

# Proton or Carbene Transfer? On the Dark and Light Reaction of Diazoalkanes with Alcohols

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**Abstract:** The formal alkylation reaction of OH groups with diazoalkanes under catalyst-free reaction conditions finds broad application in organic synthesis. However, even today, this reaction is mainly limited to the use of diazomethane as reaction partner. In this combined experimental and theoretical study, we aim at a fundamental understanding of the reaction of diazoalkanes with alcohols to make this transformation amenable to a generalized approach towards formal alkylation reactions of alcohols with diazoalkanes. Experimental and theoretical studies suggest a direct proton

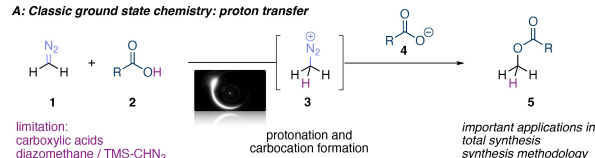
transfer only in exceptional cases. In a more general setting, such O–H functionalization proceed both under dark and photochemical conditions via a key hydrogen-bonded singlet carbene intermediate that undergoes a protonation–addition mechanism. We conclude with applications of this approach in O–H functionalization reactions of alcohols, including simple fluorinated, halogenated and aliphatic alcohols and showcase functional-group tolerance of this method in the reaction of biologically active and pharmaceutically relevant alcohols.

## Introduction

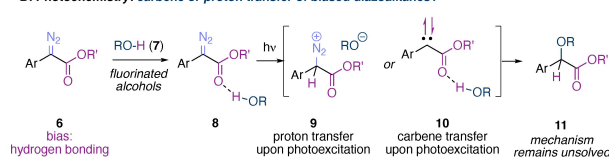
The reaction of carboxylic acids with diazomethane is a classic reaction in organic synthesis.<sup>[1–3]</sup> It features extraordinary reaction efficiency, selectivity and functional group tolerance and is of high relevance for the synthesis of methyl esters across the chemical disciplines.<sup>[3]</sup> It proceeds via initial proton transfer from a carboxylic acid **2** to the basic diazomethane **1** to give an electrophilic diazonium ion **3** and nucleophilic carboxylate **4**. In a next step, the methylation of the carboxylate occurs to furnish the desired methyl ester **5** in a highly atom-efficient fashion with nitrogen as the sole by-product (Scheme 1A).<sup>[2]</sup>

Despite its elegance, this reaction concept has only been scarcely explored for diazoalkanes other than diazomethane. A rather simple exchange of diazomethane with today's most commonly applied diazoalkane, methyl phenyldiazoacetate, already results in a complete stall of the reaction progress<sup>[4]</sup> and either metal-catalyzed,<sup>[5]</sup> thermal,<sup>[6]</sup> or photochemical<sup>[7,8]</sup> conditions are required to perform such reactions. Only recently, our group uncovered the reactivity of donor-acceptor diazoalkanes with fluorinated alcohols **7** under photochemical conditions.<sup>[4]</sup> In this case, the preformation of a hydrogen-bonding complex

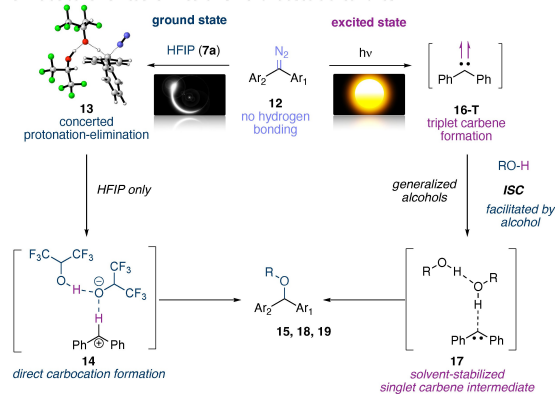
### A: Classic ground state chemistry: proton transfer



### B: Photochemistry: carbene or proton transfer of biased diazoalkanes?



### C: This work: elucidation of reaction mechanism of unbiased diazoalkanes



- general approach towards alkylation reactions
- broad synthetic utility
- high functional group tolerance
- control experiments & computational studies
- elucidation of reaction mechanism in dark and light
- proton transfer for HFIP only
- alcohol-assisted intersystem crossing key for high efficiency

Scheme 1. Alkylation reactions with diazoalkanes.

**8** between donor-acceptor diazoalkanes with fluorinated alcohols was identified vital to achieve high reaction efficiency (Scheme 1B). However, the underlying reaction mechanism remained elusive and the participation of proton or carbene transfer reaction mechanism remains an open question of

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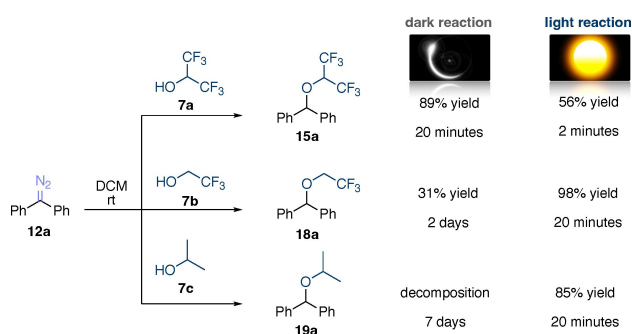
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fundamental interest. Detailed experimental and theoretical studies are thus highly demanded to obtain an understanding of this reactivity and further exploration of this concept and the development of new applications.

We hypothesized that aryl/aryl diazoalkanes (**12**) could serve as suitable substrates to study the fundamentals of the reaction of diazoalkanes with alcohols. Aryl/aryl diazoalkanes should be a particularly well-suited class of substrates, as electronic properties of the diazoalkane can be very subtly adjusted by introduction of electron-donating or -withdrawing groups.<sup>[9–11]</sup> Moreover, the absence of the pendant ester moiety – which is present in aryl diazoacetates intrinsically – suppresses a preformation of a reactant complex via hydrogen bonding<sup>[4,12]</sup> that could otherwise significantly bias reaction pathways in favor of proton transfer reactions (Scheme 1C).

## Results and Discussion

We therefore studied the reaction of diphenyl diazomethane (**12a**) with hexafluoro isopropanol (HFIP, **7a**), trifluoro ethanol (TFE, **7b**) and iso-propanol (**7c**) under dark<sup>[13]</sup> and photochemical conditions (Scheme 2). In the case of HFIP, a high-yielding reaction occurred in the dark within 20 minutes reaction time. This reaction could be significantly accelerated by irradiation with visible light (470 nm) to give the same product **15a** within in less than two minutes reaction time. TFE proved rather unreactive and the diazoalkane was consumed only after two days of reaction time and a rather low yield of the trifluoro ethyl ether **18a** was obtained, with the majority of the diazoalkane forming an unidentifiable mixture of different products. In this case, irradiation with visible light led to an even higher rate acceleration (150x fold) and the reaction product was obtained in almost quantitative yield. An even more pronounced effect was observed in the reaction with iso-propanol – in the dark, the ether product was not formed after seven days reaction time and diazoalkane **12a** slowly decomposed, while a rapid O–H functionalization reaction occurred under photochemical conditions within 20 minutes to yield **19a** in high yield. When investigating metal catalysts based on rhodium or copper, we observed the decomposition of **12a** and no product formation was observed for **7a–c**.<sup>[14]</sup> Furthermore, we studied the reaction in the dark at elevated temperature yet



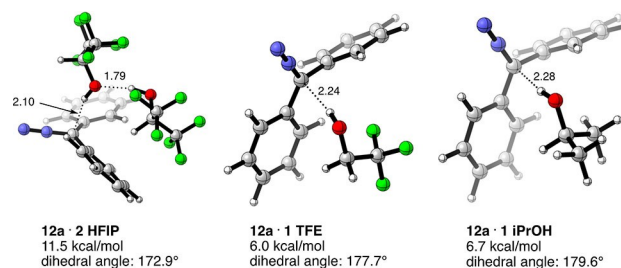
**Scheme 2.** Dark and light reactions of diphenyl diazomethane with alcohols.

yields for the reaction of **7a** with **12a** decreased with higher temperature and in the reaction of **7b** and **7c** no product formation was observed and **12a** decomposed within 2 h reaction time (for details, see Supporting Information).

## Mechanistic Studies

The above observation prompted us to perform mechanistic studies on this O–H functionalization reaction to understand the underlying reaction pathways and to evaluate the possibility of proton and carbene transfer reaction mechanism under dark and light conditions. According to Mayr's nucleophilicity scale diphenyl diazomethane should be much less nucleophilic as compared to diazomethane (*N* parameter for Ph<sub>2</sub>CN<sub>2</sub> = 5.29 vs. 10.48 for CH<sub>2</sub>N<sub>2</sub>).<sup>[15]</sup> Taking the acidity of alcohols **7a–c** into account (p*K*<sub>a</sub> for HFIP/TFE/iPrOH = 9.3/12.6/17.1),<sup>[16]</sup> we consider hydrogen bond interactions and proton transfer reactions as key. We therefore examined the potential of hydrogen bond interactions between the alcohol and diphenyl diazomethane and studied the formation of a reactant complex by coordination of one, two, or three molecules of HFIP, TFE or iPrOH to diphenyl diazomethane (Scheme 3 and Figure S2). According to the structures of these complexes, diphenyl diazomethane undergoes a weak hydrogen bonding (length: 2.10 to 2.28 Å) between the OH group and the carbon atom bearing the diazo group (**12a·2HFIP**, **12a·1TFE**, **12a·1iPrOH**).<sup>[17]</sup> This observation is mirrored in the free energy for the formation of this hydrogen bond complex, which is in all cases an endergonic process due to the absence of strong hydrogen bond acceptors.

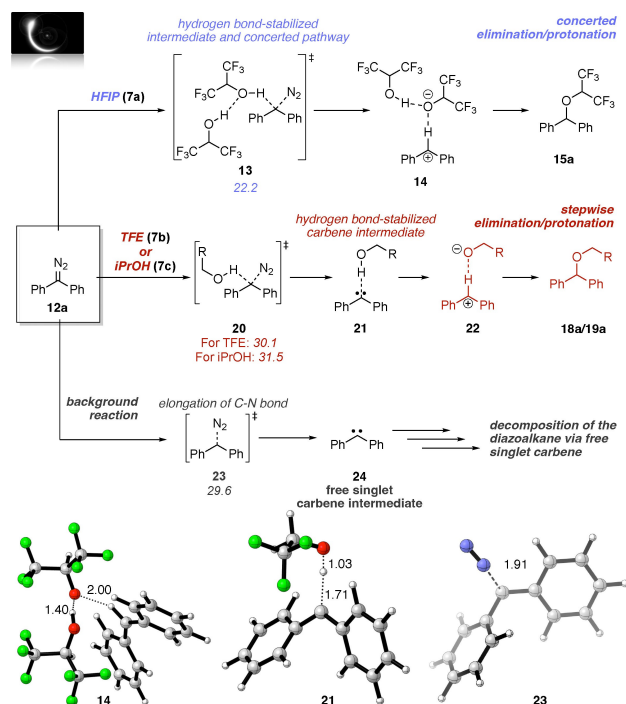
We then examined the first reaction step with the aim of understanding the participation of carbocation or carbene intermediates in the course of the dark reaction. In the reaction of diphenyl diazomethane with HFIP, the lowest-lying transition state was identified as **13** with an activation free energy of 22.2 kcal/mol, which is reasonably low to occur at room temperature and involves the participation of two molecules of HFIP. Transition states with one or three molecules of HFIP are significantly higher in energy and thus do not contribute to the reaction product (Figure S4 and S6). All three transition states involve a proton transfer reaction from the mildly acidic HFIP to the nucleophilic carbon of the diazo functional group with concomitant release of nitrogen in a concerted, asynchronous reaction mechanism to give the benzhydryl cation / hexafluoro



**Scheme 3.** Structures and key parameters of reactant complex as determined by DFT calculations.

isopropoxide ion pair **14**. For the energetically preferred reaction pathway, the hexafluoro isopropoxide ion further engages in a hydrogen bond to a second molecule of HFIP, which stabilizes this intermediate by 6.4 kcal/mol over the respective intermediate with one molecule of HFIP (Figure S4). Thus a second molecule of HFIP takes up two distinct roles in the dark reaction with diphenyl diazomethane: it facilitates the proton transfer and stabilizes the intermediate ion pair **14** by hydrogen bonding (Scheme 4).

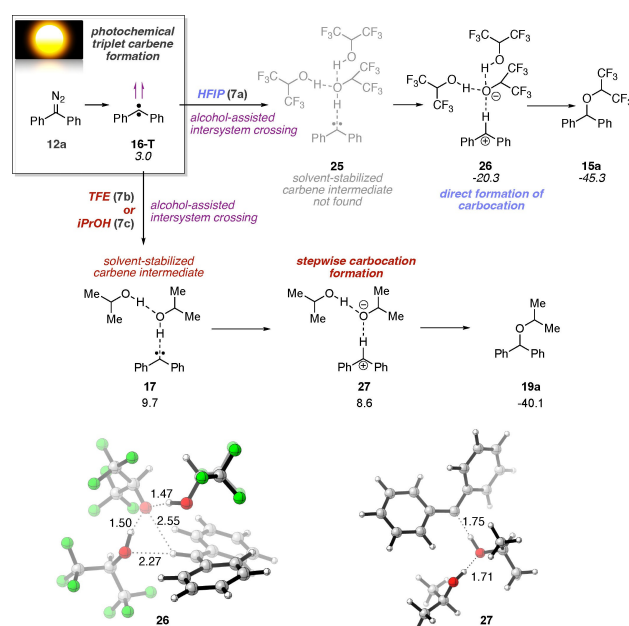
In the case of TFE, the reaction outcome similarly depends on the number of alcohol molecules involved in the transition state. Transition state **20** involves one molecule of TFE and is preferred over transition states involving more molecules of alcohol by at least 2.5 kcal/mol, but leads to the initial formation of a hydrogen-bonded, singlet carbene intermediate **21** ( $\Delta G^\ddagger = 30.1$  kcal/mol). Importantly, the activation free energy for the hydrogen bonding to one molecule of alcohol stabilizes this singlet carbene **21**, similar to observations by Nuernberger and Sander in flash photolysis and QM/MM studies.<sup>[18]</sup> Finally, the hydrogen-bonded carbene undergoes a stepwise protonation–addition reaction. Importantly, the activation free energy for the formation of **21** lies within the same range as the background decomposition reaction of diphenyl diazomethane **12a** ( $\Delta G^\ddagger = 29.6$  kcal/mol) to give a free singlet carbene **24**, which thus easily undergoes decomposition and reasons the observed experimental data. These calculations also reason the decomposition reaction in the presence of iPrOH. The formation of the hydrogen-bonded singlet carbene is energetically unfavored ( $\Delta G^\ddagger = 31.5$  kcal/mol) and background decomposition to a free carbene intermediate is favored. For both TFE and iPrOH the direct transfer of a proton was not observed, which



Scheme 4. Theoretical studies on the O–H functionalization in the dark.

we assume to be reasoned by the reduced acidity of these alcohols.

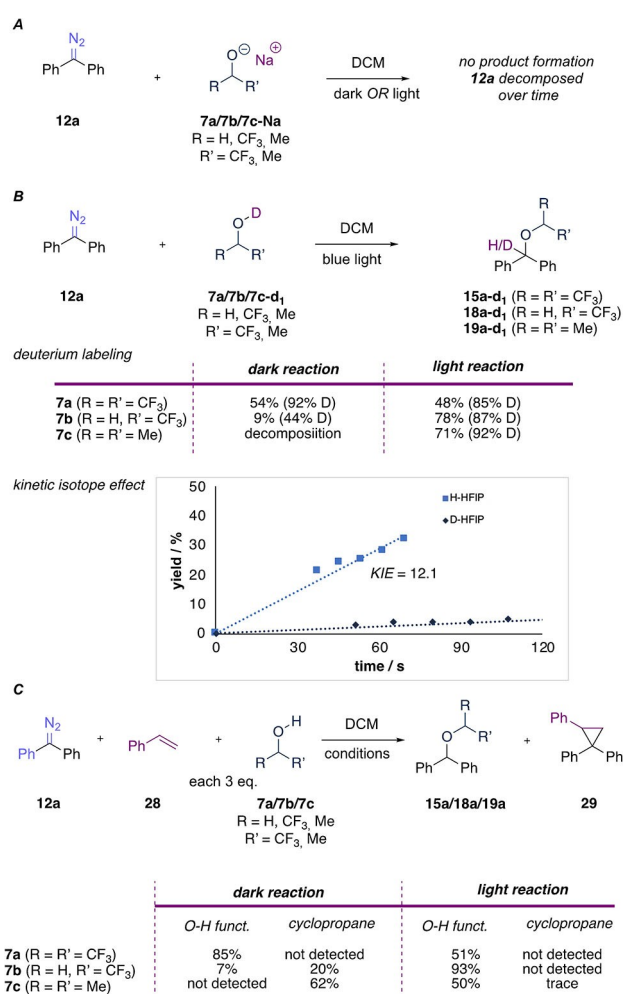
We next aimed at rationalizing the distinct reaction outcome under photochemical conditions and examined the excited state chemistry of diphenyl diazomethane (Scheme 5 and Figure S13–S17). Photoexcitation initially leads to an electronic and vibronic excited singlet state that subsequently undergoes internal conversion to the vibronic ground state of the first excited state. During this process, intersystem crossing occurs to give intermediate **12a-T** on the triplet spin surface. Consecutive extrusion of nitrogen gives the triplet carbene **16-T** as the direct product of photolysis (Figure S13).<sup>[19]</sup> The generated triplet carbene intermediate **16-T** absorbs at 315 nm,<sup>[18c]</sup> therefore we consider that photoexcitation of **16-T** by visible light is not taking place under the present conditions. The reaction of this triplet carbene **16-T** with HFIP leads to a facile alcohol-assisted intersystem crossing that is directly followed by a proton transfer to give the benzhydryl cation **26** without formation of intermediates as studied by hypothetical hydrogen-bonding structure optimization analysis. For TFE and iPrOH, a closely related pathway is observed – however, in this case a step-wise mechanism via a hydrogen-bonded singlet carbene intermediate followed by protonation occurs, which is similar to previous results by Nuernberger and Sander using QM/MM methods.<sup>[18b]</sup> The analysis of pathways that involve the protonation of the excited state could be identified, yet are significantly disfavored over the pathway involving carbene formation – protonation – C–O bond formation. Moreover, oxonium ylide formation pathways followed by proton transfer may also account for the photochemical O–H insertion reaction. However, the calculation results show that pathways involving ylide formation have considerably higher energy barriers



Scheme 5. Theoretical studies on the O–H functionalization under photochemical conditions.

compared to direct protonation of a carbene species, which renders this reaction pathway unlikely (Figure S15 and S16).

For validation of the above theoretical data and the importance of the hydrogen bonding and proton transfer in the course of the reaction, we conducted different control experiments. First, we examined sodium salts of HFIP, TFE, and *i*PrOH under dark and light reaction conditions (Scheme 6A), yet in all cases the decomposition of diazoalkane **12a** was observed. Next, we examined deuterium labeling experiments (Scheme 6B). In the dark reaction, a high incorporation of deuterium in the reaction product was observed for HFIP. A significant reduction was observed in the case of TFE, which might be related to trace amounts of water present in the reaction mixture and the long reaction time that may result in background exchange processes. *i*PrOH showed only the decomposition of **12a**. In the light reaction, a high level of deuterium incorporation was observed for all alcohols under investigation. The further analysis of isotope effects for the dark reaction of HFIP revealed a marked kinetic isotope effect, which indicates a proton transfer to be the rate determining step and is in line with the above computational results.<sup>[20]</sup>



**Scheme 6.** Control experiments. A) Studies on alkoxide salts. B) Deuterium labelling experiments. C) Competition experiments.

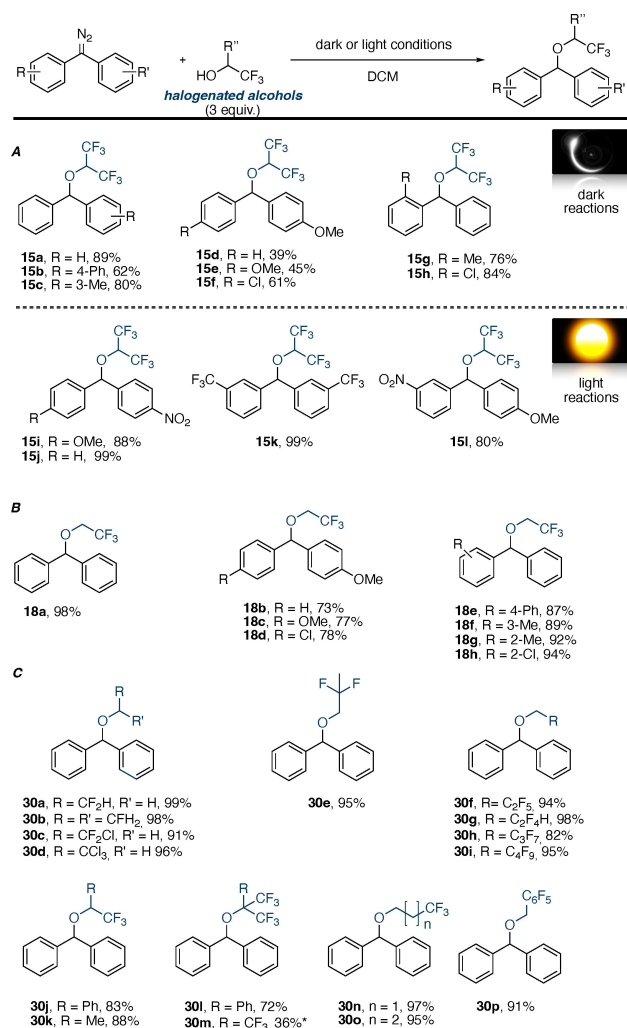
We then studied competition experiments using equimolar amounts of alcohol and styrene (**28**) as a carbene-trapping reagent (Scheme 6C). While the reaction of HFIP proceeded in a highly chemoselective fashion and only the product of O–H functionalization was observed, the reaction of TFE led to a mixture of O–H functionalization and cyclopropanation product **29** in low yield. More importantly, the latter is formed as the major product and thus suggests the participation of carbene intermediates in the reaction with TFE. In the case of *i*PrOH selective cyclopropanation was observed, which is in line with the previous observation and calculations for the dark reaction of *i*PrOH. Under photochemical conditions a markedly different reaction outcome was observed and in all cases only the product of O–H functionalization was observed and only traces of cyclopropane product **29** were formed. This hints at the participation of alcohols via hydrogen bonding in the intersystem crossing that ultimately leads to selective O–H functionalization.

In summary, the theoretical and experimental data underlines the importance of proton transfer reactions and hydrogen bonding in the course of the O–H functionalization of diphenyldiazomethane with alcohols. Differences in the acidity of the alcohol and dark or light reaction conditions then play a key role in the modulation of the reaction pathway. Only in the case of the dark reaction of HFIP a direct protonation and carbocation formation was observed as the main reaction pathway. In all other cases – disregarding dark or light reaction conditions – a carbene intermediate is formed that is key for the downstream reactivity. However, the formation of a hydrogen-bonded carbene intermediate is important to access the O–H functionalization under dark or light reaction conditions. The light reaction is however superior over the dark reaction as a triplet carbene is initially formed that can only undergo intersystem crossing in the presence of a hydrogen bond donor and thus directly leads towards the key hydrogen-bonded singlet carbene intermediate that in turn leads to chemoselective O–H functionalization.

## Application in Synthesis

After establishing a rationale for the O–H functionalization of diazoalkanes with fluorinated alcohols, we next investigated the application of the reaction of aryl/aryl diazoalkanes with alcohols in synthesis (Scheme 7).

We first studied the influence of the electronic properties of aryl/aryl substituted diazoalkanes **12** on the reaction with HFIP and whether the reaction can be conducted under light or dark reaction conditions (Scheme 7A). A range of different electron-donating and electron-neutral substituents on the diazoalkane reaction partner were tolerated under dark reaction conditions and the corresponding ethers **15a–h** were obtained in good to excellent yield. Importantly, the introduction of an electron-withdrawing group, such as a nitro or trifluoromethyl group resulted in an almost complete stall of the dark reaction and only trace amounts of the ether product were observed after several days reaction time with the majority of the diazoalkane



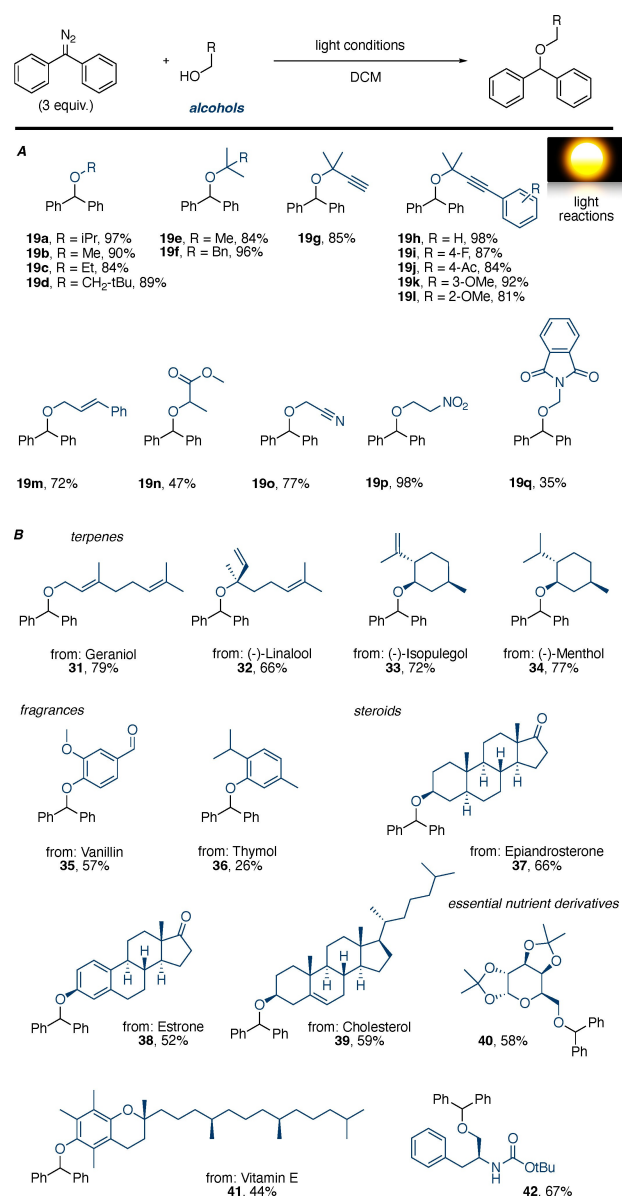
**Scheme 7.** Studies on the applicability: A) reaction with HFIP. B) reaction with TFE. C) reaction with fluorinated and halogenated alcohols.

undergoing decomposition. However, under photochemical conditions, a rapid high-yielding reaction to the corresponding ether was observed (15i-l).

Next, we examined the reaction of TFE with aryl/aryl substituted diazoalkanes (Scheme 7B). In this case, only a very slow reaction was observed in the dark, even in the presence of two strong electron-donating groups. To render this process synthetically useful, we turned our attention to the photochemical reaction conditions. In the case of TFE, a high yield of the O–H functionalization product was obtained, disregarding of the substitution pattern of the diazoalkane (18a–h). Similarly, perfluorinated derivatives of methanol smoothly reacted to the corresponding ether products under photochemical conditions. In this context, we also studied the reaction of difluoro ethanol, monofluoro ethanol, chlorinated derivatives of ethanol, different longer chain halogenated alcohols, and pentafluorobenzyl alcohol. In all cases, the desired ether products were obtained in high isolated yield under photochemical conditions (Scheme 7C). Even the tertiary alcohol proved highly reactive to give the O–H functionalization product 30i in high yield. Non-

fluoro-*tert*-butanol displayed a unique reactivity and the reaction was complete in the dark within few seconds after addition of nonfluoro-*tert*-butanol to a solution of diphenyl diazomethane.

We then studied alcohols that undergo even weaker hydrogen bonding (Scheme 8A). Consistent with our above mechanistic data, alcohols such as methanol or isopropanol did not undergo O–H functionalization in the dark. Instead, photochemical conditions have to be applied, which now gives a high-yielding approach towards the mild introduction of diphenylmethyl protecting groups onto alcohol-containing molecules, when using an excess of the diazoalkane reaction partner (19a–q).<sup>[21]</sup> This excess can be rationalized by weaker hydrogen bonding of the simple aliphatic alcohols with the intermediate carbene species, resulting in unwanted side



**Scheme 8.** Studies on the applicability: A) reaction with aliphatic alcohols. B) reaction with natural products and biologically relevant molecules.

reactions. Under these conditions, a variety of functional groups were tolerated, such as nitrile, nitro, or aldehyde groups. Moreover, in the presence of unsaturated bonds, selective O–H functionalization occurred and double or triple bonds remained untouched.

We last embarked on investigations towards the applicability of natural products and biologically active compounds (Scheme 8B). Different alcohols based on terpenes (31–34), steroids (37–39), fragrances (35,36), or derivatives of nutrients (40–42) smoothly underwent the O–H functionalization in good to high yield and showcase applications of this photochemical method for the introduction of benzhydryl protecting groups under mild conditions.

## Conclusion

O–H Functionalization reactions of alcohols with aryl/aryl diazoalkanes under catalyst-free conditions are reported. Experimental and computational studies revealed that this reaction can proceed under dark reaction conditions via proton transfer processes similar to classic O–H functionalization reaction of carboxylic acid with diazomethane. However, this dark process is essentially limited to the use of hexafluoroisopropanol. Photoexcitation of the diazoalkane leads to a substantial acceleration of this O–H functionalization reaction and opens a general approach towards O–H functionalization with aryl/aryl diazoalkanes. This photochemical reaction proceeds via initial formation of a triplet carbene intermediate that undergoes alcohol-assisted intersystem crossing leading to a hydrogen-bond-stabilized singlet carbene followed by rapid protonation and C–O bond formation. Both approaches for O–H functionalization were then examined in a broad substrate scope, including fluorinated, halogenated, and aliphatic alcohols. Further applications with natural products and biologically active alcohols further demonstrate the versatility of this approach (65 examples, up to 99% yield).

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** alcohols · carbenes · DFT calculations · protonation reactions

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- [20] KIE analysis of TFE and iPrOH was not conducted due to the low reactivity under dark reaction conditions.
- [21] For the optimization of the reaction with aliphatic alcohols, see Table S2 in the Supporting Information.

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