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The development of efficient carbene transfer reactions under mild reaction conditions is very important to access small molecules for applications in organic synthesis and drug discovery. Herein, we describe the application of blue light in photochemical carbene transfer reactions of donor acceptor diazoalkanes under mild reaction conditions with propargylic alcohols, which provides – in contrast to conventional metal-catalyzed carbene transfer reactions – an access to cyclopropenes.

Carbene transfer reactions are an important fundamental transformation in organic synthesis and open up different reactivity patterns ranging from cycloadditions, insertion reactions to rearrangement reactions.^{1–4} Today, the majority of these carbene transfer processes are conducted in the presence of expensive precious metal^{1–3} catalysts and more lately catalysts based earth-abundant iron or cobalt have emerged as a sustainable alternative.⁴ Most of these transformations require the strict exclusion of moisture and air, which is far from being operationally simple.

The UV photolysis of diazoalkanes is a classical alternative to metal-catalyzed carbene transfer reactions, yet applications are very limited due to side reactions related to the high energy UV light.⁴ Although diazoalkanes are intensely colored and absorb light in the visible region, the application of low-energy visible light as a sustainable and metal-free alternative to carbene transfer reactions has received only little interest until now.^{5–9} Only recently, the Davies,⁷ He⁸ and our group⁹ reported on the use of low-energy blue light to liberate carbenes from donor–acceptor diazoalkanes for applications cycloaddition, X–H and C–H insertion, olefination and Doyle–Kirmse rearrangement reactions. Most remarkably, visible light mediated carbene transfer reactions are operationally very straightforward can be conducted using simple p.A. grade solvents in the presence of air without the need of any additional precautions.⁹

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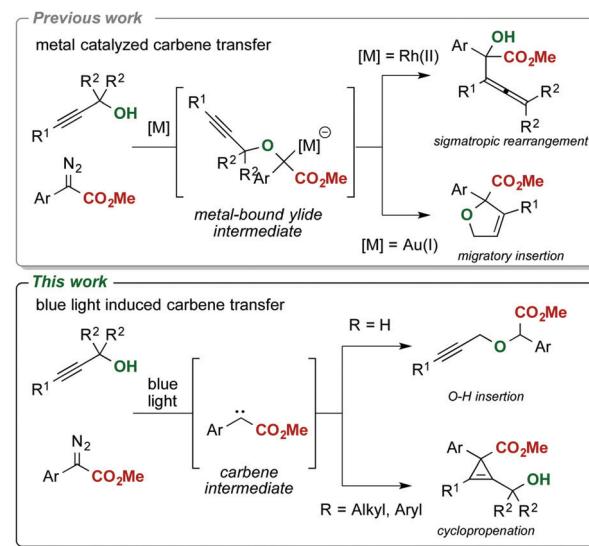
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9cc00927b

Visible light mediated, metal-free carbene transfer reactions of diazoalkanes with propargylic alcohols†

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The carbene transfer reaction of diazoalkanes with propargylic alcohols is a valuable transformation to access a variety of different rearrangement reactions.^{10,11} To date, different gold(I),^{10a} palladium(II)^{10b} and rhodium(II)^{10c} catalysts have been described in this transformation and provide, depending on the nature of the catalyst, an access to alkenes^{10c} or dihydrofurans.^{10a,b} Mechanistically, these rearrangements proceed *via* formation of a metal carbene complex that delivers an electrophilic metal-bound carbene to the nucleophilic alcohol substrate under formation of an ylide intermediate, which undergoes either a 2,3-sigmatropic rearrangement or a migratory insertion reaction (Scheme 1a and b).

Against this background and building on our experience in carbene transfer reactions,¹² we became intrigued in studying the reaction of propargylic alcohols with diazoalkanes under irradiation with low-energy blue light and set out our studies by examining the reaction of propargylic alcohols with donor–acceptor diazoalkanes.



Scheme 1 Reaction of propargylic alcohols with metal carbene complexes and free carbenes.

Table 1 Reaction optimization

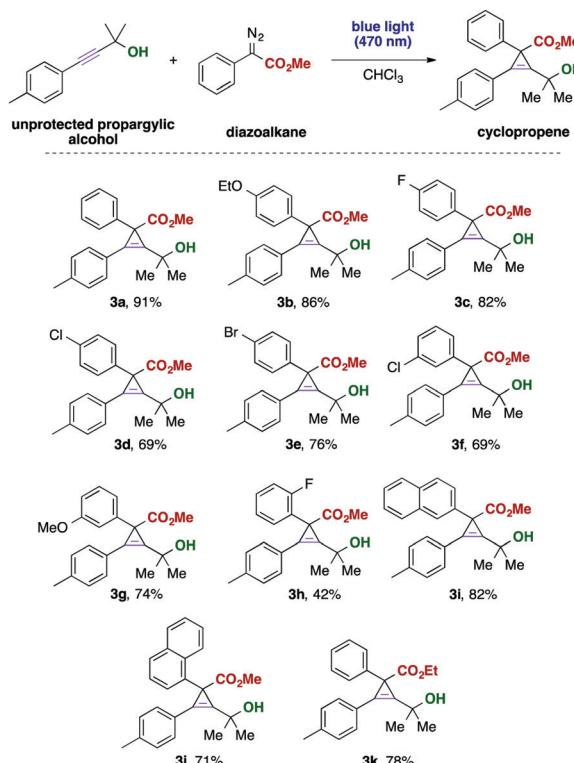
| # ^a | Solvent | R ¹ | R ² | Substrate | Ratio 1 : 2 | Yield (3) | Yield (4) |
|-----------------|-------------------|----------------|----------------|-----------|-------------|-----------|-----------|
| 1 | DCE | Me | Me | 1a | 1 : 1 | 51% | — |
| 2 | DCE | Me | Me | 1a | 1 : 2 | 82% | — |
| 3 | DCE | Me | Me | 1a | 1 : 4 | 86% | — |
| 4 | DCE | Me | Me | 1a | 4 : 1 | 59% | — |
| 5 | EtOAc | Me | Me | 1a | 1 : 4 | 71% | — |
| 6 | THF | Me | Me | 1a | 1 : 4 | Traces | — |
| 7 | DCM | Me | Me | 1a | 1 : 4 | 86% | — |
| 8 | CHCl ₃ | Me | Me | 1a | 1 : 4 | 91% | — |
| 9 ^b | CHCl ₃ | Me | Me | 1a | 1 : 4 | 82% | — |
| 10 | Hexane | Me | Me | 1a | 1 : 4 | 44% | — |
| 11 | Toluene | Me | Me | 1a | 1 : 4 | 55% | — |
| 12 | CHCl ₃ | H | H | 1b | 1 : 4 | — | 54% |
| 13 | CHCl ₃ | Me | H | 1c | 1 : 4 | 53% | — |
| 14 ^c | CHCl ₃ | Me | Me | 1a | 1 : 4 | no ret. | — |

^a Propargyl alcohol 1a-c (0.3 mmol) and diazoalkane 2 (2.0 eq., 0.4 mmol) were dissolved in 3 mL of solvent and stirred at room temperature for 12 hours under irradiation with blue LEDs (470 nm, 3 W). Yields were reported for isolated products. ^b Reaction scale: 10 mmol. ^c Reaction in the dark.

Surprisingly, we observed a markedly altered reactivity in this metal-free transformation and could observe a highly chemoselective cyclopropanation reaction of the tertiary alcohol 1a (Table 1, entry 1). The formation of this tetra-substituted cyclopropene is remarkable; in general, cyclopropanation reactions¹³⁻¹⁹ can be readily performed in the presence of different Rh(II),¹⁴ Au(I),¹⁵ Ir(III),¹⁶ Ag(I)¹⁷ or other precious metal based catalysts, yet applications are mostly limited towards alkynes bearing only a single sterically demanding substituent. In particular, a systematic study on the synthesis of such densely substituted cyclopropenes bearing an adjacent fully substituted carbon atom is not reported even today. Initial applications, dating back to 1960 describe limited examples of photocatalytic cyclopropanation reactions, yet limited in both substrate scope and yield.²⁰

Inspired by these unexpected observations, we decided to study the influence of reaction parameters, such as stoichiometry and solvent to alter the course of the reaction. Under optimized conditions, cyclopropene 3a could be obtained using propargyl alcohol 1a in excellent yield using chloroform as solvent without the need of alcohol protection, including the gram-scale application (Table 1, entry 9). In a control experiment in the dark, no reaction was observed (Table 1, entry 14).

Notably, we were unable to observe the formation of the O-H insertion product 4 or identify any product arising from a rearrangement reaction under all reaction conditions investigated. This observation emphasizes important differences in reactivity of light-mediated and metal-catalyzed carbene transfer reactions and highlights complementary reactivities of these carbene species. Switching to the primary alcohol 1b resulted in

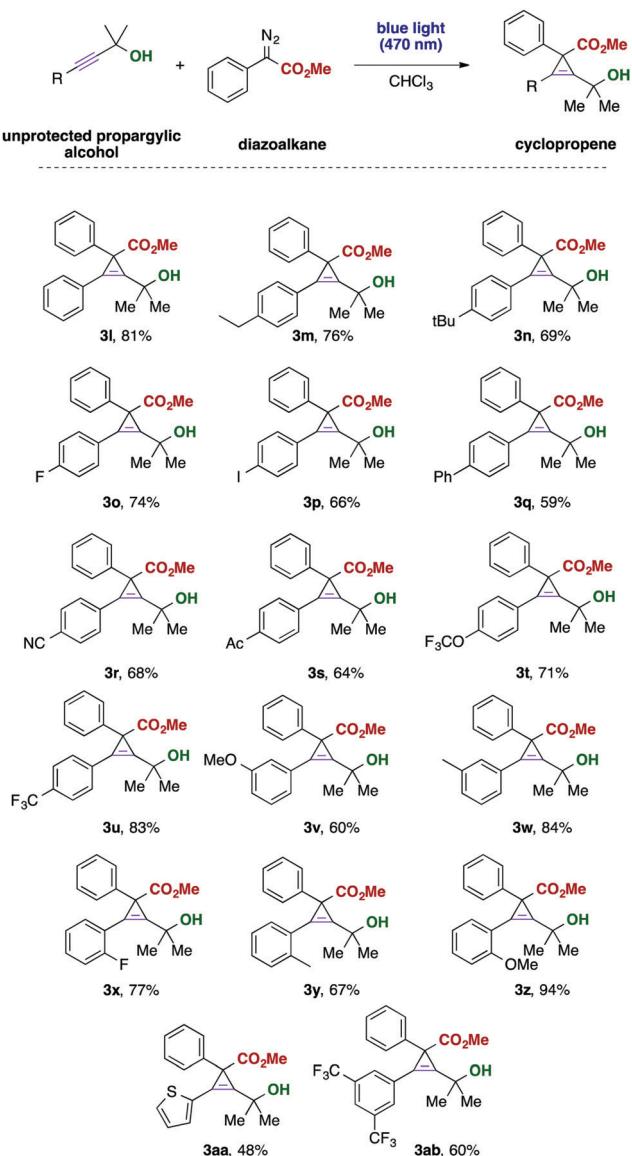


Scheme 2 Visible light mediated carbene transfer reactions with propargylic alcohols. Propargyl alcohol 1a (0.3 mmol) and diazoalkane (4.0 eq., 1.2 mmol) were dissolved in 3 mL of CHCl₃ and stirred at room temperature for 12 hours under irradiation with blue LEDs (470 nm, 3 W). Yields were reported for isolated products.

exclusive formation of the propargylic ether 4 via O-H insertion of the carbene intermediate without formation of the cyclopropene or rearrangement product (Table 1, entry 12). The secondary alcohol 1c, however, reacted under formation of the cyclopropene product and formation of both diastereoisomers in a 1 : 1 mixture (Table 1, entry 13). Protection of the alcohol as a methyl ether or a silyl ether resulted in no product formation. Cinnamyl alcohols did not undergo the respective cyclopropanation product in satisfactory selectivity and provided either no cyclopropanation or only sluggish cyclopropanation reactions.²¹

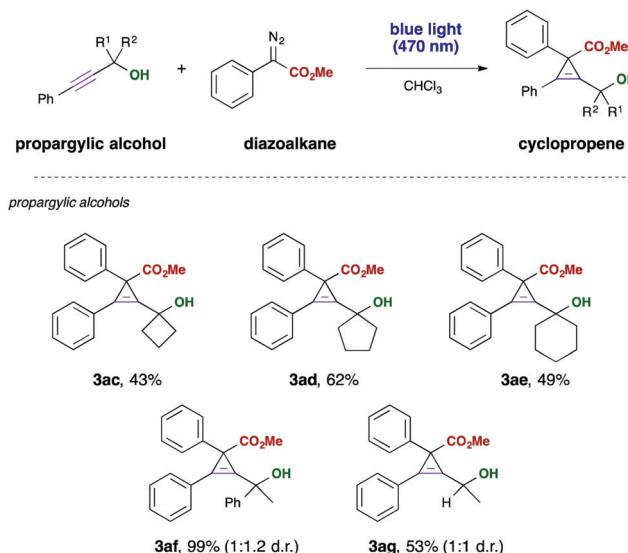
In subsequent investigations, we examined the applicability of different donor-acceptor diazoalkanes in this cyclopropanation reaction of unprotected propargylic alcohols. Different electron-donating substituents and halogens in *para*- and *meta*-positions of the aromatic ring were well-tolerated. In the case of an *ortho* substitution of the aromatic ring of the aryl diazoacetate, the yield of the corresponding cyclopropene was only moderate, which might be attributed to overcrowding due to the high steric demand of the alkyne substrate and the carbene reaction partner. Similarly, different carbocycles were tolerated or ester diazoalkanes (Scheme 2). Importantly, trifluoromethyl-substituted donor-acceptor diazoalkanes reacted sluggishly to the corresponding cyclopropene and only a mixture of compounds could be obtained.

Subsequently, we examined the substrate scope of unprotected propargylic alcohols. Gratifyingly, a broad range of functional



Scheme 3 Investigations with different propargylic alcohols. Propargyl alcohol **1** (0.3 mmol) and diazoalkane **2** (4.0 eq., 1.2 mmol) were dissolved in 3 mL of CHCl_3 and stirred at room temperature for 12 hours under irradiation with blue LEDs (470 nm, 3 W). Yields were reported for isolated products.

groups is compatible with the present reaction conditions and the desired cyclopropenes were isolated in good yields. Even reactive and labile or strongly electron-withdrawing and thus deactivating functional groups, such as iodide (**3p**), nitrile (**3r**), trifluoromethoxy (**3t**) or an acetyl (**3s**) group, are well tolerated and the desired cyclopropenes could be obtained as the only product. The position of the substituent at the aromatic ring only had a minor effect on the reaction outcome and in all cases the desired products were obtained in good yield. Interestingly, also heterocyclic alkynes, such as the thiophene substrate (Scheme 3, **3aa**) smoothly reacted to the desired cyclopropene without formation of unwanted byproducts.



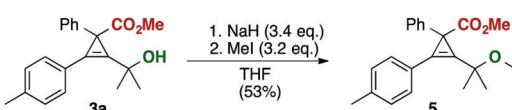
Scheme 4 Investigations on with different substitution patterns at the alcohol position. Propargyl alcohol **1** (0.3 mmol) and diazoalkane **2** (4.0 eq., 1.2 mmol) were dissolved in 3 mL of CHCl_3 and stirred at room temperature for 12 hours under irradiation with blue LEDs (470 nm, 3 W). Yields were reported for isolated products.

Finally, we investigated different aliphatic substituents at the propargyl moiety. Different cyclic substrates reacted in this visible light mediated cyclopropanation reaction with moderate yield, giving access to interesting polycyclic building blocks containing one tetra-substituted cyclopropene ring. We furthermore examined a phenyl, methyl disubstituted alkyne, which gave the desired cyclopropene in almost quantitative yield, yet the product was obtained only in a 1:1 diastereomeric mixture (Scheme 4).

Finally, we examined the derivatization of the cyclopropene **3a** in methylation reactions. Using sodium hydride as a base, the methylation product **5** was obtained in 53% yield (Scheme 5).

In summary, we herein report on photochemical carbene transfer reactions that open up orthogonal reaction pathways to metal-catalyzed carbene transfer reactions. Under metal-free conditions and without the need to exclude moisture or air, diazoalkanes readily undergo a high-yielding photochemical cyclopropanation reaction with sterically demanding propargylic alcohols, which underlines the unique reactivity of carbenes generated under photochemical conditions. Under the present reaction conditions, a broad variety of functional groups are well tolerated and tetra-substituted cyclopropenes (33 examples) can be accessed in up to 99% isolated yield.

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Scheme 5 Reaction of propargylic alcohols with metal carbene complexes and free carbenes.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- Selected review articles: (a) H. M. L. Davies and J. R. Manning, *Nature*, 2018, **451**, 417; (b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981; (c) M. P. Doyle, R. Duffy, M. Ratnikov and Z. Zhou, *Chem. Rev.*, 2010, **110**, 704; (d) L. Mertens and R. M. Koenigs, *Org. Biomol. Chem.*, 2016, **14**, 10547; (e) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810; (f) K. J. Hock and R. M. Koenigs, *Angew. Chem., Int. Ed.*, 2017, **56**, 13566; (g) Z. Sheng, Z. Zhang, C. Chu, Y. Zhang and J. Wang, *Tetrahedron*, 2017, **73**, 4011.
- Selected review articles: (a) H.-J. Knölker and I. Bauer, *Chem. Rev.*, 2015, **115**, 3170; (b) S.-F. Zhu and Q.-L. Zhou, *Natl. Sci. Rev.*, 2014, **1**, 580; (c) R. Shang, L. Ilies and E. Nakamura, *Chem. Rev.*, 2017, **117**, 9086; (d) O. F. Brandenberg, R. Fasan and F. H. Arnold, *Curr. Opin. Biotechnol.*, 2017, **47**, 102.
- Selected references: (a) B. Morandi and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 938; (b) M. S. Holzwarth, I. Alt and B. Pliethke, *Angew. Chem., Int. Ed.*, 2012, **51**, 5351; (c) J. Day, B. McKeever-Abbas and J. Dowden, *Angew. Chem., Int. Ed.*, 2016, **55**, 5809; (d) J. R. Griffin, C. I. Wendell, J. A. Garwin and M. C. White, *J. Am. Chem. Soc.*, 2017, **139**, 13624; (e) D. M. Carminati, D. Intrieri, A. Caselli, S. Le Gac, B. Boitrel, L. Toma, L. Legnani and E. Gallo, *Chem. - Eur. J.*, 2016, **22**, 13599; (f) K. J. Hock, L. Mertens, R. Hommelsheim, R. Spitzner and R. M. Koenigs, *Chem. Commun.*, 2017, **53**, 6577; (g) C. Empel, K. J. Hock and R. M. Koenigs, *Org. Biomol. Chem.*, 2018, **16**, 7129; (h) C. Empel, K. J. Hock and R. M. Koenigs, *Chem. Commun.*, 2019, **55**, 338.
- Selected references: (a) N. R. Candeias and C. A. M. Afonso, *Curr. Org. Chem.*, 2009, **13**, 763; (b) O. S. Galkina and L. L. Rodina, *Russ. Chem. Rev.*, 2016, **85**, 537; (c) J. Brunner, H. Senn and F. M. Richards, *J. Biol. Chem.*, 1980, **255**, 3313; (d) Y. Liang, L. Jiao, S. Zhang and J. Xu, *J. Org. Chem.*, 2005, **70**, 334; (e) J. Wang, G. Burdzinski, J. Kubicki and M. S. Platz, *J. Am. Chem. Soc.*, 2008, **130**, 11195; (f) K. Nakatani, S. Maekawa, K. Tanabe and I. Saito, *J. Am. Chem. Soc.*, 1995, **117**, 10635.
- L. W. Ciszewski, K. Rybicka-Jasińska and D. Gryko, *Org. Biomol. Chem.*, 2019, **17**, 432.
- Selected references on metal-free carbene transfer reactions: (a) Z. Wang, A. G. Herraiz, A. M. del Hoyo and M. G. Suero, *Nature*, 2018, **554**, 86; (b) Z. Liu, H. Tan, L. Wang, T. Fu, Y. Xia, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 3056; (c) Y. Zheng, R. Bian, X. Zhang, R. Yao, L. Qiu, X. Bao and X. Xu, *Eur. J. Org. Chem.*, 2016, 3872; (d) C. Tortoreto, D. Rackl and H. M. L. Davies, *Org. Lett.*, 2017, **19**, 770; (e) X. Zhang, Y. Zheng, L. Qiu and X. Xu, *Org. Biomol. Chem.*, 2017, **16**, 70; (f) Y. S. Vaske, M. E. Mahoney, J. P. Konopelski, D. L. Rogow and W. J. McDonald, *J. Am. Chem. Soc.*, 2010, **132**, 11379.
- I. Jurberg and H. M. L. Davies, *Chem. Sci.*, 2018, **9**, 5112.
- T. Xiao, M. Mei, Y. He and L. Zhou, *Chem. Commun.*, 2018, **54**, 8865.
- (a) R. Hommelsheim, Y. Guo, Z. Yang, C. Empel and R. M. Koenigs, *Angew. Chem., Int. Ed.*, 2019, **58**, 1203; (b) S. Jana and R. M. Koenigs, *Asian J. Org. Chem.*, DOI: 10.1002/ajoc.201900099; (c) Z. Yang, Y. Guo and R. M. Koenigs, *Chem. - Eur. J.*, DOI: 10.1002/chem.201900597.
- Selected references on rearrangement reactions: with Au catalysts: (a) J. Wang, X. Yao, T. Wang, J. Han, J. Zhang, X. Zhang, P. Wang and Z. Zhang, *Org. Lett.*, 2015, **17**, 5124; with Pd catalysts: (b) J. Wang, X. Yao, T. Wang, J. Han, J. Zhang, X. Zhang, P. Wang and Z. Zhang, *Chem. Commun.*, 2015, **51**, 15204. With Rh catalysts: (c) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 15497.
- Selected further references: (a) Y. Sha, S. Feng, Z. Liu, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 7891; (b) Z.-S. Chen, X.-H. Duan, P.-X. Zhou, S. Ali, J.-Y. Luo and Y.-M. Liang, *Angew. Chem., Int. Ed.*, 2012, **51**, 1370.
- Selected references on our work: (a) K. J. Hock, A. Knorrseidt, R. Hommelsheim, J. Ho, M. Weissenborn and R. M. Koenigs, *Angew. Chem., Int. Ed.*, 2019, **58**, 3660; (b) K. J. Hock, L. Mertens and R. M. Koenigs, *Chem. Commun.*, 2016, **52**, 13783.
- Selected review articles: (a) M. Rubin, M. Rubina and V. Gevorgyan, *Synthesis*, 2006, 1221; (b) I. Marek, S. Simaan and A. Masarwa, *Angew. Chem., Int. Ed.*, 2007, **46**, 7364.
- References on cyclopropenation reactions of alkynes using Rh catalysts: (a) J. F. Briones and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 11916; (b) T. Goto, K. Takeda, N. Shimada, H. Nambu, M. Anada, M. Shiro, K. Ando and S. Hashimoto, *Angew. Chem., Int. Ed.*, 2011, **50**, 6803; (c) Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawryluk and E. J. Corey, *J. Am. Chem. Soc.*, 2004, **126**, 8916; (d) H. M. L. Davies and G. H. Lee, *Org. Lett.*, 2004, **6**, 1233; (e) M. K. Palleria and J. M. Fox, *Org. Lett.*, 2007, **9**, 5625; (f) B. Morandi and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 4294; (g) M. P. Doyle, M. Protopopova, P. Müller, D. Ene and E. A. Shapiro, *J. Am. Chem. Soc.*, 1994, **116**, 8492; (h) M. P. Doyle, D. G. Ene, C. S. Peterson and V. Lynch, *Angew. Chem., Int. Ed.*, 1999, **38**, 700; (i) S. Chuprakov and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 4463; (j) K. J. Hock, R. Spitzner and R. M. Koenigs, *Green Chem.*, 2017, **19**, 2118; (k) U. P. N. Tran, R. Hommelsheim, Z. Yang, C. Empel, K. J. Hock, T. V. Nguyen and R. M. Koenigs, *ChemRxiv*, DOI: 10.26434/chemrxiv.7545623.v1.
- Cyclopropenation reactions with Au catalysts: J. F. Briones and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 11916.
- Cyclopropenation reactions with Ir catalysts: M. Uehara, H. Suematsu, Y. Yasutomi and T. Katsuki, *J. Am. Chem. Soc.*, 2011, **133**, 170.
- Cyclopropenation reactions with Ag-catalysts: (a) J. F. Briones and H. M. L. Davies, *Org. Lett.*, 2011, **13**, 3984; (b) Z. Liu, Q. Li, P. Liao and X. Be, *Chem. - Eur. J.*, 2017, **23**, 4756.
- Other catalytic cyclopropenation reactions: (a) L. Maestre, E. Ozkal, C. Ayats, A. Beltran, M. M. Diaz-Requejo, P. J. Perez and M. A. Pericas, *Chem. Sci.*, 2015, **6**, 1510; (b) X. Cui, X. Xu, H. Lu, S. Zhu, L. Wojtas and P. X. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 3304.
- Metal-free thermal cyclopropanations: R. Barroso, A. Jimenez, M. C. Perez-Aguilar, M.-P. Cabal and C. Valdes, *Chem. Commun.*, 2016, **52**, 3677.
- Selected references: (a) W. E. von Doering and T. Mole, *Tetrahedron*, 1960, **10**, 65; (b) W. B. DeMore, H. O. Pritchard and N. Davidson, *J. Am. Chem. Soc.*, 1959, **81**, 5874.
- For details on other alcohols investigated, please see the ESI†.