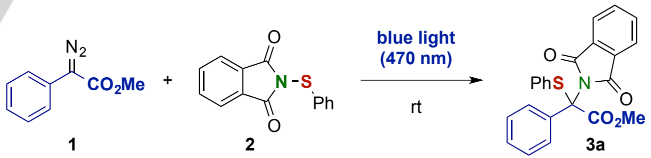
The Stevens rearrangement,[10] is well-described with ammonium ylides and numerous reports showcase the potential of this formal insertion reaction into carbon-nitrogen bonds ranging from synthetic methodology, total synthesis to applications in medicinal chemistry.[11] To date, limited approaches towards Stevens rearrangement reactions of sulfur ylides with donor-acceptor diazo derivatives have been reported that are limited to high temperature processes with precious metal catalysts and to formal heteroatom-heteroatom insertion reactions.[12] Moreover, the Stevens rearrangement leading to a formal insertion of a carbene fragment into a carbon-sulfur bond is much less investigated and current approaches are limited to the application of acceptor-only diazoalkanes, yet limited due to the regioselectivity of competing [1,2]- and [2,3]-sigmatropic rearrangement process[13a] or to specific, highly reactive substrates.[13b] To the best of our knowledge, the development of a highly regioselective Stevens rearrangement reactions of donor-acceptor carbenes is highly demanded and it would pave the way towards formal insertion reactions into carbon-sulfur bonds leading to fully substituted carbon centers.



**Scheme 1.** Photochemical sigmatropic rearrangement reactions.

We became intrigued in studying metal-free [1,2]-sigmatropic rearrangement reactions using blue light to generate carbenes from α-aryldiazoacetates (Scheme 1). We initiated our investigations by studying the reaction of phenyl diazoacetate **1** and *N*-sulfenyl phthalimide **2** under metal-free reaction conditions and irradiation with blue LEDs. We were delighted to observe that the S-N insertion product could be isolated in good yield at ambient temperature and using conventional p.A. grade solvents und an air atmosphere (Table 1).

**Table 1.** Reaction Optimization.



| entry[a] | solvent | changes from standard conditions | yield |
|---|---|---|---|
| 1 | THF | - | 39% |
| 2 | Toluene | - | 29% |
| 3 | MeCN | - | 44% |
| 4 | DCM | - | 56% |
| 5 | DCM | 5 eq. **2** | 85% |
| 6 | DCM | 10 eq. **2** | 89% |
| 7 | DCM | 5 eq. **2**, in the dark | *no rct.* |

[a] *Reaction conditions*: diazoalkane (0.2 mmol) and *N*-sulfenyl phthalimide (2.0 eq.) were dissolved in 2 mL DCM and irradiated with blue LEDs (470 nm, 3 W) for 12 h. Yields refer to isolated product.

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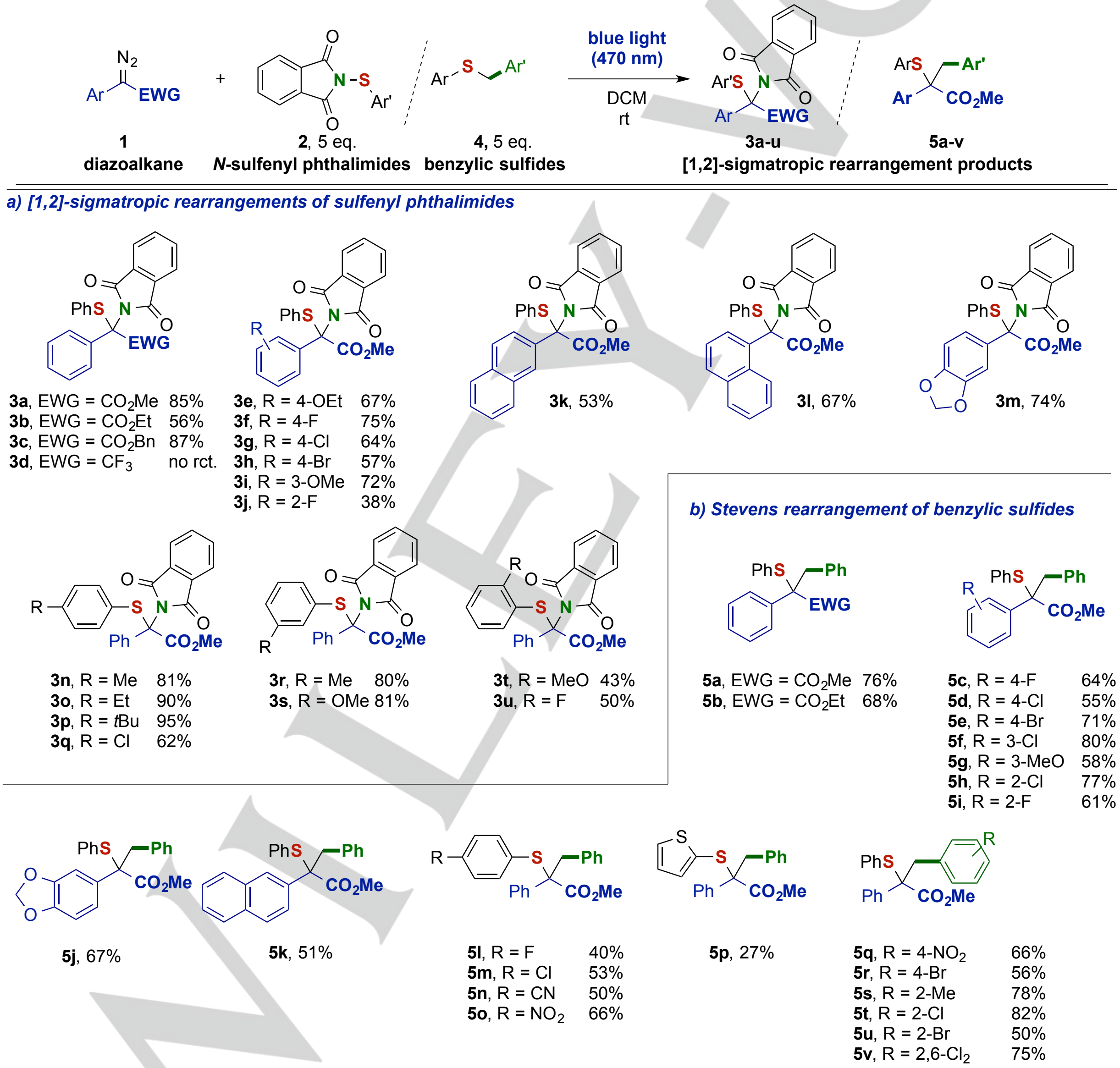
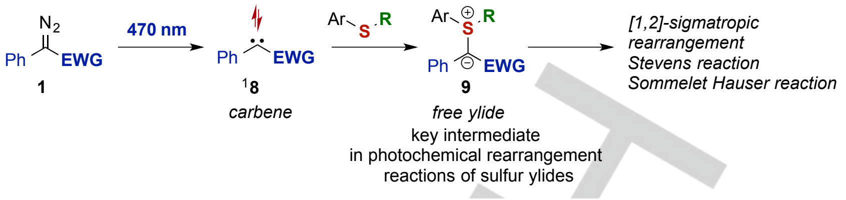
Different polar and apolar solvents were compatible and the reaction product was obtained in moderate yield, only in chloroform and hexane no reaction was observed. While the missing reactivity in hexane can be explained by the low solubility of *N*-sulfenyl phthalimide in hexane and thus dimerization of the α-aryldiazoacetates, the outcome in chloroform solvent can be rationalized by reaction of the carbene intermediate with solvent molecules.[14,15] Under optimal conditions (table 1, entry 6), we were able to isolate the desired α-mercapto ester **3a** in very good yield.[16] In the absence of light, no reaction was observed (Table 1, entry 7).

With the optimal conditions in hand, we next studied the applicability of this transformation and studied the reaction of different α-aryldiazoacetates and *N*-sulfenyl phthalimides in this [1,2]-sigmatropic rearrangement reaction. Halogens (**3f**, **3g**, **3h**, **3j**, **3q**, **3u**), ethers (**3e**, **3i**, **3s**, **3t**) and aliphatic (**3n**, **3o**, **3p**, **3r**) substituents at the phenyl ring as well as different carbocycles (**3k**, **3l**, **3m**) had only little influence on the reaction outcome and the product of the [1,2]-rearrangement could be isolated in up to 95% yield in case of *meta*- or *para*-substitution pattern on both reaction partners. The introduction of an *ortho*-substituent resulted in slightly reduced yields of the rearrangement product, which might be attributed to steric hindrance of the rearrangement process due to the high steric demand of substituents involved in the rearrangement process (**3j**, **3t**, **3u**).



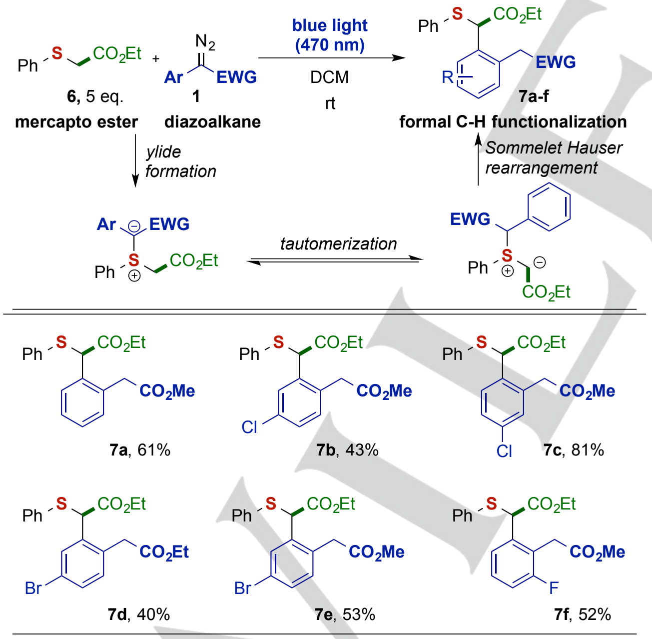
**Scheme 2.** Investigation on [1,2]-sigmatropic rearrangement reactions. *Reaction conditions*: sulfide (**2** or **4**) (5 eq.) and diazoalkane (0.2 mmol) were dissolved in 2 mL DCM and irradiated with blue LEDs (470 nm, 3 W) for 12 h. Yields refer to isolated products.

To investigate the generality of light-induced [1,2]-sigmatropic rearrangement reactions, we next focused on benzylic sulfides, which would provide an entry into the formal insertion reaction of a carbene fragment into a C-S bond. The rearrangement reaction of benzylic sulfides is particularly challenging (*vide supra*) and we were delighted to observe that benzyl phenyl sulfides **4** and α-aryldiazoacetates reacted with a perfect chemoselectivity in a [1,2]-sigmatropic rearrangement. Different substitution patterns with broad functional group tolerance were tolerated for both coupling partners, including halogens (**5c**, **5d**, **5e**, **5f**, **5h**, **5i**, **5l**, **5m**, **5r**, **5t**, **5u**, **5v**), nitro (**5o**, **5q**) or nitrile (**5n**) functional groups, and the desired Stevens rearrangement products were isolated as the sole rearrangement product in yields of up to 80% (scheme 2b) Similarly, different carbocyclic diazoesters (**5j**, **5k**) were well tolerated and the corresponding reaction products were isolated in good yield. Notably, even the sterically demanding 2,6-dichloro substituted benzylic sulfide reacted smoothly in this sigmatropic rearrangement reaction (**5v**). In all reactions, no products of [2,3]-sigmatropic rearrangement reaction were observed, as it is the case for acceptor-only diazo derivative.[13b]



**Scheme 4.** Mechanistic hypothesis of rearrangement reactions of sulfur ylides.

When switching to the α-mercapto ester **6**, we observed a switch from [1,2]-sigmatropic to [2,3]-sigmatropic rearrangement under otherwise identical reaction conditions. This observation can be rationalized by ylide formation followed by tautomerization, which is a prerequisite for the subsequent Sommelet-Hauser rearrangement and rearomatization steps (Scheme 3). Finally, we investigated a small set of different α-aryldiazoacetates, which smoothly underwent this formal *ortho* C-H functionalization reaction and the desired reaction products were isolated in moderate to high yield (Scheme 3, **7a-f**).



**Scheme 3.** Visible light mediated Sommelet-Hauser rearrangement reactions. *Reaction conditions*: diazoalkane (0.2 mmol) and **6** (5.0 Eq.) were dissolved in 2 mL DCM and irradiated with blue LEDs (470 nm, 3 W) for 12 h. Yields refer to isolated products.

Based on the above data, we hypothesize that under the photochemical conditions an electrophilic carbene $^{1}$**8** is generated, which might be reversibly stabilized by solvent molecules.[14-15,18] This highly reactive carbene can subsequently be trapped by sulfur nucleophiles under formation of a free ylide intermediate **9**, which then undergoes, depending on the substitution pattern, different sigmatropic rearrangement reactions (Scheme 4).

In summary, we herein report on photochemical rearrangement reactions of sulfides with α-aryldiazoacetates. The photolysis of α-aryldiazoacetates enables a metal-free access to carbenes that, upon formation of a free ylide intermediate with sulfur-based nucleophiles, readily undergo highly chemoselective rearrangement reactions in up to 95% yield (47 examples). This photochemical protocol now opens up new and operationally simple methods for the formal insertion reactions of carbenes into S-N, S-C or C-H bonds.

## Acknowledgements

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**Keywords:** photochemistry • carbene • diazoalkane • rearrangement • metal-free

[1] Selected articles on photochemical reactions: a) S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, 9748-9815; b) R. Remy, C. G. Bochet, *Chem. Rev.* **2016**, *116*, 9816-9849; c) M. D. Kärkäs, J. A. Porco Jr., C. R. J. Stephenson, *Chem. Rev.* **2016**, *116*, 9683-9747; d) T. P. Nicholls, D. Leonori, A. C. Bissember *Nat. Prod. Rep.* **2016**, *33*, 1248-1254.

[2] Selected articles on photocatalytic reactions: a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075-10166; b) L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018**, *57*, 10034-10072; *Angew. Chem.* **2018**, *130*, 10188-10228.

[3] Selected articles on photochemical radical transfer reactions: a) J. Davies, S. P. Morcillo, J. J. Douglas, D. Leonori, *Chem. Eur. J.* **2018**, *24*, 12154-12163; b) M. D. Kärkäs, *ACS Catal.* **2017**, *7*, 4999-5022; c) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58-102; *Angew. Chem.* **2016**, *128*, 58-106.

10.1002/chem.201900597

[4] W. B. DeMore, H. O. Pritchard, N. Davidson, *J. Am. Chem. Soc.* **1959**, *81*, 5874-5879.

[5] Selected references: a) N. R. Candeias, C. A. M. Afonso, *Curr. Org. Chem.* **2009**, *13*, 763-787; b) O. S. Galkina, L. L. Rodina, *Russ. Chem. Rev.* **2016**, *85*, 537-555; c) J. Brunner, H. Senn, F. M. Richards, *J. Biol. Chem.* **1980**, *255*, 3313-3318; d) Y. Liang, L. Jiao, S. Zhang, J. Xu, *J. Org. Chem.* **2005**, *70*, 334-337; e) J. Wang, G. Burdzinski, J. Kubicki, M. S. Platz, *J. Am. Chem. Soc.* **2008**, *130*, 11195-11209; f) K. Nakatani, S. Maekawa, K. Tanabe, I. Saito, *J. Am. Chem. Soc.* **1995**, *117*, 10635-10644.

[6] L. W. Ciszewski, K. Rybicka-Jasińska, D. Gryko, *Org. Biomol. Chem.* **2019**, *17*, 432-448.

[7] Selected references: (a) Z. Wang, A. G. Herraiz, A. M. del Hoyo, M. G. Suero, *Nature* **2018**, *554*, 86-91. b) Y. S. Mimieux Vaske, M. E. Mahoney, J. P. Konopelski, D. L. Rogow, W. J. McDonald, *J. Am. Chem. Soc.* **2010**, *132*, 11379-11385.

[8] a) I. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112-5118; b) T. Xiao, M. Mei, Y. He, L. Zhou, *Chem. Commun.* **2018**, *54*, 8865-8868; c) D. Liu, W. Ding, Q.-Q. Zhou, Y. Wei, L.-Q. Lu, W.-J. Xiao, *Org. Lett.* **2018**, *20*, 7278-7282; d) R. Hommelsheim, Y. Guo, Z. Yang, C. Empel, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 1203-1207; *Angew. Chem.* **2019**, *131*, 1216-1220; e) S. Jana, R. M. Koenigs, *Asian J. Org. Chem.* **2019**, DOI: 10.1002/ajoc.201900099.

[9] Selected review articles on metal-catalyzed carbene transfer reactions: a) A. DeAngelis, R. Panish, J. M. Fox, *Acc. Chem. Res.* **2016**, *49*, 115-127; c) A. Ford, H. Miel, A. Ring, A. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981-10080; d) H. U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151-1196; e) H. M. L. Davies, J. R. Manning, *Nature* **2018**, *451*, 417-424; f) M. P. Doyle, R. Duffy, M. Ratnikov, Z. Zhou, *Chem. Rev.* **2010**, *110*, 704-724; g) L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.* **2016**, *14*, 10547-10556; h) K. J. Hock, A. Knorrscheidt, R. Hommelsheim, J. Ho, M. J. Weissenborn, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 3630-3634; *Angew. Chem.* **2019**, *131*, 3669-3673; i) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810-13889.

[10] a) Z. Sheng, Z. Zhang, C. Chu, Y. Zhang, J. Wang, *Tetrahedron* **2017**, *73*, 4011-4022; b) J. D. Neuhaus, R. Oost, J. Merad, N. Maulide, *Top. Curr. Chem.* **2018**, *376*, 15; c) R. Bach, S. Harthong, J. Lacour, *Comprehensive Organic Synthesis II*, **2014**, *3*, 992; d) T. H. West, S. S. M. Spoehrle, K. Kasten, J. E. Taylor, A. D. Smith, *ACS Catal.* **2015**, *5*, 7446-7479; e) K. J. Hock, L. Mertens, R. Hommelsheim, R. Spitzner, R. M. Koenigs, *Chem. Commun.* **2017**, *53*, 6577-6580; f) C. Empel, K. J. Hock, R. M. Koenigs, *Chem. Commun.* **2019**, *55*, 338-341; g) A. V. Stepakov, A. P. Molchanov, J. Magull, D. Vidovic, G. L. Starova, J. Kopf, R. R. Kostikov, *Tetrahedron,* **2006**, *62*, 3610-3618; h) J.-P. Qu, Z.-H. Xu, J. Zhou, C.-L. Cao, X.-L. Sun, L.-X. Dai Y. Tang, *Adv. Synth. Catal.* **2009**, *351*, 308-312; i) V. Nair, S. M. Nair, S. Mathai, J. Liebscher, B. Ziemer, K. Narsimulu, *Tetrahedron Lett.* **2004**, *45*, 5759-5762; j) K. K. Ellis-Holder, B. P. Peppers, A. Y. Kovalesky, S. T. Diver, *Org. Lett.* **2006**, *8*, 2511-2514.

[11] a) J. B. Sweeney, *Chem. Soc. Rev.* **2009**, *38*, 1027-1038; b) E. Tayama, *Chem. Rec.* **2015**, *15*, 789-900.

[12] a) Z. Song, Y. Wu, T. Xin, C. Jin, X. Wen, H. Sun, Q.-L. Xu, *Chem. Commun.* **2016**, *52*, 6079-6082; b) H. Yuan, T. Nuligonda, H. Gao, C.-H. Tung, Z. Xu, *Org. Chem. Front.* **2018**, *5*, 1371-1374; c) Y. Li, Z. Huang, X. Wu, P. Xu, J. Wang, Y. Zhang, *Org. Lett.* **2011**, *13*, 1210-1213.

[13] a) M. Liao, L. Peng, J. Wang, *Org. Lett.* **2008**, *10*, 693-696; b) X. Xu, C. Li, M. Xiong, Z. Tao, Y. Pan, *Chem. Commun.* **2017**, *53*, 6219-6222; c) Y. Huang, X. Li, X. Wang, Y. Yu, J. Zheng, W. Wu, H. Jiang, *Chem. Sci.* **2017**, *8*, 7047-7051.

[14] Photolysis of donor-acceptor complex provides initially a singlet carbene, which can be stabilized by solvent molecules. This process might increase the lifetime of the carbene intermediate. For references, please see N. J. Turro, Y. Cha, I. R. Gould, *J. Am. Chem. Soc.* **1987**, *109*, 2101-2107.

[15] M. B. Jones, J. E. Jackson, N. Soundararajan, M. S. Platz, *J. Am. Chem. Soc.* **1988**, *110*, 5597

[16] As comparable yields were obtained with only 5 eq. of *N*-sulfenyl phthalimide **2**, we decided to continue our investigations with 5 eq. of the sulfides.

[17] a) Z. Zhang, Z. Sheng, W. Yu, G. Wu, R. Zhang, W.-D. Chu, Y. Zhang, J. Wang, *Nature Chem.* **2017**, *9*, 970-976; b) X. Zhang, Z. Qu, Z. Ma, W. Shi, X. Jin, J. Wang, *J. Org. Chem.* **2002**, *67*, 5621-5625; c) K. J. Hock, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2017**, *56*, 13566-13568; *Angew. Chem.* **2017**, *129*, 13752-13754.

[18] For a discussion of the interconversion of donor acceptor singlet and triplet carbenes, please see: a) Z. Zhu, T. Bally, L. L. Stracener, R. J. McMahon, *J. Am. Chem. Soc.* **1999**, *121*, 2863-2874.

[19] D. Werlé, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 15452-15456; *Angew. Chem.* **2015**, *127*, 15672-15676.

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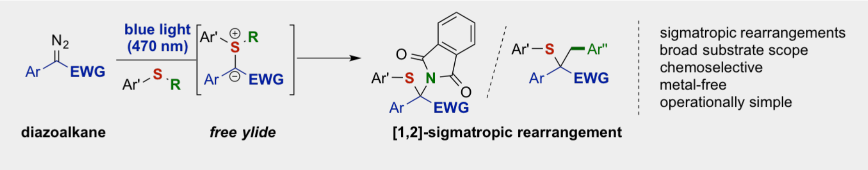
## COMMUNICATION



The photolysis of α-aryldiazoacetates enables efficient sigmatropic rearrangement reactions with sulfides. Depending on the substitution pattern of the sulfide different rearrangement products can be obtained under metal-free and operationally simple conditions in an air atmosphere.

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