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Alcohol, Aldehyde, and Ketone Liberation and Intracellular Cargo Release through Peroxide-Mediated α-Boryl Ether Fragmentation

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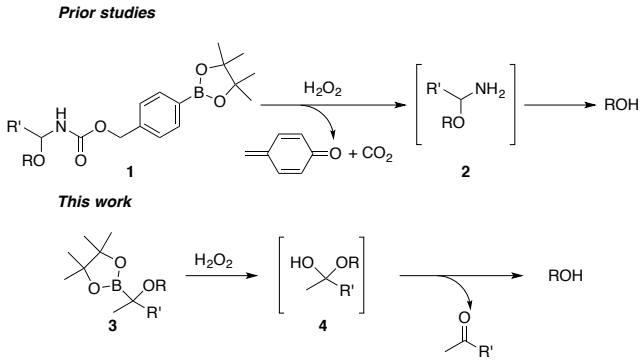
ABSTRACT: α-Boryl ethers, carbonates, and acetals, readily prepared from the corresponding alcohols that are accessed through ketone diboration, react rapidly with hydrogen peroxide to release alcohols, aldehydes, and ketones through the collapse of hemiacetal intermediates. α-Boryl acetals containing a latent fluorophore readily allow the demonstration that cargo can be released inside cells in the presence of exogenous or endogenous hydrogen peroxide. These experiments show that this protocol can be used for drug activation in an oxidative environment without generating toxic by-products.

INTRODUCTION

Reactive oxygen species (ROS), including hydrogen peroxide, are linked to a number of disparate medical conditions including neurological diseases,[1] cancer,[2] aging,[3] and diabetes.[4] ROS-rich environments are also created through exposure to ionizing radiation, as encountered in radiotherapy.[5] Hydrogen peroxide's unique reactivity properties and importance in these conditions have resulted its utilization to initiate a number of processes in biological and materials chemistry. Initial studies from Chang's group demonstrated that aryl boronates can be converted to fluorescent phenols by cellular H_2O_2.[6] This result, coupled with Lo's employment of the boronate to phenol conversion to effect benzylic leaving group departure,[7] led to the development of numerous compounds that release fluorophores and other diagnostic tools in oxidatively stressed cells.[8] Additional applications of oxidatively triggered self-immolative spacers[9] have been developed to promote particle breakdown[10] and signal amplification.[11] H_2O_2 is an attractive agent for initiating prodrug unraveling in many cases because it is small and can access sterically hindered sites in structures that are inaccessible to enzymes, which are commonly utilized for this purpose. Cargo release from antibodies[12] serves as an example of a process that can benefit from activation by a small molecule. Peroxide-mediated drug release has been explored to a limited extent.[13] However substrates for these processes employ aryl or vinyl boronates as oxidative triggers to promote release from the benzylic or allylic position. Therapeutic applications of these systems, therefore, can be complicated by the significant toxicity of the resultant quinone methide[14] or acrolein[15] by-products. Thus alternative structural motifs that release compounds in the presence of H_2O_2 without generating toxic by-products would be valuable for applications in oxidative drug release.

We have initiated a program with the objective of designing readily accessible structures that have the capacity to localize toward a cellular target and decompose under oxidative conditions to release a biological effector. Our initial design for alcohol release[13b] (Scheme 1) employed acyl aminal substrates (**1**) that are available through reductive multicomponent unions of nitriles, chloroformates, and alcohols.[16] Aryl or vinyl boronate oxidation with H_2O_2 releases a quinone methide or acrolein and CO_2 to form an unstable hemiaminal (**2**) that collapses to release the alcohol. We reasoned that oxidation of α-boryl ethers or carbonates (**3**) would provide a similar unstable hemiacetal (**4**) that releases an alcohol directly or through carbonate breakdown with less by-product generation. This approach allows for the selection of a non-toxic ketone by-product to serve as a guide in substrate design.

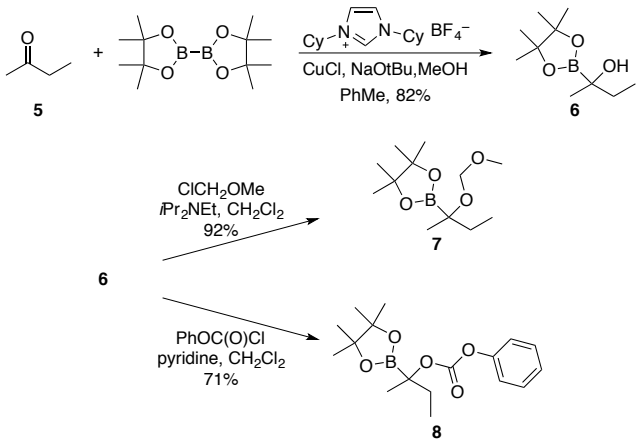


Scheme 1. Alcohol release through boronate oxidation.

This manuscript describes the realization of this approach through the release of several diverse structures via oxidative fragmentation of α-boryl ethers, carbonates, and acetals. Specific advances include 1) the development of experimentally facile conditions for the synthesis of α-boryl alcohols through a variant of a known ketone diboration protocol, 2) the preparation of α-boryl ethers and carbonates through conditions that avoid strong base, 3) the demonstration that α-boryl ethers decompose rapidly and efficiently in the presence of H_2O_2 under mildly basic conditions while α-boryl carbonates decompose more slowly, 4) the elaboration of several protocols for preparing cyclic boryl-substituted acetals, 5) the observation that the acetals can liberate aldehydes and ketones in the presence of H_2O_2, 6) the application of the acetal breakdown to release fluorophores at low substrate and peroxide concentrations, 7) the validation of the capacity of the acetals to release cargo in cells through stimulation with exogenous H_2O_2, and 8) the demonstration that cargo can be released in cells by endogenous H_2O_2 resulting from chemically stimulated oxidative stress. These results clearly illustrate that α-boryl ethers, carbonates, and acetals are viable substrates for releasing biological effectors in cells in response to oxidative conditions while avoiding the generation of toxic by-products.

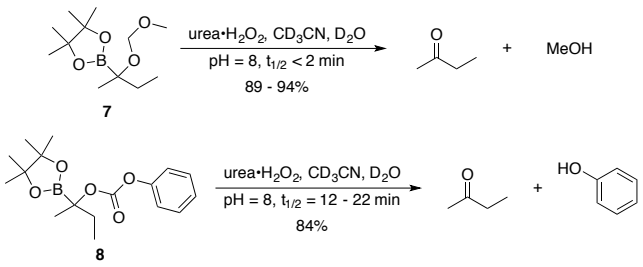
RESULTS AND DISCUSSION

Ether, carbonate, and cyclic acetal substrate synthesis and decomposition. The success of this project was contingent upon identifying suitable approach to α-boryl alcohol formation.[17] We initially employed Clark's ketone-relevant variation[18] of the Sadighi carbonyl diboration protocol[19] for the conversion of **5** to boryl alcohol **6** (Scheme 2).[20] These conditions (PinB–BPin, (ICy)CuCl, NaO*t*Bu, PhMe, 50 °C followed by borate protodeboration on silica gel) provided **6**, but were deemed to be unacceptable due to the low reaction rate and because of the technical difficulty associated with the need to initiate the reaction in a glove box. We reasoned that the relevant copper carbene catalyst could be prepared in situ by deprotonating the imidazolium salt in the presence of CuCl, thereby obviating the need to isolate this sensitive species. Moreover adding MeOH to the reaction mixture substantially increased the rate of the reaction, in accord with Molander's observations.[21] These changes resulted in the conversion of **5** to **6** in 82% yield within 1 h and *without recourse to glove box or Schlenk line techniques*. The experimental facility of this protocol appreciably enhances access to α-boryl alcohols. This is significant because boronates and related species with α-heteroatom substitution are useful as substrates for cross-coupling[21] and chain elongation reactions,[22] and as surrogates of functionalized carboxylic acids for applications in medicinal chemistry.[23] The hydroxy groups can be functionalized readily, as demonstrated through the formation of methoxymethyl ether **7** and phenyl carbonate **8**.



Scheme 2. α-Boryl alcohol synthesis and functionalization.

The oxidative breakdown of compounds **7** and **8** was achieved by subjecting them (~25 mM) to urea•H_2O_2 (300 mM) in a mixture of CD_3CN and aqueous (D_2O) buffer (pH = 8.0). The buffer was selected to mimic the experimentally determined pH of mitochondria.[24] in consideration of potential applications to mitigating neuronal oxidative stress. Initial experiments were conducted in a 5:1 ratio of CD_3CN and buffer (Scheme 3). Reaction progress was monitored by ^{1}H NMR through following the disappearance of the signals for diastereotopic hydrogens from the methylene group in the starting materials and the appearance of the corresponding enantiotopic hydrogens in butanone. Conversions were calculated by comparison to the internal standard 1,2-dimethoxyethane.



Scheme 3. Oxidative alcohol release.

Methoxymethyl ether **7** fragmented quite rapidly in the presence of hydrogen peroxide. Over 50% of the starting material was consumed in less than 2 minutes (Figure 1A), and complete conversion was observed within 20 min with an 89% NMR yield of butanone. Changing the solvent to a 1:1 ratio of CD_3CN to buffer did not slow the reaction and resulted in a slightly increased NMR yield of 94%. Moreover lowering the pH to a cytosolic-relevant value of 7.2 had only a minimal effect on the rate despite the diminished peroxy anion concentration (Figure 1B), providing a 91% NMR yield of butanone.

Carbonate **8**, however, broke down much more slowly under the oxidative conditions.[25] Consumption of 50% of the starting material required 22 min when the reaction

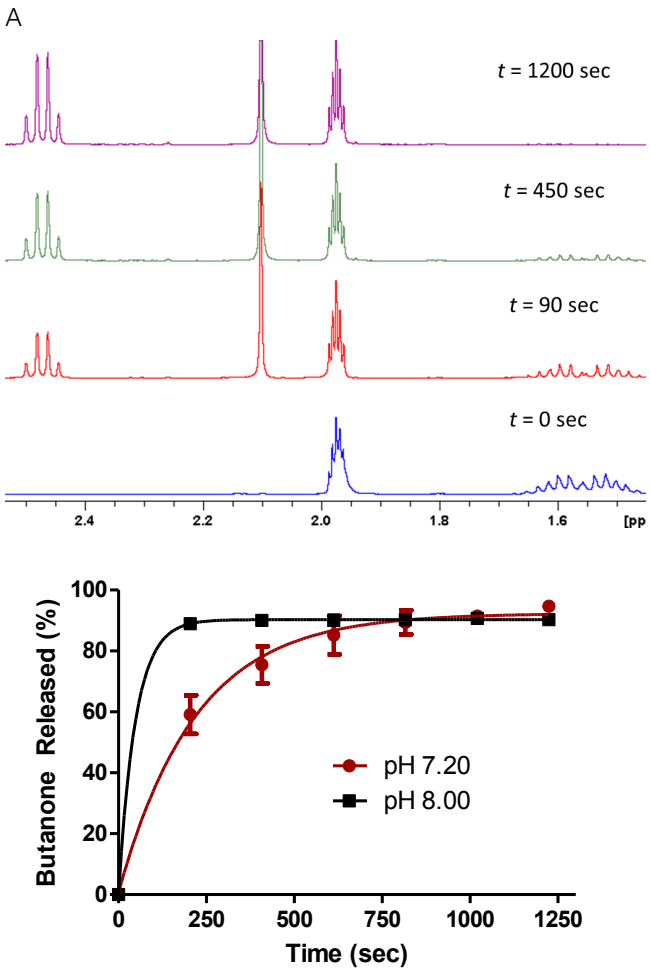


Figure 1. Oxidative breakdown of **7**. (A) Reaction progress as determined by ^{1}H NMR. (B) Reaction progress as a function of pH.

was conducted in a 5:1 mixture of CD_3CN and buffer. Changing the solvent to a 1:1 mixture of CD_3CN and buffer resulted in a slightly increased rate, with 50% of the starting material being consumed within 12 min. The reactions were quite efficient, with both providing an 84% yield of the desired products.

The rate difference for alcohol release between acetal and carbonate substrates indicates that the rate determining step in these processes is boronate oxidation rather than hemiacetal collapse. The slow breakdown of the carbonate could result from intramolecular coordination between the carbonyl oxygen and the boron, as illustrated by **9** (Figure 2) thereby inhibiting the approach of HOO^- to the boron. Crystal structures show this type of coordination in α-boryl amides,[26] and intramolecular coordination has been shown to confer stability to boronates.[27] However the ^{11}B chemical shift of **8** (δ 32.2 ppm) is nearly identical to the ^{11}B chemical shift in **7** (δ 32.1 ppm), and is significantly different from amido pinacolboronates, which show ^{11}B chemical shifts of approximately 15 ppm.[26,28] Alternatively the breakdown could be slowed by a diminished migratory aptitude resulting from the presence of an electron withdrawing acyl group. No evidence of a persistent peroxyboronate intermediate, such as **10**, was observed upon monitoring the progress of the reaction with ^{11}B NMR, however. Regardless of the origin of the effect, the capacity to control the breakdown rate through a simple structural modification provides kinetic versatility in drug release strategy.

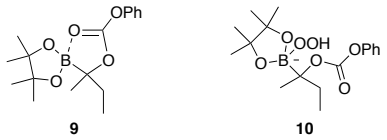
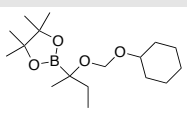
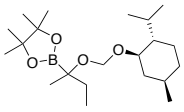
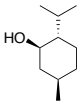
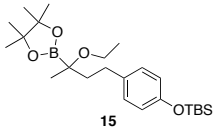
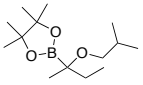
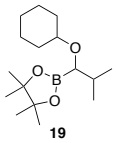
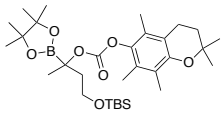
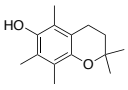
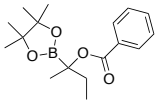
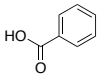


Figure 2. Structures **9** and **10** as potential origins for the slow breakdown of **8**.

Several additional substrates were prepared to define the scope of the process (Table 1). Secondary alcohols such as cyclohexanol (from the breakdown of **11**) and the more complex menthol (from the breakdown of **13**) are released smoothly. Although the formation and fragmentation of alkoxymethyl ethers proceeds rapidly and smoothly, direct release of alcohols would be desirable for avoiding the generation of toxic formaldehyde,[29] particularly if the cargo is not intended to effect a cytotoxic response. Primary and secondary alcohols can be released directly, as shown in entries 3-5. The use of an aldehyde-derived boronate in entry 5 facilitated the synthesis of the ether. The oxidative cleavage of **15** and **20** (entries 3 and 6) are also significant because they show that functionalized substrates participate well in this process, providing potential handles for incorporating tissue-, cell-, or organelle-targeting functional groups. Boronate **20** releases the antioxidant pentamethyl chromanol (**21**),[30] showing that this method could be applied to the release of radical scavengers in the presence of environments that are rich in reactive oxygen species, such as mitochondria. As previously discussed, this release was predictably somewhat slow due to the carbonate linker. The release of carboxylic acids (entry 7), while possible, is substantially slower than the release of alcohols or carbonates and is therefore not likely to be useful. Compound **22** showed a chemical shift of 27.0 ppm in the ^{11}B NMR spectrum, indicating that coordination between the boron and the carbonyl group is likely to play a role in preventing oxidative cleavage through peroxide attack.

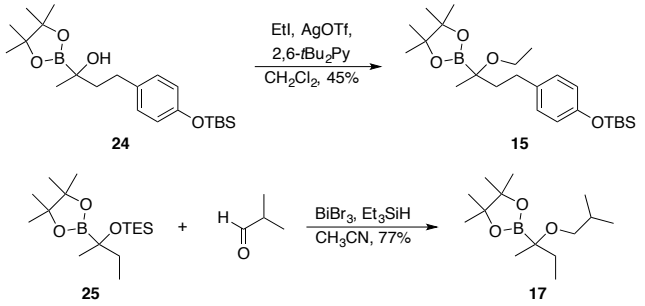
Table 1. Alcohol release scope.[a]

entry	substrate[b]	product	$t_{1/2}$ (min)[c]	yield (%)[d]
1	 **11**	 **12**	<2	84

2	 13	 14	<2	85
3	 15	 16	<2	89
4	 17	 18	<2	89
5	 19	 12	<2	83
6	 20	 21	90	79
7	 22	 23	>936	16

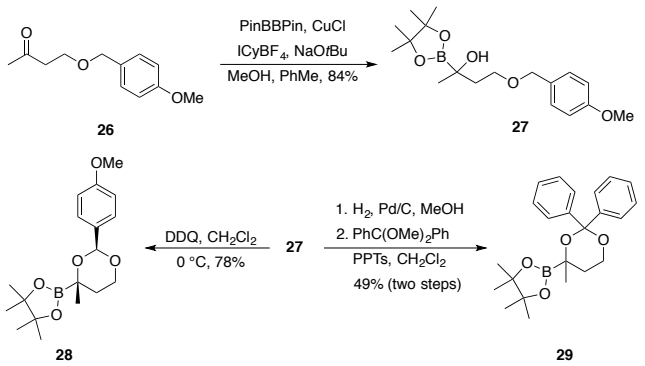
[a] Reactions run with 6 – 12 equiv H_2O_2•urea at pH = 8.0 in CD_3CN and D_2O (5:1) at rt. [b] See the Supporting Information for the preparation of the substrates. [c] As determined by monitoring substrate consumption. [d] Determined by ^1H NMR through comparing to the internal standard 1,2-dimethoxyethane.

The synthesis of alkyl ethers is challenging in comparison to the synthesis of alkoxymethyl ethers because direct Williamson ether syntheses with α-boryl alcohols are prone to undergo bora-Brook rearrangements[31] that render the oxygen non-nucleophilic. Direct etherification requires sufficiently potent electrophiles to subvert the need for alkoxide generation. This can be achieved (Scheme 4) by activating halide leaving groups with AgOTf,[32] allowing for hindered pyridines to be used as proton scavengers. This is illustrated by the ethylation of α-boryl alcohol **24** to yield **15**. Alternatively, reductive etherification of α-boryl silyl ethers in the presence of $BiBr_3$[33] is a versatile method for preparing these substrates under non-basic conditions. Thus silyl ether **25**, readily available from **6**, can be condensed with isobutyraldehyde in the presence of Et_3SiH to yield **17**. An additional benefit of the reductive annulation protocol lies in the enhanced stability of α-boryl silyl ethers in comparison to α-boryl alcohols. This allows for the substrate scope to be broadened to include aldehyde-derived boronates such as **19**.



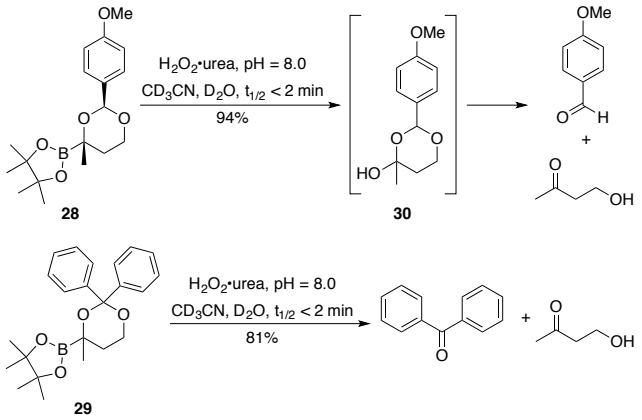
Scheme 4. Etherification in the absence of strong base.

The functional group tolerance of the process and the capacity for α-boryl alcohols to add into oxocarbenium ions suggested that the scope could be expanded further to promote aldehyde and ketone release. The preparation of the substrates for these studies is illustrated in Scheme 5. Cyclic acetal substrates can be prepared either through oxidative or classical exchange reactions. Ketone **26**, available from commercially available 4-hydroxy-2-butanone,[34] underwent copper-catalyzed borylation smoothly to yield alcohol **27**. DDQ-mediated oxidative cyclization[35] provided acetal **28** in 78% yield. Removing the PMB group from **27** under hydrogenolytic conditions followed by acetal exchange with the dimethyl acetal of benzophenone provided acetal **29** in 49% yield over two steps.



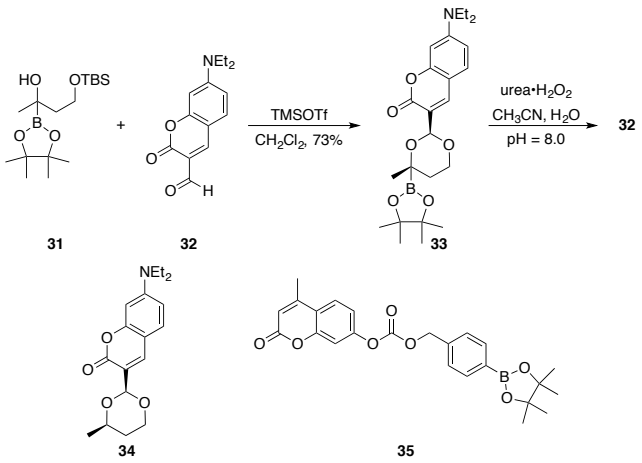
Scheme 5. Synthesis of cyclic acetal substrates.

The boryl-substituted acetals release their cargo readily, as shown in Scheme 6. Boronate **28** reacted with H_2O_2 at pH = 8.0 to provide hemiacetal **30**, which broke down to form anisaldehyde and 1-hydroxy-3-butanone in 94% yield. Over 50% of the starting material was consumed within 90 sec, and complete conversion occurred in <15 min. Similarly boronate **29** reacted to form benzophenone quickly and efficiently. Therefore this variation of the protocol significantly extends the range of structures that can be released in the presence of hydrogen peroxide. Moreover this strategy illustrates a new approach to designing prodrugs for aldehydes and ketones, as previous efforts have largely centered on the use of oximes and derivatives.[36,37]



Scheme 6. Aldehyde and ketone release through oxidative acetal cleavage.

Latent fluorophore synthesis and release. All studies to this point were conducted at relatively high concentrations of substrate and peroxide. Determining whether these processes can proceed at biologically relevant concentrations requires an analytical technique that is more sensitive than ^{1}H NMR. Therefore we explored the potential for the release of a fluorophore at low substrate and peroxide concentrations. The synthesis of a latent fluorophore is shown in Scheme 7. Silyl ether **31**, which was prepared from the TBS ether of 4-hydroxy-2-butanone, coupled with aldehyde **32** (prepared from commercially available materials in two steps)[38] in the presence of TMSOTf[39] to yield acetal **33**. This acetal was formed as a single stereoisomer, with the relative configuration being determined through a NOESY experiment. The Noyori acetalization conditions were significantly superior to Brønsted acid-mediated protocols due to the absence of protodeboration as a prominent competing reaction. Acetalization induces significantly different fluorescence properties relative to the aldehyde, with λ_{ex} values of 448 nm and 402 nm and λ_{em} values of 510 nm and 452 nm for **32** and **33**, respectively, thereby facilitating the monitoring of oxidative breakdown. Acetal **34** was prepared through a similar protocol to serve as a control compound in evaluating the importance of the oxidative trigger in peroxide-



Scheme 7. Synthesis of a latent fluorophore.

mediated decomposition. We also prepared benzylic carbonate **35**.This compound releases its fluorophore through the common oxidative 1,6-elimination pathway and was synthesized to compare the background stability of **33** with a well-vetted latent fluorophore motif.

Fluorophore release was studied at a concentration of 25 μM for **33** at pH = 7.4 with H_2O_2 concentrations of 100 μM and 200 μM. The concentration of **32** was monitored by excitation at 448 nm and emission at 499 nm (a wavelength where **33** shows only slight emission), with product release being quantitated by comparison to a standard curve. The fluorophore release experiments are summarized in Figure 3. The breakdown of **33** was conducted in 1% DMSO in aqueous phosphate buffer. Fluorophore concentration increased steadily with time. The rate and extent of fluorophore release showed the expected dependency upon H_2O_2 concentration. Lowering the H_2O_2 concentration from 200 μM to 100 μM slowed fluorophore release to a small but noteworthy extent. The yield of **32** was 88% with 200 μM H_2O_2 and 78% with 100 μM H_2O_2. Fluorophore release was minimal in the absence of H_2O_2. A similar study of carbonate **35** showed that ratio of fluorophore release in the presence and absence of H_2O_2 was nearly equivalent to the ratio that was observed for **33**.[25] This indicates that the inherent stability of the α-boryl ether moiety is comparable to a well established oxidative trigger. Fluorophore release in the absence of H_2O_2 was studied at pH = 6.0 and 4.5 to determine the stability of the acetal toward acid. Fluorophore release was slightly inhibited at lower pH values (see the Supporting Information for a graphic with an expanded y-axis), which is significant for biological applications in consideration of the capacity of endosomes to achieve pH values as low as 4.9.[40]

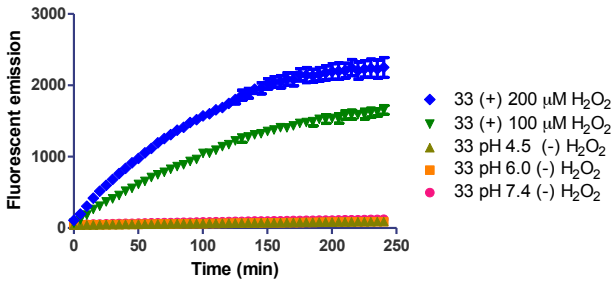


Figure 3. Fluorophore release at low substrate and peroxide concentrations and pH stability studies.

Acetal **34** did not release **32** at any H_2O_2 concentration over the time span of the experiment,[25] thereby validating the importance of boronate oxidation in cargo release. Separate studies in the presence of a large excess of H_2O_2 (10 mM) allowed for the determination of a pseudo-first order rate constant of 1.47×10^{-3} sec^{-1} for the decomposition of **33**.[25] This rate compares favorably to the peroxide-mediated decomposition of boryl-substituted benzylic carbamates to generate quinone methides via 1,6-elimination.[8a] The 1,6-elimination pro-

tocol is likely to be significantly slower for releasing aliphatic alcohols, however, in consideration of their lower nucleofugacity and our prior observation[13b] that the rates of these processes are strongly correlated with the rate of benzylic C–O bond cleavage.[41]

Exposing **33** to a number of reactive oxygen species showed that the breakdown is selective for H_2O_2 (Figure 4). Solutions of H_2O_2, NaOCl, KO_2, and *t*BuOOH were prepared by diluting commercially available material. Hydroxyl and *t*-butoxyl radicals were prepared by mixing the corresponding peroxide with $FeSO_4 \bullet 5H_2O$ and adding catalase to consume residual peroxide.[8a] The chart shows the ratio of fluorescence intensity after 30 min to the initial value. Aside from H_2O_2 only hydroxyl radical showed a notable fluorophore release, albeit significantly lower in magnitude compared to H_2O_2-mediated release.

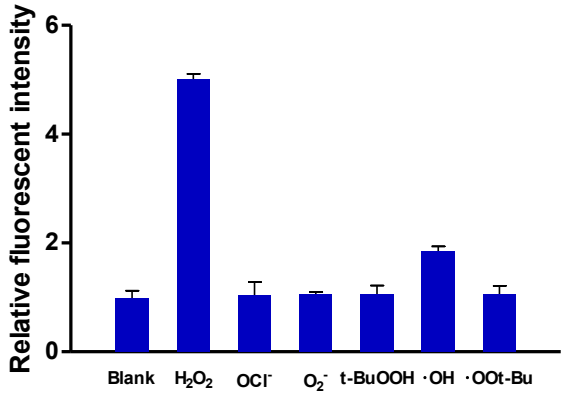


Figure 4. Comparison of fluorophore release by different oxidants. $[\mathbf{33}]_0$ = 40 μM, $[\text{oxidant}]_0$ = 200 μM, pH = 7.4.

Cellular fluorophore release. These results led us to study the release of the fluorophore in cells to provide an easily visualized demonstration of these compounds' capacity to release cargo in a biologically relevant environment. This was demonstrated in accord with Chang's protocol,[42] whereby HeLa cells were incubated with **33** (10 μM) for 45 min and fluorophore release was imaged in the absence and presence of exogenous 100 μM H_2O_2. The results are shown in Figure 5. Very little fluorophore release occurred within 30 min in the absence of external H_2O_2 with the small response most likely being attributable to the endogenous peroxide that is present in cancer cells.[43] Significant fluorophore release was observed in the presence of H_2O_2, however. This demonstrates that α-boryl acetals are cell-permeable and can release cargo within cells. Conducting these studies with control acetal **34** resulted in no fluorophore release,[25] thereby providing further evidence for the proposed release mechanism.

We repeated this experiment with HEK293T cells, derived from the transformation of non-cancerous embryonic kidney tissue with sheared adenovirus DNA and stable transfection with the SV40 T antigen,[44] with **33** to test whether

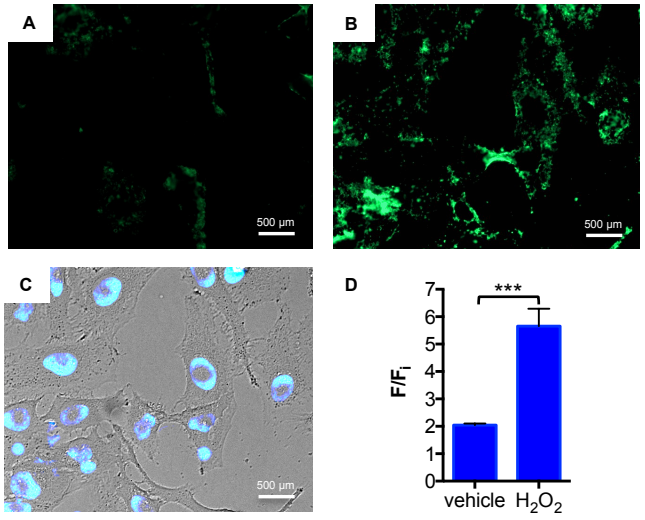


Figure 5. Fluorophore release in HeLa cells treated with exogenous H_2O_2. Cells were incubated with **33** (10 μM) in DPBS buffer for 45 min at 37°C, followed by replacement with fresh DPBS containing (A) vehicle or (B) H_2O_2 (100 μM). After 30 min, fluorescence was imaged (Zeiss Axio Observer Z1, 20x objective, GFP filter (Set 38 HE; ex. 470 nm; em. 525 nm)). (C) Bright-field image of cells in (B) stained with Hoechst 33258 (1 μM) and imaged using a DAPI filter (Set 68; ex. 377 nm; em. 464 nm). (D) Mean fluorescence intensities were calculated from three individual HeLa cells and set relative to the mean fluorescence intensity prior to treatments (F/F_i). Error bars denote standard deviations, *** $P < 0.001$.

differentiation between cell lines is possible. HeLa cells, directly derived from cancerous cervical tissue, are expected to contain slightly elevated levels of endogenous H_2O_2[43] and, therefore show higher background emission.

Quantitation of fluorophore release in the absence and presence of exogenous H_2O_2 (Figure 6) indeed showed that the background signal was significantly reduced in the absence of exogenous H_2O_2. These results further validate the stability of α-boryl acetals in the absence of oxidants, as required for selective applications to drug release in

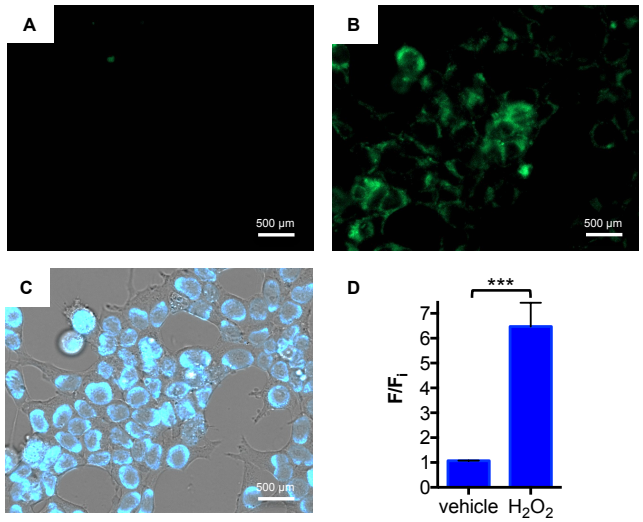


Figure 6. Fluorophore release in HEK293T cells through treatment with exogenous H_2O_2. Cells were treated with **33** (10 μM) in DPBS buffer for 45 min at 37 °C, followed by replacement with fresh DPBS containing (A) vehicle or (B) H_2O_2 (100 μM). After 30 min incubation, cellular fluorescence was imaged on a Zeiss Axio Observer Z1 microscope using a 20x objective and a GFP (Set 38 HE) filter (ex. 470 nm, em. 525 nm). (C) Bright-field image of cells in (B) stained with Hoechst 33258 (1 μM) and imaged using a DAPI (Set 68) filter (ex. 377 nm, em. 464 nm). (D) Mean fluorescence intensities were calculated from individual ROIs (n = 3) and set relative to the mean fluorescence intensity prior to treatments (F/F_i). Error bars denote standard deviations.

oxidatively stressed environments. Conducting these studies with the control acetal **34** again resulted in no fluorophore release.[25]

While these studies provide compelling evidence for the capacity of α-boryl acetals to release cargo in cells, the results would have significantly more impact if fluorophore release could be achieved through endogenous H_2O_2 generation. Phorbol myristate acetate (PMA) promotes intracellular H_2O_2 generation.[45] Therefore HeLa cells were incubated with PMA (1 μM) for 60 min followed by the addition of **33** (10 μM). Fluorophore release in cells that were treated with PMA was evidenced by a significant increase of fluorescence (Figure 7), in contrast to the lack of fluorophore release in cells that were not treated with PMA. *These results clearly show the capacity of α-boryl acetals to release compounds inside of cells in response to endogenous concentrations of H_2O_2.*

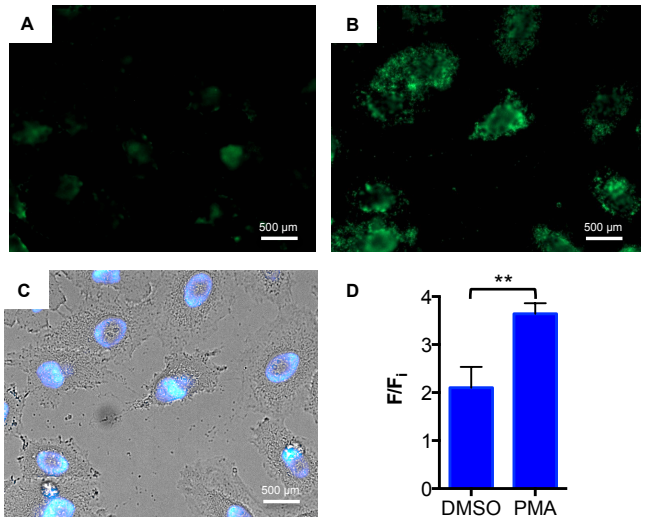


Figure 7. Cellular fluorophore release in HeLa cells by endogenous, PMA-stimulated H_2O_2 generation. Cells were pretreated in DMEM containing (A) DMSO or (B) PMA (1 uM) and incubated at 37°C for 60 minutes. Media was replaced with fresh DPBS containing **33** (10 uM) and cells were incubated for an additional 60 min at 37°C before fluorescence was imaged (Zeiss Axio Observer Z1, 20x objective, GFP filter (Set 38 HE; ex. 470 nm; em. 525 nm)). (C) Bright-field image of cells in (B) stained with Hoechst 33258 (1 μM) and imaged using a DAPI filter (Set 68; ex. 377 nm; em. 464 nm). (D) Mean fluorescence intensities were calculated from three individual HeLa cells and set relative to the mean fluorescence intensity prior to treatments (F/F_i). Error bars denote standard deviations, ** $P < 0.01$.

Conclusions

We have shown that α-boryl ethers and related structures are excellent vehicles for releasing molecular cargo in an oxidative environment. These compounds are accessed from α-boryl alcohols that can be prepared by operationally facile ketone or aldehyde borylation reactions. Although these alcohols cannot be functionalized via their alkoxides, they can be alkylated or acylated in the presence of weak amine bases. Reductive alkylation provides an attractive alternative to boryl ether formation under acidic conditions. α-Boryl ethers release alcohols extremely rapidly in the presence of H_2O_2 while α-boryl carbonates decompose somewhat more slowly, providing a predictable mechanism for controlling the rate of alcohol release. The capacity to functionalize α-boryl alcohols under acidic conditions provides a pathway to generate α-boryl acetals. These acid-stable structures readily release aldehydes and ketones upon exposure to H_2O_2. The ability to liberate cargo at low substrate and peroxide concentrations was validated through the release of a fluorescent aldehyde. Fluorophore release can also be achieved inside cells with exogenous H_2O_2 or with endogenous, chemically stimulated H_2O_2 generation. The presence of the boronate group is essential to these processes, in support of the proposed pathway for the breakdown. The capacity to release molecules inside cells with a sterically non-demanding oxidant while generating non-toxic by-products indicates that these compounds will be valuable for drug release in oxidatively stressed cells.

ASSOCIATED CONTENT

Supporting Information

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

Schemes for compound synthesis, characterization of all compounds, general protocols for compound release, procedures for fluorophore release in cells.

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Notes

The authors have applied for a provisional patent that covers the drug delivery applications of this work.

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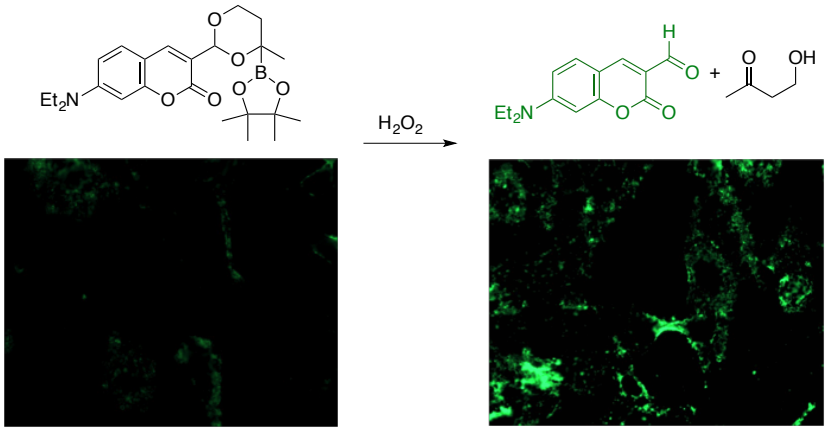
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