EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Bromomethyl Silicate: A Robust Methylene Transfer Reagent for Radical-Polar Crossover Cyclopropanation of Alkenes

Authors: Wenping Luo, Yewen Fang, Li Zhang, Tianhang Xu, Yongjun Liu, Yan Li, Xiaoping Jin, Jiakan Bao, Xiaodong Wu, and Zongyong Zhang

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000134

Link to VoR: http://dx.doi.org/10.1002/ejoc.202000134

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.202000134

COMMUNICATION

WILEY-VCH

Bromomethyl Silicate: A Robust Methylene Transfer Reagent for Radical-Polar Crossover Cyclopropanation of Alkenes

Wenping Luo,[a] Yewen Fang,[b,*] Li Zhang,[c] Tianhang Xu,[b] Yongjun Liu,[a] Yan Li,[a,*] Xiaoping Jin,[c,*] Jiakan Bao,[b] Xiaodong Wu,[b] and Zongyong Zhang[b]

[a] W. Luo, Y. Liu, Prof. Dr. Y. Li
Hubei Collaborative Innovation Center for Advanced Organic Chemical Materials and Ministry-of-Education Key Laboratory for Synthesis and Application of Organic Functional Molecules
Hubei University
No. 368 Youyi Dadao, Wuhan 430062, China
Email: liyanok@hubu.edu.cn

[b] Prof. Dr. Y. Fang, T. Xu, J. Bao, X. Wu, Z. Zhang
School of Materials and Chemical Engineering
Ningbo University of Technology
No. 201 Fenghua Road, Ningbo 315211, China
E-mail: fang@nbut.edu.cn

[c] Dr. L. Zhang, Prof. Dr. X. Jin
Department of Pharmaceutical Engineering
Zhejiang Pharmaceutical College
No. 888 Yinxian Avenue East, Ningbo 315100, China
E-mail: jinxp@mail.zjpc.net.cn

Supporting information for this article is given via a link at the end of the document.

Abstract: A general protocol for visible-light-induced cyclopropanation of alkenes was developed with bromomethyl silicate as a methylene transfer reagent, offering a robust tool for accessing highly valuable cyclopropanes. In addition to *α*-aryl or methyl substituted Michael acceptors and styrene derivatives, the unactivated 1,1-dialkyl ethylenes were also shown to be viable substrates. Apart from realizing the cyclopropanation of terminal alkenes, the methyl transfer reaction has been furtherly demonstrated to be amenable to the internal olefines. The photocatalytic cyclopropanation of 1,3-bis(1-arylethenyl)benzenes was also achieved, giving polycyclopropane derivatives in excellent yields. With late-stage cyclopropanation as the key strategy, the synthetic utility of this transformation was also demonstrated by the total synthesis of LG100268.

Due to the facile generation and termination of radicals in sustainable way during photoredox catalysis process, photocatalytic single electron transfer (SET) reactions are becoming increasingly prevalent over the past decade.[1] Consequently, spectacular progress dealing with SET process has been achieved in the development of versatile radical precursors,[2] new photocatalysts,[3] asymmetric photoredox catalysis,[4] merging photoredox with other catalysis,[5] application of new technology,[6] and mechanism investigations.[7] Among these numerous efforts devoting to the visible-light-driven photoredox catalysis, development and application of practical and efficient organic transformations are always in high demand.[8]

Efficient strategy that allows for a rapid and selective construction of strained pharmacophores represents valuable tools for drug discovery and high throughput screenings (Figure 1).[9] Recently, we and other groups devoted significant efforts to the cyclopropanation of alkenes by means of photoredox catalysis.[10] Surprisingly, only a few general and successful methods were described concerning alkene cyclopropanation with a methylene transfer reagent. In 2017, Suero and co-workers reported a photocatalytic methodology for the stereoconvergent cyclopropanation of styrene derivatives and Michael acceptors using diiodomethane as a methylene source (Scheme 1a).[11] In contrast to the above reductive generation of iodomethyl radical, the general access of halomethyl radical was realized via oxidative SET process with halosilicate as the methylene source (Scheme 1b).[12,13] Of note, these cyclopropanation reactions based on photooxidative generation of halomethyl radical proceed efficiently via redox-neutral radical-polar crossover[14] without any aid of external additives. Due to the superior leaving group ability of iodide over bromide and chloride, the use of high reactive iodomethyl radical has more opportunities to prevent the formation of the undesired noncyclized Giese-type addition product.[13] During our recent investigation of nucleofuge character of halides, at least 10-times higher reactivity of bromide compared with chloride was observed in the 3-*exo-tet* cyclization.[12b] Furthermore, compared to chloromethyl and iodomethyl radicals, a good balance between atom economy and cyclization efficiency could be expected employing the less investigated bromomethyl radical as a bifunctional C1 reagent. With this idea in hand, we set out to explore the application of bromomethyl silicate as the CH_2 source in photoredox-catalyzed cyclopropanation of alkenes.

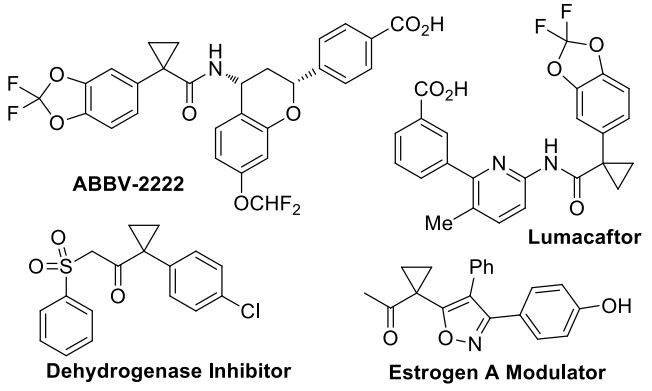
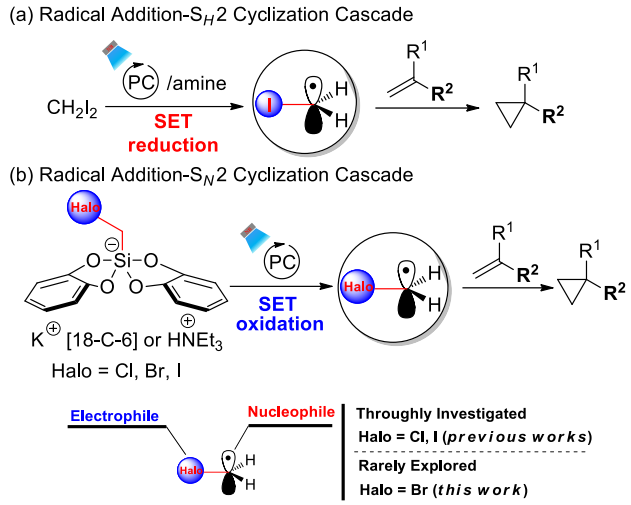
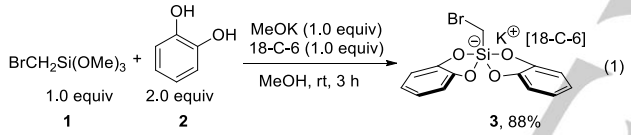


Figure 1. Examples of biologically active cyclopropane-containing molecules.



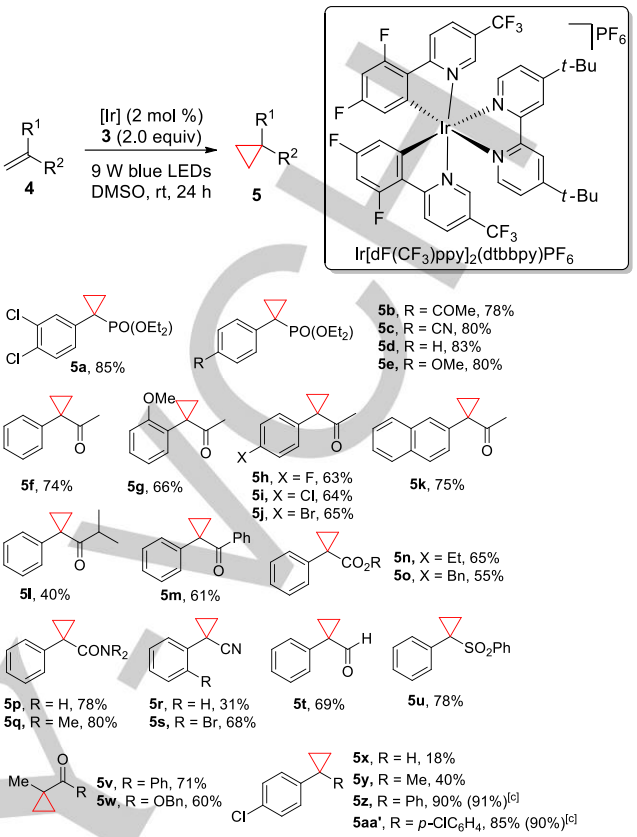
Scheme 1. Generation of halomethyl radical and the applications in cyclopropanation reactions.

Bis-catecholato bromomethyl silicate **3** was easily obtained from the reaction of the readily prepared bromomethyltrimethoxysilane **1**[13] with catechol **2** in the presence of 18-crown-6 and potassium methoxide in methanol (eq 1).[15] Bromomethyl silicate **3** was isolated in 88% yield without any chromatography as free-flowing and bench-stable powder.



With bis-catecholato bromomethyl silicate **3** in hand, photocatalytic cyclopropanation of vinylphosphonates[16] with **3** as the methylene source was initially explored for modular synthesis of cyclopropylphosphonates (Table 1). Gratifyingly, 1-aryl substituted cyclopropylphosphonates **5a-e** were cleanly prepared under our previous reported reaction conditions (2 mol % Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, 9 W blue LEDs irradiation, DMSO, 24 h). Regardless of the electron-donating or -withdrawing characters of the substituents on the aromatic ring, no contamination of the undesired noncyclized Giese-type addition product was observed.[12a] Furthermore, the protocol was extended to the access of cyclopropylketones which can be found in a number of bioactive substances by exalting crucial hydrophobic interactions.[17] In addition to the efficient formation of **5f** from 2-phenyl-1-buten-3-one, 2-methoxyphenyl substituted methyl vinyl ketone was nicely cyclopropanated to cyclopropylketone **5g** in 66% yield. Moreover, the cyclopropanaiton was also suitable for 2-aryl-1-buten-3-one containing halogens on aryl group, producing **5h-j** in 63-65% yields. 2-Naphtyl acetylcyclopropane **5k** could be efficiently accessed in 75% yield. In addition, cyclopropylketones **5l** and **5m** were prepared from 2-phenyl substituted vinyl isopropyl ketone and vinyl phenyl ketone, respectively. After realizing cyclopropanation of *α,β*-unsaturated ketones, the cyclopropanation of 2-phenyl substituted acrylates was also successful, delivering cyclopropylcarboxylates **5n-o** in 55-65%

Table 1. Cyclopropanation of Michael acceptors and styrene derivatives.[a,b]

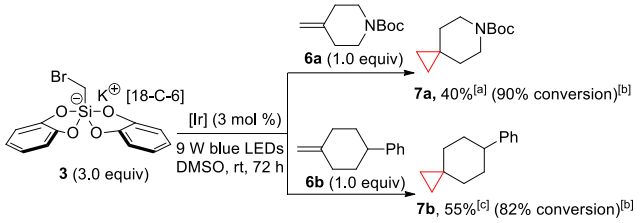


[a] *Reaction conditions*: a reaction mixture of **4** (0.2 mmol), **3** (0.4 mmol), [Ir] (2 mol %), and DMSO (6.0 mL) was irradiated by 9 W blue LEDs for 24 h at room temperature (cooling with a fan). [Ir]: Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6.

[b] Isolated yield.

[c] bis-catecholato chloromethyl silicate (2.0 equiv) was used instead of **3**.

yields. *α,β*-Unsaturated amides were converted to their cyclopropanes **5p-q** in high efficiency. Of note, compared to the formation of 1-phenylcyclopropylnitrile **5r**, higher efficiency for the preparation of **5s** containing *ortho*-bromo substituted arene was observed. Interestingly, this methylene transfer reaction could be further extended to the cyclopropanation of *α*-phenylacrolein, giving **5t** in 69% yield. Vinylsulfone also reacted with **3** to produce **5u** in 78% yield. In addition to the above *α*-aryl substituted Michael acceptors, 2-methyl-1-phenyl-2-propenone and benzyl 2-methylacrylate were also shown to be viable substrates, giving **5v** and **5w** in 71% and 60% yields, respectively. In the case of the reaction of 4-chlorostyrene derivatives, low yield of the cyclopropane product **5x** was obtained, plauged by the possible formation of polymers/oligomers. Clearly, incorporation of an alkyl or aryl substituent at the *α*-position of 4-chlorostyrene has a positive effect for the efficiency of cyclopropanation. 1,1-Diarylethylenes exceptionally worked well, affording 1,1-diaryl cyclopropanes **5z** and **5aa'** in high yields. Interestingly, chloromethyl silicate[12a] was a suitable methylene source for the cyclorpropanation of 1,1-diaryethylenes, giving **5z** and **5aa'** in 91% and 90% yields, respectively. Of note, no cyclopropanation of 1,1-diphenylethylene could be observed with CH_2I_2 as the CH_2 source via radical addition-S$_H$2 cyclization process.[11a]

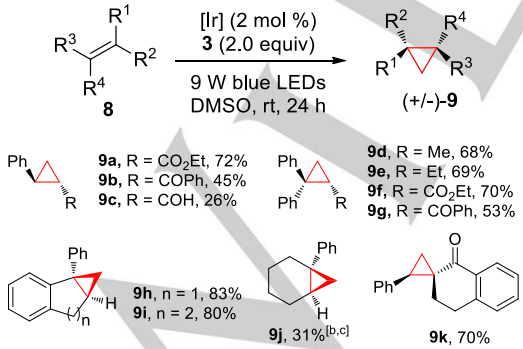


Scheme 2. Cyclopropanation of 1,1-dialkyl ethylenes. a) Isolated yield. b) The conversions given in parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture. c) NMR yield (500 MHz) was reported by use of *p*-nitroacetophenone as an internal standard.

After achieving the cyclopropanation of Michael acceptors and styrene derivatives, the unactivated 1,1-dialkyl ethylenes were subjected to the present methylene transfer reaction conditions. To the best of our knowledge, there is no literature precedent for CH_2 transfer reaction of 1,1-dialkyl ethylenes by means of photoredox catalysis. Impressively, the expected spirocyclopropanes **7a** and **7b** were accessed in good yields (Scheme 2). Unfortunately, their full conversions were not achieved by varying the reaction parameters (catalyst loading, reaction time, and equivalent of bromomethyl silicate). It is worth noting that no **7a** could be observed with chloromethyl silicate as the methylene source under similar conditions.

Apart from realizing the cyclopropanation of terminal alkenes **4** and **6**, the methyl transfer reaction has been furtherly demonstrated to be amenable to the internal olefines **8** (Table 2). Generally, the double bond geometry of **8** was retained during cyclopropanation. With (*E*)-*β*-phenyl substituted Michael acceptors as the substrate, *trans*-cyclopropanes **9a-c** were isolated in 26-72% yields. Furtherly, efficient cyclopropanation could be realized employing trisubstituted alkenes, delivering diphenyl substituted **9d-g** in 53-70% yields. As a further extension, assembling polycyclic structures bearing cyclopropyl motif was also successful, giving **9h-j** in moderate to high yields. Interestingly, spirocyclopropane **9k** was easily prepared in 70% yield. As a limitation, the tetrasubstituted 1,1-dimethyl-2,2-diphenylethene was not suitable for this cyclopropanation protocol.

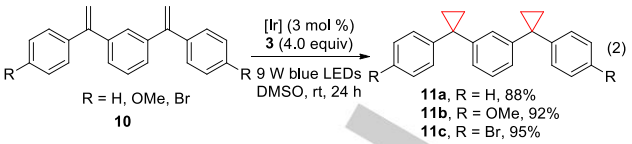
Table 2. Methylene transfer reaction of internal alkenes.[a]



[a] Isolated yield.

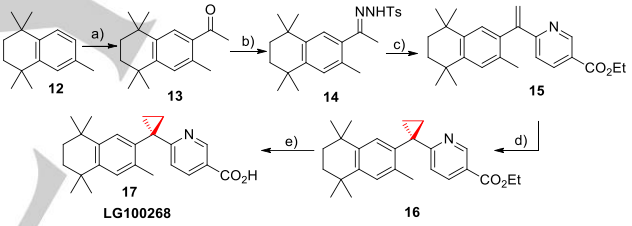
[b] The reaction was run with **3** (3.0 equiv) in the presence of [Ir] (3 mol %) for 72 h.

[c] Yield of **9j** was determined by ^{1}H NMR integration against *p*-nitroacetophenone as an internal standard.



In light of the exceptional mildness of the photocatalytic conditions, we embarked on the cyclopropanation of polyalkenes. Notably, the cyclopropanation of 1,3-bis(1-arylethenyl)benzenes **10** produced bis(cyclopropane) derivatives **11** in 88-95% yields in the presence of 3 mol% iridium catalyst with 4.0 equivalent bromomethyl silicate **3** (eq 2). These results showcase the promising application of the present protocol in the preparation of polycyclopropanes.[18]

Synthetic utility of this methylene transfer reaction has been demonstrated by the total synthesis of LG100268, being a high affinity, selective retinoid X receptor (RXR) agonist (Scheme 3).[19] The requisite *N*-tosylhydrazone **14**[20] was prepared in 2 steps with commercially available 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene **12** as the starting material. Fortunately, the coupling of hydrazone **14** with ethyl 6-bromoronicotinate furnished the expected 1,1-diarylethylene **15** in 78% yield in the presence of a catalytic amount of both $PdCl_2(CH_3CN)_2$ and *t*-Bu_2(Me)$PHBF_4$. Nicely, **15** underwent smooth cyclopropanation to give **16** in 86% yield under the standard reaction conditions. Meanwhile, chloromethyl silicate was aslo demonstrated to be viable methylene source, producing **16** in 74% yield. The LG100268 **17** was obtained in 93% yield by simple hydrolysis of the resulting diarylcyclopropane **16**.



Scheme 3. Synthesis of LG100268. Reagent and conditions: a) CH_3COCl, $AlCl_3$, CH_2Cl_2, 5 h, reflux, 96%; b) $TsNHNH_2$, CH_3OH, 2 h, reflux, 82%; c) ethyl 6-bromonicotinate, $Pd(CH_3CN)_2Cl_2$, *t*-Bu_2(Me)$PHBF_4$, *t*-BuOLi, dioxane, 90 °C, 3 h, 78%; d) **3**, [Ir], 9 W blue LEDs, DMSO, 24 h, rt, 86%; e) NaOH, MeOH, 12 h, reflux, 93%.

In conclusion, with easily accessible bromomethyl silicate as the methylene transfer reagent, cyclopropanation of an array of alkenes has been reported by means of photoredox-neutral catalysis. With radical-polar crossover process as the strategy for the cyclopropanation of alkenes, various Michael acceptors and styrene derivatives were demonstrated to be viable substrates. The unactivated electron-rich 1,1-dialkyl ethylenes were also successfully transformed into the corresponding cyclopropanes. We have also realized that this methylene transfer reaction was efficient to construct bis(cyclopropane) derivative in one pot with diene as the substrate. The reactions are operationally simple and tolerate a diversity of functional groups under photoredox-catalyzed mild conditions. New applications of bromomethyl silicate as a bifunctional C1 feedstock will be reported in due course.

Experimental Section

To an oven dried transparent 10 mL Schlenk tube equipped with stirring bar, $Ir[dF(CF_3)ppy)]_2(dtbbpy)PF_6$ (4.5 mg, 0.004 mmol, 0.02 equiv), potassium [18-C-6] bis(catecholato)bromomethylsilicate (**3**) (256.6 mg, 0.4 mmol, 2 equiv), and the corresponding alkene (0.2 mmol, 1.0 equiv) were added. The tube was evacuated and filled with nitrogen for 3 times. The tube was then charged with degassed DMSO (6.0 mL, 0.033 M) via a syringe. The tube was irradiated with a 9 W blue LED light strip spiraled within a bowel for 24 h (cooling with a fan). After the reaction was complete, the reaction solution was diluted with saturated Na_2CO_3 aqueous solution (10.0 mL), and was extracted with EtOAc (4 x 10 mL). The organic layers were combined and dried over $MgSO_4$, concentrated *in vacuo*. Flash chromatography over silica gel afforded the product.

Acknowledgements

This work was supported by the Zhejiang Provincial Natural Science Foundation of China (No. LY20B020008), the Ningbo Natural Science Foundation (Nos. 2019A610130 and 2019A610203), Science and Technology Innovation 2025 Major Project of Ningbo (No. 2019B10112), and the National Training Programs for Innovation and Entrepreneurship for Undergraduates. The authors acknowledge Professor Chaozhong Li (SIOC) for valuable discussions.

Keywords: photoredox • bromomethyl radical • redox-neutral • radical-polar crossover • cyclopropanation

[1] For selected reviews, see: a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363; b) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617-1622; c) S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, 9748-9815; d) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075-10166.

[2] a) A. C. Sun, R. C. McAtee, E. J. McClain, C. R. J. Stephenson, *Synthesis* **2019**, *51*, 1063-1072; b) P.-Z. Wang, J.-R. Chen, W.-J. Xiao, *Org. Biomol. Chem.* **2019**, *17*, 6936-6951; c) J.-P. Goddard, C. Ollivier, L. Fensterbank, *Acc. Chem. Res.* **2016**, *49*, 1924-1936; d) J. K. Matsui, S. B. Lang, D. R. Heitz, G. A. Molander, *ACS Catal.* **2017**, *7*, 2563-2575.

[3] a) D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688-6699; b) J. Ma, X. Zhang, X. Huang, S. Luo, E. Meggers, *Nat. Protoc.* **2018**, *13*, 605-632; c) C. B. Kelly, N. R. Patel, D. N. Primer, M. Jouffroy, J. C. Tellis, G. A. Molander, *Nat. Protoc.* **2017**, *12*, 472-492; d) J. Luo, J. Zhang, *ACS Catal.* **2016**, *6*, 873-877.

[4] a) X. Huang, E. Meggers, *Acc. Chem. Res.* **2019**, *52*, 833-847; b) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41-49.

[5] a) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035-10074; b) J. A. Milligan, J. P. Phelan, S. O. Badir, G. A. Molander, *Angew. Chem. Int. Ed.* **2019**, *58*, 6152-6163; *Angew. Chem.* **2019**, *131*, 6212-6224.

[6] Z. J. Garlets, J. D. Nguyen, C. R. J. Stephenson, *Isr. J. Chem.* **2014**, *54*, 351-360.

[7] a) M. A. Cismesia, T. P. Yoon, *Chem. Sci.* **2015**, *6*, 5426-5434; b) L. Buzzetti, G. E. M. Crisenza, P. Melchiorre, *Angew. Chem. Int. Ed.* **2019**, *58*, 3730-3747; *Angew. Chem.* **2019**, *131*, 3768-3786.

[8] B. König, *Eur. J. Org. Chem.* **2017**, 1979-1981.

[9] a) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651-11679; b) L. A. Wessjohann, W. Brandt, T. Thiemann, *Chem. Rev.* **2003**, *103*, 1625-1648; c) F. Brackmann, A. de Meijere, *Chem. Rev.* **2007**, *107*, 4493-4537; d) D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631-4642.

[10] A. G. Herraiz, M. G. Suero, *Synthesis* **2019**, *51*, 2821-2828.

[11] a) A. M. del Hoyo, A. G. Herraiz, M. G. Suero, *Angew. Chem. Int. Ed.* **2017**, *56*, 1610-1613; *Angew. Chem.* **2017**, *129*, 1632-1635; b) A. M. del Hoyo, M. G. Suero, *Eur. J. Org. Chem.* **2017**, 2122-2125.

[12] a) T. Guo, L. Zhang, X. Liu, Y. Fang, X. Jin, Y. Yang, Y. Li, B. Chen, M. Ouyang, *Adv. Synth. Catal.* **2018**, *360*, 4459-4463; b) W. Luo, Y. Yang, Y. Fang, X. Zhang, X. Jin, G. Zhao, L. Zhang, Y. Li, W. Zhou, T. Xia, B. Chen, *Adv. Synth. Catal.* **2019**, *361*, 4215-4221.

[13] J. P. Phelan, S. B. Lang, J. S. Compton, C. B. Kelly, R. Dykstra, O. Gutierrez, G. A. Molander, *J. Am. Chem. Soc.* **2018**, *140*, 8037-8047.

[14] L. Pitzer, J. L. Schwarz, F. Glorius, *Chem. Sci.* **2019**, *10*, 8285-8291.

[15] V. Corcé, L.-M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier, L. Fensterbank, *Angew. Chem. Int. Ed.* **2015**, *54*, 11414-11418; *Angew. Chem.* **2015**, *127*, 11576-11580.

[16] a) T. Guo, L. Zhang, Y. Fang, X. Jin, Y. Li, R. Li, X. Li, W. Cen, X. Liu, Z. Tian, *Adv. Synth. Catal.* **2018**, *360*, 1352-1357; b) L. Zhang, Y. Fang, X. Jin, H. Xu, R. Li, H. Wu, B. Chen, Y. Zhu, Y. Yang, Z. Tian, *Org. Biomol. Chem.* **2017**, *15*, 8985-8989; c) Y. Fang, L. Zhang, J. Li, X. Jin, M. Yuan, R. Li, R. Wu, J. Fang, *Org. Lett.* **2015**, *17*, 798-801.

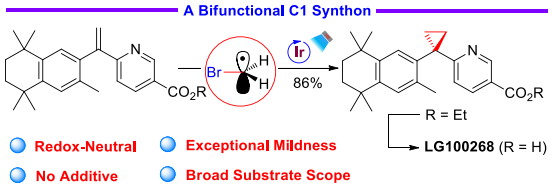
[17] A. N. Baumann, F. Schüppel, M. Eisold, A. Kreppel, R. de Vivie-Riedle, D. Didier, *J. Org. Chem.* **2018**, *83*, 4905-4921.

[18] a) G. Bojase, T. V. Nguyen, A. D. Payne, A. C. Willis, M. S. Sherburn, *Chem. Sci.* **2011**, *2*, 229-232; b) T. Kurahashi, S. I. Kozhushkov, H. Schill, K. Meindl, S. Rühl, A. de Meijere, *Angew. Chem. Int. Ed.* **2007**, *46*, 6545-6548; *Angew. Chem.* **2007**, *119*, 6665-6668.

[19] H. Yoshida, Y. Takemoto, K. Takaki, *Chem. Commun.* **2014**, *50*, 8299-8302.

[20] M. Roche, A. Hamze, O. Provot, J.-D. Brion, M. Alami, *J. Org. Chem.* **2013**, *78*, 445-454.

Cyclopropanation



A new bifunctional C1 synthon: With bromomethyl silicate as a CH_2 source, visible-light-induced cyclopropanation has been demonstrated to be amenable to the alkenes including Michael acceptors, styrene derivatives, and unactivated 1,1-dialkyl ethylenes. In addition to the broad substrate scope, this radical-polar crossover process is also characterized by its redox-neutral process , mild conditions, and good functional-group compatibility.