

# Dark and Light Reactions of Carbenes—Merging Carbene Transfer Reactions with N-Heterocyclic Carbene Catalysis for the Synthesis of Hydroxamic Acid Esters

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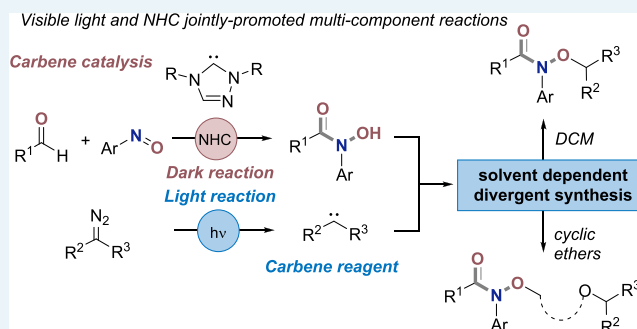
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**ABSTRACT:** Herein, we report visible light and N-heterocyclic carbene (NHC) jointly promoted multicomponent carbene transfer reactions. Under the optimized reaction conditions, two kinds of important hydroxamic acid esters were obtained in good yields depending on the reaction media used. The key to this success was driven by the blue light-promoted generation of free carbene species and the fast in situ formation of hydroxamic acid under NHC-catalyzed conditions. The mild reaction conditions, excellent functional group tolerance, useful synthetic transformations, and successful modification of natural products and drug molecules proved the utility and practicality of this method.

**KEYWORDS:** carbene transfer reactions, carbene catalysis, photochemistry, diazoalkane, hydroxamic acid, computational studies



## Introduction

Carbenes are reactive, divalent carbon-based compounds and play a key role in chemistry as ligands, catalysts, or reagents.<sup>1–5</sup> They possess unique electronic properties that are of particular importance for ligand design and for controlling the reactivity of transition-metal complexes.<sup>2,3</sup> Moreover, they can be used as nucleophilic organocatalysts and to investigate new reaction concepts in metal-free synthesis.<sup>5</sup> For applications as reagents, the high reactivity of free carbenes has long been considered a key limitation, and the use of transition-metal catalysts in carbene transfer reactions is a long-standing key paradigm.<sup>1,2</sup> Only recently it was shown that free carbenes can be generated by visible light photolysis of diazoalkanes, which allows selective transformations with nucleophilic reaction partners, such as alcohols, amines, electron-rich olefins, group VI elements, and others, in two-component reactions.<sup>5–7</sup> The development of more complex multicomponent reactions via photogenerated carbene intermediates, however, remains hitherto severely limited as the high reactivity of the photogenerated carbene species easily leads to undesired byproducts.<sup>6</sup> As such, the development of concepts to enable programmable and modular multicomponent reactions is of high relevance to exploring the reactivity and applications of free carbene intermediates for the rapid construction of complex organic molecules.

Against this background, we hypothesized that a combination of two carbenes—one being used as a reagent, the other used as a nucleophilic catalyst—could serve as a handle to overcome present limitations in multicomponent reactions of free carbene intermediates. We considered that a nucleophilic

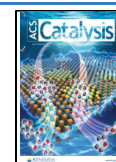
carbene catalyst could serve as a handle in Umpolung reactions of electrophiles via a Breslow intermediate.<sup>7</sup> Specifically, we presumed that the reaction of a Breslow intermediate with nitrosobenzenes could provide unprecedented access to protected hydroxamic acids,<sup>8</sup> which in turn could react with a photogenerated carbene intermediate and provide general access to hydroxamic acid esters (Scheme 1c). The latter are privileged structures in drug discovery and hold a broad spectrum of pharmacological activities, including antibacterial, antifungal, and anticancer properties (e.g., clomazone herbicide A and cycloserine antibiotic B, Scheme 1a).<sup>9–11</sup> They can also be used as versatile synthetic intermediates and chiral ligands.<sup>12–16</sup> The synthesis of hydroxamic acid esters remains a challenge to organic synthesis and involves either classic condensation reaction of O-protected hydroxylamines or catalytic approaches, which, however, require the use of stoichiometric activating agents, protecting group installation and removal, strong bases, or high reaction temperatures (Scheme 1b).<sup>17</sup> Thus, methods that allow for a mild and versatile synthesis of hydroxamic acid esters are in high demand.

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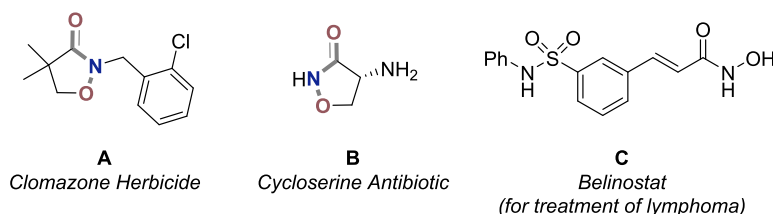
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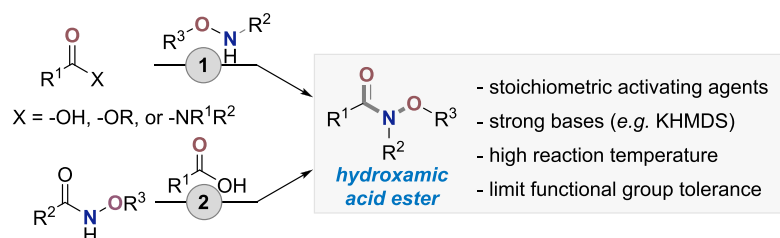
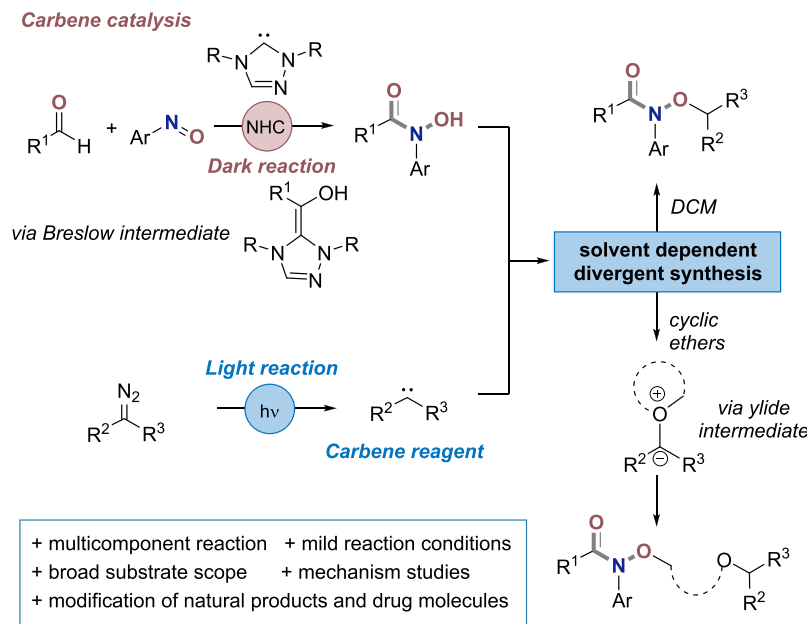


## Scheme 1. Hydroxamic Acid Derivatives—Applications, Synthesis, and Multicomponent Reactions

## (a) selected bioactive hydroxamic acid derivatives



## (b) Classic synthetic methods

(c) **This work:** photochemical, NHC-catalyzed hydroxamic acid esters synthesis two different carbenes with different roles

Herein, we report on our studies on the combination of a carbene catalyst and a carbene reagent for the synthesis of hydroxamic acid esters. In the first organocatalytic reaction, benzaldehydes undergo a carbene-catalyzed Umpolung reaction and addition to nitrosoarenes to give a hydroxamic acid, which can then be used as in the esterification reaction with photogenerated carbenes, or ylides thereof. This protocol featured a good functional group tolerance and was explored in a broad substrate scope, including the modification of natural products and existing drugs. The present study further serves as an entry to allow future investigations on the combination of photochemical carbene transfer reactions with other catalytic strategies, which still remains only poorly understood.<sup>18</sup>

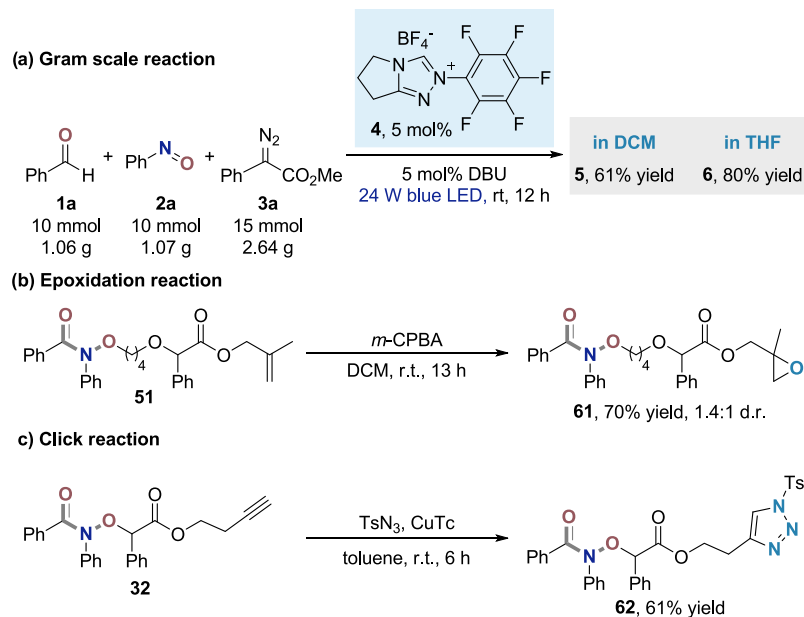
In an initial set of experiments, we examined the reaction of benzaldehyde (**1a**), nitrosobenzene (**2a**), and donor/acceptor diazoalkane (**3a**). Gratifyingly, in the presence of triazolium salt **4** and DBU as base and irradiation with blue light-emitting

diode (LEDs) (24 W), we could successfully demonstrate that such a multicomponent reaction can indeed be realized via the interplay of carbene catalysis and carbene transfer reactions in a DCM solvent. A strong influence of the base on the reaction efficiency was observed and shows that the efficiency of the carbene catalysis significantly impacts the outcome of this three-component reaction. Of all bases studied, DBU gave by far the best results, which we assume to be related to the deprotonation of the triazolium salt **4** to liberate the active carbene catalysts. Other commonly used reaction media were also investigated, and dichloromethane proved to be the best choice for this three-component reaction. Strikingly, a four-component reaction occurred in a THF solvent, in which one molecule of THF was incorporated into the reaction product (**6**, Table 1, entry 6) via the formation of oxonium ion intermediate (vide supra) and related to the previously reported reactions of an oxonium ylide intermediates.<sup>6</sup>

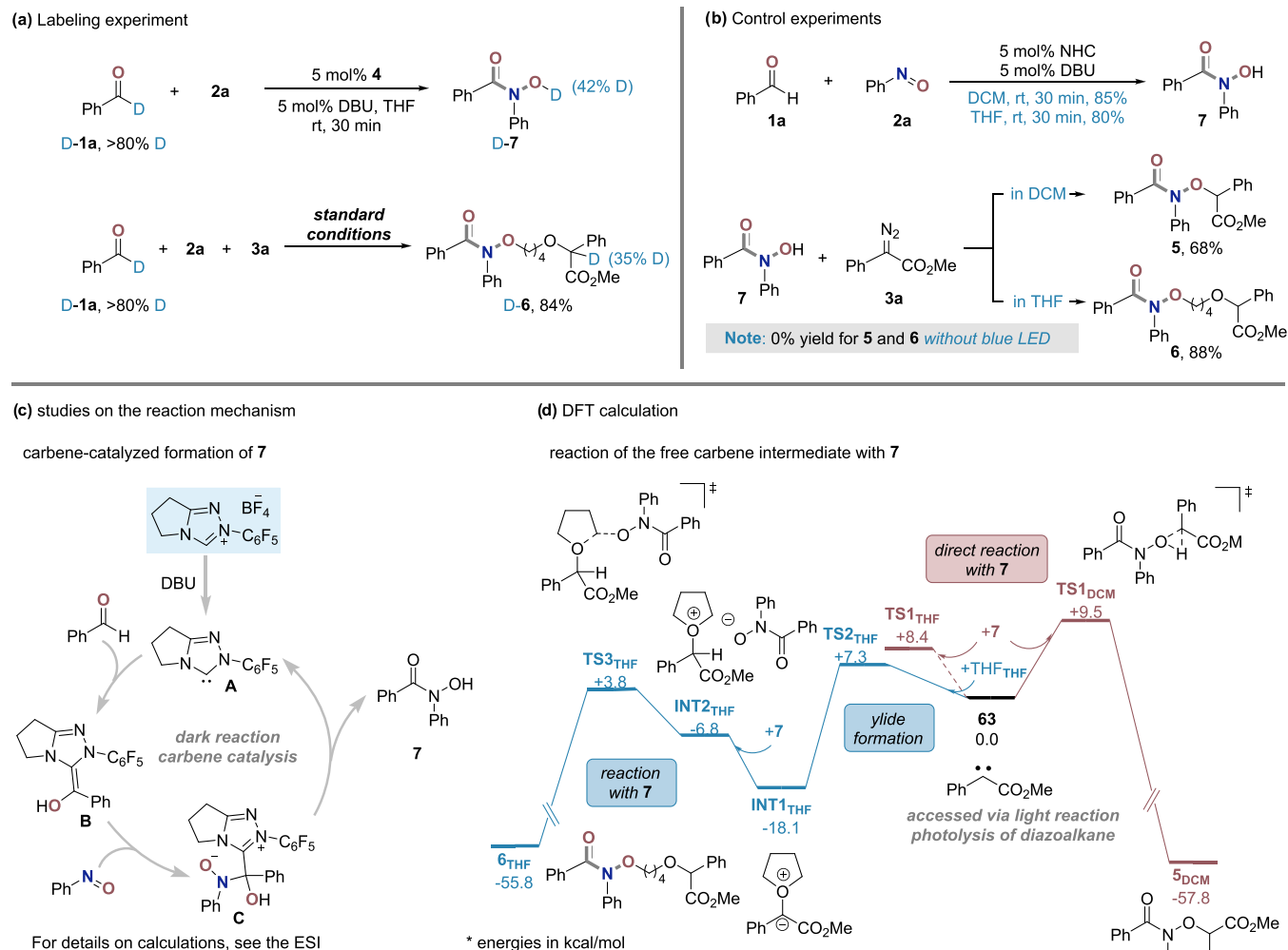




## Scheme 4. Applications on the Gram-Scale and Derivatization Reactions



## Scheme 5. Mechanism Studies



efficiency (40–45). With regard to the aryl diazoacetate components, different substituents of the aromatic ring were

well tolerated, and the reaction proceeded in high yields (46, 47). In addition, we found that different alkyl esters (48–50)



and alkyl groups containing sensitive double bonds (**51**) showed good compatibility. Next, we employed this multi-component reaction with a set of biologically active compounds, and derivatives of vitamin E, propofol, 1-(-)-borneol, citronellol, cinnamaldehyde, and melonal could be successfully accessed via this four-component reaction (**52–57**).

We then evaluated the reactivity of other cyclic ethers to further broaden the application of this 4-component reaction (Scheme 3). Indeed, 2,5-dihydrofuran, 1,4-dioxane, and other six-membered ring cyclic ethers smoothly underwent the respective four-component reaction (**58–60**). Contrarily, tetrahydrothiophene, epoxides, or 2-methyl THF were found incompatible, which we assume to be related to increased nucleophilicity, reactivity, or stability, respectively.

To show the potential applications of this strategy, we first engaged in the synthesis of products **5** and **6** on a gram scale, which smoothly proceeded without a significant decrease in the reaction efficiency (Scheme 4a). We then examined the applications of the hydroxamic acid ester products. Notably, the formed hydroxamic acid ester was found stable under various conditions, which provided opportunities to further increase the molecular complexity. For instance, treatment of **51** with *m*-CPBA at room temperature afforded hydroxamic acid ester **61** bearing an ethylene oxide moiety in a 70% yield (Scheme 4b). In addition, a copper-mediated click reaction was studied to introduce an important triazole scaffold into **32** (Scheme 4c).

Last, we embarked on studies to elucidate the reaction mechanism. First, we performed a deuterium labeling experiment using deuterated benzaldehyde (>80% D) to give **6-d** in a 84% yield with a 35% deuterium label, which is indicative that the hydrogen atom adjacent to the ester group in hydroxamic acid esters originates from the aldehyde (Scheme 5a). For deconvolution of the reaction steps, we examined the reaction of **1a** and **2a** in the presence of triazolium salt **4**, which resulted in a fast and highly efficient formation of hydroxamic acid **7** within 30 min in either a DCM or THF solvent. We also examined this reaction with **D-1a**, which gave **D-7** with a 42% of the deuterium label. In a further step, we examined the reaction of **7** with **3a**. This step only gives the reaction product **5** or **6**—depending on the solvent—under photochemical conditions, while no reaction was observed in the dark (Scheme 5b).

Based on the above experimental results and computational studies, we propose the following mechanism (Scheme 5c,d): Under the basic reaction conditions, deprotonation of triazolium salt **4** readily gives the NHC catalyst **A**, which activates aldehyde to form the nucleophilic Breslow intermediate **B**. Then, nucleophilic addition of **B** to nitroarenes afforded **C**. Our density functional theory (DFT) analysis of this process shows that independent of the solvent, the addition of the carbene catalyst to the aldehyde to form the Breslow intermediate is highest in activation free energy (in DCM: 20.6 kcal mol<sup>-1</sup>; in THF: 18.8 kcal mol<sup>-1</sup>, for a complete profile of the formation of **7**, please see the Supporting Information). As suggested by the experimental data, hydroxamic acid **7** now plays a key role in the reaction with a photochemically-generated carbene intermediate. We therefore, examined different reaction pathways of the free singlet carbene with hydroxamic acid **7**, depending on the solvent (Scheme 5d).

We then examined the reaction of a free singlet carbene **63**, which can be readily obtained via the photolysis reaction. The reaction of the free carbene intermediate with **7** is in the DCM and THF solvent, a highly favored reaction, and proceeds via transition states with very low activation free energy to directly lead to the three-component product **5**<sub>DCM</sub>. In the THF solvent, however, the reaction of the free carbene with solvent molecules is slightly favorable over the direct reaction with **7**. Taking into account the activation free energy of less than 10 kcal mol<sup>-1</sup>, the reaction with the solvent and the reaction with hydroxamic acid are both diffusion limited, and the huge excess of solvent molecules thus results in favorable ylide formation. The ylide can then react in a proton transfer reaction leading to the ion pair **INT2**<sub>THF</sub>. The close proximity of the anionic hydroxamate and oxonium ion then results in the formation of the four-component reaction product **6**<sub>THF</sub>.

In summary, we have described a concept for multi-component reactions that builds on the distinct reactivity of two carbenes. While the first N-heterocyclic carbene reacts as an organocatalyst in the synthesis of hydroxamic acids, the second carbene—which is formed via the photolysis of a diazoalkane—takes up a reagent role. The in situ-formed hydroxamic acid and carbene then react in a solvent-dependent multicomponent reaction to deliver biologically important hydroxamic acid esters. Compared to previously developed routes for the hydroxamic acid ester synthesis, the method developed herein occurred under very mild conditions with a high atom economy. The photochemical gram-scale synthesis, successful modification of natural products and drug molecules, and synthetic transformations further proved the utility and practicality of the developed method. The current process would serve as an entry to further study the synthetic potential for catalyst-free photogenerated carbene species, especially their applications in multicomponent transformations.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.2c02875>.

General; preparation and spectral data of starting materials; condition optimization; general procedure and spectral; follow-up chemistry; mechanism studies; copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra (PDF)

Computational detail; schemes of computed reaction pathways; computed energy of all stationary points; 3D structure and coordinates of all stationary points (PDF)

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## Author Contributions

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## Notes

The authors declare no competing financial interest.

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