

Photochemistry

International Edition: DOI: 10.1002/anie.201915161
German Edition: DOI: 10.1002/ange.201915161

Photoinduced Proton-Transfer Reactions for Mild O-H Functionalization of Unreactive Alcohols**

Sripati Jana[†], Zhen Yang[†], Fang Li, Claire Empel, Junming Ho, and Rene M. Koenigs*

Abstract: Hexafluoroisopropanol is typically considered as an unreactive solvent and not as a reagent in organic synthesis. Herein, we report on a mild and efficient photochemical reaction of aryl diazoacetates with hexafluoroisopropanol that enables, under stoichiometric reaction conditions, the synthesis of fluorinated ethers in excellent yield. Mechanistic studies indicate there is a preorganization of hexafluoroisopropanol and the diazoalkane acts as an unreactive hydrogen-bonding complex. Only after photoexcitation does this complex undergo a protonation-substitution reaction to the reaction product. Investigations on the applicability of this photochemical transformation show that a broad variety of acidic alcohols can be subjected to this transformation and thus demonstrate the feasibility of this concept for O-H functionalization reactions (54 examples, up to 98% yield).

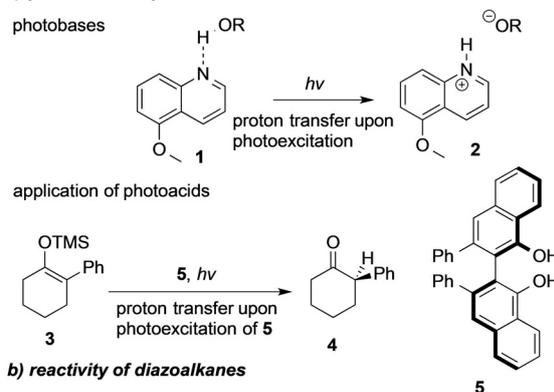
Excited-state reactivity has developed into a fundamental reaction principle over the past few years and is today an indispensable tool to conduct organic synthesis by facilitating elementary reactions steps, for example, photoinduced electron- or proton-transfer reactions.^[1–3] With the resurgence of photoredox catalysis over the past decade, photoinduced electron-transfer reactions have found their way into the standard repertoire of organic chemistry.^[2] In contrast, photoinduced proton transfer (PPT) is much less investigated,^[2,3] although it is of fundamental interest in the development of photoacids^[2] and photogenerated bases (1),^[3,4] with applications to trigger, for example, protein folding,^[5] pH jumps,^[6] or to regulate enzymes.^[7]

PPT reactions in organic synthesis are limited and the first examples^[8,9] have shown that the protonation of silyl enol ether 3 can be achieved, although in low yields, by UV

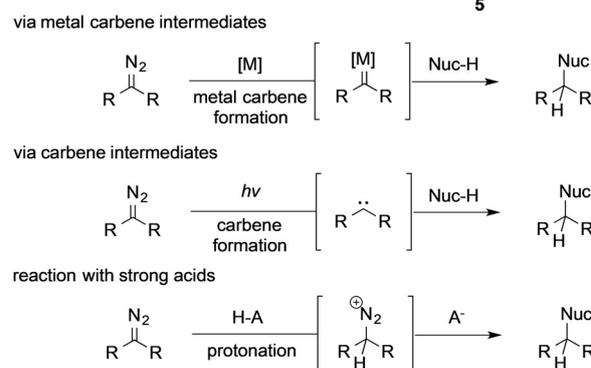
excitation of the binaphthol derived catalyst 5 (Scheme 1 a).^[9] In contrast, PPT reactions for the purpose of forming carbon–carbon or carbon–heteroatom bonds and/or the activation of unreactive precursors has, to the best of our knowledge, not been described. This approach would open up a conceptually new approach in organic synthesis, ideally with the use of mild, low-energy visible light.

We hypothesized that photoexcitation of aryl diazoacetates 6 with visible light should generate a photoexcited state that might act as a photobase in a PPT reaction with mild acids to deliver a diazonium ion and a pendant nucleophilic anion

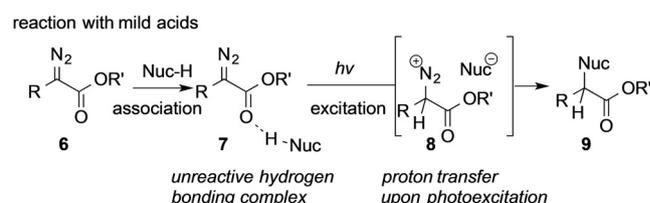
a) photoinduced proton transfer reactions



b) reactivity of diazoalkanes



c) Photoinduced proton transfer



Scheme 1. a) Concept of photobasicity and applications of photoacids in organic synthesis, b) reactivity modes of diazoalkanes, c) photoinduced proton-transfer reactions.

[*] S. Jana,^[†] Z. Yang,^[†] F. Li, C. Empel, Prof. Dr. R. M. Koenigs
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: rene.koenigs@rwth-aachen.de

Dr. J. Ho
School of Chemistry, University of New South Wales
Sydney, NSW 2052 (Australia)

[†] These authors contributed equally to this work.

[**] A previous version of this manuscript has been deposited on a preprint server (<https://doi.org/10.26434/chemrxiv.10317947.v1>).

Supporting information and the ORCID identification numbers for the authors of this article can be found under:
<https://doi.org/10.1002/anie.201915161>.

© 2019 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited, and is not used for commercial purposes.

(ion pair **8**). The latter should undergo a nucleophilic substitution to deliver the reaction product (**9**). This concept would open up a new reactivity pattern of diazoalkanes and add to known X-H functionalization reactions (Scheme 1 b). Such a reaction has been described by a carbene insertion mechanism under metal-catalyzed and photochemical conditions.^[10,11] More recently, Jurberg and Davies reported that acidic carboxylic acids react with strong Brønsted acids even in the dark through the classic protonation mechanism.^[11]

To address this challenge, we sought to study the reaction of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with diazoalkanes under photochemical conditions. HFIP possesses distinct hydrogen-bonding ability, low nucleophilicity, mild acidity, and is typically considered unreactive towards functionalization and should, therefore, be a suitable starting point to investigate this concept.^[12] Typically, reactions with HFIP as a reagent are conducted in HFIP solvent^[13] and the development of mild and efficient functionalization reactions of HFIP using stoichiometric amounts of HFIP is in high demand. Only recently, Waldvogel and co-workers reported an electrochemical process for the functionalization of HFIP, but in HFIP as solvent.^[14] Our approach would use HFIP as a reagent in organic synthesis and allow the direct introduction of hexafluoro isopropyl ether groups into organic molecules. We thus commenced our studies by investigating the reaction of HFIP with methyl phenyldiazoacetate (**6a**) under photochemical conditions^[15] and were delighted to observe that the functionalization with HFIP readily occurred in excellent yield and without the need for further purification within 4 h at ambient temperature (Table 1, entry 1). We subsequently reduced the amount of HFIP to 1.0 equivalent and obtained the desired product **10a** as an analytically pure sample after simple evaporation of the solvent (Table 1, entries 2–4). Control experiments using *i*PrOH revealed only a very sluggish reaction and poor yield of the corresponding isopropoxy ether, even with a large excess of *i*PrOH (10 equiv; Table 1, entry 9). No background reaction between

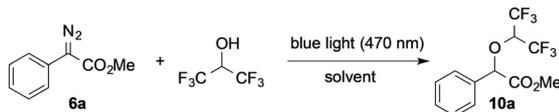
HFIP and methyl phenyldiazoacetate (**6a**) was observed in the dark even after a reaction time of 24 h (Table 1, entry 10).

Further control experiments with Rh^{II} resulted in unproductive reaction pathways. Small amounts of the hexafluoro isopropoxy ether **10a** were observed when a copper catalyst and a large excess of HFIP were used, although substantial amounts of by-product were formed, which is in line with observations of the Doyle group.^[16] Under comparable reaction conditions (1 equiv HFIP), only negligible amounts of the desired product were obtained (Table 1, entry 8).

Intrigued by this unexpected observation and the outstanding yield even when using a 1:1 mixture of HFIP and the diazoalkane, we wondered if the hydrogen-bond-donor properties of HFIP might play a role in promoting this reaction. Indeed, early studies on the interaction of diazoalkanes with hydrogen-bond donors indicated this potential interaction.^[17,18] We then studied the reaction of **6a** with different alcohols in a 1:1 ratio by UV/Vis spectroscopy, but no significant differences (Table 2) were observed. We next carried out NMR studies in [D₁]chloroform. These studies revealed a distinct pK_A-related perturbation of the chemical shift of the alcohol O-H proton. HFIP was the most acidic substrate and a chemical shift perturbation of 1.04 ppm was observed, whereas the shift for the less-acidic trifluoroethanol (TFE) was 0.34 ppm. The least acidic *i*PrOH showed only a very minor chemical shift perturbation of 0.03 ppm (Table 2). Importantly, a similar trend was observed for the ester carbonyl and methyl groups in the ¹³C NMR spectra (Table 2). A similar observation of chemical shift perturbation was made for different mildly acidic halogenated alcohols or phenols, for example, trichloroethanol, tribromoethanol, 3,3,3-trifluoropropanol, or 2,6-difluorophenol (for details, see Table S1 and S2 in the Supporting Information).^[19] None of the samples underwent a spontaneous O-H functionalization reaction of the alcohol in the dark.

Subjecting the samples to the photolysis reaction conditions led to the clean and quantitative conversion of HFIP

Table 1: Realization of the photobasicity concept.

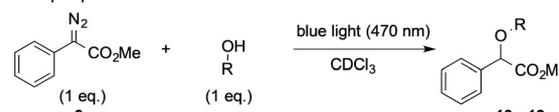


| Entry ^[a] | Conditions | Solvent | Equiv | Yield [%] |
|----------------------|---|-------------------|------------------------|-----------|
| 1 | 470 nm light | DCM | 10 | > 99 |
| 2 | 470 nm light | DCM | 5 | > 99 |
| 3 | 470 nm light | DCM | 1 | > 99 |
| 4 | 470 nm light | CHCl ₃ | 1 | > 99 |
| 5 ^[b] | Rh ₂ (OAc) ₄ (3 mol %) | DCM | 10 | NR |
| 6 ^[b] | Rh ₂ (esp) ₂ (3 mol %) | DCM | 10 | NR |
| 7 ^[b] | Cu(MeCN) ₄ PF ₆ (5 mol %) | DCM | 10 | 28 |
| 8 ^[b] | 2,2-bipyridine (7 mol %) | DCM | 1 | < 5 |
| 9 ^[c] | 470 nm light | DCM | 10 (<i>i</i> PrOH) | 9 |
| 10 ^[d] | reaction in the dark | DCM | 10 | NR |

[a] **6a** (0.4 mmol) and the hexafluoroisopropanol were dissolved in the solvent indicated and then irradiated with 470 nm LEDs (3 W).

[b] Reaction with indicated catalysts in the dark. [c] Reaction with *i*PrOH instead of HFIP. [d] Reaction in the dark.

Table 2: Influence of the alcohol on the reaction yield and selected physical properties.



| Entry ^[a] | Alcohol | Yield [%] ^[a] | Δδ (O-H) [ppm] ^[b] | Δδ (C=O) [ppm] ^[c] | λ _{ex} [nm] ^[d] |
|----------------------|---------------|--------------------------|-------------------------------|-------------------------------|-------------------------------------|
| 1 | – | – | – | – | 433 |
| 2 | HFIP | > 99 (10a) | 1.04 | 0.70 | 430 |
| 3 | TFE | 96 (11a) | 0.34 | 0.14 | 432 |
| 4 | DFE | 95 (12a) | 0.08 | 0.07 | 433 |
| 5 | <i>i</i> PrOH | 5 (13a) | 0.03 | 0.00 | 432 |

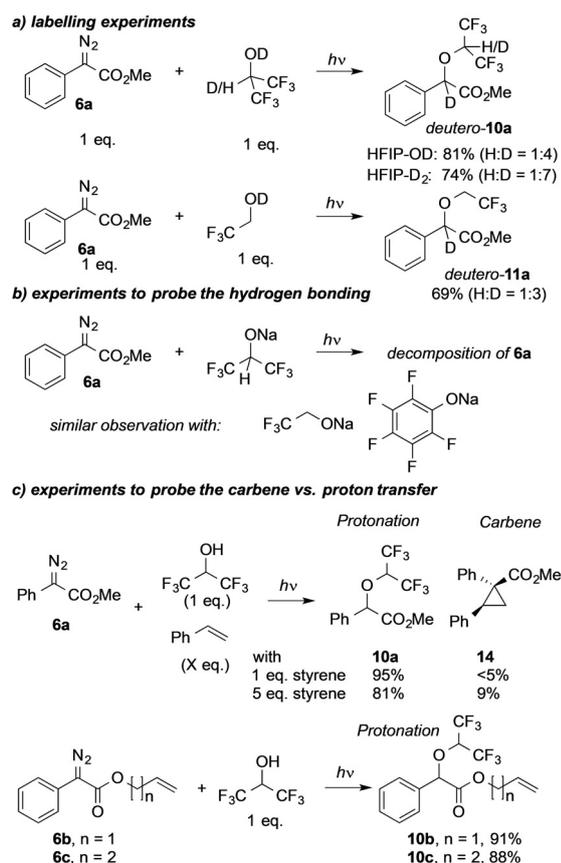
[a] **6a** (0.4 mmol) and the respective alcohol (1 equiv) were dissolved in CDCl₃. Yields based on ¹H NMR spectroscopic analysis of the crude reaction mixtures after irradiation. [b] Determined by ¹H NMR spectroscopy before irradiation with 470 nm LEDs (3 W). [c] Determined by ¹³C NMR spectroscopy before irradiation with 470 nm LEDs.

[d] Absorption maximum of a 1:1 mixture of **6a** and alcohol in DCM solvent (c = 0.1 mol L⁻¹). TFE = trifluoroethanol, DFE = difluoroethanol.

and trifluoroethanol into the O-H functionalization product, without formation of by-product. Difluoroethanol (DFE) underwent the O-H functionalization to give product in 95% yield, with about 5% of the diazine being observed in the ^1H NMR spectrum. The reaction of methyl phenyldiazoacetate (**6a**) with the least acidic *i*PrOH gave only minor amounts of the O-H functionalization product; in this case, the diazine by-product was formed instead.

To further probe this reaction mechanism, we performed a set of control experiments. We first studied labeling experiments using deuterium-labeled HFIP and trifluoroethanol under stoichiometric conditions. In both cases, a high preservation of the deuterium label was observed, which is indicative of deuterium transfer or an O-D insertion reaction (Scheme 2a). Replacing the weakly acidic proton under basic conditions to form the sodium salt, led to the desired reaction product not being obtained, only decomposition of diazoacetate **6a** was observed, which further corroborates the importance of the hydrogen bonding for a high reaction efficiency. Similarly, sodium salts of other alcohols, such as trifluoroethanol or pentafluorophenol, led to decomposition of the diazoacetate (Scheme 2b).

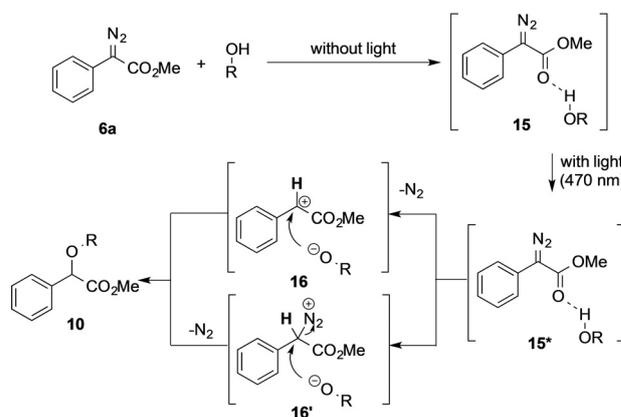
We then set out to study competition experiments to understand if the reaction proceeds through a proton- or carbene-transfer mechanism. Probing the reaction of methyl



Scheme 2. Control experiments: a) Labeling studies with deuterated HFIP and TFE, b) reaction without the possibility of hydrogen bonding, c) experiments to probe a potential inter- or intramolecular carbene-transfer reaction.

phenyldiazoacetate (**6a**) with HFIP and other halogenated alcohols in the presence of styrene as a carbene-trapping reagent led to only small amounts of the cyclopropane product **14** being obtained (for details see Table S3). Only the cyclopropane product was observed when *i*PrOH was used under the same conditions.^[19] Next, we studied allyl and homoallyl phenyldiazoacetate (**6b/c**), but no intramolecular cyclopropanation reaction occurred. Only the reaction with HFIP took place in high yield (**10b/c**, Scheme 2c). These observations are indicative of a proton-transfer mechanism taking place in this transformation.

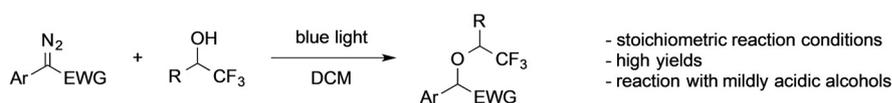
The above data now provide basic experimental evidence of a reaction mechanism involving the initial formation of a hydrogen-bonded complex **15** of the reactant. Irradiation of this complex with visible light delivered a photoexcited complex **15***, which can then act as a photobase and readily deprotonate mildly X-H-acidic reaction partners. This process can then result in the formation of ion pair **16** with concomitant extrusion of nitrogen gas or in the formation of ion pair **16'**. Both ion pairs then undergo a rapid nucleophilic substitution reaction to afford the reaction product **10** (Scheme 3).



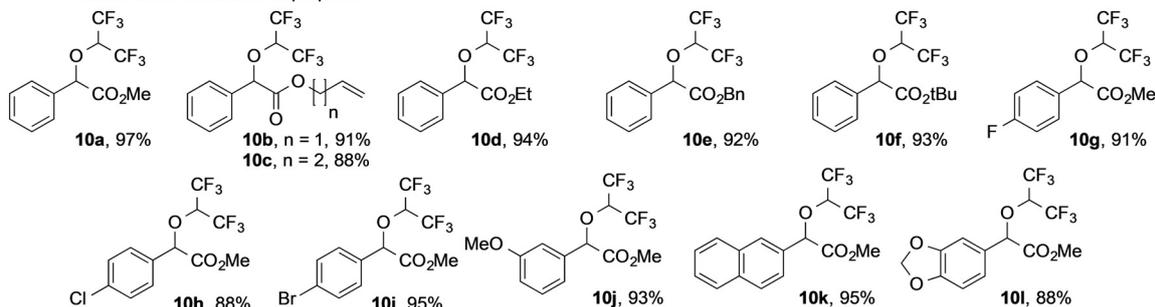
Scheme 3. Hypothesized reaction mechanism.

In subsequent investigations we probed the generality of this transformation. We set out to first investigate the stoichiometric reaction of aryl diazoacetates with HFIP, trifluoroethanol, and difluoroethanol, and were delighted to observe that the desired O-H functionalization products were isolated in all cases in excellent yield (Scheme 4, **10a–I**, **11a–h**, **12a–h**). In the majority of examples using HFIP and trifluoroethanol, no further purification was needed, which underlines the high efficiency of this photoinduced proton-transfer process. Difluoroethanol reacted similarly, but purification of the final compound by column chromatography and a slight excess (3 equiv) of the alcohol was required. TFE and DFE proved unreactive only in the case of *ortho*-substituted aryl diazoacetate, and only a small amount of product (< 10%) was observed by NMR spectroscopy (Scheme 4, **11i**, **12i**).

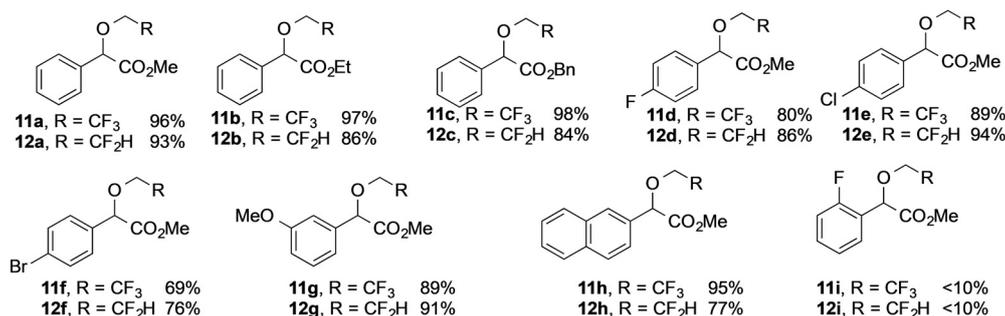
We next studied different substitution patterns of fluorinated alcohols. Perfluorinated alcohols and substituted trifluoromethylated alcohols underwent the photoinduced



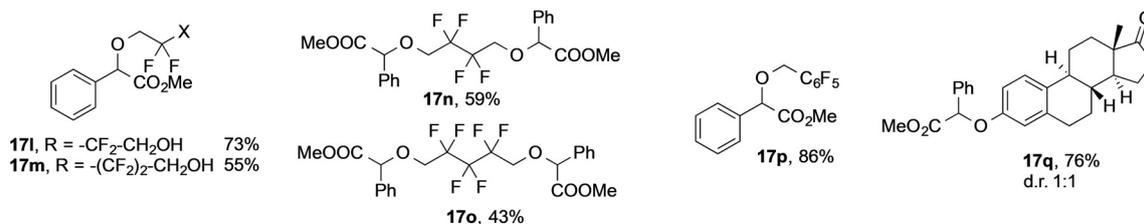
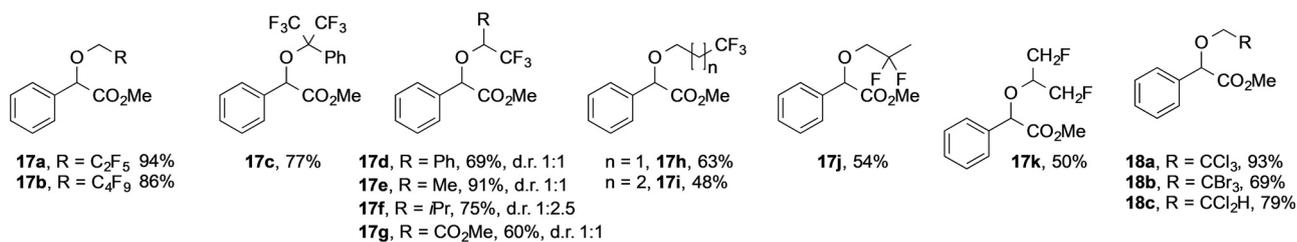
reaction with hexafluoro isopropanol



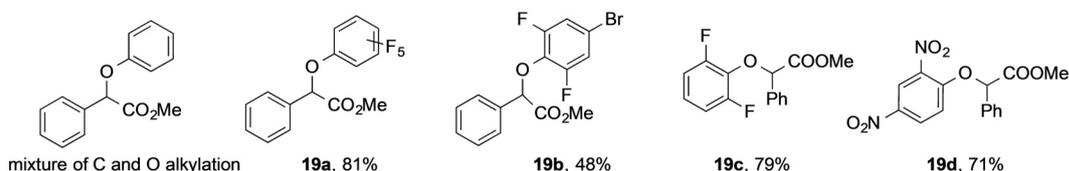
reaction with trifluoro and difluoro ethanol



reaction with halogenated alcohols



reaction with phenols

**Scheme 4.** Substrate scope of the photoinduced proton-transfer reactions of aryl diazoacetates with alcohols.

proton-transfer reaction in good to high yield (Scheme 4, **17a–q**). Importantly, even a sterically highly demanding tertiary alcohol reacted smoothly to afford the desired fluorinated ether **17c**. Similarly, the bis(monofluoromethyl)-

substituted alcohol reacted to give ether **17k** in good yield. It is noteworthy that the trifluoromethyl group can also be moved to the terminal position, with 3,3,3-trifluoro-propan-1-ol reacting to afford the desired reaction product **17h** in

moderate yield. Diols can be transformed into either the mono- or difunctionalized products in moderate to good yield, depending on the reaction stoichiometry (Scheme 4, **17l–o**). The efficiency of this proton transfer is also underlined by the reaction of one example of a tertiary fluorinated alcohol giving the desired ether **17c** in good yield.

This reaction can further be performed using chlorinated and brominated alcohols and the corresponding ethers were isolated in moderate to good yield (Scheme 4, **18a–c**). Phenol reacted readily, but gave a complex mixture of O-H and C-H functionalization products. After blocking the *ortho* and/or *para* positions of the aromatic ring with substituents, the desired O-H functionalization product of phenol was obtained in moderate to high yield (Scheme 4, **19a–d**).

In summary, we herein report photoinduced proton-transfer reactions that open up a new reactivity for aryl diazoacetates. The ester functional group reacts with mildly acidic fluorinated alcohols to form an unreactive hydrogen-bonded complex. Photoexcitation of this complex leads to a concomitant photoinduced proton-transfer reaction, followed by nucleophilic substitution to give the ether product. This hydrogen bond was identified by NMR spectroscopy, and further control experiments underpinned the importance of this hydrogen bond for high reaction efficiency, with a carbene transfer mechanism being unlikely. We studied the generality and applicability of this reaction by using diverse fluorinated and other halogenated alcohols and could obtain the desired reaction products in high yields (54 examples, up to 98% yield).

Acknowledgements

We thank the German Science Foundation, Dean's Seed Fund of RWTH Aachen, and the Boehringer Ingelheim Foundation for financial support. We thank Dr. T. Vinh Nguyen (UNSW Sydney), Prof. Frederic W. Patureau (RWTH Aachen), and Prof. Markus Albrecht (RWTH Aachen) for helpful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: diazoalkanes · fluorine · O-H functionalization · photobases · photochemistry

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 5562–5566
Angew. Chem. **2020**, *132*, 5608–5613

- [1] a) M. D. Kärkäs, J. A. Porco, Jr., C. R. J. Stephenson, *Chem. Rev.* **2016**, *116*, 9683–9747; b) T. P. Nicholls, D. Leonori, A. C. Bissember, *Nat. Prod. Rep.* **2016**, *33*, 1248–1254; c) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; d) L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018**, *57*, 10034–10072; *Angew. Chem.* **2018**, *130*, 10188–10228.

- [2] a) P. Wan, D. Shukla, *Chem. Rev.* **1993**, *93*, 571–584; b) A. C. Sedgwick, L. Wu, H.-H. Han, S. D. Bull, X.-P. He, T. D. James, J. L. Sessler, B. Z. Tang, H. Tian, J. Song, *Chem. Soc. Rev.* **2018**, *47*, 8842–8880.
- [3] J. R. Hunt, C. Tseng, J. M. Dawlaty, *Faraday Discuss.* **2019**, *216*, 252–268.
- [4] a) E. W. Driscoll, J. R. Hunt, J. M. Dawlaty, *J. Phys. Chem. Lett.* **2016**, *7*, 2093–2099; b) J. R. Hunt, J. M. Dawlaty, *J. Phys. Chem. A* **2018**, *122*, 7931–7940; c) I. Demianets, J. R. Hunt, J. M. Dawlaty, T. J. Williams, *Organometallics* **2019**, *38*, 200–204; d) W. Sheng, M. Nairat, P. D. Pawlaczyk, E. Morczka, B. Farris, E. Pines, J. H. Geiger, B. Borhan, M. Dantus, *Angew. Chem. Int. Ed.* **2018**, *57*, 14742–14746; *Angew. Chem.* **2018**, *130*, 14958–14962.
- [5] a) D. Rimmerman, D. Leshchev, D. J. Hsu, J. Hong, B. Abraham, R. Henning, I. Kosheleva, L. X. Chen, *J. Phys. Chem. B* **2019**, *123*, 2016–2021; b) N. Amdursky, *Phys. Chem. Chem. Phys.* **2015**, *17*, 32023–32032; c) B. Cohen, C. Alvarez Martin, N. Alarcos Carmona, J. A. Organero, A. Douhal, *J. Phys. Chem. B* **2011**, *115*, 7637–7647.
- [6] R. M. D. Nunes, M. Pineiro, L. G. Arnault, *J. Am. Chem. Soc.* **2009**, *131*, 9456–9462.
- [7] Y. Li, X. Feng, A. Wang, Y. Yang, J. Fei, B. Sun, Y. Jia, J. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 796–800; *Angew. Chem.* **2019**, *131*, 806–810.
- [8] A. Das, S. Ayad, K. Hanson, *Org. Lett.* **2016**, *18*, 5416–5419.
- [9] Z. M. Salem, J. Saway, J. J. Badilo, *Org. Lett.* **2019**, *21*, 8528–8532.
- [10] a) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie, Q.-L. Zhou, *Nat. Chem.* **2010**, *2*, 546–551; b) Y. Zhang, Y. Yao, L. He, Y. Liu, L. Shi, *Adv. Synth. Catal.* **2017**, *359*, 2754–2761; c) X.-L. Xie, S.-F. Zhu, J.-X. Guo, Y. Cai, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 2978–2981; *Angew. Chem.* **2014**, *126*, 3022–3025.
- [11] I. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.
- [12] S. K. Sinha, T. Bhattacharya, D. Maiti, *React. Chem. Eng.* **2019**, *4*, 244–253.
- [13] Selected examples: a) X. Creary, C. C. Geiger, *J. Am. Chem. Soc.* **1982**, *104*, 4151–4162; b) D. Bonnet-Delpon, C. Cambillau, M. Charpentier-Morize, R. Jacquot, D. Mesurer, M. Ourevitch, *J. Org. Chem.* **1988**, *53*, 754–759; c) A. Di Salvo, M. David, B. Crousse, D. Bonnet-Delpon, *Adv. Synth. Catal.* **2006**, *348*, 118–124.
- [14] Y. Imada, J. L. Röckl, A. Wiebe, T. Gieshoff, D. Schollmeyer, J. Chiba, R. Franke, S. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 12136–12140; *Angew. Chem.* **2018**, *130*, 12312–12317.
- [15] Selected review articles: a) L. W. Ciszewski, K. Rybicka-Jasińska, D. Gryko, *Org. Biomol. Chem.* **2019**, *17*, 432–448; b) C. Empel, R. M. Koenigs, *Synlett* **2019**, *30*, 1929–1934.
- [16] E. E. Gray, M. K. Nielsen, K. A. Choquette, J. A. Kalow, T. J. A. Graham, A. G. Doyle, *J. Am. Chem. Soc.* **2016**, *138*, 10802–10805.
- [17] a) C. Pecile, A. Föffani, S. Gherseti, *Tetrahedron* **1964**, *20*, 823–829; b) R. Cataliotti, S. Sorriso, G. Paliani, *Can. J. Chem.* **1976**, *54*, 2445–2450; c) J. F. McGravity, *Helv. Chim. Acta* **1980**, *63*, 1767–1778.
- [18] N. Fei, B. Sauter, D. Gillingham, *Chem. Commun.* **2016**, *52*, 7501–7504.
- [19] For details, please see the Supporting Information.

Manuscript received: November 27, 2019

Revised manuscript received: December 26, 2019

Accepted manuscript online: December 27, 2019

Version of record online: February 25, 2020