Photochemical Doyle-Kirmse reaction – a metal-free route to allenes

Katarzyna Orłowska,‡,† Katarzyna Rybicka-Jasińska,‡,† Piotr Krajewski,†,‡ and Dorota Gryko*,†

†Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52 01-224 Warsaw, Poland
‡Department of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

ABSTRACT: This report describes metal-free, blue light-induced [2,3]-sigmatropic rearrangement of sulfonium ylides generated from donor/acceptor diazoalkanes and propargyl sulfides. The reaction furnishes highly functionalized allenes from a broad range of starting materials in decent yields. Mechanistic experiments supported by the literature data suggest singlet carbenes as intermediates in this reaction.

The unique reactivity of 1,2-diene moiety and its presence in a number of natural products have attracted considerable attention over the last decades.[1-3] Allenes undergo a wide variety of reactions including cycloisomerization,[4,5] cycloaddition[6-8] and cross-coupling[9-11] reactions furnishing valuable collection of small and complex molecules with impressive regio- and diastereoselectivities.[12,13] As a result, this functionality has been often installed in biologically active molecules, such as steroids[14] or nucleosides[15] to tune their pharmacological properties.

Appealing chemistry of allenes results in a variety of synthetic methods for their preparation – starting from classical procedures[16] to more recent reports on enantioselective methods promoted by metal catalysts (e.g. copper,[17] palladium[18] or gold[19]). Prominent among these are rearrangement reactions involving sulfonium or oxonium propargyl ylides. Typically, these reactive intermediates are generated from propargyl sulfides or alcohols and extremely electrophilic metal carbenes derived from diazocarbonyl compounds.[20-24]

Unlike carbene chemistry induced by metal catalysts,[25,26] photolytic reactions are less explored, with only few examples being promoted by visible light.[27] Our group developed photocatalytic procedures for functionalization of aldehydes,[28] ketones,[29] and indols[30] evidencing that in the presence of blue light α-diazo esters can act as efficient alkylating reagents. On the other hand, decomposition of aryl diazoacetates to free carbenes under blue light irradiation proved to be feasible because these compounds absorb light in the wavelength region of 400-500 nm.[31,32] As a consequence, the reactivity of donor/acceptor diazo compounds under blue light irradiation has been extensively studied. Indeed, visible light-induced cyclopropanation,[33] cyclopropenation,[34] benzannulation,[35] cross-coupling,[36] as well as C-H,[32] O-H,[32] N-H[32,37] insertion reactions have been recently reported.

Photochemically generated carbenes react with propargyl tertiary alcohols[38] giving cyclopropenes in contrast to metal catalyzed [2,3]-sigmatropic rearrangement involving ylide intermediates (Scheme 1A).[24]

Scheme 1. Metal Catalyzed and Photochemical Reactions of Donor/Acceptor Diazoalkanes.
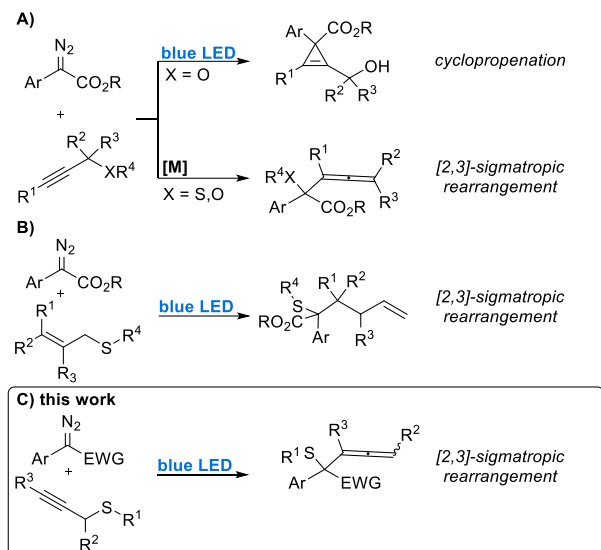
Such ylides, in general, can undergo either [1,2]- or [2,3]-sigmatropic rearrangements but for allyl sulfides the Doyle-Kirmse reaction predominates (Scheme 1B).[39,40,34]

In this line, we questioned whether in the presence of blue light propargyl sulfides, would follow a pattern of propargyl alcohols and undergo photochemical cyclopropenation reaction or rather furnish [2,3]-sigmatropic rearrangement products as reported by Kirmse[41] and Doyle[42] in metal-catalyzed reactions.

Herein, we report that under blue light irradiation the Doyle-Kirmse reaction of propargyl sulfides with donor/acceptor diazoalkanes leads to allenes, valuable building blocks towards complex molecules (Scheme 1C).

Taking into consideration optical properties of donor/acceptor diazo compounds (see SI), specifically, the local absorbance maximum for the lowest energy absorption, we selected methyl (4-cyano)phenyl diazoacetate (**1**) as a model diazoalkane and reacted it with phenyl propargyl sulfide (**2**) under blue light irradiation (Table 1). To our delight, the reaction furnished allene **3** in 76% yield (entry 1). Control experiments demonstrated the crucial role of light (entry 2). Consequently, since some diazo compounds absorb in the wavelength around 500 nm, the model reaction was irradiated with green light. The desired product **3** formed however in diminished yield. Having in mind that suitable sensitizers induce generation of carbenes, we examined if the addition of eosin Y - an organic photocatalyst - improved the reaction outcome. The yield indeed increased up to 65% (entry 4). On the other hand, under high-energetic UV light reactions with and without the addition of benzophenone - a photosensitizer – were less efficient (entries 5, 6). Presumably, in these cases photoexcitation of not only diazo ester **1** but also of propargyl sulfide **2** contributed to the loss of the reaction selectivity. DCM assured the formation of product in the highest yield. Notably, there was no need of using dry, degassed solvents (for details see SI). The yield further

improved when diazo compound **1** was added to the solution of 9 equiv. of sulfide **2** in DCM, portionwise (second portion after 3 h, entry 7).

Table 1. Background and Optimization Studies[a]
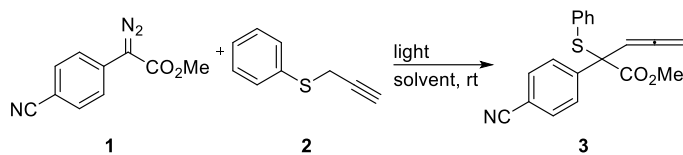
| entry	light	yield [%][b]
1	blue	76
2	no light	0
3	green	45
4[c]	green	65
5[d]	UV	12
6[d,e]	UV	22
7[f]	blue	**80**

[a]Reaction conditions: **1** (0.15 mmol), **2** (9 equiv.), DCM (0.5 mL), single blue LED, 24 h, rt. [b]Isolated yields. [c]Eosin Y (1 mol%) was added. [d]Reaction time: 8 h. [e]Benzophenone (20 mol%) was added. [f]Reaction was started with **1** (0.075 mmol) in DCM (0.25 mL), second portion of **1** (0.075 mmol) in DCM (0.25 mL) was added after 3 h.

With optimal conditions in hands, we investigated the scope of aryl diazoacetates (Scheme 2) and propargyl sulfides (Scheme 3). The visible light-induced Doyle-Kirmse reaction works well for a broad range of aryl diazo compounds regardless of a position and electronic effects of a substituent in the phenyl ring. In case of electron donating substituents (allenes **14**, **15**) as compared to those with electron withdrawing groups (products **3-6**) yields slightly decrease, as a result of lower electrophilicity of carbenes generated from diazo reagents. Halogen substituents on the phenyl ring within the diazo compound structure (**7-11**) are also well tolerated with 4-fluoro derivative giving the best result (**9**, 88%). Furthermore, the substitution position does not strongly affect the reaction yield, for 2- and 3-substituted products **10**, **11** yields decrease to same extend as compared to 4-substituted diazoalkane derivative **9**. Even allene **16** bearing heteroaromatic moiety can be synthesized in good yield in contrast to allene bearing the pyridine unit.

Various esters of aryl diazoacetate including (-)-menthyl are well tolerated with benzyl diazoester with λ_{max} = 430 nm giving allene **18** in the highest yield.

Noteworthy, under developed conditions aryl diazoketone also absorbing blue light gives allene **20** in 43% yield (Figure 1). In contrast, methyl 2-diazo-3-phenyl-propionate (λ_{max} = 410 nm, Figure 1) is not reactive under developed conditions suggesting that the absorption of light in the blue region is not the only prerequisite for an efficient reaction.

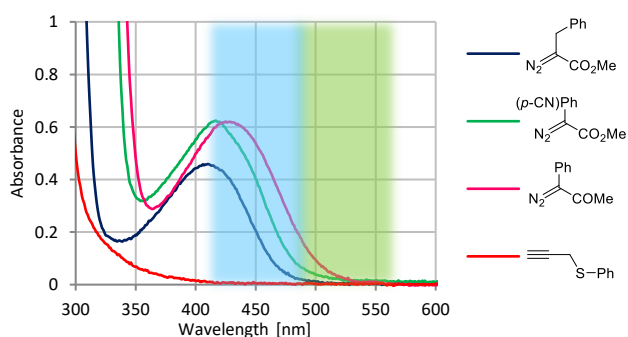**Scheme 2.** Scope of Reaction: Aryl Diazocarbonyl Compounds[a]
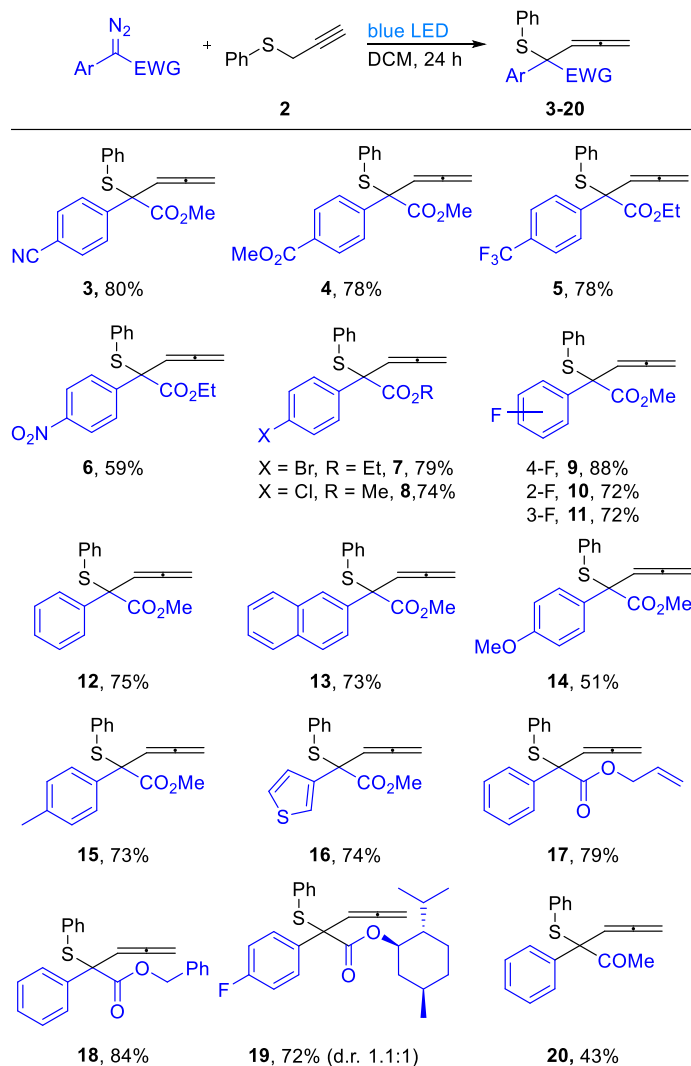
ᵃReaction conditions: diazoalkane (0.15 mmol, added in two portions), phenyl propargyl sulfide (**2**, 9 equiv.), DCM (0.5 mL), single blue LED, 24 h.
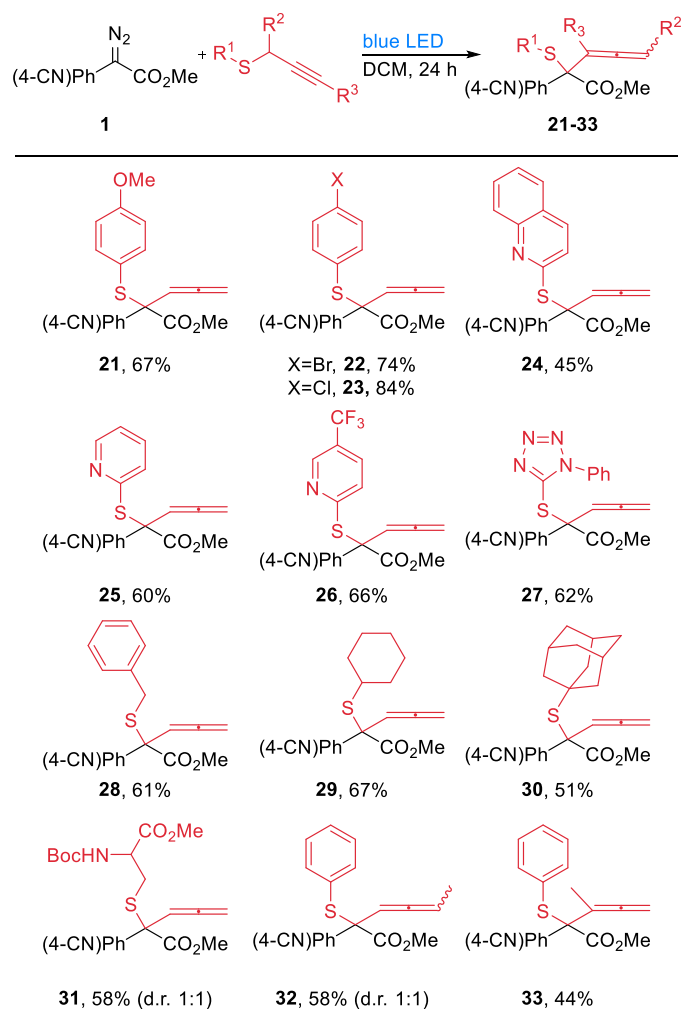
As far as propargyl sulfides are concerned, the reaction tolerates not only derivatives with substituted phenyl rings giving allens **21-23** in good yields but also nitrogen-containing heteroaromatics e.g. pyridine, tetrazole, quinolone (**24-27**) and aliphatic sulfides for which products form (**28-30**) in only slightly diminished yields. A valuable example is allene **31** bearing cysteine moiety which was obtained in 58% yield with, as expected, no diastereoselectivity.

The effect of substitution on the propargyl moiety was also examined and due to steric hindrance allenes **32** and **33** were obtained but in moderate yields.

Figure 1. Absorption spectra of various diazoalkanes (6 μmol·mL^{-1} in DCM) and phenyl propargyl sulfide **2** (3.6 μmol·mL^{-1} in DCM). For UV-Vis spectra of other aryl diazocarbonyl compounds see SI.

**Scheme 3.** Scope of Reaction: Propargylic Sulfides[a]

21, 67%

X=Br, **22**, 74%
X=Cl, **23**, 84%

24, 45%

25, 60%

26, 66%

27, 62%

28, 61%

29, 67%

30, 51%

31, 58% (d.r. 1:1)

32, 58% (d.r. 1:1)

33, 44%

[a]Reaction conditions: diazoalkane **1** (0.15 mmol, added in two portions), propargylic sulfide (9 equiv.)**,** DCM (0.5 mL), single blue LED, 24 h.

On the basis of recent reports on the reactivity of aryl diazoacetates under blue light irradiation,[32] we assume that the photoexcitation of aryl diazocarbonyl compound is also the initial step in their reaction with propargyl sulfides (Scheme 4). Under light irradiation nitrogen extrusion occurs leading to singlet carbene which can either undergo intersystem crossing to the triplet state or as such react with a propargyl sulfide generating a sulfonium ylide. Subsequent [2,3]-sigmatropic rearrangement furnishes the desired allene.

Scheme 4. Plausible Mechanism of the photochemical Doyle-Krimse reaction
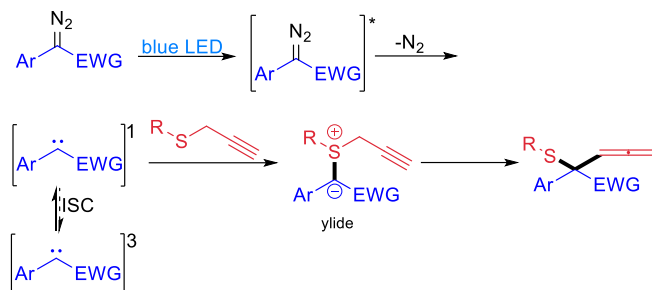
Exploring the mechanistic aspects of the reaction, we questioned the nature of carbene species involved in the visible light induced Doyle-Kirmse reaction. Our recent studies on porphyrin-photocatalyzed α-alkylation of ketones with α-diazo esters suggest generation of triplet carbenes detected as an adduct with TEMPO.[28] Concurrently, the reported reaction is not halted by the addition of TEMPO and no adducts with carbenes can be detected (see SI). Taking into consideration that direct photolysis of diazo compounds leads to generation of singlet carbenes while photosensitization furnishes triplet carbenes[43,44] we performed the reaction with and without addition of a triplet sensitizer - tetraphenyl porphyrin, TPP (Scheme 5A). When TPP was added, a decrease in the yield was indeed observed comparing to porphyrin-free reaction. Moreover, blue light irradiation of aryl diazoacetate with *trans*-stilbene led to diastereoselective cyclopropanation reaction (Scheme 5B). This outcome is typical for singlet carbene species as cyclopropanations engaging triplet carbenes are belived to be two-step processes with the loss of stereospecifity.[45] Consequently, predominant generation of singlet carbenes in the reaction course is assumed.

Scheme 5. Mechanistic Experiments
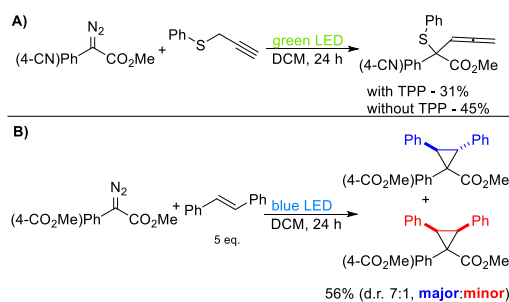
In summary, we have shown that the Doyle-Kirmse reaction of propargyl sulfides with diazo compounds can be induced by visible light and does not require any catalyst. Our method enables the synthesis of a broad range of highly functionalized allenes in good to excellent yields under mild reaction conditions.

Mechanistic considerations support involvement of singlet carbenes which with propargyl sulfides form ylides. Subsequent [2,3]-sigmatropic rearrangement leads to allenes. Our investigations contribute to broadening the knowledge of visible light induced processes employing diazo compounds as only comprehensive studies will fulfill this research area.

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