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Redox-Neutral Photocatalytic Cyclopropanation *via* Radical/Polar Crossover

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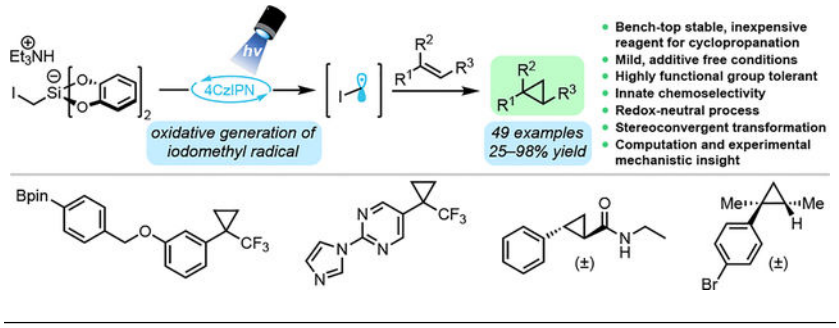
Abstract

A bench-top stable, bifunctional reagent for the redox-neutral cyclopropanation of olefins has been developed. Triethylammonium bis(catecholato)iodomethylsilicate can be readily prepared on multigram scale. Using this reagent in combination with an organic photocatalyst and visible light, cyclopropanation of an array of olefins, including trifluoromethyl- and pinacolatoboryl-substituted alkenes, can be accomplished in a matter of hours. The reaction is highly tolerant of traditionally reactive functional groups (carboxylic acids, basic heterocycles, alkyl halides, etc.) and permits the chemoselective cyclopropanation of poly-olefinated compounds. Mechanistic interrogation revealed that the reaction proceeds *via* a rapid anionic 3-*exo*-*tet* ring closure, a pathway consistent with experimental and computational data.

Graphical Abstract



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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectral data (PDF)

INTRODUCTION

The cyclopropyl group is a common motif found in many pharmaceutical products[1] and secondary metabolites.[2] It is employed to increase metabolic stability, enhance potency, and decrease plasma clearance.[1a] Consequently, cyclopropane rings appear in 10 of the top 200 highest grossing pharmaceutical products from 2016[1b] and in 124 approved or investigational drugs (Figure 1).[1c] Furthermore, the substitution pattern of these rings can impart bioisosteric properties. Trifluoromethyl-substituted cyclopropanes (TFCps) are salient examples of the unique bioisosterism possible with cyclopropanes; TFCps are *tert*-butyl isosteres that improve *in vitro* and *in vivo* stability while retaining biological activity.[3–5] A TFCp was utilized in the development of a selective, brain-penetrating T-type calcium channel blocker (ACT-709478) with a safety profile suitable for advancement into Phase I clinical trials (Figure 1).[3d]

Among the more popular strategies for cyclopropane assembly are [2+1]-type reactions with olefins. Some examples include the use of carbenoids generated from diethylzinc and halomethanes (Simmons-Smith),[6] or *via* diazo compounds.[7] In some cases, a two-step process (Michael-type addition followed by intramolecular nucleophilic displacement) can be employed for the direct cyclopropanation of olefins (e.g., sulfur ylides with enones in the Corey-Chaykovsky reaction).[7b,8] Although these routes are well-established in the literature, they are often lacking in broad functional group tolerance or operational simplicity, and rarely employ mild conditions. Specifically, state-of-the-art methods for TFCp synthesis by cyclopropanation rely on multi-step sequences involving treatment of the corresponding trifluoromethylalkene with diazomethane followed by a retro-[3+2]-cycloaddition in refluxing xylenes (Figure 2A).[3a,4] Alternate strategies that do not rely on cyclopropanation of CF3-substituted olefins do exist (e.g., cationic ring closure,[5a,b] Minisci-type alkylation[5c]), but their scope is constrained by inherent mechanistic limitations.

Single-electron approaches for the cyclopropanations of alkenes are much less well-developed. Leading methods rely on the use of diazo compounds,[9] pre-functionalized substrates,[10] or methods that require large excesses of reagents and multiple additives.[11] Thus, these methods are not easily employed in late-stage functionalization of complex molecules. Photoredox catalysis has enabled the operationally simple generation of radicals while maintaining the broad functional group tolerance and orthogonality to acidic or basic residues that is associated with processes proceeding through open shell intermediates.[12] However, no *photooxidizable* C_1 reagent for radical cyclopropanation is described in the literature. We thus directed our efforts toward designing such a species to fill this gap. We envisioned that a reagent furnishing a halomethyl radical could operate as a cyclopropanating reagent where, following radical addition to an olefin, a 3-*exo*-*tet* cyclization would forge the second C–C bond required for cyclopropanation (Figure 2B). In addition to serving as an effective cyclopropanating reagent, successful design of a reagent furnishing a halomethyl radical would allow the properties of this reactive odd-electron intermediate to be probed.[13]

DISCUSSION

Reagent Design and Development.

In devising this reagent, several parameters were considered: (*i*) an ability to be bifunctional in nature (i.e., able to engage in two distinct C–C bond forming events), (*ii*) bench stability, (*iii*) ease of photooxidation, (*iv*) a practical, inexpensive, direct preparation from commercial materials, and (*v*) potential to operate in a redox-neutral and metal-free reaction manifold. Such a reagent would not only leverage the wide functional group tolerance that is characteristic of photoredox catalyzed radical reactions, but would stand in contrast to the typical approaches to cyclopropanation (harsh bases, poor safety profiles, and/or toxic reagents). Although a variety of radical precursors were explored (e.g., potassium organotrifluoroborates, 4-alkyldihydropyridines, α-halocarboxylates, etc.), α-halomethyl bis(catecholato)silicates were ultimately identified as best fulfilling these criteria (see the Supporting Information for details on assessment of other halomethyl radical precursors). Alkylbis(catecholato)silicates can be prepared from commodity materials on multigram scale, have low, leveled oxidation potentials, and are typically free-flowing, bench-stable powders compatible with organic photocatalysts.[14] We anticipated that single electron oxidation by the excited state of the photocatalyst would furnish the desired halomethyl radical intermediate. Once formed, the radical would readily add to an alkene **2**, and an anionic (S_N2) or radical 3-*exo*-*tet* (S_H2) cyclization would furnish the desired cyclopropane **3** (Figure 2C).

To assess the feasibility of the envisioned process, three bifunctional silicates (α-chloro **1a**, α-bromo **1b**, and α-iodo **1c**) were prepared from commercially available chloromethyltrimethoxysilane (~$0.26 per mmol) in either one or two simple chemical steps. These reagents could, in all cases, be prepared on multigram scale in good yield, without any chromatography, and were isolated as free-flowing powders.

Trifluoromethyl-substituted alkenes **2** were initially selected for exploring the proposed cyclopropanation given their known compatibility with photoredox catalysis and proficiency as radical acceptors.[15,16] In addition, success here would allow the mild, one-step preparation of valuable TFCps **3** from trifluoromethyl-substituted alkenes. Given the ease with which these olefins can now easily be accessed from commercially available trifluoromethyl ketones,[15b] aryl halides,[15c] or organoboron reagents,[15a] success here would provide a regiospecific means to install the TFCp motif on virtually *any* scaffold (arene, hetereoarene, aliphatic, etc., Figure 3).

In addition to their inherent synthetic value, the known ability for trifluoromethylalkenes to undergo a competitive anionic fluoride elimination would provide a handle through which insight could be gained as to whether ring closure would occur *via* an anionic or radical pathway (Figure 2C, see Mechanistic Studies for further details).[16e–f,17]

With these considerations in mind, we evaluated the selectivity for cyclization versus fluoride elimination (Scheme 1). Using 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN)[18] as photocatalyst and dimethyl sulfoxide (DMSO) as solvent, we not only observed the desired reactivity, but found that the ratio of cyclopropane **3** to undesired *gem*-

difluoroalkene **4** was strongly dependent on the halogen leaving group; a complete inversion in selectivity was observed when moving from the chloro- to bromo- to iodosilicate (Scheme 1).

Given its innate selectivity for cyclopropanation and inexpensive nature (~$1.10 per mmol), further optimization of this annulation process utilized iodomethyl-based silicate reagent **1c**, providing reaction conditions that do not require the use of additives (see Supporting Information for details on optimization). Use of 30 W blue LEDs lamps as the light source allowed the shortest reaction times (0.5–24 h, depending on scale and substrate). The reaction proceeded equally well in the presence of other, more cost-effective, light sources (e.g., 21 W CFLs) with only the reaction time being impacted (See Supporting Information for detail on light source studies). Control reactions confirmed this indeed was a photocatalytic process; in the absence of light or photocatalyst, no reaction occurred (see Supporting Information). An additional control reaction where reaction progress was evaluated over alternating periods of irradiation and darkness (the so called “light/dark” experiment) was performed. More rigorous evaluation of the photochemical aspect of this process (e.g., Stern-Volmer emission quenching, quantum yield determination) was performed as well (see Mechanistic Studies for further details), ultimately ruling out an unassisted, self-sustaining chain process.

With these conditions in hand, the scope of the transformation was explored. A variety of structurally diverse α-trifluoromethyl alkenes were amenable to cyclopropanation, generally providing products in good yield and with excellent functional group compatibility (Table 1). Bromo-substituted arenes (**3a-3d**) reacted efficiently to provide the desired products. Steric effects did have some influence on the reaction. *ortho*-Substitution itself was not deleterious, but larger substituents did seem to have a more pronounced effect (e.g., **3c** required longer reaction times and a slightly higher loading of **1c**). The reaction tolerated a potentially reactive alkyne (**3e**) functional group. Additionally, a wide range of nitrogen-containing substrates, including aryl nitrile **3g**, Boc-protected and *N*-methyl-anilines **3h-3j**, a Boc-protected benzylic amine **3k**, and a secondary amide **3l**, all cyclopropanated successfully. The reaction even proceeds smoothly in the presence of an acidic ammonium chloride salt (**3m**). Furthermore, aldehyde **3n**, phenol **3o**, benzyl alcohol **3p**, benzoic acid **3q**, and methyl ester **3r** were all compatible, illustrating both the broad functional group tolerance and the compatibility of protic groups. Other valuable synthetic lynchpins such as an aryl Bpin (**3s**), primary alkyl iodide (**3t**), and a secondary alkyl chloride (**3u**) were also tolerated. The chemoselectivity of the transformation was evaluated using the geraniol analog **3v**, where cyclopropanation was observed exclusively at the electron-deficient trifluoromethyl-substituted olefin. The reaction was not limited to α-styryl trifluoromethyl-substituted alkenes. A representative trifluoromethyl-substituted aliphatic alkene (**3w**) also efficiently underwent cyclopropanation, albeit at an extended reaction time and with higher silicate loading. In addition, a variety of heteroaryl trifluoromethyl alkenes including indole **3x**, indazole **3y**, pyrido[2,3-*b*]pyrazine **3z**, imidazole-pyrimidine **3aa**, pyridine **3ab**,[19] a caffeine derivative **3ac**, and thiophene **3ad** were readily cyclopropanated. Finally, the reaction could be conducted on a 5 mmol scale with virtually no effect on the yield (**3a**). It should also be noted that these sorts of CF_3-subsituted olefins fail to react under previously

reported radical cyclopropanation methods (see Supporting information for comparison studies).

Alteration of the perfluoroalkyl chain was also explored. Both pentafluoroethyl and 1,1-difluoroethyl-substituted alkenes reacted to give the corresponding substituted cyclopropanes (**3ae** and **3af**, respectively). Interestingly, the more electron-deficient and sterically encumbered pentafluoroethyl **2ae** gave a 77:23 mixture of cyclopropane **3ae** and fluoride elimination product, as determined by ^{19}F NMR of the crude reaction mixture, suggesting that the side chain can perturb the relative rates of cyclization versus elimination.

Lastly, to demonstrate the user-friendly nature of this reaction, the cyclopropanation of trifluoromethyl alkene **2d** was conducted in the presence of an air atmosphere and using wet, non-degassed DMSO (Scheme 2). Although the reaction did proceed to full conversion, the product was isolated in a slightly lower yield. However, the result is still a testament to the robustness of the transformation.

We next explored the generality of this reagent for cyclopropanation, and thus other olefins were examined. Overall, various electronically distinct olefins were amenable to cyclopropanation, and the functional group tolerance matched that observed with trifluoromethyl-substituted alkenes. α,β-Unsaturated esters, amides, and ketones (**6a–6e**) readily underwent the cyclopropanation to give the corresponding trans products (Table 2). A key intermediate (**6c**) used in the synthesis of platelet aggregation inhibitor Ticagrelor (AstraZeneca, Figure 1)[20] was prepared using this reagent and isolated as an approximately 1:1 mixture of *trans*-cyclopropane diastereomers. Several alkenes bearing 1,1-disubstitution were readily cyclopropanated (**6f-6k**). The reaction was further extended to 1,1-diarylethylenes to furnish 1,1-diaryl cyclopropanes (**6i, 6j**). Even a trisubstituted alkene was converted to its corresponding cyclopropane without issue (**6k**). Additionally, *trans*-anethole reacted to give only the corresponding *trans*-cyclopropane **6l**, and terminally unsubstituted styrenes (which are typically incompatible with radical cyclopropanation)[11a] gave the corresponding mono-substituted cyclopropanes (**6m** and **6n**). Furthermore, many examples (e.g., **6a**, **6d**, **6e**, **6i**, **6l**, and **6m**) displayed more successful reactivity when using **1c** as compared to previously reported radical cyclopropanation methods.[11]

The stereochemical outcome when using *trans*-anethole prompted us to interrogate whether stereoconvergence occurred using the method outlined here. Cyclopropanation of an *E/Z* mixture of **5l** as well as a trisubstituted alkene **5o** provided *trans*-cyclopropane as the exclusive stereoisomer. In addition, use of pure *cis*- or pure *trans* β-methylstyrene resulted in the same stereochemical result. Exclusive formation of the *trans*-cyclopropane was observed, although these isomeric olefins appear to react at different rates. Stereoconvergence here is likely achieved via diastereoselective ring closure following radical addition to either isomer (made possible by the rapid interconversion of a radical intermediate). However, given that photochemical isomerization is a background reaction for some olefins (e.g., Scheme 3), stereoconvergence via preferential reaction with one alkene isomer cannot be conclusively ruled out for some systems (see Supporting Information for further details).

Mechanistic Studies.

Having explored the synthetic scope and utility of this reagent, we next turned our attention to the reaction mechanism, specifically whether the proposed 3-*exo-tet* cyclization proceeded *via* an anionic or radical (S_H2) pathway. Although the identity of the halogen of the halomethyl radical does dramatically impact the reaction pathway, that alone cannot distinguish between anionic or radical ring closure (i.e., iodide is both more prone to nucleophilic displacement *and* is more homolytically labile than bromine or chlorine). Experiments to explore the influence of electronics on product distributions were initially conducted. However, no strong electronic correlation between the ratio of cyclopropane to *gem*-difluoroalkene was observed (Scheme 4).

Of note, the reaction could also be conducted in the presence of 3 equiv of trifluoroacetic acid (TFA) *without any change* in ratio or reaction conversion. Although intriguing, these results were not sufficient to preclude one of the two cyclization pathways. We next turned to quantum mechanical calculations to evaluate these mechanistic postulates more conclusively. Specifically, we sought to determine which of the two mechanisms more accurately described the observed results (i.e., the effect on product selectivity by the structure of α-halomethyl radical, etc.). Calculations were initially performed at the UM06–2X/DGDXVP level of theory in implicit solvent.[21] Further, to assess the influence of dynamic correlation, open-shell, domain-based local pair, and natural orbital Coupled-Cluster calculations using single and double excitations with perturbative triple excitations (DLPNO-CCSD(T)) using def2-TZVPP basis using ORCA were also performed.[22] This latter method provides accurate energies (within 3 kJ mol^{-1}) with the computational cost comparable to DFT calculations.[23] Single point energy calculations in implicit solvent using (D3(BJ)-B3LYP)/def2-TZVPP and UM06-2X/ def2-TZVPP were performed in parallel for comparison, which revealed identical trends and very similar energetic profiles as the DLPNO-CCSD(T) method (see Supporting Information).[24] For simplicity, only DLPNO-CCSD(T) free energies are presented and discussed explicitly in the text. All 3D structures were generated using CYL-view.[25]

We initially sought the energetics of the radical 3-*exo-tet* cyclization. In this pathway (Figure 2C), radical intermediate **2′** presumably arises from Giese-type addition[26] of the halomethyl radical **1′** to the alkene **2**; which can undergo ring-closure *via* S_H2–type mechanism to deliver the desired TFCp **3**. Thus, we populated the potential energy surface of this pathway (Scheme 5). Note that energetics of the initial radical addition to the alkene show regioselective formation of α-radical **INT-I**, implying that α-radical formation is both kinetically and thermodynamically favored over β-radical formation (see the Supporting Information for additional details). With the exception of the iodo system (22.0 kcal mol^{-1} barrier of cyclization from **INT-I**), the barriers for the radical cyclization (SH2-type pathway, **TS-II** and **TS-III**, respectively) are not feasible under experimental conditions (barriers are 27.6 kcal mol^{-1} and 34.5 kcal mol^{-1}). All other methods predicted similar barriers (See Supporting Information). This is surprising given that formation of cyclopropane was observed with all halomethyl silicates. Even more surprising was the fact that, in all cases, the reactions are net endergonic. Notably, the barriers and (endergonic) reaction energies are consistent with the strength of the C–X bond (C–X bond dissociation

energies for C–I, C–Br, and C–Cl are ~57, ~71, and ~85 kcal mol^{-1}, respectively).[27] The computed barriers for a possible radical- mediated fluoride elimination to give the *gem*-difluoroalkene (not shown) were too high to be feasible and were universally highly endergonic (~63 kcal mol^{-1} between all adducts of halomethyl addition).

The energetic inconsistency of the radical cyclization pathway with our experimental observations led us next to investigate whether anionic pathways might be operative for both cyclization and *gem*-difluoroalkene formation (Scheme 6). In excellent agreement with experiment, the computed barriers for the anionic pathway: 1) are feasible under experimental conditions (~4–9 kcal mol^{-1}) and exergonic (~ −4 to −43 kcal mol^{-1}), and 2) qualitatively and quantitatively replicate the experimental trends (Scheme 1C). Further, although the barriers for the S_N2-type cyclization increase with the leaving group ability (I > Br > Cl), the barriers for the elimination (E1cB pathway) remained relatively unchanged for all halo systems (~7 kcal mol^{-1}). Therefore, for the iodo system, cyclopropane formation **P-IV** (*via* S_N2-type transition state) is kinetically favored by 3.8 kcal mol^{-1} over the alkene product (**P-VII**). However, for the bromo system, the energy difference between these two competing pathways decreases ($\Delta\Delta G^{\ddagger}$ is 1.1 kcal mol^{-1} for **TS-V** versus **TS-VIII**) in favor of *gem*-difluoroalkene formation. Finally, in the chloro-system, the elimination transition state (**TS-IX**) is favored by 2 kcal mol^{-1} over the substitution pathway (*via* **TS-IV**), thus further favoring the formation of the alkene.

Not only do the barriers for cyclization explain the observed selectivity (and, because of their less energy-demanding nature, rule out the S_H2-type pathway), but they agree with our experimentally observed results. Both pathways rule against *inter*molecular (bimolecular) protonation as a viable reaction outcome because the reaction is likely proceeding at catalytic concentrations of anionic and radical intermediates, and the barriers for *intra*molecular cyclization and elimination are low (<9 kcal mol^{-1}). This rationalizes not only how the reaction proceeds in the presence of an ammonium but also how it can operate even when a highly acidic species such as TFA is added. This same insensitivity toward acid likely rules out the formation of an iodomethyl anion (and thus the formation of carbene). Moreover, it explains how *gem*-difluoroalkene formation is the predominant pathway when using non-bifunctional radicals, rather than traditional Giese-type hydroalkylation.[16d,f] Finally, the very low barrier for cyclization from the iodomethyl-derived anion (Scheme 5, **TS-IV**) explains the relative insensitivity to varying electronics of the arene.

Next, we wondered whether the mechanistic findings would translate to the non-trifluoromethylated systems successfully cyclopropanated using **1c**. More specifically, the possibility of a mechanistic spectrum where the electronics of an α-substituent would control whether the cyclization proceeds through a radical or anionic pathway. Whereas photoredox Giese-type processes are established for α-carbonyl[28] and α-boryl[29] olefins, similar reactivity in more electron-rich olefins is not established. Thus, we evaluated the energetics of anionic and radical ring closure for a representative system, 1,1-diphenylethylene (Scheme 7). The result of this set of calculations rules out a mechanistic spectrum; the energetic trends are similar to the α-trifluoromethyl systems. That is, the barrier for radical cyclization is ~20 kcal mol^{-1} (*via* **TS-XIII**) from the corresponding 1,1-diphenyl-3-iodopropyl radical, while the barrier for the cyclization from the corresponding

1,1-diphenyl-3-iodopropyl anion is virtually barrierless (~3 kcal mol^{-1}; *via* **TS-X**). Importantly, the anionic mechanism is contingent on a rather fast (and favorable) SET reduction of the intermediate radical. Other halomethyl radical additions show similar trends.

The transition states for the reaction of olefin **5i** with various halomethyl radicals is suggestive that, if an anionic pathway is indeed operative, cyclization should be feasible under experimental conditions with even the less reactive chloromethyl radical. In the absence of a fluoride elimination, only intermolecular side reactions are possible in systems such as **5i**. To probe this prediction, the cyclopropanation of **5i** using chloromethylsilicate **1a** was attempted under the conditions optimized for **1c** (Table 3). Indeed, cyclopropanation of **5i** gave a comparable yield when using chloromethylsilicate **1a** in place of iodomethylsilicate **1c**. Further, examination of the cyclopropanation of other non-CF_3-bearing alkenes using **1a** resulted in varying levels of success. Overall, the isolated yields were lower when using **1a**, reflective of the higher barrier to cyclization onto an alkyl chloride versus alkyl iodide. Seemingly less stabilized anions were more likely to engage in appreciable cyclization. Substrates that proceed through stabilized enolate anions (**5a′, 5d, 5f**) provide no cyclized product. Additionally, some substrates preferentially underwent protonation to give the uncyclized, alkyl chloride Giese-type addition product (**5g, 5n**). On the whole, the observations here are consistent with the proposed anionic cyclization pathway.

To bracket the rate of radical reduction experimentally, **5p** was prepared and subjected to cyclopropanation. Surprisingly, the major product was bis-cyclopropane **6p**, albeit in low isolated yield. Giese-type adduct **7** was not observed (Scheme 8). This implies that SET reduction exceeds the known rate constant of ring opening for the related α-cyclopropyl benzyl radical of 6.1×10^4 s^{-1}, which corresponds to a barrier of ~11.1 kcal mol^{-1} at 298 K.[30] The experimental results are again borne out in the computational model (Scheme 9). The calculated thermodynamics of the ring opening process for this system shows that the barrier for SET reduction must be lower than the calculated barrier for ring-opening (13.3 kcal mol^{-1}). This is in agreement with the rate data. In addition, the low barrier for cyclization from **INT-VI** (2.7 kcal mol^{-1}) explains the facile formation of bis-cyclopropane **6p**.

With all these data in hand, we suggest the following order of events as the operative mechanism (Figure 4) under the developed reaction conditions: 1) Visible light-mediated photoexcitation of 4CzIPN to its excited state. 2) Reductive quenching of 4CzIPN* by halomethyl silicate **1**. This mode of quenching is supported by Stern-Volmer emission quenching experiments (see Supporting Information) and also by the generally low, favorable oxidation potentials of silicates ($E_{1/2}$ = +0.4 – 0.7 vs SCE) and the high, unfavorable reduction potentials of primary iodides (e.g., $E_{1/2}$ = −1.44 V vs SCE for CH_2I_2)[11a] Subsequent fragmentation of oxidized **1** furnishes halomethyl radical **1′**. 3) After radical generation, Giese-type addition by the halomethyl radical generates adducts **2′** or **5′**; 4) SET reduction of these adducts by the reduced state of 4CzIPN gives anions **2′′** or **5′′** and returns 4CzIPN to its original ground state; 6) Anionic cyclization of **2′′** or **5′′** furnishes cyclopropanes **3** or **6**. Ultimately, this process is a closed cycle and does not appear

to operate by a chain mechanism. The quantum yield of this process was determined to be 0.066, implying that an assisted chain process is not operative.

In cases where the olefin is 1,2-disubstituted or trisubstituted, stereoconvergence is observed. Stereoconvergence likely arises from rapid equilibration of Giese-adduct **2/5** to the most stable conformation followed by stereoretentive reduction and rapid ring closure (see Supporting Information for calculations supporting this hypothesis). Alternatively, because photochemical isomerization of the starting olefin is possible, a dynamic kinetic resolution-type scenario may arise.

The results obtained and subsequent mechanistic postulate stands in stark contrast to literature reports employing the iodomethyl radical, which propose ring closure through an S_H2-type 3-*exo-tet* cyclization.[11] At the request of a reviewer, a direct comparison using a representative set of substrates was made between the method reported here and the method previously reported by Suero and coworkers (Table 4). For some substrates, the reactions gave comparable yields (**6d**, **6e**, and **6l**), while for others distinctly different reactivities were observed. Specifically, alkenes **5i** and **5l** gave exclusive non-cyclized iodoalkylation products under the conditions previously reported by Suero et al., whereas under the redox-neutral, radical/polar crossover conditions reported here, the same alkenes reacted to give solely cyclopropanated product.[31]Given that the putative active species is the same in both cases, the disparity in reactivity ultimately suggests that the redox environment in which the radical is generated (i.e., the order of SET events, presence of additives, etc.) dramatically influences the reaction outcome. More broadly, this implies the redox environment can open up, or close off, alternative mechanistic pathways. This latter conclusion may be useful for methods design in other reaction manifolds beyond cyclopropanation.

CONCLUSIONS

Herein, the successful development of a new reagent for the redox-neutral cyclopropanation of olefins under mild, photocatalytic conditions is disclosed. This reagent has resulted in the generation of not only a suite of TFCps, but it has enabled radical/polar crossover cyclopropanation of a diverse range of olefins to be accomplished with ease and excellent functional group compatibility. Combined theoretical and experimental Mechanistic Studies revealed that the reaction likely proceeds *via* a photooxidatively generated iodomethyl radical addition to an olefin followed by radical SET reduction, culminating in an anionic 3-*exo-tet* ring closure. Further applications for this reagent are under development and will be reported in due course. More generally, the findings disclosed here not only enable facile access to halomethyl radicals, but begin to shed light on the unique capabilities of these C_1 synthons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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31. For a more in-depth discussion and computation analysis of the process reported in Ref 11a, see Supporting Information.

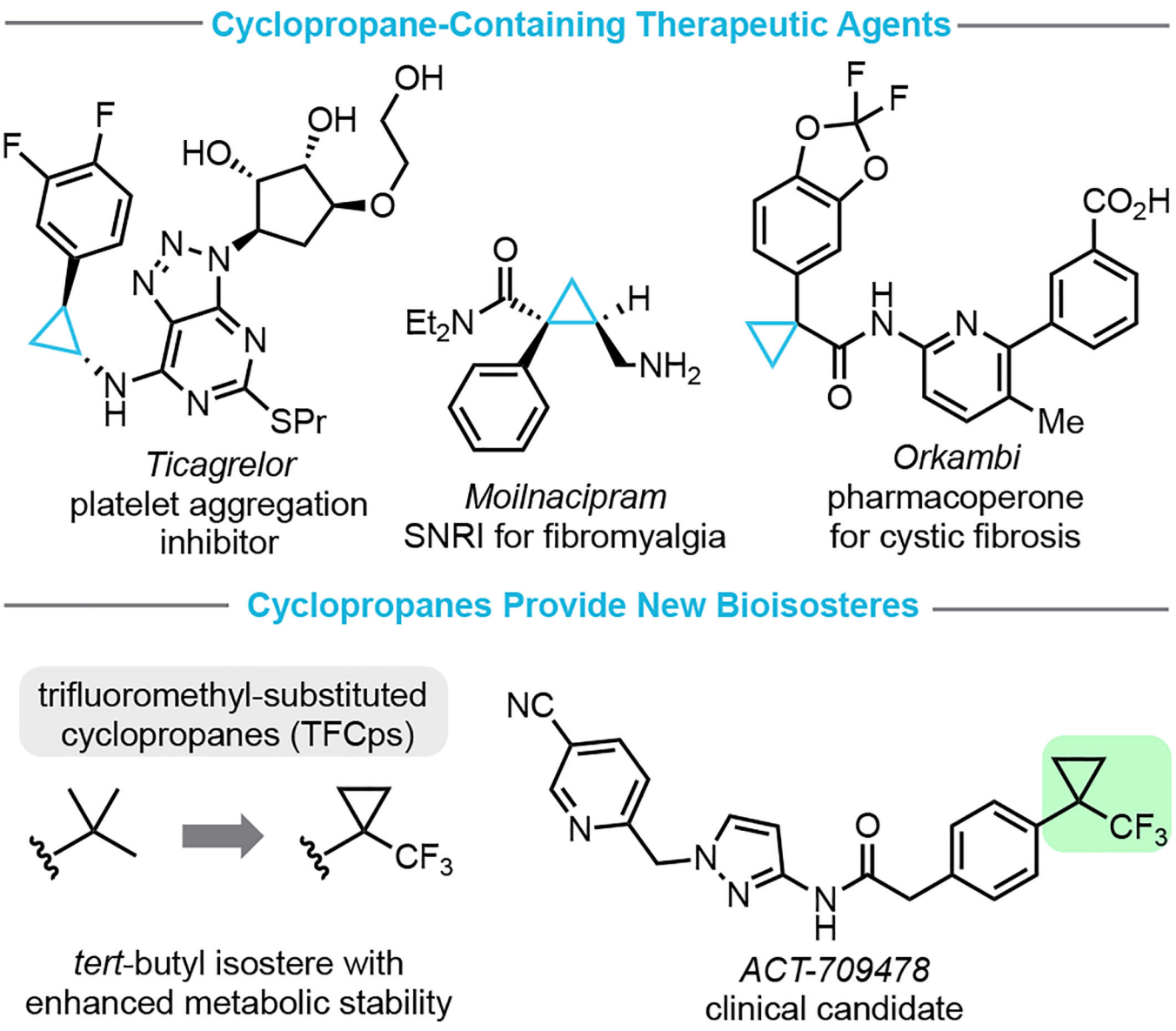


Figure 1.
Cyclopropane-containing pharmacons and trifluoromethyl cyclopropanes.

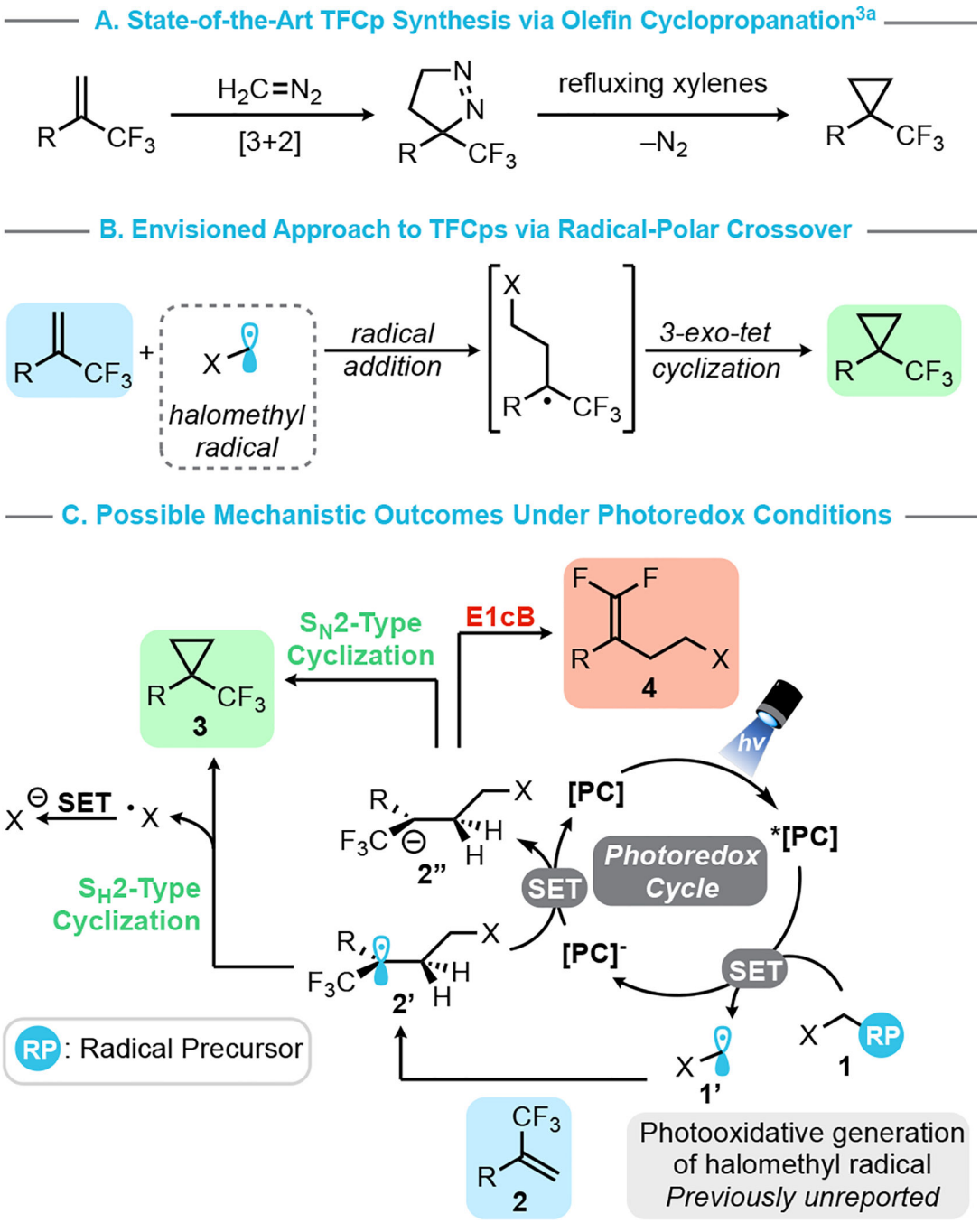


Figure 2.
Synthesis of trifluoromethyl-substituted cyclopropanes.

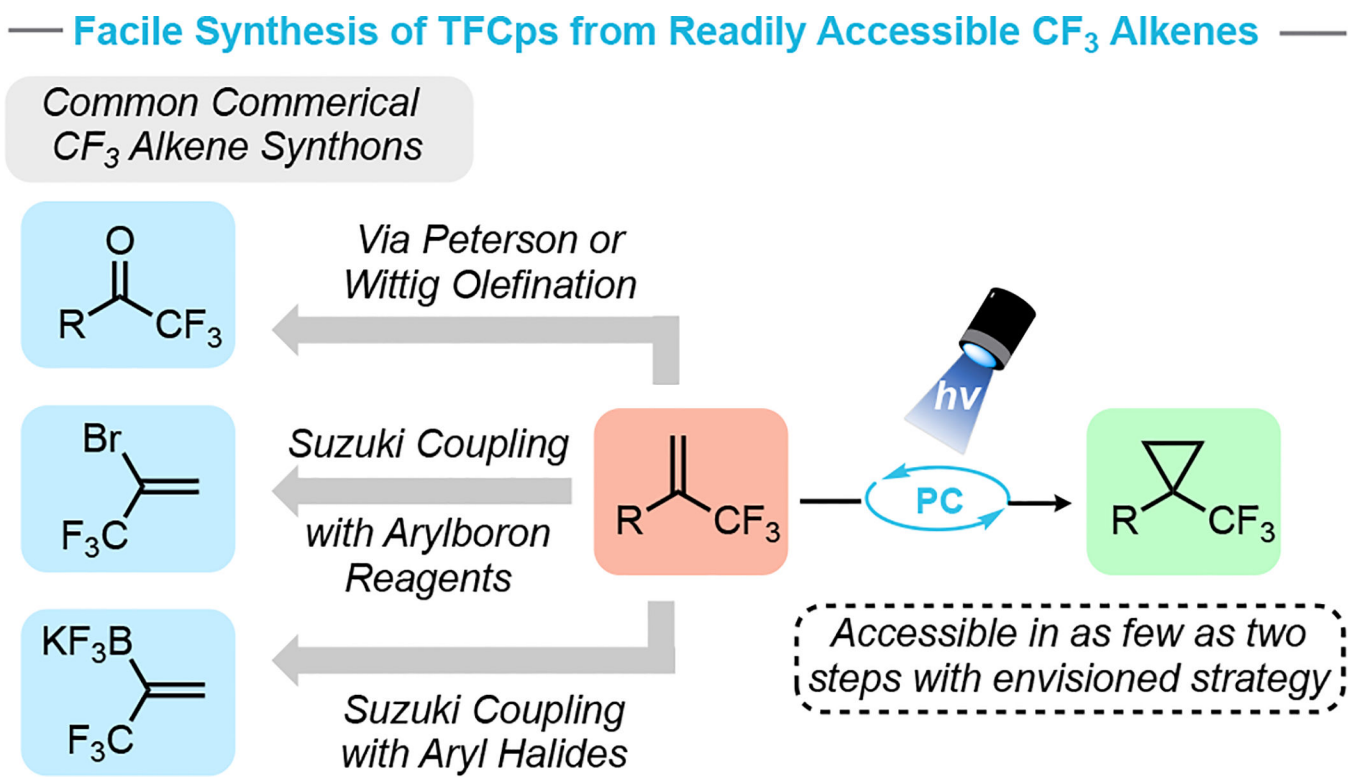


Figure 3.
Convergent strategies to TFCps from commercial materials.

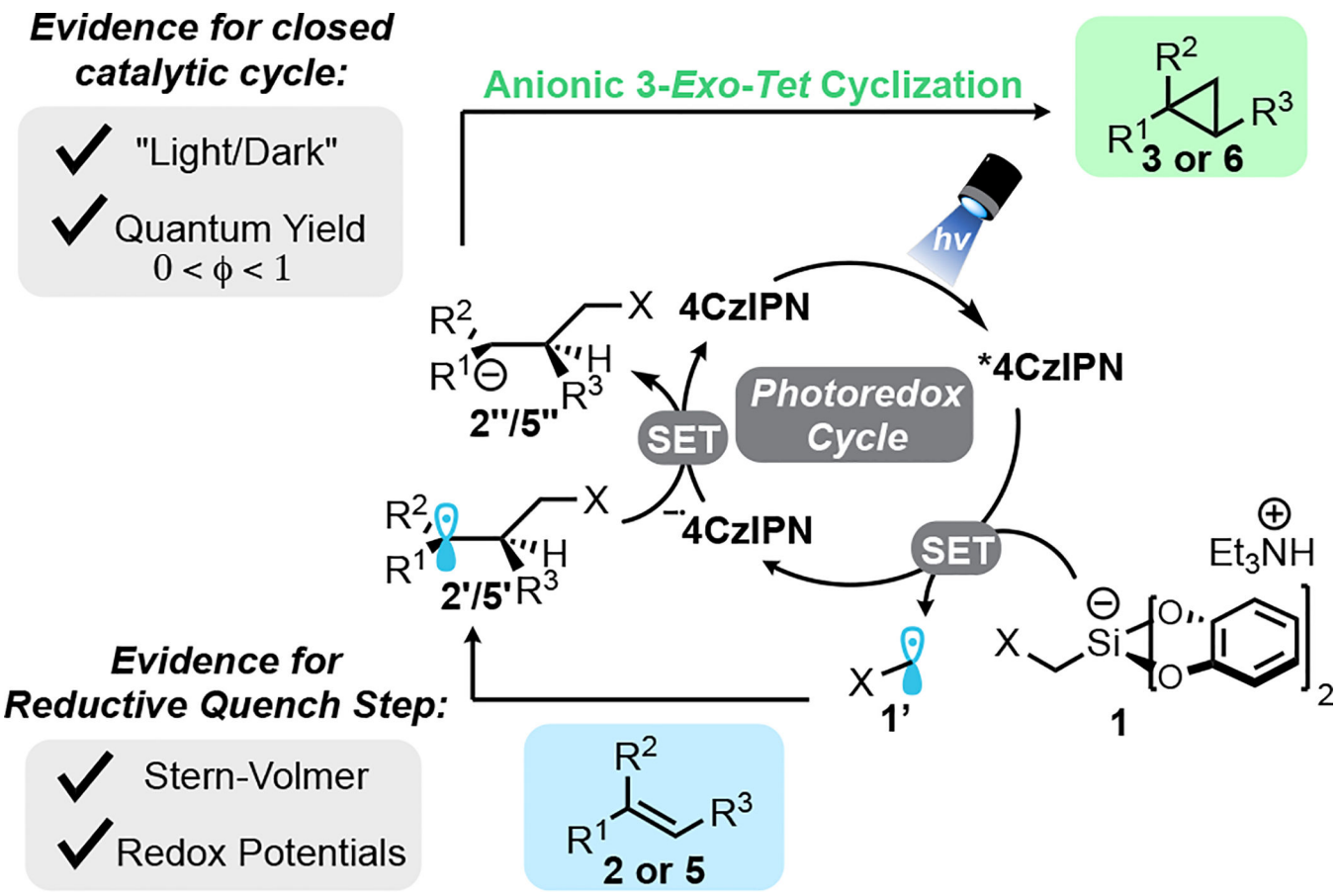


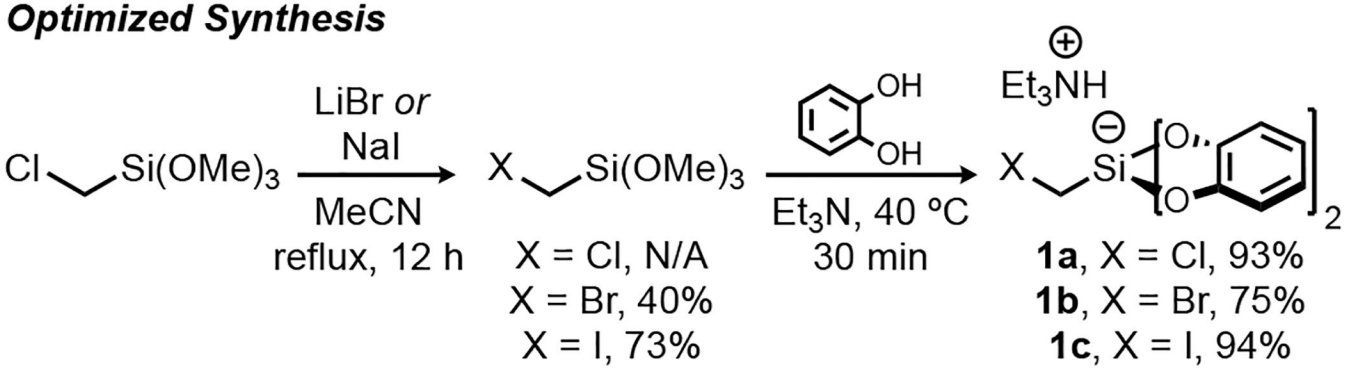
Figure 4.
Plausible Mechanism for Cyclopropanation.

Considerations in Reagent Design

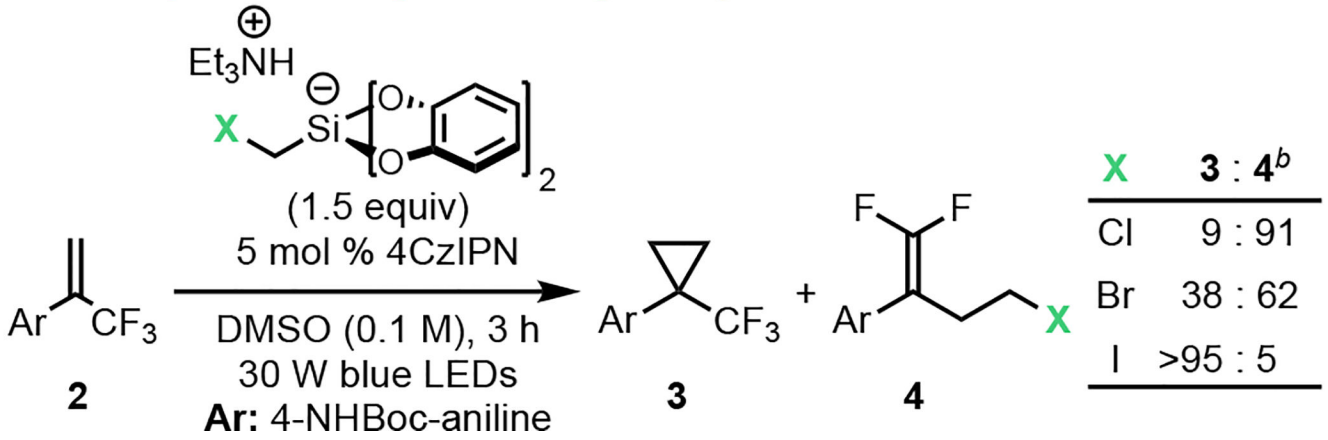
- *Inexpensive*
- *Ease of preparation*
- *Bench-top stability*
- *Low oxidation potential*

Synthesis and Evaluation of Bifunctional Silicate Reagents

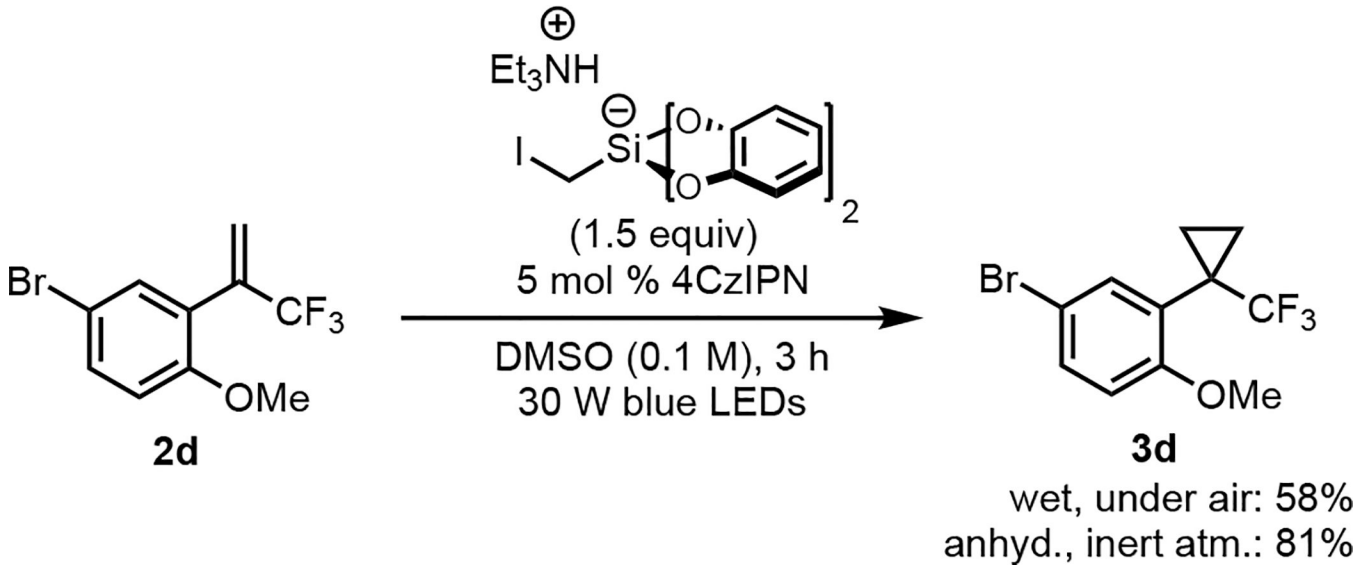
Optimized Synthesis



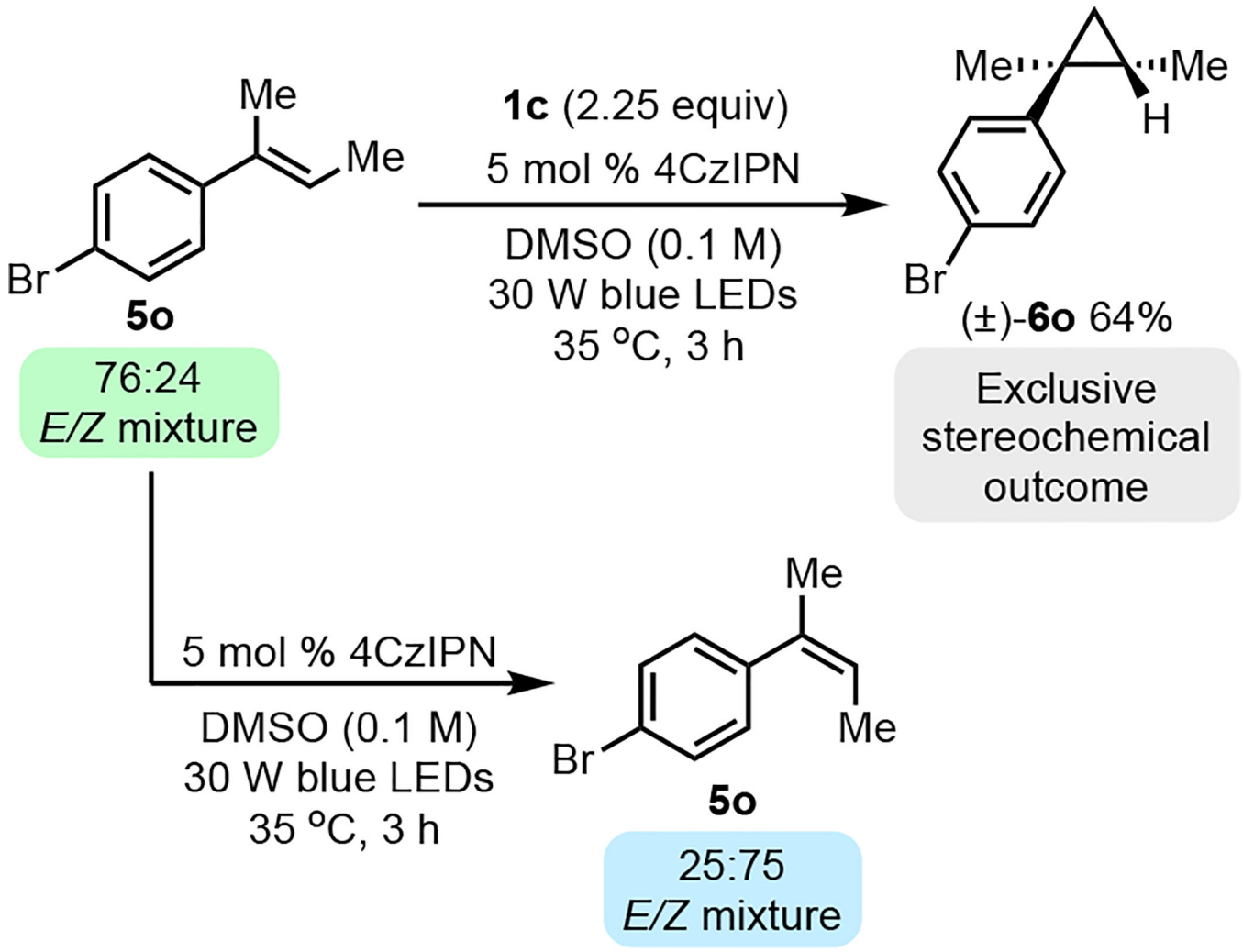
Impact of Halogen Leaving Group on Product Distribution[a]



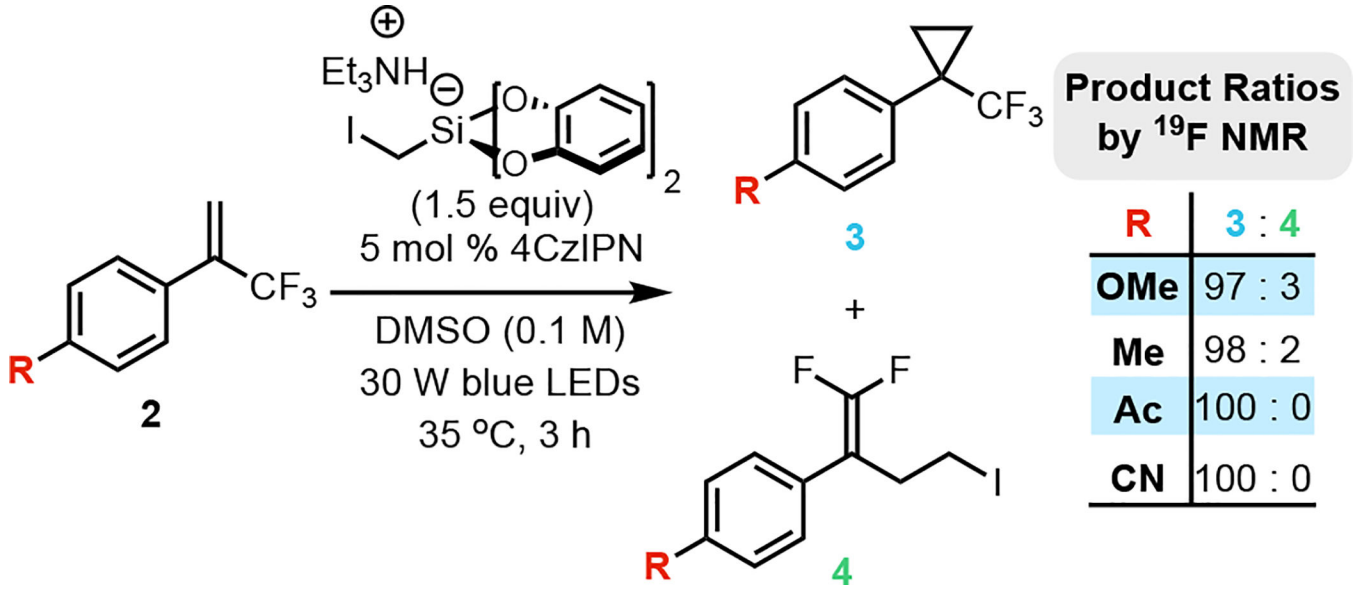
Scheme 1.
Synthesis and Optimization of the Bifunctional Silicate Reagent



Scheme 2.
Zero Precaution Reaction

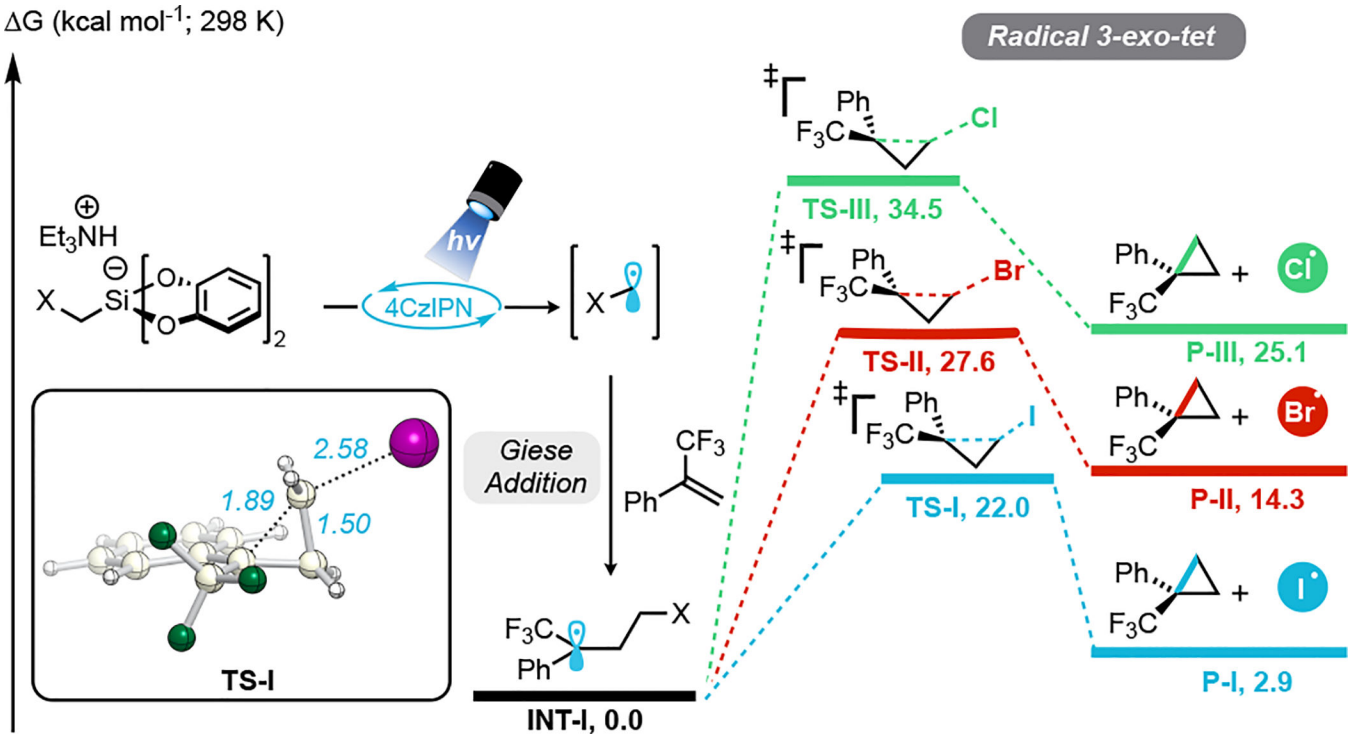


Scheme 3.
Stereoconvergent Cyclopropanation



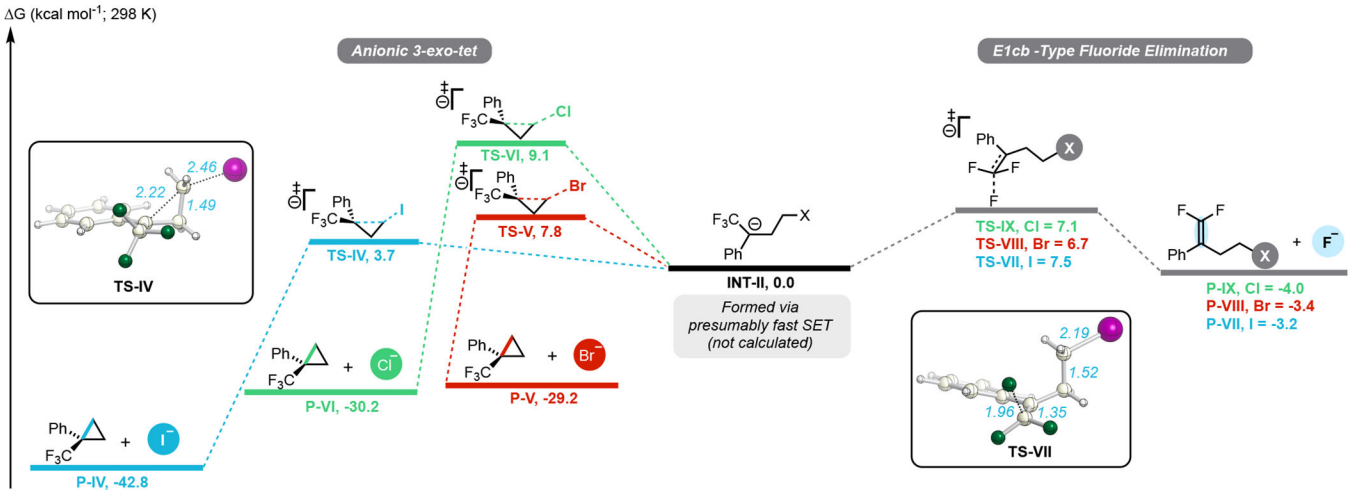
Scheme 4.

Insensitivity of Cyclopropanation to Electronics[a]



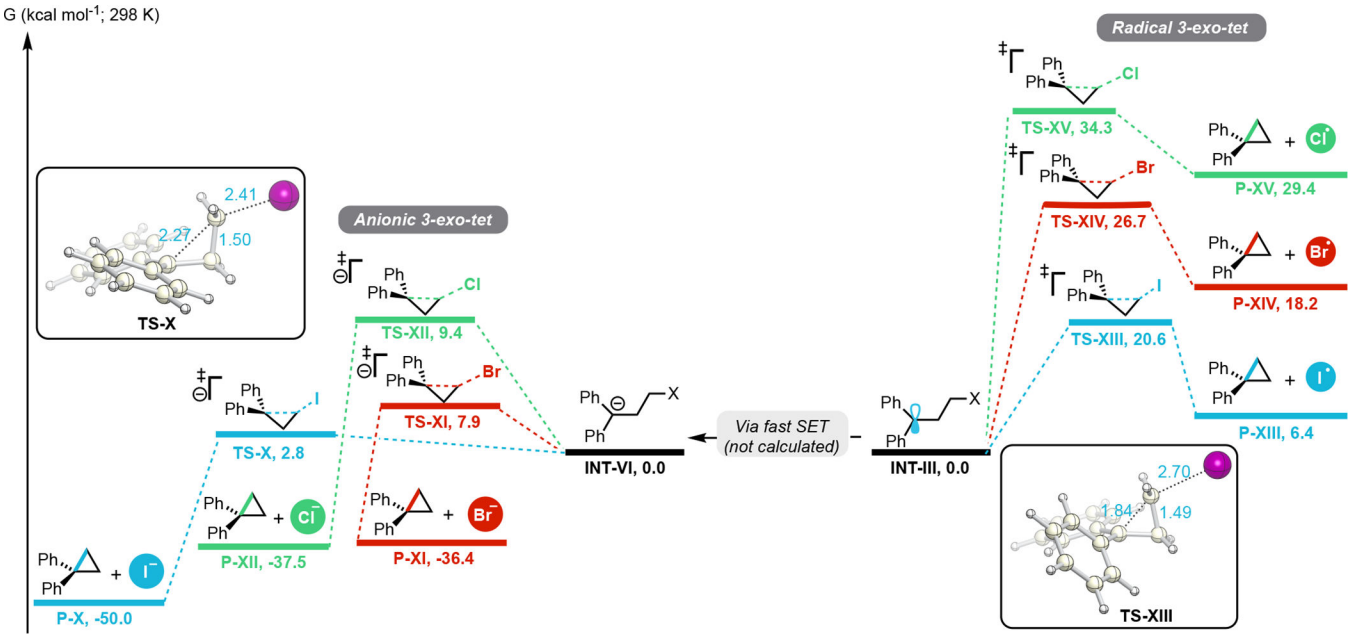
Scheme 5.

Influence of Halogen Substituent on the Barriers for the S_H2-type 3-*exo-tet* Cyclization Pathway.[a]



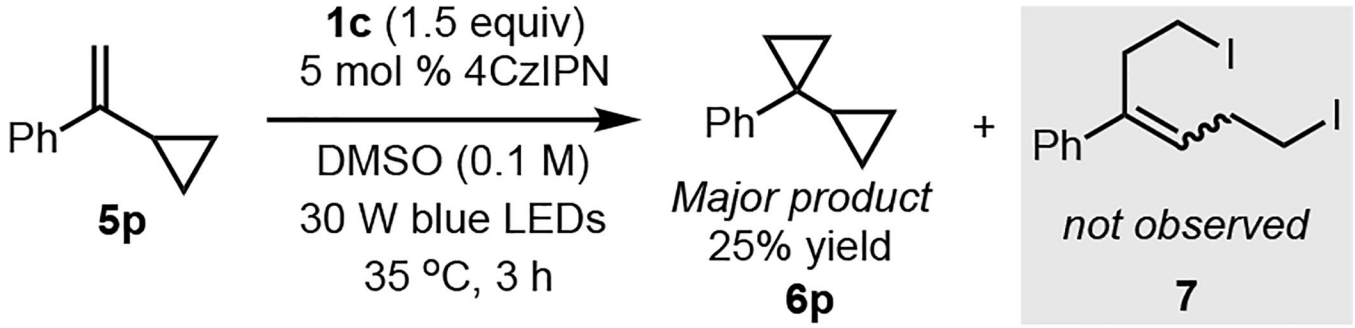
Scheme 6.

Energetics of Anionic 3-exo-tet Cyclization Versus E1cb-type Fluoride Elimination[a]

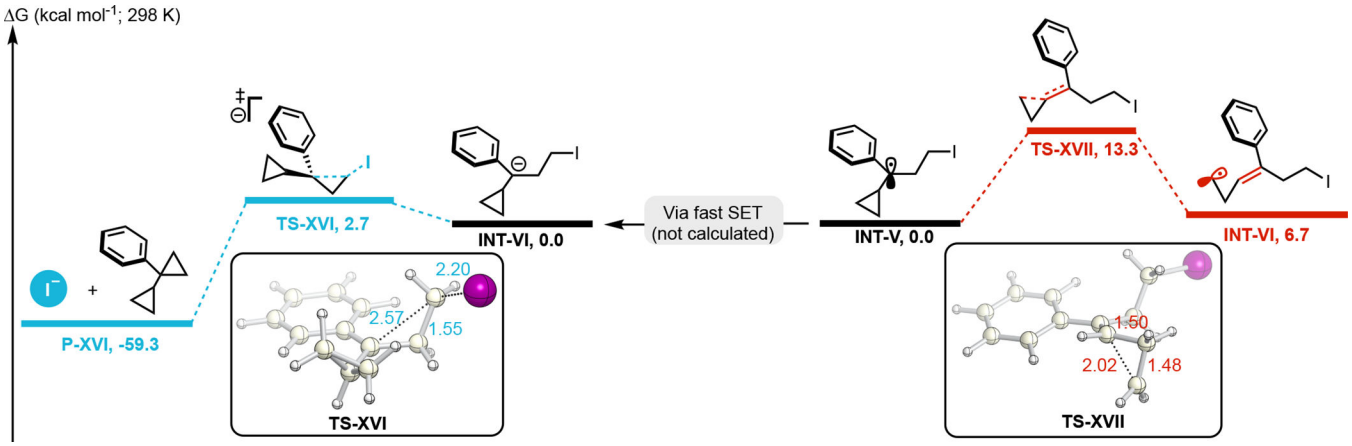


Scheme 7.

Energetics of Anionic Versus Radical 3-*exo-tet* Cyclization in a Non-α-Trifluoromethyl System[a]



Scheme 8.
Bracketing Experiment.



Scheme 9.

Energetics of Ring Opening Versus Anionic Cyclization[a]

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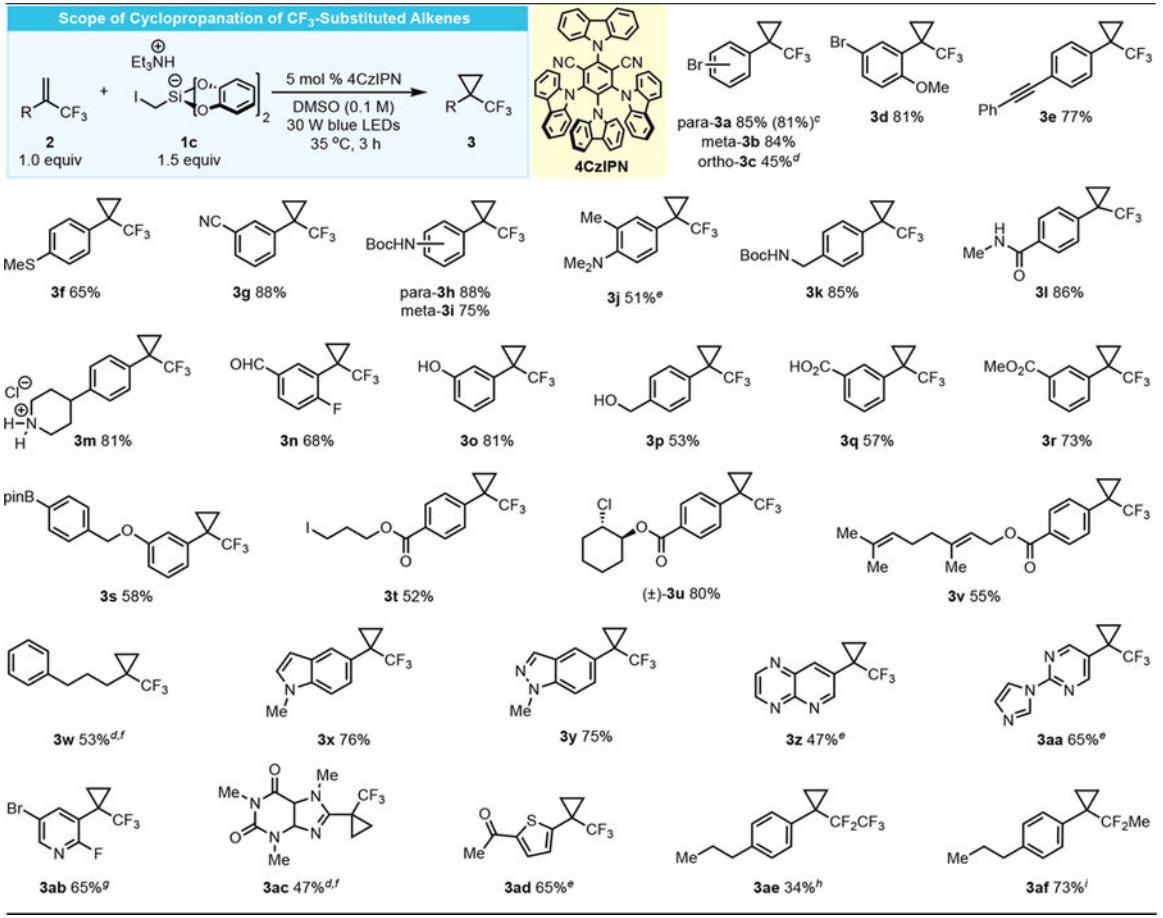
Table 1.

Iodomethylsilicate Enables Facile Synthesis of TFCps[a,b]



[a]All values indicate the yield of the isolated product. pin = 2,3-dimethylbutane-2,3-diol.

[b]General reaction conditions: iodosilicate (1.5 equiv, 0.75 mmol), alkene (1.0 equiv, 0.50 mmol), 4CzIPN (5 mol %, 0.025 mmol), DMSO (0.1 M), 3 h, irradiating with blue LEDs (30 W). See the Supporting Information for details.

[c] Isolated yield on 5 mmol scale.

[d] Conducted using 2.0 equiv of silicate.

[e] Conducted using 1.75 equiv of silicate.

[f] Reaction run for 24 h.

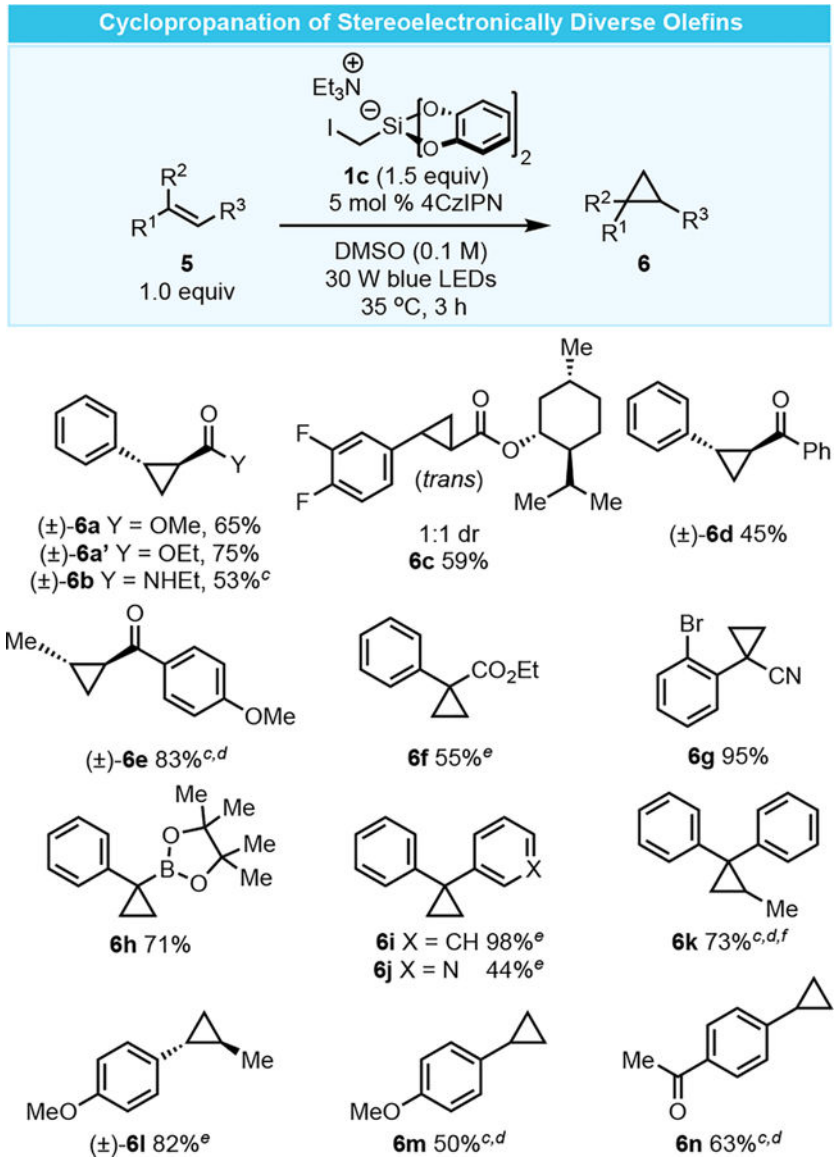
[g] Isolated as a 95:5 mixture of product and 2-methylated product.

[h] 77:23 ratio of cyclopropane to fluoride elimination *via* ^{19}F NMR of the crude reaction mixture; olefin removed *via* Ag-doped SiO_2

[i] 92:8 ratio of cyclopropane to fluoride elimination, *via* ^{19}F NMR of the crude reaction mixture; olefin removed *via* Ag-doped SiO_2.

Table 2.

Cyclopropanation of Non-α-Trifluoromethyl-Substituted Olefins[a,b]



[a] All values indicate the yield of the isolated product.

[b] General reaction conditions: iodosilicate (1.5 equiv, 0.75 mmol), alkene (1.0 equiv, 0.50 mmol), 4CzIPN (5 mol %, 0.025 mmol), DMSO (0.1 M), 3 h, irradiating with blue LEDs (30 W). See the Supporting Information for details.

[c] Conducted using 2.0 equiv of silicate.

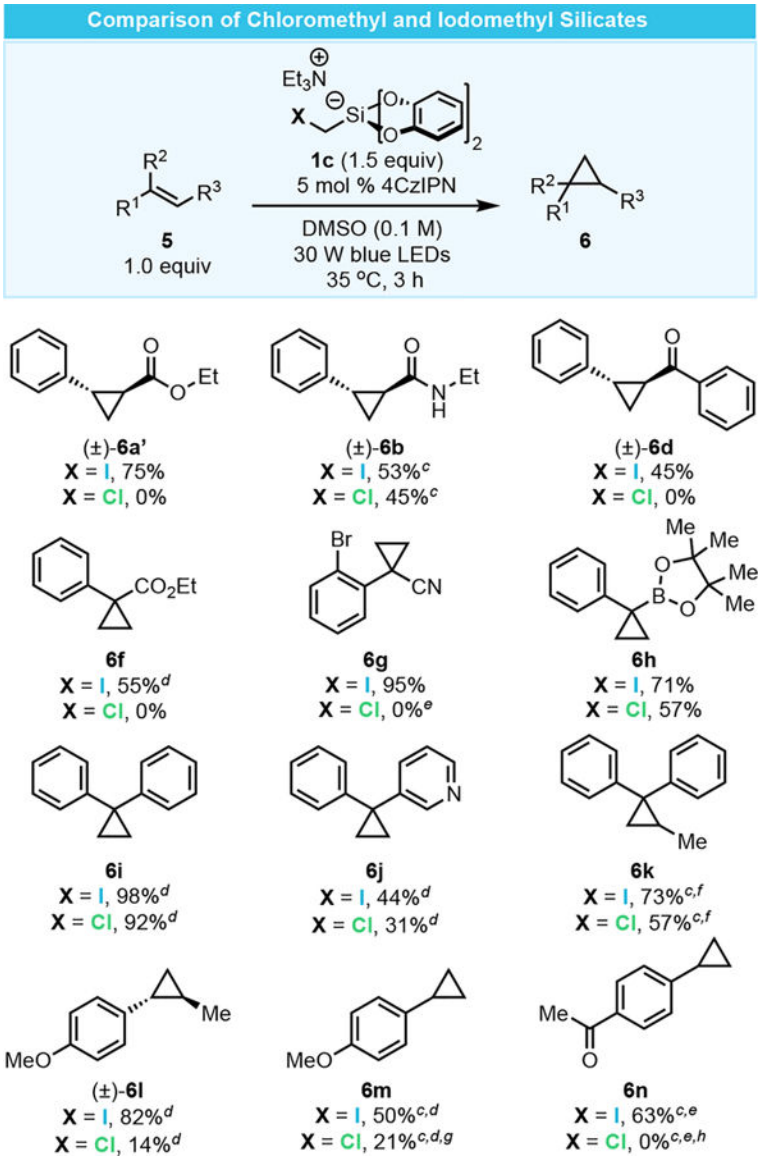
[d] Reaction run for 18 h.

[e] Conducted using 1.75 equiv of silicate.

[f]Product isolated as a 94:6 mixture of product and starting material.

Table 3.

Cyclopropanation Using Chloromethylsilicate[a,b]



[a]All values indicate the yield of the isolated product.

[b]General reaction conditions: iodosilicate (1.5 equiv, 0.75 mmol), alkene (1.0 equiv, 0.50 mmol), 4CzIPN (5 mol %, 0.025 mmol), DMSO (0.1 M), 3 h, irradiating with blue LEDs (30 W). See the Supporting Information for details.

[c]Conducted using 2.0 equiv of silicate.

[d]Conducted using 1.75 equiv of silicate.

[e]Isolated 66% yield of noncyclized Giese-type addition product.

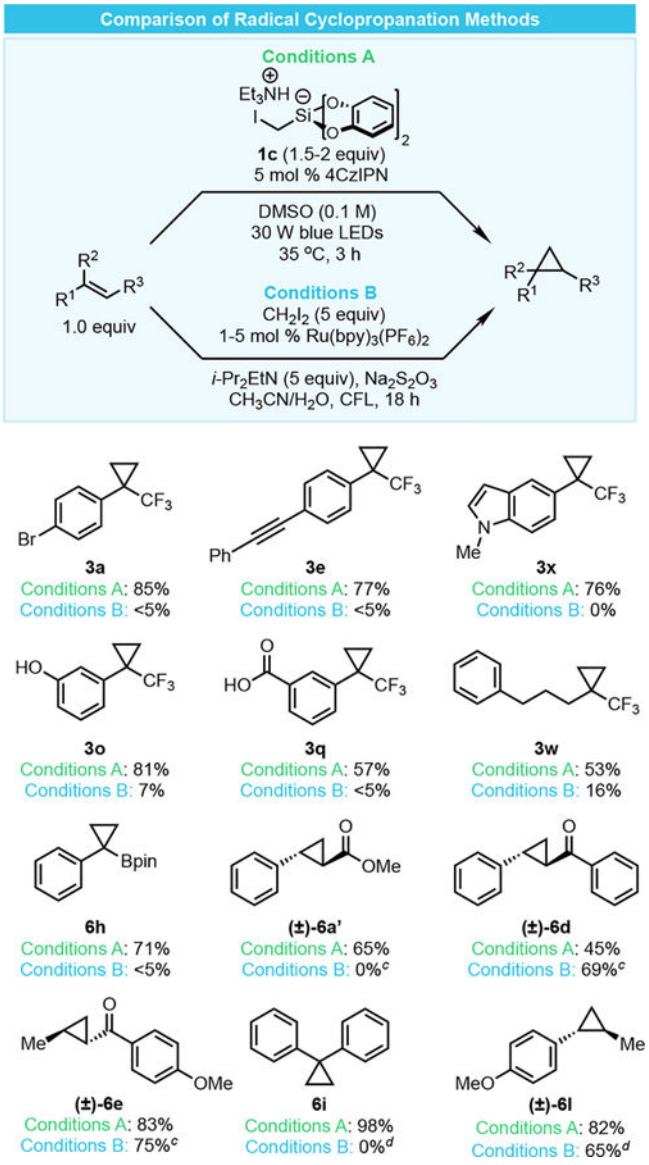
[f]Reaction run for 18 h.

[g] Isolated product contained 2% yield of non-cyclized Giese-type addition product.

[h] Isolated 60% yield of non-cyclized Giese-type addition product. See Supporting Information for details.

Table 4.

Comparison of Radical Cyclopropanation Methods[a,b]



[a] All values indicate the yield of the isolated product.

[b] Reactions using condition B were performed exactly as described in reference 11a.

[c] Yield reported in reference 11b.

[d] Yield reported in reference 11a.