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Organocatalyzed Visible Light-Mediated *gem*-Borosilylcyclopropanation

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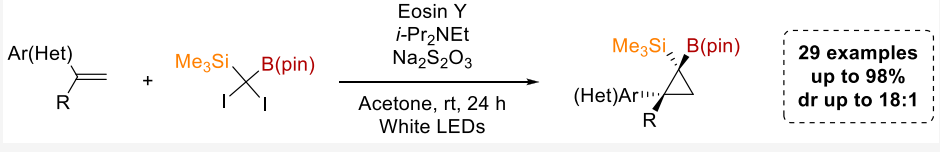


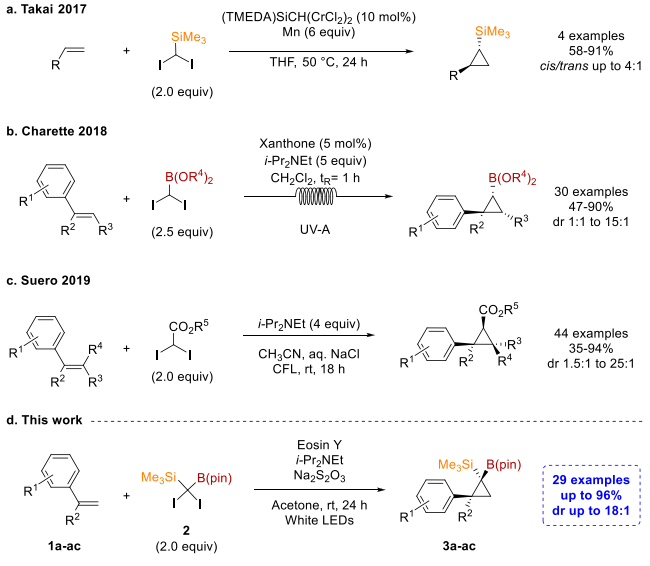
ABSTRACT: The borosilylcyclopropanation of styrene derivatives using a (diiodo(trimethylsilyl)methyl)boronic ester carbene precursor is reported herein. The key reagent was synthesized in a 4-step sequence using inexpensive and commercially available starting materials. This method enabled the preparation of novel 1,1,2-tri- and 1,1,2,2-tetrasubstituted borosilylcyclopropanes up to excellent yields and diastereoselectivity. The reaction is organocatalyzed by eosin Y in the presence of visible light. A mechanism consistent with the experimental observations was postulated based on density functional theory calculations. The versatility of these entities was highlighted through post-functionalization reactions.

INTRODUCTION

The cyclopropane moiety is an often targeted scaffold in organic and medicinal chemistry.[1] Due to its rigid three-dimensional framework with spatially distinct and well-defined substituents, this structural motif is widely prevalent in biologically active compounds.[2] Extensive effort has been made to furnish straightforward access to highly substituted cyclopropanes. Furthermore, the development of methods for their introduction into complex molecules is of significant interest.[3] Cyclopropanes are also useful synthetic handles, and boronate and silyl units are increasingly found in recent drug candidates.[4,5] For instance, boron-containing active pharmaceutical ingredients, such as bortezomib, tavaborole, and crisaborole, were approved by the FDA and European authorities in the past decades.[6] Silicon, being intrinsically non-toxic, allows the pharmacodynamic properties of drug candidates to be improved when the C−Si bond is used as a C═C bond bioisostere.[7] Novel highly substituted small ring systems, such as *gem*-borosilylcyclopropanes are attractive building blocks, and methods to access them are in demand.

From established methods, metal carbene or carbenoid transfer to alkenes is one of the most efficient approaches to prepare cyclopropanes.[4] A direct method to synthesize cyclopropylsilanes diastereoselectively was initially reported by Takai.[8a] This method employs an organochromium reagent generated from (diiodomethyl)trialkylsilane and stoichiometric amount chromium chloride. These reaction conditions were later improved to use a catalytic quantity of chromium and manganese as the stoichiometric reductant (Scheme 1a)[8b] or altered to obtain cyclopropylboronate esters.[8c] Despite the efficiency of these methods, the use of toxic chromium limits

Scheme 1. Previous Direct Cyclopropanations Using Diiodomethyl Reagents[a]



[a]TMEDA: *N,N,N′N′*-tetramethylethylenediamine; CFL: compact fluorescent lamp; pin: pinacol.

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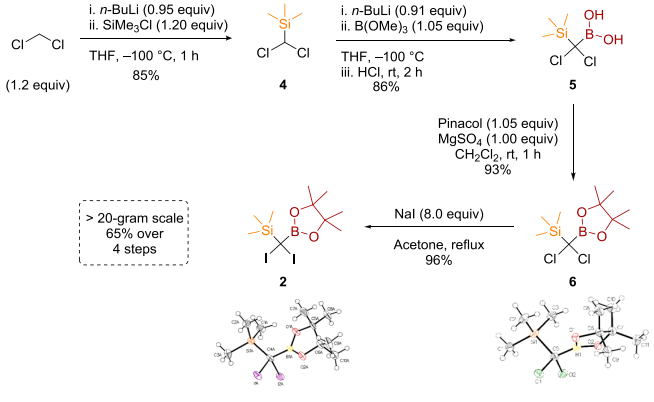
the applicability of these methods. A Simmons−Smith type borocyclopropanation was meanwhile reported where coordination of the zinc carbenoid and the allylic ether oxygen of the substrate led to excellent diastereoisomeric ratios.[9] In the last century, chemists were inspired by the blueprints of light-harvesting biomolecules found in nature, which allowed use of transition-metal complexes and organic dyes that employ photons to drive chemical transformations.[10] Photochemical methods were applied to a convenient and scalable metal-free borocyclopropanation using UVA light, an organic photocatalyst, and continuous flow technology with modest diastereoselectivity (Scheme 1b).[11] In 2019, Suero and coworkers described a photocatalyst-free light-mediated synthesis of cyclopropylcarboxylates that were obtained using a diiodomethylcarboxylate reagent (Scheme 1c).[12] Yet, from all the previous cyclopropanation methods using diiodoalkyl reagents, lower diastereoselectivity was obtained under mild reaction conditions. To the best of our knowledge, no example of *gem*-borosilylcyclopropanes has been reported in the literature so far.

Herein, we report a metal-free and visible-light mediated synthesis of *gem*-borosilylcyclopropanes (Scheme 1d). A user-friendly setup utilizing household white LEDs *vs* a specific photoreactor allowed the cyclopropanation of numerous styrene derivatives. Optimized organocatalytic and visible light-activated conditions resulted in a broad range of novel silylcyclopropylboronate esters with good yields and excellent diastereoselectivity driven by hindrance of the silylated group. Complementary to previous borocyclopropanations,[11] *cis*-borocyclopropanes were obtained in good yields (Scheme 3).

RESULTS AND DISCUSSION

Synthesis of Reagent Diiodomethyl Reagent 2. The chromatography-free synthesis of (diiodo(trimethylsilyl)-methyl)boronic ester **2** was completed in a 4-step sequence inspired by the previously published synthesis of diiodomethylpinacol boronate used for borocyclopropanation (Scheme 2).[9,13] The first step is the formation of a dichloromethyl anion

Scheme 2. Synthesis of Diiodomethyl Reagent 2[a]



[a]Thermal ellipsoids are plotted at the 50% probability level.

starting from dichloromethane, which is then quenched with trimethylsilyl chloride to obtain the commercially available, but expensive dichloromethyltrimethylsilane **4** in 85% yield. The subsequent addition of boronic acid using commercial trimethyl borate followed by pinacol protection on the boronic acid afforded product **6** in good yield. Finally, a double Finkelstein reaction with sodium iodide in acetone produced the diiodomethylsilylboronate ester reagent **2** in 65% overall yield from dichloromethane on a 20 g scale.[14] The structures of **6** and **2** were unambiguously confirmed by X-ray crystallographic analysis. Reagent **2** was kept at −20 °C and did not show any sign of degradation over 3 years.

Optimization Studies. Upon investigating several reaction parameters, it was determined that the cyclopropanation of styrene **1a** using diiodoboromethylsilane **2** afforded **3a** in good yield at room temperature with eosin Y as the photocatalyst, *i*-Pr_2NEt, sodium thiosulfate, and white LED irradiation (Table 1, entry 1). This transformation was unsuccessful using either dichloromethyl reagent **6** or its chloroiodomethyl analog (Table 1, entries 2, 3). This transformation was possible with a ruthenium photocatalyst affording product **3a** in a slightly lower yield (entry 4). Considering the high cost and low sustainability of transition metal-based photoredox catalysts,[15] the optimization with the latter was not further pursued and other organophotocatalysts were tested. A decrease of the yield was observed with rose bengal or xanthone as a photocatalyst (entries 6, 7) and interestingly, a 43% yield of cyclopropane **3a** was obtained without any photocatalyst (entry 7). When lowering the stoichiometry of **2** to one equivalent, a decreased 44% yield along with a diastereoisomeric ratio of 9:1 were observed (entry 8). Similar yields were obtained with 2 or 3 equivalents of diiodoboromethylsilane **2** (entries 1 *vs* 9). On the other hand, using reagent **2** as the limiting reagent and alkene **1a** in excess led to only 63% yield of the desired product (entry 10). These conditions facilitated the purification process, and often times the crude silylcyclopropylboronate ester could be used directly in further derivatization reactions (Scheme 4). Using sodium bisulfite instead of sodium thiosulfate or the absence of a reducing agent resulted in 73% yield in both cases (Table 1, entries 11, 12). Yields were slightly decreased to 75% and 84% when the reaction solvent was dichloromethane and acetonitrile, respectively (entries 13, 14). Since acetone is a recommended solvent based on ecotoxicity, health, and safety,[16] it was chosen for the subsequent scope study. A survey of other amine bases indicated that *i*-Pr_2Net was optimal in this reaction (entry 15). This transformation required a minimum of 24 h of irradiation to be completed as 16 h led to a lower yield (entry 16). Different light sources were then tested and although the maximum absorbance of eosin Y is at 520 nm,[17] a decreased yield was obtained with green LED irradiation (entry 17). It is noteworthy that the maximum absorbance of reagent **2** is at 326 nm, in the UVA region.[18] As expected, a control experiment also indicated that no product was observed when the reaction was left in the dark at room temperature for 24 h (entry 18).

Additionally, the relative configuration of the major diastereoisomer was confirmed by X-ray crystallography. As expected from the bulkier nature of the silylated group compared to the boronate ester, the crystal revealed a *trans* relationship between the phenyl and the silyl substituents.

Scope. To explore the generality of the reaction, an array of diverse styrenes were submitted to the visible-light mediated borosilylcyclopropanation under the optimized conditions using 2 equivalents of diiodoboromethylsilane **2** (Table 1, entry 9). Borosilylcyclopropanes arising from electron-rich substituted styrenes (**3b−f**) or styrenes bearing a halogen (**3h−j**) were obtained in 58−96% yields and excellent diastereoselectivity (Scheme 3). The reaction conditions are

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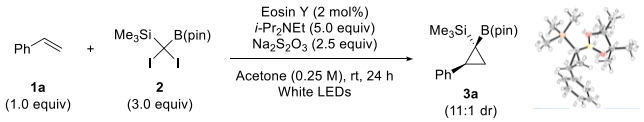
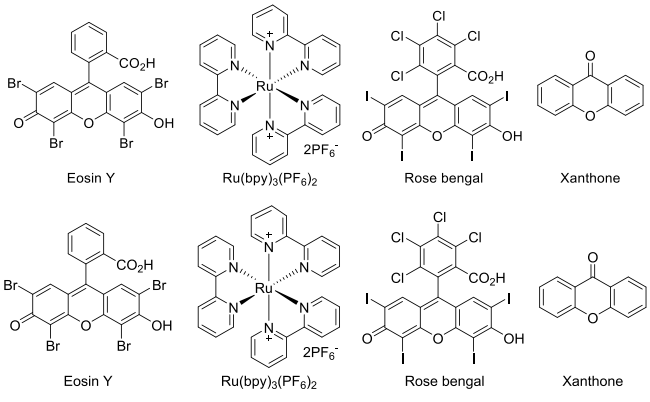
Table 1. Optimization Studies and Control Experiments[a]



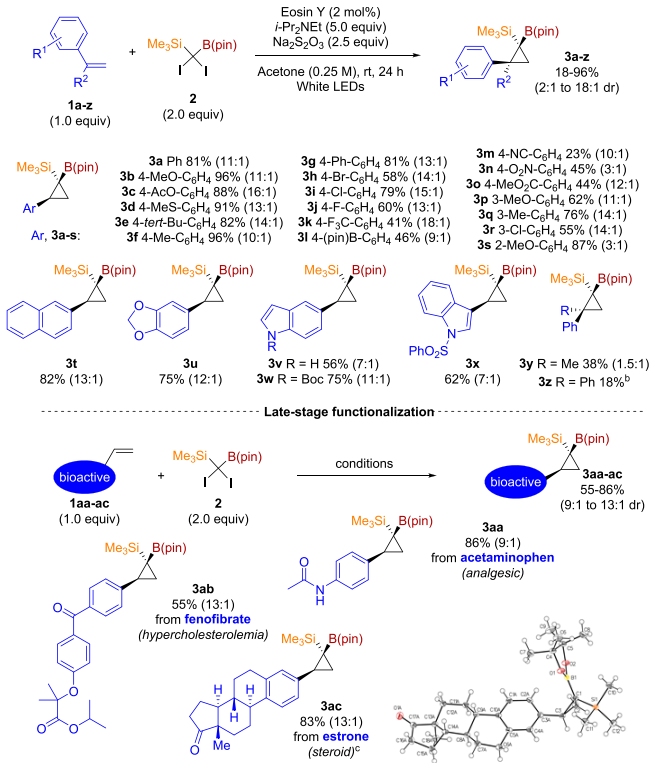
Entry	Deviation from reaction conditions	Yield (%)
1	None	91
2	**6** instead of **2**	0
3	ICl**B**(pin)(SiMe$_3$) instead of **2**	0
4	Ru(bby)$_3$PF$_6$ instead of Eosin Y	75
5	Rose bengal instead of Eosin Y	63
6	Xanthone instead of Eosin Y	32[b]
7	No photocatalyst	43
8	1 equiv of **2**	44[c]
9	2 equiv of **2**	87
10	5 equiv of **1a** and 1 equiv of **2**	63 (80)[d]
11	$NaHSO_3$ instead of $Na_2S_2O_3$	73
12	No $Na_2S_2O_3$	73
13	CH_2Cl_2 instead of acetone	75
14	MeCN instead of acetone	84
15	Et_3N instead of *i*-Pr$_2$Net	0
16	16 h instead of 24 h	68
17	Green LEDs instead of white LEDs	61
18	In the dark (without irradiation)	0



[a]All entries were conducted on a 0.17 mmol scale. Thermal ellipsoids are plotted at the 50% probability level. ^{1}H NMR yield of combined diastereoisomers was determined using triphenylmethane as the internal standard. [b]Under continuous flow, using 5 mol% of xanthone, no $Na_2S_2O_3$, CH_2Cl_2 as the solvent, and irradiated with UVA during 1 h. [c]9:1 dr. [d]Isolated yield on a 1.0 mmol scale after 48 h.

compatible with the presence of a boronate ester substituent on the styrene moiety and **3l** was obtained in 83% by ^{1}H NMR and 46% isolated yield. It is worth mentioning that this *bis*(boronate ester) was particularly unstable over silica because of the aromatic boronate, and decomposition was observed upon purification (**3l**).[19] Interestingly, styrenes with strong electron-withdrawing groups were less reactive and *para*-trifluoromethyl **3k**, *para*-cyano **3m**, and *para*-nitro **3n** were synthesized in 23−45% yield. To our delight, sterically

Scheme 3. Borosilylcyclopropanation of Various Styrene Derivatives[a]



[a]Isolated yields of combined diastereoisomers. Diastereoisomeric ratio shown in parentheses and determined in crude ^{1}H NMR. Reactions done on a 0.20 mmol scale. [b]64 h reaction time. [c]Thermal ellipsoids are plotted at the 50% probability level.

hindered alkenes were well tolerated, and both *ortho*- and *meta*-substituted styrenes delivered products **3p**−**3s** in 55−87% yield with modest to excellent diastereoselectivity. Naphthyl- and benzodioxole-substituted alkenes provided the desired borosilylcyclopropanes **3t**−**u**. Moreover, unprotected and protected indolyl-substituted alkenes were compatible with the reaction conditions and afforded cyclopropanes **3v**−**x** in good yields. Notably, 1,1-disubstituted alkenes were tolerated, albeit the tetrasubstituted cyclopropanes **3y** and **3z** were obtained in moderate yields and low diastereoselectivity (**3y**). Unfortunately, both *cis*- and *trans*-1,2-disubstituted and alkyl-substituted alkenes were unsuccessful.[20] Due to the increased stability of the product and to the improvement of the reaction efficiency, overall yields were significantly improved compared to a recently developed borocyclopropanation, specifically up to a 31% increase for the corresponding substrate of **3c**.[11] The functional group tolerance of the reaction makes it suitable for late-stage functionalization reactions. Alkenes derived from fenofibrate, acetaminophen, and estrone were successfully cyclopropanated, affording drug-like molecules **3aa**−**ac** in 55% to 86% yield.

Application of Borosilylcyclopropanes. To further highlight the synthetic utility of *gem*-borosilylcyclopropanes, product **3a** was derivatized to produce diverse functionalized 1,1,2-trisubstituted or 1,2-disubstituted cyclopropanes **7**−**12** (Scheme 4A). The trimethylsilyl functional group underwent smooth proto-desilylation upon treatment with a fluoride source and heat[21] to produce borocyclopropane **7** in 58% yield in a 3:1 diastereoselective ratio. This method is therefore

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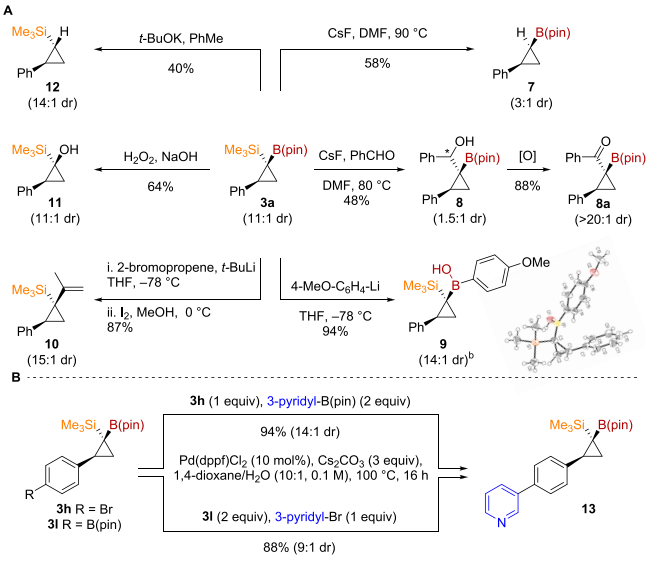
Scheme 4. Post-functionalization[a]



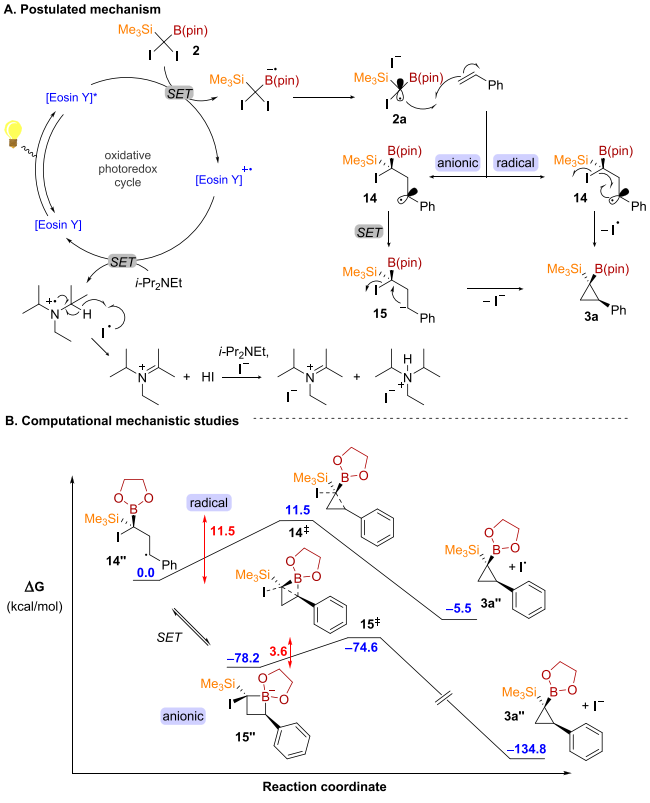
[a]Isolated yields. A. Post-functionalization of *gem*-borosilylcyclopropane **3a**. [b]Thermal ellipsoids are plotted at the 50% probability level. B. Distal Suzuki−Miyaura cross-coupling on cyclopropanes **3h,l**.

complementary to those affording the *trans* isomer.[9,11] When the desilylation reaction was done in the presence of benzaldehyde, cyclopropylmethanol **8** was obtained in 48% yield and a diastereoisomeric ratio of 1.5:1.[22] Further oxidation of **8** afforded the corresponding ketone quantitatively as a single cyclopropyl diastereoisomer (**8a**). This sequence confirmed that the change in the diastereomeric ratio arose from a mixture at the benzylic alcohol position center and the relative configuration of the cyclopropane substituents remained unaltered. Functionalization of the boronate ester was subsequently investigated.[23] Notably, the addition of (4-methoxyphenyl)lithium led to borinic acid **9**, which was isolated in 94% yield. The structural assignment was confirmed by NMR and X-ray crystallography. Further lithiation-borylation[5,24] delivered *gem*-vinylsilylcyclopropane **10** as a single diastereoisomer in 87% yield. The boronate ester moiety could be oxidized to the alcohol to give highly valuable *gem*-silylcyclopropanol **11** in 64% yield.[25] Proto-deboration of **3a** was achieved in 40% yield upon treatment with *t*-BuOK thus producing **12** in a 14:1 dr. Orthogonal reduction of **3a** to the boronate **7** or silane **12** provided the *cis*- or *trans*-cyclopropane products selectively that could be engaged subsequently in known silyl- or borocyclopropane post-functionalization reactions.[25b,26] While silane reduction eroded the stereoselectivity in product **7**, no isomerization was observed for other transformations including substitution of the silane (**8a**) and transformation on the boronate motif in adducts **9**−**12**.

Various classical and atypical Suzuki−Miyaura cross-coupling conditions, including strategies such as the activation of the boronate with *tert*-butyllithium[25b] or via the trifluoroborate,[27] were unsuccessful with borocyclopropane **3a**. The steric hindrance of the silyl functionality was hypothesized as the root cause. However, the robustness of the boronic ester was leveraged to functionalize orthogonally. A fruitful distal coupling left the shielded boronic ester on the cyclopropane subsequently available for further potential functionalization (Scheme 4B). When *para*-bromo-phenyl-borocyclopropane **3h** was used as the electrophilic partner and 3-pyridinylboronate pinacol ester as the nucleophile, the coupled adduct **13** was obtained in a 94% yield. Alternatively, the same set of conditions using 4-B(pin)phenylcyclopropane **3l** as the nucleophilic partner and 3-bromopyridine as the electrophile furnish the desired heteroaryl product **13** in an excellent 88% isolated yield. This latter result underlines the difference in reactivity between the two B(pin) moieties in **3l**.

Mechanistic Studies. A postulated photoredox mechanism for borosilylcyclopropanation is depicted in Scheme 5A.

Scheme 5. Mechanistic Studies[a]



[a]A. Photoredox cycle, propagation and termination mechanism. B. Calculated free energy profile for radical and anionic pathways using Gaussian 16.C.01 (SMD-MeCN-M06-2X/DGDZVP). Computational studies using a model substrate where the pinacolic methyl groups were replaced with hydrogen were conducted to elucidate whether the stereo-determining step was anionic or radical. Pathways were surveyed with SMD-MeCN-M06-2x/DGDZVP[31] using Gaussian 16.C.01.[32]

Having a quantum yield of 0.32, eosin Y performs most of its electronic transfers from its singlet state.[17] After visible-light irradiation, excited eosin Y ($E^{S1}_{Ox(eosinY)}$ = −1.58 V vs SCE (saturated calomel electrode))[17] is oxidized by diiodoboromethylsilane **2** ($E^{Red}_{1/2}{}^{2}$ = −1.28 V vs SCE),[28] leading to a transient radical anion that fragments into iodo-boromethylsilane radical **2a**. The ground state of eosin Y ($E^{Ox}_{1/2(eosinY)}$ = +0.76 V vs SCE) is recovered upon reduction by *i*-Pr_2NEt ($E^{Ox}_{1/2(i\text{-}Pr2NEt)}$ = +0.63 V vs SCE).[11] The reduction quenching cycle was excluded since eosin Y in its ground state is not able to oxidize diiodoboromethylsilane **2** ($E^{red}_{1/2(eosinY)}$ = −1.08 V vs SCE compared to $E^{red}_{1/2(2)}$ = −1.28 V vs SCE).[17,29] Then, apart from the photoredox cycle, homolytic substitution of styrene by radical **2a** to give radical intermediate **14**, which would undergo cyclopropanation to obtain cyclopropane **3a**.

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The remaining iodide radical would be quenched by termination by *i*-Pr_2NEt radical cation. The subsequent cyclopropanation step could take place *via* either an anionic or radical pathway. In a deuterated β-styrene borocyclopropanation experiment conducted by Ooi and coworkers, the concerted cyclopropanation of a singlet-carbene intermediate was excluded, thus leading to a stepwise cyclopropanation.[30] In the radical pathway, as suggested by Suero *et al*,[29] radical **14** would directly go through the cyclization step by propagation. However, in an anionic pathway, intermediate **14** would go through a single electron transfer with the *i*-Pr_2NEt radical cation to give a benzylic anion. Cyclization would take place by substitution and expulsion of iodide to obtain desired product **3a**. Since the anionic pathway begins with radical **14** as the starting material, even the observed radical inhibition by TEMPO could not exclude one cyclization mechanism over the other.

Both computed pathways predominantly lead to the *E*-isomer of the product **3a** consistent with the experimental results.[33] To determine which pathway might be involved, the anionic and radical pathways for the *E*-isomer were compared directly (Scheme 5B). In the radical pathway, the difference in free energy from intermediate **14″** to its transition state **14**‡ was calculated to be 11.5 kcal/mol (Scheme 5B, top). In the thermodynamic cycle, formation of the anion from radical through a fast electron transfer is possible. The resulting benzylic anion was stabilized by the boron atom and led to a four-membered ring intermediate **15”**, with a free energy of −78.2 kcal/mol (Scheme 5B, bottom). Since the anionic transition state **15**‡ was calculated to have a relative free energy of −74.6 kcal/mol, the barrier from intermediate **15″** to its transition state is 3.6 kcal/mol. Notably, the barrier of the anionic pathway is 7.9 kcal/mol lower than the barrier of the radical pathway (**15″** vs **14”**). Hence, likely due to the stabilization of the carbanion by the boron atom, the anionic pathway appears to be predominant. Adding an electron-withdrawing group on **3a** might decrease the free energy of **15** and might increase the cyclization step activation energy. This explains the lowered yields of **3k**, **3m**, and **3n**.

CONCLUDING REMARKS

In summary, a highly efficient *gem*-borosilylcyclopropanation of a broad scope of styrene derivatives was developed in a diastereoselective manner. Metal-free, user-friendly, and mild reaction conditions taking advantage of photochemistry and using acetone as the solvent produced novel borosilylcyclopropanes motifs. The key reagent was synthesized in a chromatography-free 4-step sequence starting from inexpensive and readily available commercial reactants. To illustrate the potential of the reaction in late-stage functionalizations, 29 borosilylcyclopropanes, three of them being alkenyl derivatives from natural or drug-like molecules, were synthesized in up to 96% yield. Complementary to established *trans*-borocyclopropanations, the first method to produce borosilylcyclopropane gives access to *cis*-borocyclopropanes after proto-desilylation. Computational mechanistic studies determined that the cyclopropanation step was anionic, stabilized by a four-membered ring boronate anion. Orthogonal and distal functionalization of borosilylcyclopropanes allowed synthesis of distinctly valuable synthetic targets and addition of complexity. Further functionalization reactions are currently being conducted and will be reported in due course.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02535.

Experimental procedures, mechanism experimental procedures, UV−Vis spectra, cyclic voltammetry, NMR spectra copies, computational procedures (PDF)

Accession Codes

CCDC 2144795−2144804 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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