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Research Article

Photocatalytic Oxidative Activation of Bicyclo[1.1.0]butanes for Formal [2σ+2π] Cycloadditions

Maxim Golfmann, Marius Reinhold, Jorn D. Steen, Malte S. Deike, Behrend Rodemann, Christopher Golz, Stefano Crespi,* and Johannes C. L. Walker*

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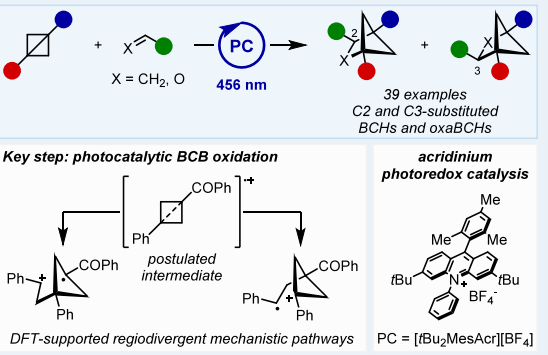
ABSTRACT: We report the discovery of an example of oxidative bicyclo[1.1.0]butane activation. This reactivity stands in contrast to well-established strain-release nucleophile addition and reductive activation and opens up further possibilities for exploiting bicyclo[1.1.0]butanes in synthesis. Using a strongly oxidizing acridinium organophotocatalyst, the formal [2σ+2π] cycloaddition between bicyclo[1.1.0]butanes and alkenes or aldehydes leads to the corresponding bicyclo[2.1.1]hexanes or oxabicyclo[2.1.1]hexanes. The subtle interplay between bicyclo[1.1.0]-butane and alkene identity dictates the mechanism of the reaction, with regiodivergent pathways providing complementary reaction products in up to >20:1 regioselectivity. A mechanistic investigation including electrochemical, photophysical, radical trapping, and computational studies support the oxidative mechanisms proposed.



KEYWORDS: *Bicyclo[1.1.0]butane, Bicyclo[2.1.1]hexane, Oxabiyclo[2.1.1]hexane, Photoredox catalysis, Oxidation*

INTRODUCTION

Bicyclo[1.1.0]butanes (BCBs) are powerful building blocks in organic synthesis, and provide a flexible starting point to a wide range of structural motifs.[1] They count as some of the most highly strained isolable organic compounds (64 kcal mol^{-1}),[2] and this ring strain manifests itself in the weak and highly reactive central C−C bond. The chemistry of BCBs is typically based on cleavage of this strained C−C bond, with the accompanying strain-release the major energetic driving force (Scheme 1A). BCBs have been widely investigated in the context of polar reactivity with nucleophiles[3] and electrophiles,[4] and equivalent additions of radicals have also been reported.[5] More recently, energy transfer photocatalysis has emerged as a powerful method of BCB activation, leading to cleavage of the central C−C bond and formation of a putative diradical intermediate.[6,7] Reductive BCB activation via single-electron reduction of bridgehead carbonyls has been achieved though transition metal,[8a,d] photoredox,[8b,9] and pyridine boryl catalysis approaches,[8c] and reductive boronyl catalysis has also been used to activate pyridine-substituted BCBs.[10] Gryko and co-workers also reported an Umpolung approach to BCB activation, using a Co(I) catalyst to reduce electron-poor BCBs.[11] Despite the rapidly expanding interest in BCB chemistry and the opportunities to be gained by developing new methods for their activation, the alternative *oxidative* activation pathway has remained largely uninvestigated.[12] Gassmann and co-workers first reported the single-electron oxidation of a BCB in 1979,[13] but preparative applications of the BCB radical cation have since then remained few and far between (Scheme 1B). One early example was the photochemical oxidation of 1,2,2-trimethylbicyclo[1.1.0]butane with stoichiometric 1-cyanonaphthalene in methanol, giving the methanol addition product,[14] and similar reactivity has also been reported for bridged BCB derivatives.[15] Gollnick and Weber also proposed electron-transfer as one possible mechanism for the photooxygenation of BCBs in an O_2 atmosphere.[16,17] Very recently, Glorius and co-workers reported a dearomative cycloaddition reaction between BCBs and phenols, where BCB oxidation was proposed as one potential reaction pathway.[18]

In line with our interest in preparing saturated polycyclic motifs,[19] we were attracted to BCBs as a general entry to bridged bicyclic scaffolds. Interest in such saturated, three-dimensional compounds has surged in recent times as they have been proposed as promising fragments for drug discovery in the context of the "escape from flatland" hypothesis[20] and as benzene bioisosteres.[21] The presence of substituent vectors not native to aromatic chemical space also enables the construction of compounds with unusual substituent geometries.[21e]

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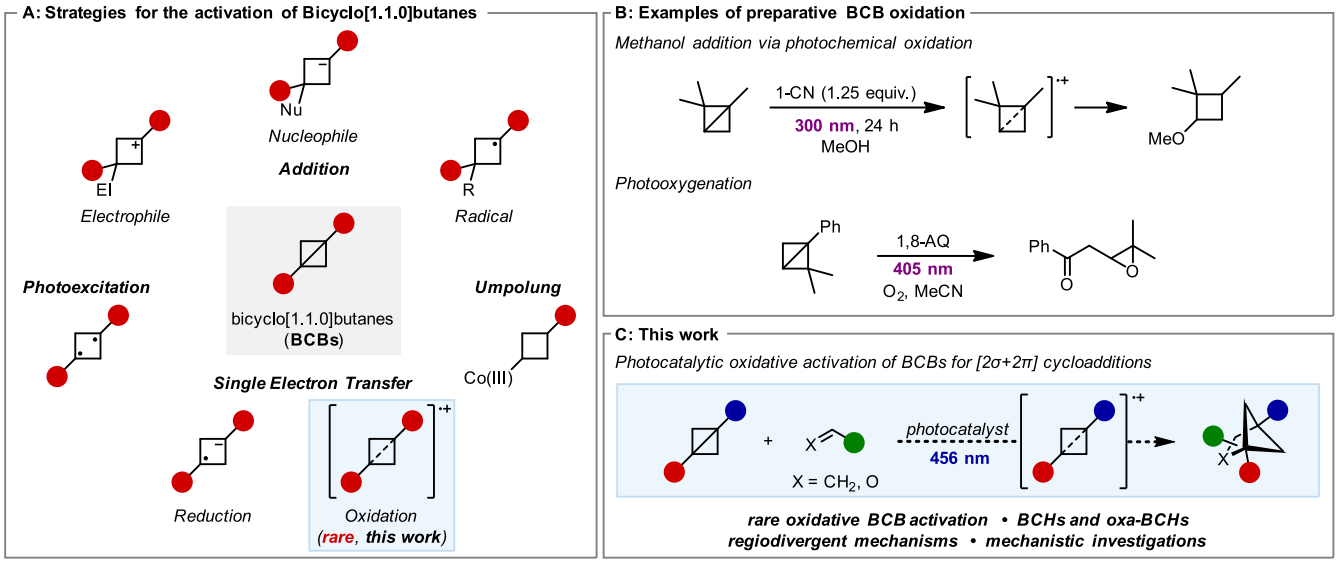
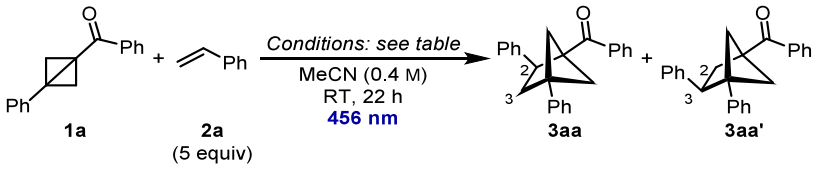
Scheme 1. Modes of Bicyclo[1.1.0]butane Activation[a]



[a](A) Strategies for the activation of bicyclo[1.1.0]butanes. (B) Examples of preparative BCB oxidation.[14b,16] (C) This work: photocatalytic oxidative activation of BCBs for [2σ+2π] cycloadditions. 1-CN = 1-cyanonaphthalene. 1,8-AQ = 1,8-anthraquinone.

Table 1. Optimization of Reaction Conditions[a]



entry	conditions	yield (%)[b]	3aa:3aa′
1[c]	$[Ru(bpy)_3](PF_6)_2$ (5 mol %), $Gd(OTf)_3$ (1 equiv), TMEDA (1 equiv)	<5	
2[c]	4CzIPN (5 mol %), $Gd(OTf)_3$ (1 equiv), TMEDA (1 equiv)	3	n.d.
3[c,d]	4CzIPN (5 mol %)	77	7:1
4[c,d]	$[t\mathrm{Bu_2MesAcr}][BF_4]$ (5 mol %)	94	3.9:1
5	**$[t\mathrm{Bu_2MesAcr}][BF_4]$ (5 mol %)**	**quant.**	4.2:1
6	as entry 5 but 0.2 mmol scale and 5 h	74[e]	2.1:1
7	as entry 5 but 1.0 mmol scale and 36 h	67[e]	2.5:1
8	as entry 6 but no photocatalyst	<5	
9	as entry 6 but no 456 nm LEDs	<5	
10	$Gd(OTf)_3$ (1 equiv), no 456 nm LEDs	<5	

[a]General reaction conditions: 0.05 mmol **1a**, 5 equiv. **2a**, MeCN (0.1 M), RT, 456 nm, 22 h. [b]Yield estimated by ^{1}H NMR spectroscopy relative to CH_2Br_2 as an internal standard. [c]0.05 M concentration. [d]10 equiv **2a**. [e]Isolated yield. n.d. = not determined. bpy = 2,2′-bipyridine, Tf = trifluoromethanesulfonate, TMEDA = tetramethylethylenediamine.

We began by considering the reaction between BCBs and alkenes. Cairncross and Blanchard,[22a] de Meijere and co-workers,[22b] and Wipf and co-workers[22c] had previously demonstrated the thermal insertion of alkenes into BCBs to yield bicyclo[2.1.1]hexanes (BCHs). Recently, this reactivity has become more widely investigated. Brown and co-workers reported the formal [2σ+2π] cycloaddition between BCBs and alkenes via energy transfer photocatalysis and BCB photoexcitation.[7] Glorius and Bach have reported complementary photocatalytic energy transfer [2σ+2π] cycloadditions based on coumarin,[23a] quinolone,[23b] or azaarene photoexcitation.[23c] In these cases, the photoexcited intermediates react with the ground state BCB. Direct excitation of cyclobutenones and reaction with ground state BCBs has also been explored.[24] Lewis-acid-catalysis offers an alternative method of activating BCBs, and has proven successful for formal cycloadditions with ketenes[25] and indoles.[26] The addition of ester enolates also led to the corresponding 2-oxa-BCHs via an addition/intramolecular acyl substitution mechanism.[27] In the single-electron transfer regime, Procter,[8a] Shi,[8b] Wang,[8b] Zheng,[8d] and Li[10] all developed reductive routes to BCHs from BCBs, based on the catalytic reduction of pendant carbonyls or pyridines. Formal cycloadditions with aldehydes, imines, triazolinedione or nitrosoarenes have also been reported under various conditions, and provide access to sought-after heterocyclic BCB derivatives.[28] Oxidative approaches to these formal [2σ+2π] cycloaddition reactions have remained unreported, however. During final preparation of this manuscript, Glorius and co-workers reported related results focusing on the oxidative activation of ester-substituted BCBs for [2σ+2π] cycloaddition reactions with electronically unbiased alkenes.[29]

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Herein, we disclose the discovery of a rare example of a photocatalytic oxidative activation of BCBs, using a visible light-activated acridinium organophotocatalyst (Scheme 1C). Compared to the work of Glorius and Houk, our investigation focuses on ketone-substituted BCBs and we show that the radical cation intermediates react not only with alkenes but also with aldehydes to form both high-value BCH and oxaBCH scaffolds. In our case, ketone-substituted BCBs do not show reactivity with unbiased alkenes. Interestingly, the mechanistic picture for ketone-substituted BCBs is markedly more complex, and their radical cations demonstrate alternative and complementary electrophilic behavior to their ester-substituted counterparts. Through careful mechanistic investigations, we have uncovered two additional and new mechanistic pathways for this reaction, in addition to that reported by Glorius and Houk. Overall, depending on the combination of BCB and alkene used, one or more of three competing and regiodivergent pathways lead to the targeted products in up to >20:1 regioselectivity.

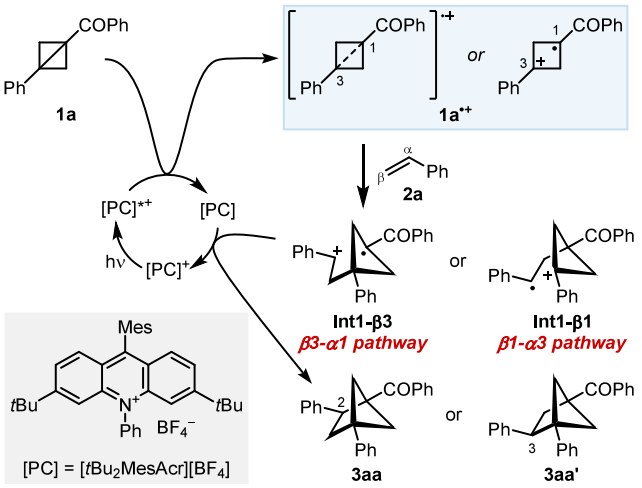
REACTION OPTIMIZATION

We began our study with the initial plan to develop a reductive activation of ketone-substituted BCB **1a**, initiating ring-opening via the ketyl radical anion. Use of conditions first described by Yoon and co-workers for the (3 + 2) cycloaddition of cyclopropyl ketones and styrenes led to no formation of the desired BCH **3aa** (Table 1, Entry 1).[30] By switching the ruthenium photocatalyst for 4CzIPN,[31] we were able to form the desired BCH **3aa** in 3% yield (Entry 2), and after removing $Gd(OTf)_3$ and TMEDA from the reaction and increasing the equivalents of styrene (**2a**), BCH **3aa** could be formed in 77% yield (Entry 3). At this stage, we identified the formation of two regioisomeric products: the C2 phenyl-substituted regioisomer **3aa** and the C3 phenyl-substituted regioisomer **3aa'**. However, further investigation of the substrate scope with 4CzIPN was limited by the efficient dimerization of styrenes.[19a] Screening other photocatalysts then led to the discovery that the acridinium photocatalyst 9-Mesityl-3,6-di*tert*-butyl-10-phenylacridinium tetrafluoroborate ($[tBu_2MesAcr][BF_4]$) was able to catalyze the reaction more efficiently and furnish BCH **3aa** in 94% yield, with only small amounts of styrene dimerization observed (Entry 4).[32] With this catalyst, the equivalents of styrene (**2a**) could also be lowered and the reaction concentration increased, leading to quantitative conversion to BCH **3aa** as a 4.2:1 regioisomeric mixture (Entry 5). When performing the reaction on 0.2 mmol scale, BCH **3aa** could be isolated in 74% yield (2.1:1 rr) (Entry 6), and on 1.00 mmol scale in 67% (2.5:1 rr) (Entry 7). In the absence of either photocatalyst or light, no reaction was observed (Entries 8 and 9), and with only $Gd(OTf)_3$ present, no product was formed, suggesting that Lewis acid-mediated donor−acceptor-type reactivity was not responsible for product formation (Entry 10, for further details of the optimization, see the Supporting Information).

BCB OXIDATION AND REACTION WITH ALKENES

In light of our original starting point, we were intrigued by the reactivity of the oxidizing acridinium catalyst. Measurement of the oxidation potential of BCB **1a** ($E_{p/2}$ = +1.47 V vs SCE) revealed that oxidation by $[tBu_2MesAcr][BF_4]$ ($E(\mathbf{PC}^{*+}/\mathbf{PC})$ = +2.08 V vs SCE) was indeed feasible.[32] Our preliminary mechanistic hypothesis for the reaction and formation of regioisomeric products focused on the formation of the putative radical cation intermediate $\mathbf{1a}^{\bullet+}$ (Scheme 2). We

Scheme 2. Preliminary Mechanistic Hypothesis[a]



[a]Mes = 2,4,6-trimethylphenyl.

considered two forms of radical cation $\mathbf{1a}^{\bullet+}$: a delocalized system and one with distinct radical and cationic centers based on the natural polarity of carbonyl-based compounds. We proposed that the two BCH regioisomers (**3aa** and **3aa'**) originated from regiodivergent reaction pathways from radical cation $\mathbf{1a}^{\bullet+}$. Either 1) nucleophilic attack from the β-position of styrene (**2a**) onto the C3-position of $\mathbf{1a}^{\bullet+}$ to give **Int1-β3**, followed by reduction and cyclization to C2-regioisomer **3aa** (β3-α1 pathway) or 2) radical-type attack from the C1-position of $\mathbf{1a}^{\bullet+}$ onto the β-position of styrene (**2a**) to give **Int1-β1**, followed by reduction and cyclization to C3-regioisomer **3aa'** (β1-α3 pathway).

The reaction between BCB **1a** and styrene (**2a**) delivered a 2.1:1 (**3aa**:**3aa'**) mixture of regioisomers, with the C2-regioisomer **3aa** being favored. Investigation of the substrate scope revealed that with other electron-neutral or electron-rich styrenes, the C2-regioisomers **3** were similarly favored (Scheme 3).[33] Styrenes bearing silane (to **3ab**), alkyne (to **3ac**), benzyl ether (to **3ad**), benzyl alcohol (to **3ae**), methoxy (to **3af**), and arene substituents (to **3ag**) could all be used to yield BCHs as their majority C2-regioisomer. A 1,1-disubstituted styrene could also be used to afford BCH **3ah**, also as the majority C2-regioisomer. The influence of steric hindrance of the alkene reactant on the reaction was investigated through use of differently substituted methylstyrenes. Substitution in all *para-* (to **3ai**), *meta-* (to **3aj**), and *ortho-* positions (to **3ak**) was tolerated, with only slightly lower conversion to the product for *meta-* and *ortho-* derivatives. Styrenes containing halogen functional groups also gave BCHs with the C2-regioisomer dominating, although here the selectivity was lower. Chlorine (to **3al**), fluorine (to **3am**), and trifluoromethyl substituents (to **3an**) were all tolerated. Indene (**2n**) displayed unusual reactivity, with BCH C3 regioisomer **3ao'** formed in high selectivity. The unusual selectivity of this reaction could be unambiguously confirmed by X-ray crystallography analysis of **3ao'**. Electron-poor styrenes continued the previously observed trend, delivering BCHs **3'**, predominantly as their C3-regioisomers. This included styrenes with nitrile (to **3ap'**), ester (to **3aq'**), and

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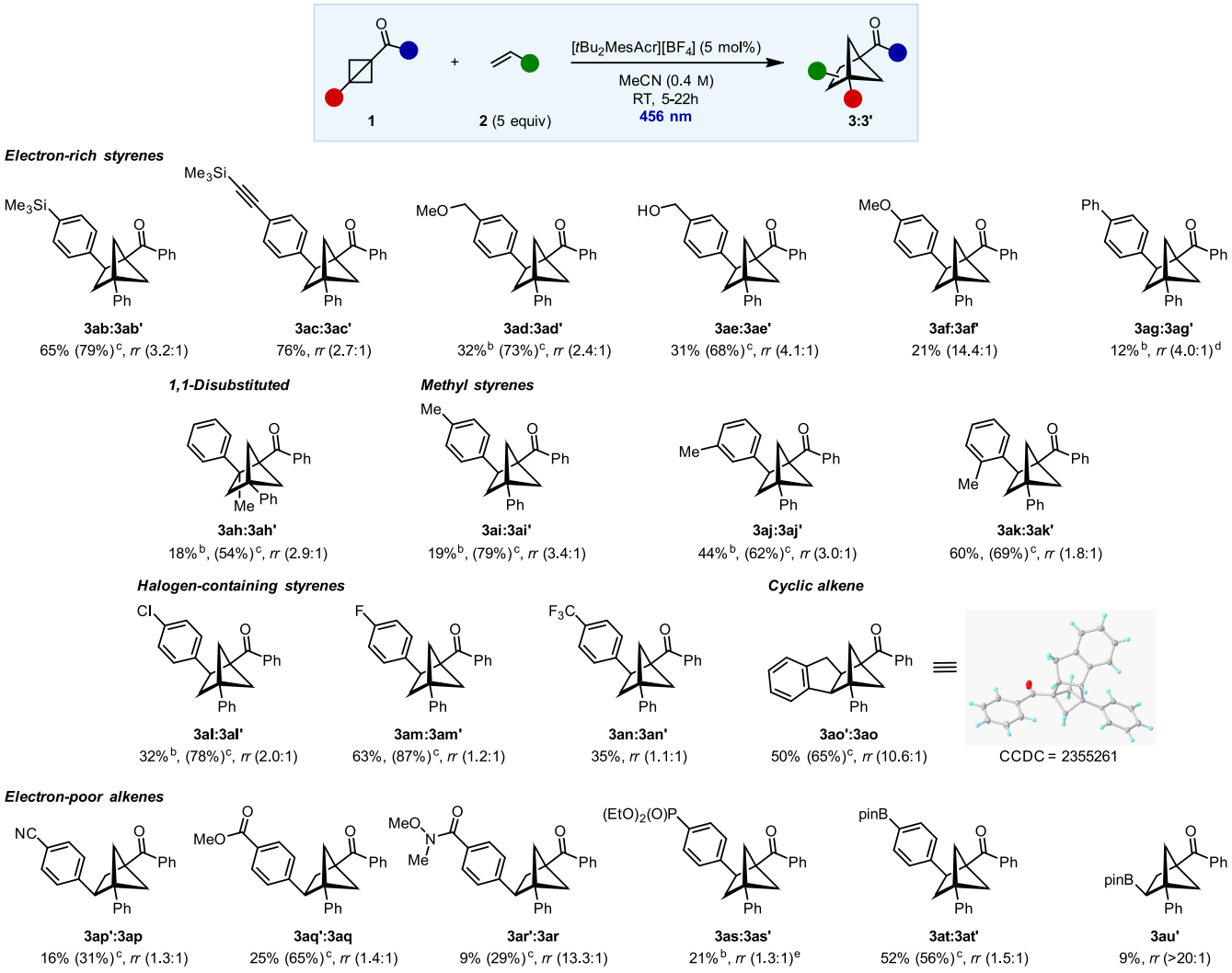
Scheme 3. Substrate Scope: Variation of Alkenes[a]



[a]Reactions were performed as described in Table 1, entry 6. *rr* was obtained by ^{1}H NMR spectroscopy of the crude reaction mixture, and yields are given after purification by flash column chromatography unless otherwise stated. [b]Yield after purification by HPLC. [c]Yield estimated by ^{1}H NMR spectroscopy of the crude reaction mixture relative to CH_2Br_2 as an internal standard. [d]*rr* obtained by ^{1}H NMR spectroscopy of purified material. [e]*rr* obtained by HPLC of purified material.

Weinreb amide substituents (to **3ar'**). The reduced nucleophilicity and increased electrophilicity of these styrene likely favors the β1-α3 radical attack mechanism and disfavors the β3-α1 nucleophilic attack mechanism from Scheme 2. A phosphonate ester-substituted styrene gave a slight preference for the C2-regioisomer **3as**, as did a pinacol boronate (as in **3at**). Reactions of BCB **1a** with a much more electron-deficient vinyl pinacol boronate ester showed exclusive (>20:1) selectivity for the C3-regioisomer **3au'**. Here, the β3-α1 pathway is seemingly completely suppressed. Unactivated aliphatic alkenes and electronically activated alkenes such as enol acetates and vinyl silanes were not suitable substrates for the reaction with BCB **1a** (for details, see Supporting Information).

We then moved to investigating BCBs with different substitution patterns (Scheme 4). BCBs with electron-rich and electron-poor aryl ketone substituents delivered the corresponding BCHs **3ba** and **3ca** in in 72% and 77% yield respectively, with no marked changes in regioselectivity compared to the electronically neutral model substrate **3aa**. An electron-poor bridgehead aryl substituent (as in **1d**) lead to a preference for the β3-α1 nucleophilic attack pathway, as seen in the formation of **3da** in 62% yield and 6:1 C3:C2 regioselectivity. We propose that the electron-poor arene increases the electrophilicity of radical cation **1d**$^{\bullet+}$. Variation of both BCB and styrene was possible, as seen for BCH **3el**, which was formed in 69% yield and 1.5:1 C3:C2 regioselectivity. Exchange of each aromatic substituent on the BCB was then assessed. The bridgehead methyl group in BCB **1f** led to a full selectivity switch to the β3-α1 nucleophilic attack pathway, with BCH **3aa** formed exclusively as the C2-regioisomer. As with BCB **1d**, we propose that the electrophilicity of radical cation **1d**$^{\bullet+}$ is increased. However, methyl ketone-substituted BCB **1g** led to BCH **3ga'** in 66% yield and moderate preference for the C3-regioisomer. In this case, we propose that the lack of an aryl substituent on the ketone decreases radical stability in **1a**$^{\bullet+}$ and **Int1-β3**, leading to a preference for the β1-α3 pathway. This trend is further observed with non-ketone-substituted BCBs **1h–k**, which delivered exclusively the C3-regioisomers of the BCHs.

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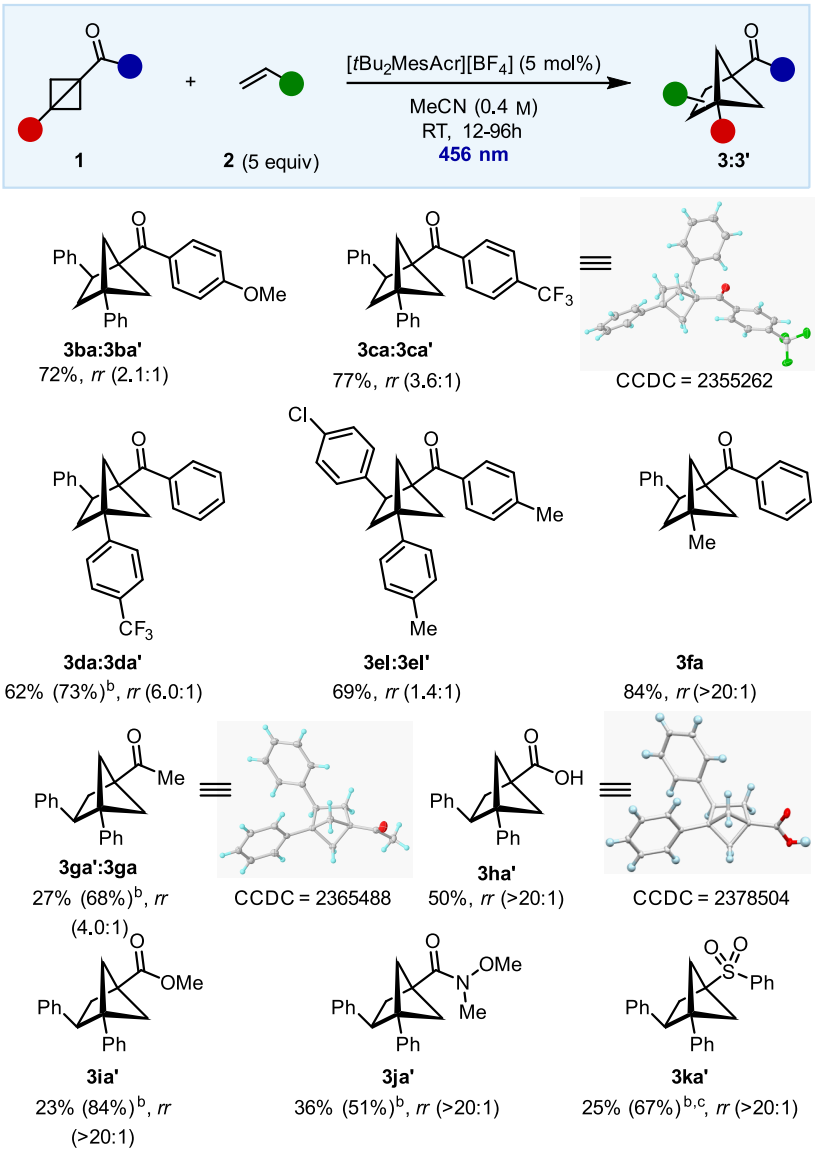
Scheme 4. Substrate Scope: Variation of BCBs[a]



[a]Reactions were performed as described in Table 1, entry 6. *rr* was obtained by ^{1}H NMR spectroscopy of the crude reaction mixture, and yields are given after purification by flash column chromatography. [b]Yield estimated by ^{1}H NMR spectroscopy of the crude reaction mixture relative to CH_2Br_2 as an internal standard. [c]10 mol % [tBu_2MesAcr][BF_4].

Carboxylic acid (**1h**), ester (**1i**), amide (**1j**), and sulfone-substituted BCBs (**1k**) all reacted with styrene (**2a**) to produce BCHs **3ha'−ka'** in >20:1 selectivity. In these cases, the reactivity via β3-α1 pathway is apparently completely suppressed. Monosubstituted BCBs were not suitable substrates for this reaction (for details, see Supporting Information).

BCB OXIDATION AND REACTION WITH ALDEHYDES

The use of cinnamaldehyde did not lead to BCH **3av** as anticipated, but rather *oxa*BCH **5av** via formal cycloaddition of the aldehyde moiety (Scheme 5). *oxa*BCH **5av** was isolated in 53% yield and as the majority C2-regioisomer. A short reaction optimization revealed CH_2Cl_2 to generally lead to higher isolated yields than MeCN, although for some oxaBCHs it also led to reduced regioselectivity (for details, see Supporting Information). Benzaldehyde could be used in this reaction, leading to *oxa*BCH **5aa** in 64% yield and full regioselectivity, and both electron-poor (to **5ab**) and electron-rich (to **5ac**) benzaldehyde derivatives were also tolerated. With *para*-methoxy benzaldehyde (**4c**), the C3-regiosomer was now favored. A halogenated benzaldehyde derivative delivered *oxa*BCH **5ad** and ethyl glyoxylate led to *oxa*BCH **5ae**. Use of alkyl ketone-substituted BCB **1g** led to *oxa*BCH **5ga** in 59% yield as a mixture of diastereomers and ester-substituted BCB **1i** led to formation of *oxa*BCH **5ia** in 43% yield as a single regioisomer. The regioselectivity of aldehyde addition is generally consistent with either nucleophilic attack of the radical cation $\mathbf{1a}^{\bullet+}$ by the aldehyde or radical attack of the aldehyde by $\mathbf{1a}^{\bullet+}$, in analogy to the mechanisms proposed in Scheme 2.[34]

MECHANISTIC STUDIES

To gain a better understanding of the mechanism of the reaction, a series of mechanistic studies were performed. Cyclic

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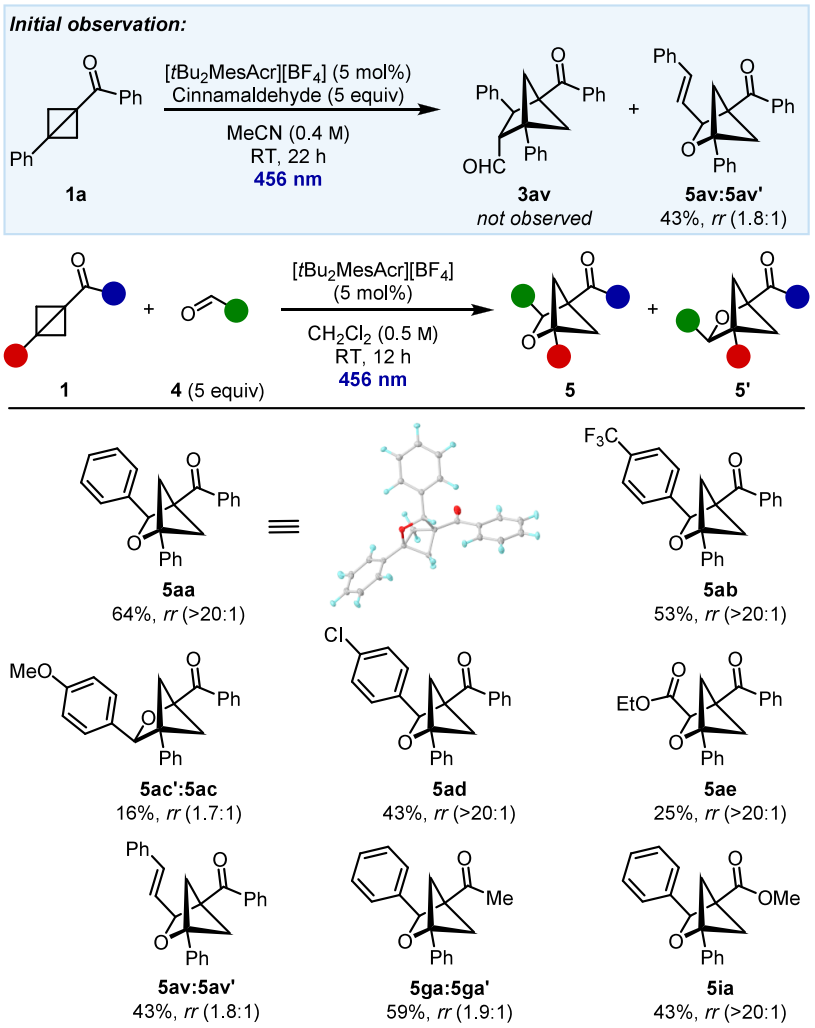
Scheme 5. Substrate Scope: BCB Oxidation and Reaction with Aldehydes[a]



[a]Reactions conditions: **1** (0.2 mmol), **4** (1.0 mmol), [tBu$_2$MesAcr][BF$_4$] (5 mol %) in CH_2Cl_2 (0.5 M) under argon atmosphere, at room temperature for 12 h with irradiation by 456 nm LEDs. *rr* was obtained by ^{1}H NMR spectroscopy of the crude reaction mixture, and yields are given after purification by flash column chromatography.

voltammetry confirmed that oxidation of phenyl ketone-substituted BCB **1a** ($E_{p/2}$ = +1.47 V vs SCE) by [tBu$_2$MesAcr]-[BF$_4$] (E([PC]*/[PC]$^-$) = +2.08 V vs SCE)[32] is thermodynamically feasible (Scheme 6A, cyclic voltammograms can be found in the Supporting Information). Although styrene (**2a**) oxidation is in principle also possible (+1.97 V vs SCE),[35] it is thermodynamically less favorable than for BCB **1a**, and styrene (**2a**) is also a less efficient quencher of the photocatalyst than BCB **1a** (*vide infra*). We therefore propose that styrene (**2a**) oxidation is unlikely to be a dominant pathway in most reactions. In addition, density functional theory (DFT) calculations indicate that the reactant complex [**1a**$^+$ + **2a**] is 4.6 kcal mol^{-1} more stable than [**1a** + **2a**$^+$], suggesting that even were styrene (**2a**) oxidation to take place, electron transfer from BCB (**1a**) to oxidized styrene (**2a**$^+$) would likely be facile (see Supporting Information for further details). No significant change in oxidation potential was seen for methyl ketone **1g** ($E_{p/2}$ = +1.49 V vs SCE), with slightly higher, although still accessible, oxidation potentials measured for ester **1i** ($E_{p/2}$ = +1.56 V vs SCE), sulfone **1k** ($E_{p/2}$ = +1.67 V vs SCE), and methyl-substituted BCB **1f** ($E_{p/2}$ = +1.67 V vs SCE). The higher oxidation potentials for these substrates reflect the ability of bridgehead phenyl and carbonyl substituents to stabilize the radical cation intermediate through delocalization. The reduction potential of the BCBs (e.g., $E_{p/2}$ (**1a**) = −1.63 V vs SCE) is too high for BCB reduction by the reduced photocatalyst (E([PC]$^+$/[PC]) = −0.59 V vs SCE)[32] to be thermodynamically feasible and the proposed low triplet excitation energy of acridinium photocatalysts (E_T ∼ 45 kcal mol^{-1})[36] similarly suggests triplet energy transfer to styrene (E_T = 61 kcal mol^{-1})[37] or BCB is unlikely.[7] Interestingly, Stern−Volmer quenching studies suggested that quenching of photoexcited [tBu$_2$MesAcr][BF$_4$] by all of BCBs **1a**, **1g** and **1i**, indene (**2o**), and styrene (**2a**) is possible to varying degrees (Scheme 6B). The most efficient quencher is indene (**2o**), followed by phenyl-substituted BCBs **1a** and **1i** (ketone or ester substitution appears to have little impact on quenching ability), styrene (**2a**), and methyl-substituted BCB **1g**. The stronger quenching ability of indene (**2o**) compared to BCBs **1a** hints at a possible change in mechanism toward BCHs **3ao**, which was formed in 10.6:1 rr. Separate Stern−Volmer quenching studies for the aldehyde insertion reaction demonstrated that the aldehyde component (either benzaldehyde (**4a**) or the more electron-rich *p*-anisaldehyde (**4c**)) does

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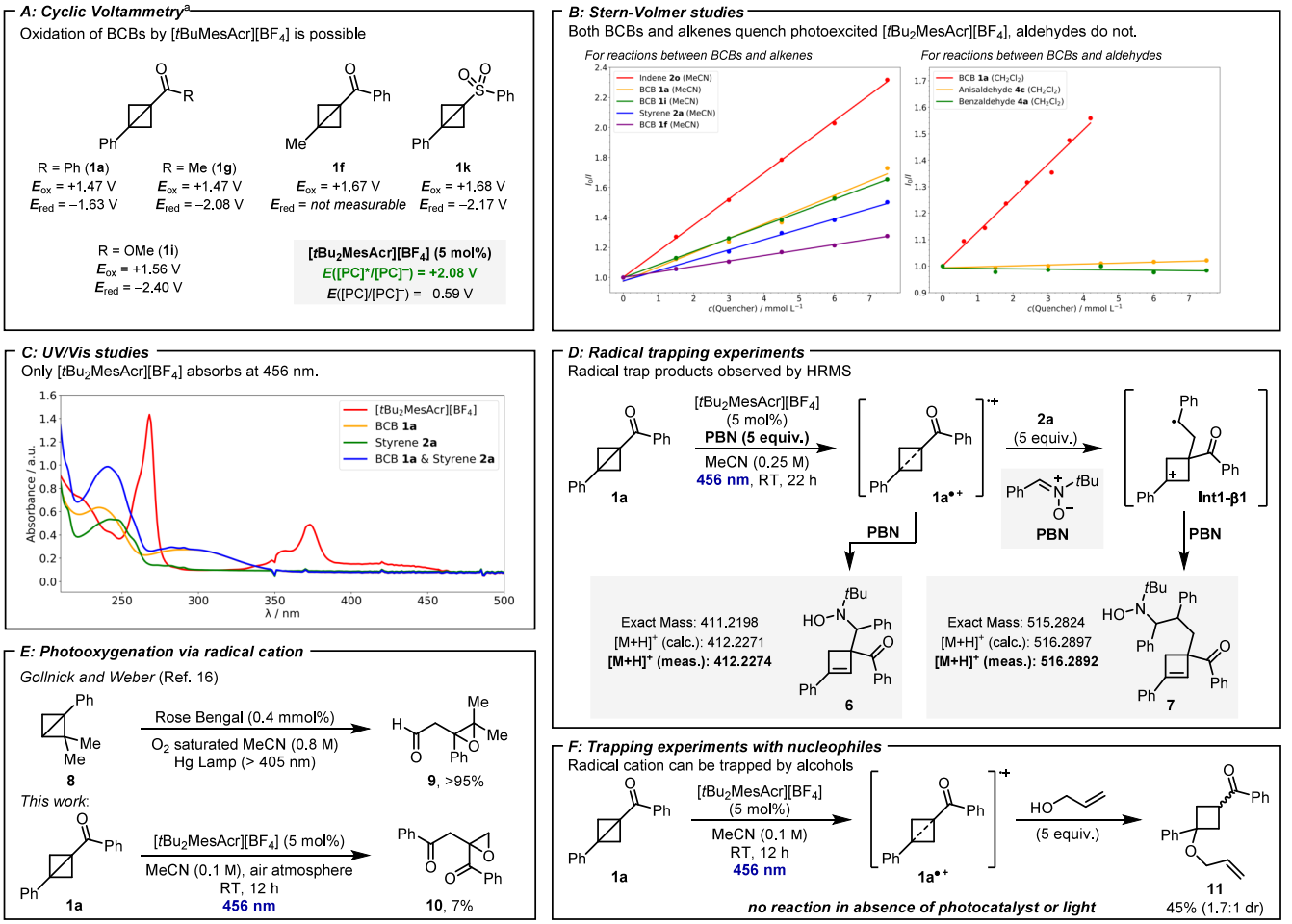
Scheme 6. Mechanistic Investigations[b]



[a]Irreversible redox potentials are all given as half potentials vs SCE. PBN = *N*-*tert*-butyl-α-phenylnitrone. [b](A) Cyclic voltammetry. (B) Stern−Volmer studies. (C) UV/Vis studies. (D) Radical trapping experiments. (E) Photooxygenation via radical cation. (F) Trapping experiments with nucleophiles.

not quench the photoexcited photocatalyst. UV/vis spectra demonstrated that only the [tBu$_2$MesAcr][BF$_4$] catalyst can absorb around 456 nm; neither BCB **1a** or styrene (**2a**) alone, nor the two in combination showed any absorption at this wavelength (Scheme 6C). We then performed radical-trapping experiments to provide evidence for the formation of the proposed radical cation intermediates (Scheme 6D). Five Equivalents of *N*-*t*Bu-α-phenylnitrone (PBN) were added to the reaction with BCB **1a**, both with and without styrene (**2a**). In the absence of styrene (**2a**), a peak consistent with PBN−adduct **6** (arising from **1a**$^{\bullet+}$) was observed by high-resolution mass spectrometry. In the presence of 5 equiv. styrene, a peak consistent with this adduct could again be observed, along with a peak for PBN−styrene−BCB adduct **7** (arising from **Int1**−**3aa**). The presence of these peaks is consistent with the formation of the radical intermediates **1a**$^{\bullet+}$ and **Int1-β3** (or **Int1-β1**) proposed. Further reactivity consistent with the formation of a radical cation could also be observed. Reaction of BCB **1a** in an air atmosphere led to formation of epoxyketone **10**, which mirrors the previous result of Gollnick and Weber, who reported the photooxygenation of BCB **8** to epoxyaldehyde **9** via an intermediate radical cation (Scheme 6E).[16] Finally, reaction between BCB **1a** and allyl alcohol led to formation of ether **11** in 45% yield as a mixture of *syn* and *anti*-diastereomers (Scheme 6F). In the absence of light or photocatalyst, no reaction was observed, which is consistent with ether formation via nucleophilic attack of the photoredox-generated radical cation. The regioselectivity of the reaction was confirmed by 2D-NMR spectroscopy, and is consistent with our proposal of nucleophilic attack at C3-position of radical cation **1a**$^{\bullet+}$ en-route to the C3-regioisomers of BCHs **3** (cf. Scheme 2).

COMPUTATIONAL STUDIES

Studying the proposed radical cation **1a**$^{\bullet+}$ by DFT revealed that the reaction with styrene (**2a**) involves the interaction of the **1a**$^{\bullet+}$ characterized by a relatively flat geometry at the four-membered ring, with a pronounced bond-breakage between the C1 and C3 carbons of the BCB core (see Supporting Information, Table S13). This conformer is slightly favored compared to the folded radical cation (0.29 kcal mol^{-1} at the ωB97M-V/def2-QZVP/CPCM(CH$_3$CN)//r^{2}SCAN-3c/CPCM(CH$_3$CN) level). The first bond formation most likely involves the interaction between the β-carbon of styrene and either C1 or C3 of **1a**$^{\bullet+}$, with the first transition states (**TS1**) characterized by the lowest energies 13.5 and 5.5 kcal mol^{-1} respectively (Scheme 7). Transition states involving attack of the styrene α-carbon are much higher in energy. The second

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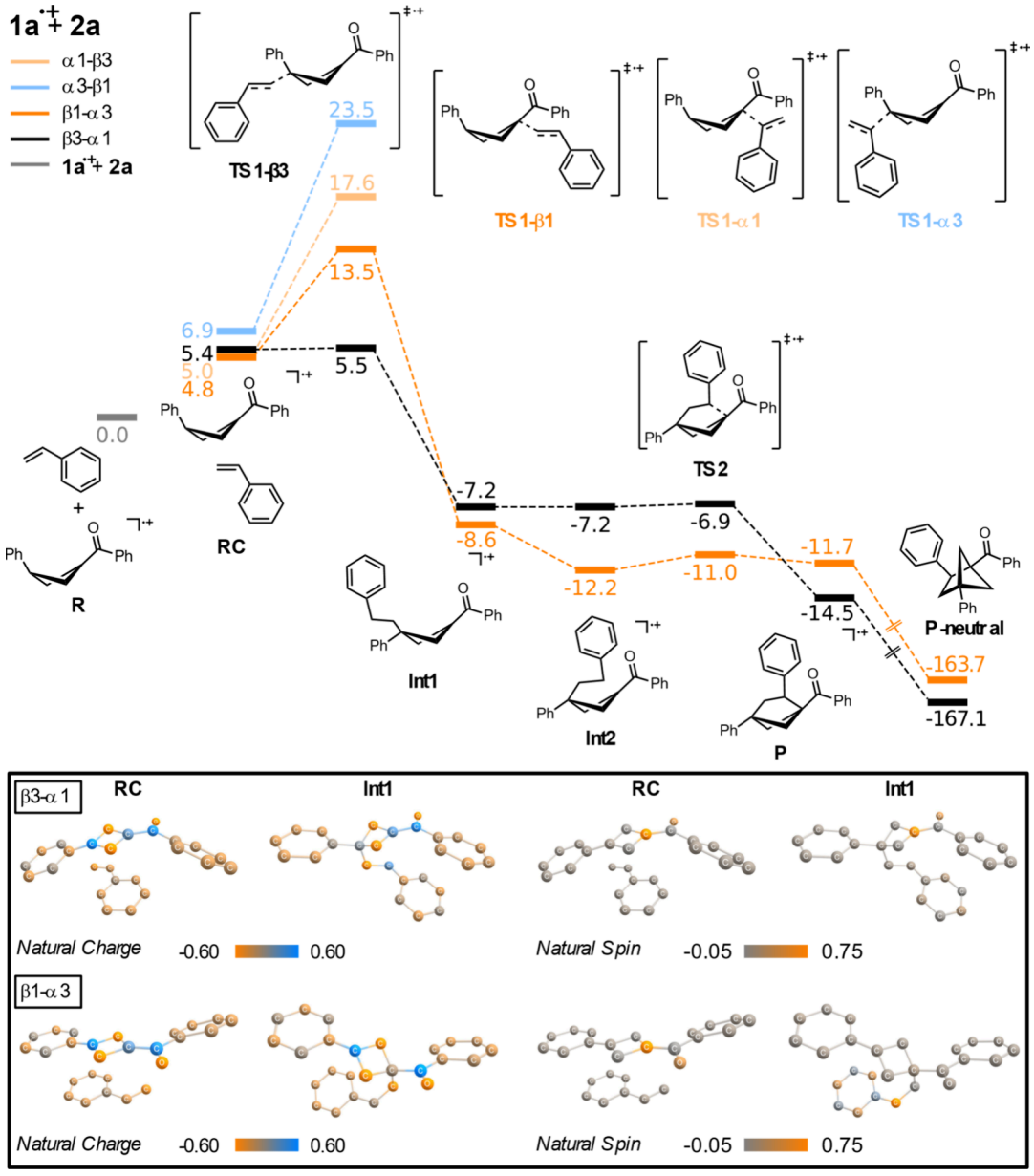
Scheme 7. Energy Diagram of the Four Radical Cation Pathways Towards Formation of the Product of 1a with 2a[a]



[a]All geometries optimized at the ωB97M-V/def2-QZVP/CPCM(CH_3CN)//r^{2}SCAN-3c/CPCM(CH_3CN) level. The values are Gibbs free energies in kcal mol^{-1}. The reference is the combined energies of the separately computed **1a**$^{\bullet+}$ and **2a**. Inset shows the natural charge (orange to blue) and spin density (gray to orange) obtained from a natural bond orbital (NBO) calculation at the ωB97M-V/def2-TZVP/CPCM(CH_3CN) level.

bond formation involves a transition state (**TS2**) with a practically negligible activation barrier. Consequently, we propose that the reaction (and, therefore, the selectivity) is dominated by the barrier toward the first bond formation. The reaction proceeds on the radical cation surface until the oxidized product is reduced to yield the final, neutral product.

For the model reaction between BCB **1a** and styrene (**2a**), pathways to both C2 (**3aa**) and C3 (**3aa'**) regioisomers (via $\beta3$-$\alpha1$ and $\beta1$-$\alpha3$ pathways respectively) are accessible at room temperature. The **TS1** for the $\beta3$-$\alpha1$ pathway is, however, significantly lower in energy than that for $\beta1$-$\alpha3$ (by 8 kcal mol^{-1}) and it is therefore expected that the C2 regioisomer dominates, as experimentally observed (Supporting Information, Figure S18). Natural spin density and charge density calculations show that the spin density of the reactant complex involving an open **1a**$^{\bullet+}$ is primarily located at the C1 position of **1a**$^{\bullet+}$, with cationic regions centered on C3. This result is in good agreement with the structure of radical cation **1a**$^{\bullet+}$ proposed earlier (see Scheme 2), and is also consistent with C3 being more electrophilic for ketone-substituted BCBs, as seen by the regioselectivity of allyl alcohol attack (see Scheme 6F). Interestingly, the ester-substituted radical cation **1h**$^{\bullet+}$ was found to be 0.62 kcal mol^{-1} *more* stable in the folded conformer than the open one, in accordance with the computational results presented by Houk and Glorius.[29]

The reduced regioselectivity that is experimentally observed for the reaction of **1a** with more electron-deficient alkenes such as **2p** can be explained by the calculated energies of the four

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reaction pathways (Supporting Information, Figure S21). For the reaction with **2p**, **TS1** for the β1-α3 pathway is merely 1.5 kcal mol^{-1} higher in energy than to for β3-α1, and since **TS2** is comparatively negligible for both pathways, we would expect no selectivity toward either regioisomer product. The natural spin and charge density were also calculated for the first intermediates for both β3-α1 and β1-α3 pathways. The higher spin densities adjacent to the styrene-derived aromatic ring in intermediates **Int1** from the β1-α3 pathway will be better stabilized by electron-poor arenes, and this is consistent with the reduced **TS1** energy barrier seen for 4-cyanostyrene (**2p**) and supports the increased levels of the C3-isomers **3'** seen with electron-deficient alkenes.

Given the highly unusual C3-regioselectivity observed for indene (**2o**), along with its comparatively low oxidation potential of +1.66 V vs SCE[35] and excellent quenching ability (see Scheme 6B), we wanted to study this particular reaction in more detail. Initially, we calculated the same pathways involving the flat geometry associated with **1a**$^{\bullet+}$ (Supporting Information, Figure S22). However, we found that the lowest energy transition state for the first attack (**TS1**) belongs to the β3-α1 pathway, which is in contradiction with the experimental results that yield C3-regioisomer **3ao'** as the major product. We then compared the energy of the reactant complexes with BCB [**1a**$^{\bullet+}$ + **2o**] or indene being predominantly oxidized [**1a** + **2o**$^{\bullet+}$], and found that the complex with oxidized indene is slightly favored by 1.85 kcal mol^{-1}. For this reason, we also investigated the reaction pathways in which **TS1** involves the folded (unoxidized) BCB **1a** (Supporting Information, Figure S23) and the radical cationic **2o**$^{\bullet+}$. Gratifyingly, **TS1** belonging to the β1-α3 pathway was now lower in energy by 5.1 kcal mol^{-1} than the β3-α1 path, in accordance with the experimental results. Together with the only slightly higher oxidation potential of indene (**2o**) compared to BCB **1a** and its much better quenching ability, these calculations support a mechanism in which indene oxidation occurs, leading to a reversal of regioselectivity compared to styrene (**2a**). NBO calculations for the corresponding intermediate **Int1** show that cationic regions are centered on C3 of the BCB fragment with spin density located at Cα of the indene. This is consistent with electrophilic activation of the BCB by the indene radical cation, with the regioselectivity of addition governed by natural polarity of the C−C bond. Our hypothesis is also consistent with the mechanism of electrophilic activation of BCBs by singlet difluorocarbenes proposed by Anderson and co-workers.[4c]

CONCLUSIONS

In conclusion, we have developed a rare example of catalytic oxidative BCB activation. The radical cationic intermediates can be intercepted by both alkenes and aldehydes, leading to formal [2σ+2π] cycloadditions to high-value (*oxa*-)BCH products. Subtle modification of the electronic characteristics of both BCB and alkene/aldehyde reactants leads to changes in the regiochemical outcome of the reaction, with both C2 and C3 BCH regioisomers obtainable in up to 20:1 *rr* depending on the substrate used. The understanding of BCB radical cation behavior gained during this study sets the stage for further exploitation of this underutilized and unusual BCB reactivity manifold for the preparation of complex molecular structures.

MATERIALS AND METHODS

General Procedure for the Synthesis of BCHs 3. A flame-dried 4 mL screw-cap vial was charged with BCB **1** (0.2 mmol), [*t*Bu$_2$MesAcr][BF$_4$] (5 mol %) and alkene **2** (1.0 mmol), if solid. The vial was evacuated and backfilled with argon three times. If BCB **1** or alkene **2** were liquid, they were added at this point. MeCN (0.4 M) was then added and the mixture was sparged with argon for 5 min, sealed with tape and irradiated with a Kessil lamp (blue LEDs, 456 nm) for 5−96 h as stated. The reaction mixture was concentrated *in vacuo* and directly purified by FCC to afford the title compound(s).

General Procedure for the Synthesis of *oxa*BCHs 5. A flame-dried 4 mL screw-cap vial was charged with BCB **1** (0.2 mmol), [*t*Bu$_2$MesAcr][BF$_4$] (5 mol %) and aldehyde **4** (1.0 mmol), if solid. The vial was evacuated and backfilled with argon three times. If BCB **1** or aldehyde **4** were liquid, they were added at this point. CH_2Cl_2 (0.5 M) was then added and the mixture was sparged with argon for 5 min, sealed with tape and irradiated with a Kessil lamp (blue LEDs, 456 nm) for 12 h. The reaction mixture was concentrated in vacuo and directly purified by FCC to afford the title compound(s).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c05067.

Details of reaction screening, experimental procedures, characterization data, cyclic voltammetry data, Stern−Volmer data, UV/vis data, details of computational calculations, and crystal structure data (PDF)

Zip file containing related CIF files (ZIP)

AUTHOR INFORMATION

Corresponding Authors

Stefano Crespi − *Department of Chemistry - Ångström Laboratory, Uppsala University, 751 20 Uppsala, Sweden;* orcid.org/0000-0002-0279-4903; Email: stefano.crespi@kemi.uu.se

Johannes C. L. Walker − *Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, 37077 Göttingen, Germany;* orcid.org/0000-0003-1045-7234; Email: johannes.walker@chemie.uni-goettingen.de

Authors

Maxim Golfmann − *Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, 37077 Göttingen, Germany*

Marius Reinhold − *Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, 37077 Göttingen, Germany*

Jorn D. Steen − *Department of Chemistry - Ångström Laboratory, Uppsala University, 751 20 Uppsala, Sweden;* orcid.org/0000-0002-7568-9370

Malte S. Deike − *Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, 37077 Göttingen, Germany*

Behrend Rodemann − *Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, 37077 Göttingen, Germany*

Christopher Golz − *Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, 37077 Göttingen, Germany*

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Author Contributions

M.G., M. R., M.S.D., B.R., and J.C.L.W. performed the experimental work. J.D.S. and S.C. performed the computational calculations. C.G. carried out the single crystal X-ray structure determinations. M.G., J.D.S., S.C., and J.C.L.W. wrote the manuscript. All authors have given approval to the final version of the manuscript. J.C.L.W. conceived the project.

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Notes

The authors declare no competing financial interest.

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