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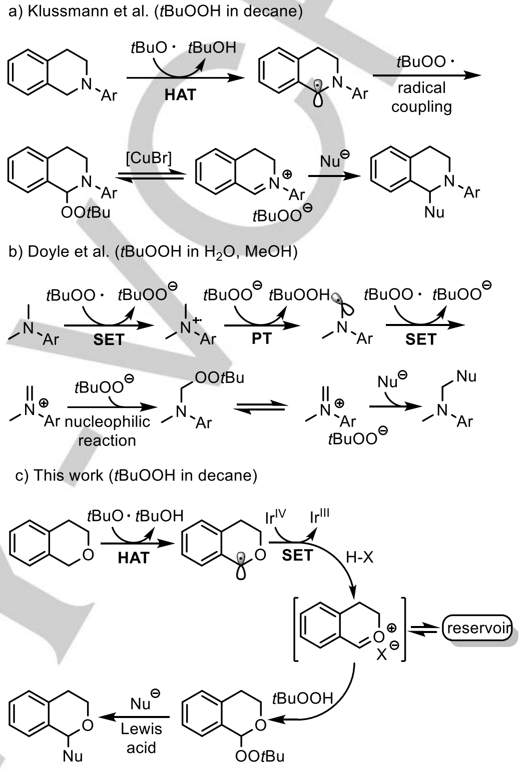
Merging Photoredox with Brønsted Acid Catalysis: The Cross-Dehydrogenative C–O Coupling for sp^3 C-H Bond Peroxidation

Qing Xia, Qiang Wang, Changcun Yan, Jianyang Dong, Hongjian Song, Ling Li, Yuxiu Liu, Qingmin Wang,* Xiangming Liu, Haibin Song

Abstract: A photoredox and Brønsted acid synergistically catalyzed cross-dehydrogenative C–O coupling reaction is developed, in which isochroman peroxyacetals are formed through the sp^3 C-H bond peroxidation. The reported method is characterized by its extremely mild reaction conditions, excellent yields and broad substrate scope. An oxocarbenium ion *p*-chlorobenzenesulfonate was speculated to be the reactive intermediate. The role of hemiacetals and oxygenated dimers on the effective stabilization of the oxocarbenium ion was investigated; the presence of added acid appeared capable of establishing equilibrium between hemiacetals and oxygenated dimers with the oxocarbenium ion pairs. Broad applicability will highlight the capacity of the protocol in future molecule synthesis.

Introduction

Cross dehydrogenative coupling (CDC) reaction, which using only C-H bonds to construct C-C bonds, represents a new generation of coupling reaction. It can omit the preparation of functional groups and thus make synthetic schemes shorter and more efficient.[1] Since 2004, Li's group has contributed lots of elegant work on CDC, which allowed the connection of C_{sp}-H, C_{sp2}-H, and even C_{sp3}-H bonds with each other.[2] Focusing on the *tert*-butyl hydroperoxide (TBHP)-engaged copper(I)-catalyzed CDC Mannich-type reaction of tertiary amines developed by Li's group,[2c,2d] Klussmann and co-workers demonstrated the existence of an on-cycle aza-peroxyacetal and revealed the mechanism of this CDC reaction to be a hydrogen atom transfer (HAT) and a subsequent radical coupling (Scheme 1a).[3] However, Doyle and co-workers later proposed a different mechanism in which the intermediate aza-peroxyacetal was supposed to form through a single electron transfer (SET) and a subsequent nucleophilic reaction (Scheme 1b).[4] In addition, many other groups also presented elegant work on the CDC reactions using the substrates of tertiary amines and ethers.[5] In general, mechanistic studies of these reactions are rare and still controversial, and the lack of a detailed understanding makes further developments difficult.



Scheme 1. Different Approaches toward the Cross Dehydrogenative Coupling

Numerous peroxide-containing natural products have been isolated, and many of them possess highly potent antitumor, antibacterial, and antimalarial activities.[6] For example, artemisinin (qinghaosu) has been proven a highly effective drug for eradicating malaria, one of the most widespread and life-threatening parasitic diseases.[7] Focused on the special peroxide structure, many pharmaceuticals and molecules with peroxide moieties have been designed and synthesized.[8] Surpassingly, the Dussault's group established series of methods for the construction of organic peroxides.[9] The group of Deng have made significant advances in asymmetric synthesis of organic peroxides by using cinchona alkaloid derivatives as organocatalysts.[10] Elegant work have also been contributed by the groups of Li, List and Antilla.[11] The development of improved methods for peroxidation should have value for the synthesis of natural products and the development of new pharmaceuticals.

The rapid growth of organic photoredox catalysis has prompted a renewed interest in radical transformations initiated by outer sphere electron transfer (ET).[12] Seminal studies of MacMillan's group demonstrated that the incorporation of HAT catalysis and transition metal with the amine or ether substrates enables photocatalytic formation of α-amino radical[13] or α-oxyalkyl radical[14] and subsequent C-C bond formation. Inspired by this work, herein we present a method for constructing

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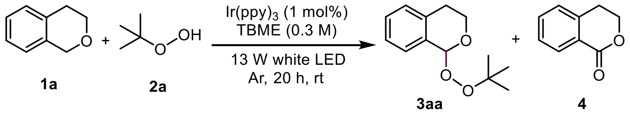
Supporting information for this article is given via a link at the end of the document.

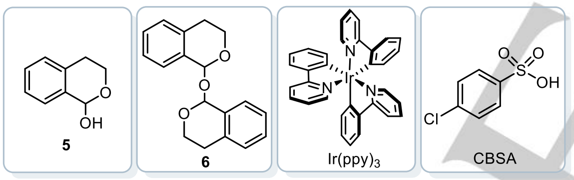
isochroman peroxyacetals which merging photoredox catalysis with cross-dehydrogenative C–O coupling reaction (Scheme 1c). Primary mechanism studies demonstrated a plausible pathway that photoredox and Brønsted acid dually catalyzed this peroxidation, and we also elucidated the structure of the reactive intermediate as well as the stabilizing effect of reservoir.

Results and Discussion

Table 1. Optimization of the Reaction Conditions[a]



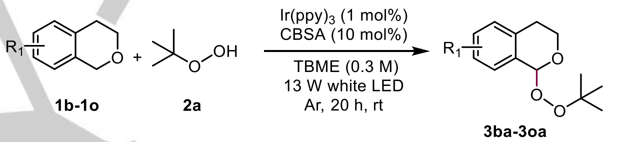
entry	deviation from standard conditions	**3aa** (%)[b]	**4** (%)[b]
1	none	64	20
2	DME instead of TBME	63	13
3	2 equiv of TBHP	52	36
4[c]	10 mol% of CBSA	**80**	**7**
5[c]	none	45	19
6[c]	10 mol% of MSA	73	8
7[c]	10 mol% of PTSA	72	9
8[c]	5 mol% of CBSA	76	13
9	no photocatlyst	trace	8
10	no light	trace	7

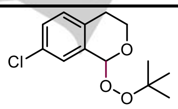


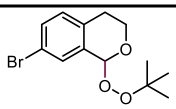
[a]Standard conditions: **1a** (0.5 mmol), **2a** (1.5 mmol, 5.5 M in decane), Ir(ppy)$_3$ (0.005 mmol, 1 mol%) in TBME (1.5 mL) were irradiated by 13 W white LED for 20 h under argon atmosphere. [b]Isolated yield. [c]Reaction time 10 h. See Supporting Information for the details of optimization studies.

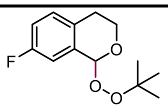
Our initial studies focused on the construction of isochroman *tert*-butylperoxyacetal (**3aa**, Table 1). When a solution of isochroman (**1a**) and TBHP (**2a**, 3 equiv) in the presence of Ir(ppy)$_3$ (1 mol%) as photocatalyst in TBME (0.3 M) was illuminated with a 13 W white LED under argon atmosphere at room temperature for 20 h, **3aa** was obtained in 64% yield along with 20% yield of by-product isochromanone (**4**) (Table 1, entry 1; For the details of optimization studies, see Supporting Information). The efficiency of the reaction was highly dependent on the solvent. Ether solvents performed applicably for this reaction, and TBME outperformed both DME and dioxane (entry 2 and Table S2). Reduce the amount of TBHP to 2 equivalent apparently lowered the yield of **3aa** (entry 3). With the condition of entry 1 in Table 1, besides **3aa** and **4**, a modicum of hemiacetal **5** (7%) and oxygenated dimer **6** (4%) was also isolated. According to precedent mechanistic studies on the ether oxidation,[15] we speculated that the generated oxocarbenium ion may not stable enough. With water as nucleophile, **5** and **6** were generated and established equilibrium with the unstable oxocarbenium ion, therefore displaying a stabilizing effect.[3b,16] Inspired by this speculation, we were encouraged to investigate the influence of Brønsted acid additives which could facilitate the breakdown of **5** and **6** into oxocarbenium ion and on the other hand promote the electrophilicity of oxocarbenium ion through binding a suitable Brønsted acid anion (X^-).[15b,17] Unsurprisingly, when 10 mol% of *p*-chlorobenzenesulfonic acid (CBSA) was added to the reaction mixture, after 10 h up to 80% yield of **3aa** was obtained (entry 4). Comparatively, only 45% yield of **3aa** was generated in the absence of Brønsted acid additive (entry 5). Extensive screening of Brønsted acid was conducted but no higher yield was observed (entries 6 and 7 and Table S5). Decreasing the amount of CBSA to 5 mol% slightly reduced the yield of **3aa** (entry 8). Last, control experiments revealed the absolute necessity of photocatalyst and light in this new peroxidation protocol (entries 9 and 10).

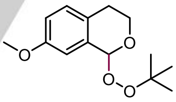
Table 2. Scope of the Substituted Isochroman[a][b]

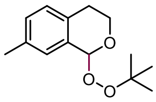


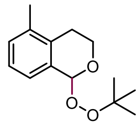

3ba, 84% yield

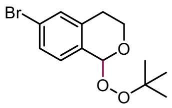

3ca, 80% yield

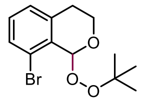

3da, 86% yield

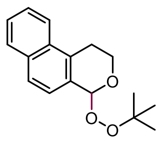

3ea, 66% yield

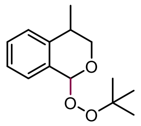

3fa, 77% yield

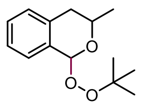

3ga, 71% yield

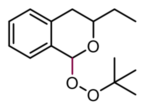

3ha, 80% yield

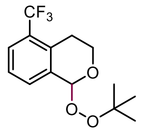

3ia, 88% yield

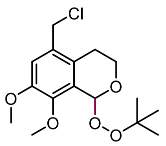

3ja, 72% yield


3ka, 93% yield
dr = 1.5 : 1[c]


3la, 94% yield
dr = 10 : 1[c]


3ma, 93% yield
dr = 2 : 1[c]


3na, 79% yield


3oa, 76% yield

[a]Conditions: **1b-1o** (0.5 mmol), **2a** (1.5 mmol, 5.5 M in decane), Ir(ppy)$_3$ (0.005 mmol, 1 mol%) and CBSA (0.05 mmol, 10 mol%) in TBME (1.5 mL) were irradiated by 13 W white LED for 20 h under argon atmosphere.

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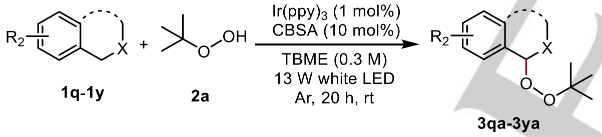
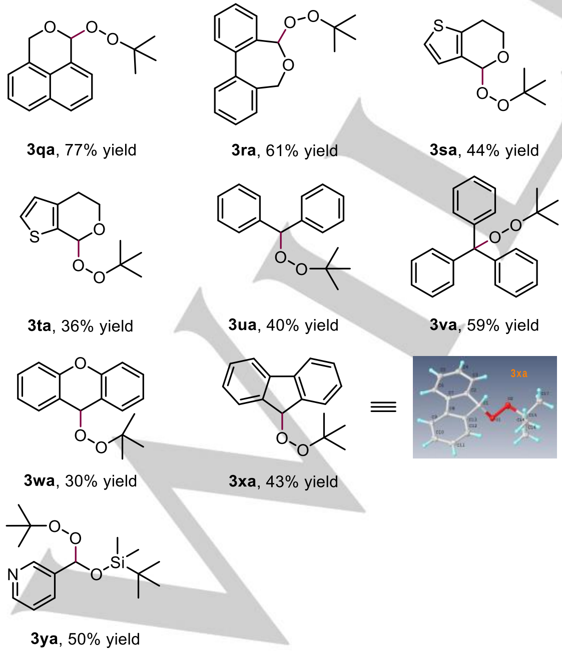
[b]Isolated yield. [c]Diastereoisomer ratios (dr) determined by ^{1}H NMR.

Encouraged by these results, we turned our attention to the influence of substituted isochroman through this protocol (Table 2). In general, the reactions proceeded smoothly to generate the desired isochroman *tert*-butylperoxyacetals in good yields (66-94%). The electron-withdrawing substituents as well as electron-donating substituents performed satisfactorily, and the position effect of substituents was inconspicuous. The substrate 3-methyl isochroman was oxidized smoothly, affording **3la** in 94% yield with moderate diastereoselectivity (dr = 10: 1). Analogously, 3-ethyl and 4-methyl isochromans reacted well and provided satisfactory yield of **3ma** (93% yield) and **3ka** (93% yield) but with low diastereoselectivity (dr = 2:1 and 1.5:1 respectively).

Furthermore, the substrate scopes including other ethers and even benzylic systems were investigated (Table 3). When six- and seven-membered cyclic benzyl ethers were used, single addition of the *tert*-butylperoxide proceeded selectively to form **3qa** (77% yield) and **3ra** (61% yield). The mild peroxidation method could also selectively functionalize the very electron-rich thienopyrans to give the dehydrogenative α-peroxidation products **3sa** and **3ta** in acceptable yields (44% and 36%) without affecting the sensitive heterocyclic ring. Besides the substituted ethers, the substrate scope could be extended to series of benzylic systems without adjacent oxygen (**3ua**-**3xa**, 30-59% yields).[18] In addition, 3-pyridinemethyl silyl ether **1y** was infrequently applicative for this reaction and gave a 50% yield of peroxyacetal product **3ya**.

Table 3. Scope of the Substituted Ethers and Benzylic Methylene Compounds[a][b]





3qa, 77% yield

3ra, 61% yield

3sa, 44% yield

3ta, 36% yield

3ua, 40% yield

3va, 59% yield

3wa, 30% yield

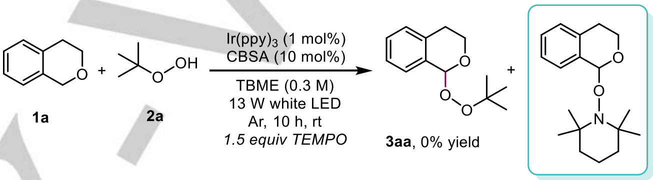
3xa, 43% yield

3ya, 50% yield

[a]Conditions: **1q-1y** (0.5 mmol), **2a** (1.5 mmol, 5.5 M in decane), Ir(ppy)$_3$ (0.005 mmol, 1 mol%) and CBSA (0.05 mmol, 10 mol%) in TBME (1.5 mL) were irradiated by 13 W white LED for 20 h under argon atmosphere. [b]Isolated yield.

Mechanistic investigations

This observed broad substrate scope in such mild reaction conditions was unprecedented, which prompted us to investigate the mechanism of the reaction. We firstly conducted the radical-trapping experiments. When using 1.5 equiv of TEMPO as the radical-trapping reagent, the reaction was totally shut down, along with the formation of trapping product of α-isochroman radical detected by HRMS analysis (Scheme 2 and Supporting Information). These results strongly supported that α-isochroman radical **7** existed in the reactions.



detected by HR-MS

Scheme 2. Radical-trapping Experiments for Mechanistic Studies

Empirically, the C-H functionalization of noncyclic benzylic ethers proceeded through oxocarbenium ion intermediates along with the generation of hemiacetal and subsequent hydrolysis. Therefore, the corresponding benzaldehyde and alcohol were obtained (Scheme 3a).[19] Conversely, compared with the noncyclic benzylic hemiacetals, the cyclic benzylic hemiacetals like **6** and oxygenated dimer **5** are more stable (Scheme 3b).[16] Inspired by this speculation, we thought utilizing our photoredox catalyzed peroxidation protocol to test the noncyclic benzylic ether substrates would be a reliable evidence for the existence of oxocarbenium ion in this reaction. After putting noncyclic benzylic ethers into the standard reactions (entry 4, Table 1), unsurprisingly, all of them decomposed smoothly to corresponding benzaldehydes (Scheme S1). Thus, there is sufficient evidence for that the oxocarbenium ion intermediates do exist in our photoredox catalyzed peroxidation strategy.

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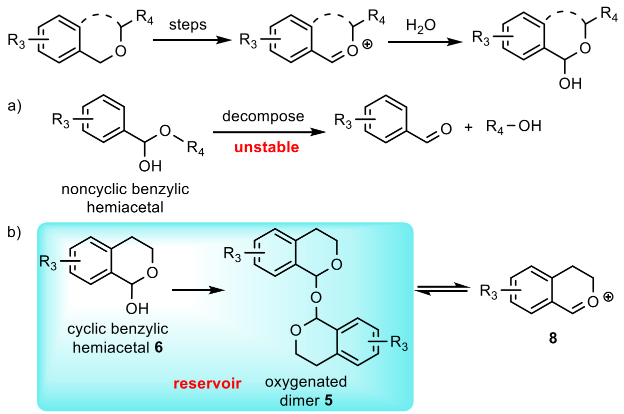
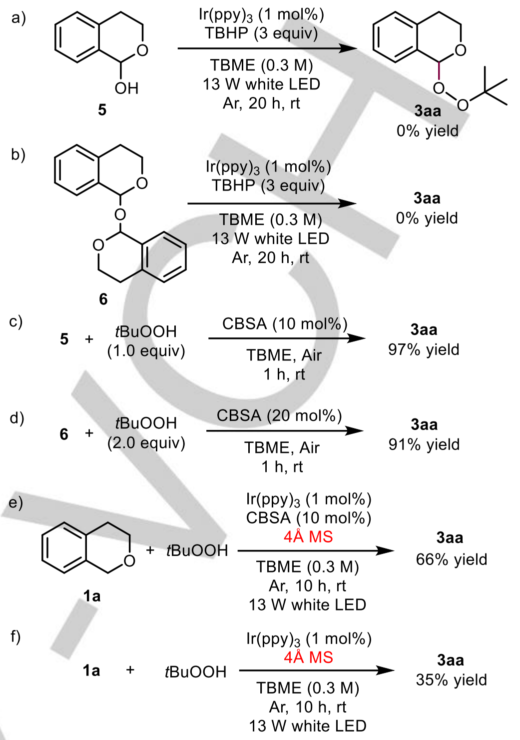


Scheme 3. Pathway of the Cyclic and Noncyclic Benzylic Ether

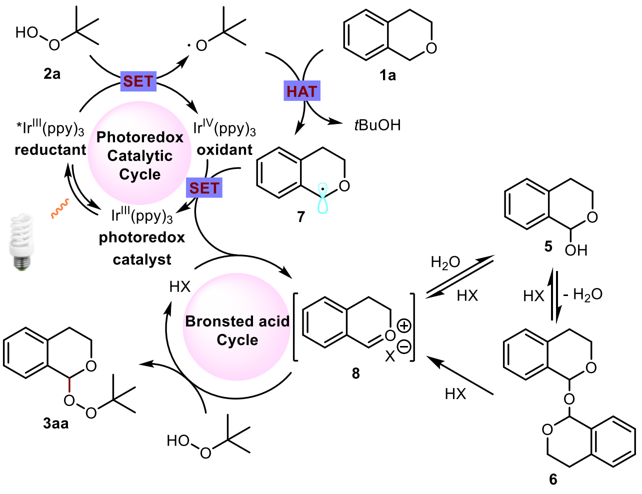
In order to further understand this reaction, we firstly gain mechanistic insights into the peroxidation with the absence of Brønsted acid. Empirically **5** and **6** acted as stable reservoirs for the reactive oxocarbenium ion intermediate. However, after **5** or **6** (previously synthesized, see Supporting Information) was injected respectively to the reaction system without Brønsted acid additives, no **3aa** was detected (Scheme 4a and 4b). These results demonstrated that **5** and **6** could not be broken down to form the oxocarbenium ion, thus they were not the true intermediates of this peroxidation in the absence of Brønsted acid. Although the reaction could generate 64% yiled of **3aa** when the reaction time was extended to 20 h, this peroxidation still performed inefficiently compared with that in the presence of CBSA (entry 4, Table 1). We speculated that with the absence of Brønsted acid, the low production yield probably resulted from the irreversible generation of **5** and **6** as byproducts. Furthermore, undesired decomposition reactions of the unstable oxocarbenium ion could also reduce the reaction yield.

Next, for further figuring out the potential role of Brønsted acid, more mechanistic studies were conducted. After quenched the reaction in the standard conditions (entry 4, Table 1) 1 h later, **5** and **6** were detected by HRMS analysis (Supporting Information). Subjecting **5** or **6** to TBHP in the presence of catalytic amounts of CBSA gave **3aa** in nearly quantitative isolated yield after 1 h (Scheme 4c and 4d). These results indicated that with the presence of CBSA, **5** and **6** can be discounted as a true reactive intermediate in the catalytic cycle. They can obviously act as stable reservoirs for the reactive oxocarbenium ion pairs, which could improve the yield and diminish undesired decomposition reactions.[20] Then for investigating the effect of counterion, we included 4 Å molecular sieves into the reaction conditions to eliminate the impact of reservoir. With the presence of CBSA, about 66% yield of **3aa** was isolated after 10 h (Scheme 4e); comparatively, 35% yield of **3aa** was obtained with the absence of CBSA (Scheme 4f). These results suggested that CBSA may provide a suitable counterion to improve the electrophilicity of oxocarbenium ion and reduce the undesired decomposition reactions. In general, condition experiments verified our assumption that the catalytic amounts of Brønsted acid not only facilitated the reservoir participating in catalytic cycle, but also enhanced the electrophilicity of oxocarbenium ion.

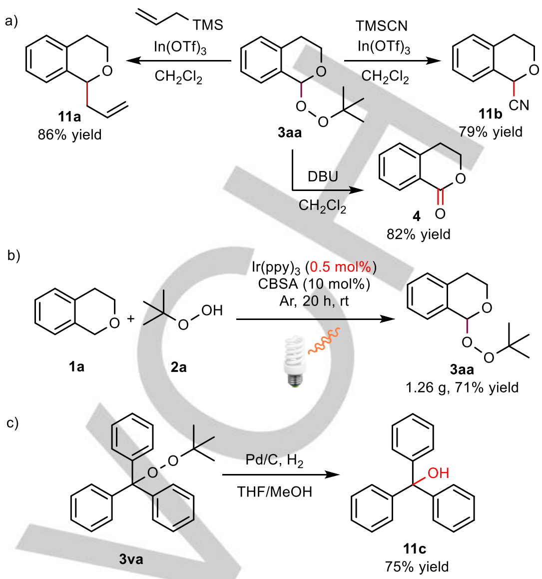


Scheme 4. Identification of the Reaction Intermediates

Based on above results, a plausible catalytic cycle can be proposed which contains two synergistic catalytic cycles (Scheme 5). The sequence would be initiated through visible light irradiation of $Ir^{III}(ppy)_3$ to give the excited state $^*Ir^{III}(ppy)_3$.[21] Then *t*-BuOOH could be reduced by $^*Ir^{III}(ppy)_3$ [$E_{1/2}(Ir^{IV}/Ir^{III})$ = −1.73 V vs SCE in CH_3CN][21] via SET, which would in turn induce scission of its weak O-O bond to generate *tert*-butoxyl radical (*t*BuO•) along with oxidant $Ir^{IV}(ppy)_3$. Subsequently, *t*BuO• might abstract a hydrogen atom from **1a** via HAT to produce **7** and *tert*-butanol (*t*BuOH). Then an electron could transfer from **7** to $Ir^{IV}(ppy)_3$ [$E_{1/2}(Ir^{IV}/^*Ir^{III})$ = + 0.77 V vs SCE in CH_3CN][21] via another SET process to regenerate $Ir^{III}(ppy)_3$ and complete the photoredox catalytic cycle. Meanwhile, the Brønsted acid catalytic cycle could be initiated via the isochroman oxocarbenium ion combined with H-X to form the oxocarbenium ion *p*-chlorobenzenesulfonate **8**. Subsequently, **8** could undergo nucleophilic attack by TBHP to generate **3aa** and complete the Brønsted acid catalytic cycle. Accordingly, **8** appears to be the reactive species in the catalytic cycle which is in off-cycle equilibrium with **5** and **6** in the presence of water. This balance seems to provide a reservoir, which could have a stabilizing effect of **8** and meanwhile release X^- to participate in Bronsted acid cycle again.[3a] As far as we are concerned, the by-product isochromanone (**4**) was probably formed through the oxidation of **5** and **6** by TBHP. In addition, it cannot be ruled out that **7** was generated through HAT of *tert*-butylperoxyl radical (*t*BuOO•), and the mechanism was shown in Scheme S2.[3c]



Scheme 5. Proposed Mechanism



Scheme 6. Synthetic Application of *tert*-Butylperoxyl Compounds

Practical applications

Intrigued by the common existence of 1-substituted isochromans that constitute the framework of many natural and synthetic bioactive products,[22] the versatility and potential application of the isochroman peroxyacetals were illustrated for the construction of various 1-substituted isochromans and other isochroman framework (Scheme 6a). In the presence of Lewis acid, the C-OO bond could be broken down, and isochroman oxocarbenium ion could be regenerated and attacked by nucleophile to form various 1-substituted isochromans such as 1-allylisochroman (**11a**) and isochroman-1-carbonitrile (**11b**) in favorable yields (86% and 79%). In addition, DBU could catalyze Kornblum-DelaMare rearrangement to construct smoothly isochromanone (**4**) with 82% yield.[23] Gram scale experiment was also conducted, which produced 1.26 g (71% yield) **3aa** in one pot with the use of 0.5 mol% of photoredox catalyst (Scheme 6b). Furthermore, the decomposition of a peroxy linkage through the Pd/C-catalyzed hydrogenation can give the corresponding tertiary alcohol **11c** with good efficiency (75% yield, Scheme 6c).

Conclusions

In summary, the photoredox and Brønsted acid catalyzed peroxidation has allowed successful and general introduction of an interesting *tert*-butylperoxyl group into isochroman to form the versatile peroxyacetals. The mild reactions proceed under visible light at ambient temperature with excellent yields, and they exhibit a broad scope with respect to both the substituted ethers and benzylic methylene compounds with high functional group tolerance. Preliminary mechanistic studies suggest an innovative dual catalytic cycles. The isochroman oxocarbenium ion pairs **8** appears to be the reactive intermediate in the catalytic cycle, and two intermediates **5** and **6** are illustrated to be the off-cycle equilibrium of **8**, which have stabilizing effect as a reservoir. We hope the present work will contribute to the development of proxides with highly sustainable conditions and synthetically important applications.

Experimental Section

See the Supporting Information for full experimental details.

Acknowledgements

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Keywords: photoredox catalysis • Brønsted acid • synergistic catalysis • peroxidation • reservoir

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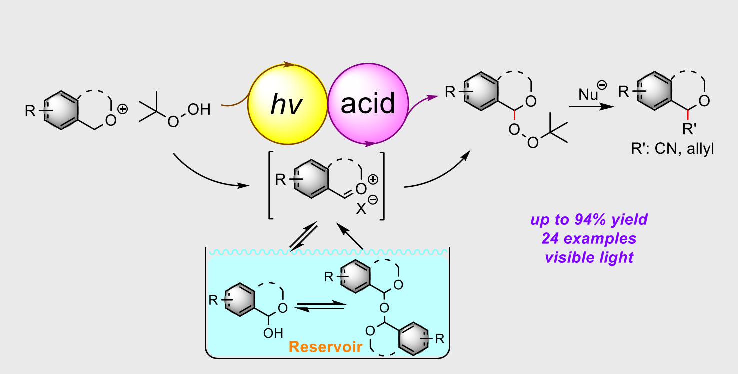

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Merging Photoredox with Brønsted Acid Catalysis: The Cross-Dehydrogenative C–O Coupling for sp^3 C-H Bond Peroxidation

Synergistic catalysis: Isochroman peroxyacetals can be accomplished by photoredox and Brønsted acid synergistically catalyzed cross-dehydrogenative C–O coupling reaction. The role of hemiacetals and oxygenated dimers on the effective stabilization of the oxocarbenium ion was investigated; the presence of added acid appeared capable of establishing equilibrium between hemiacetals and oxygenated dimers with the oxocarbenium ion pairs. Broad applicability will highlight the capacity of the protocol in future molecule synthesis.