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Aerobic Catalytic Features in Photoredox- and Copper-Catalyzed Iodolactonization Reactions

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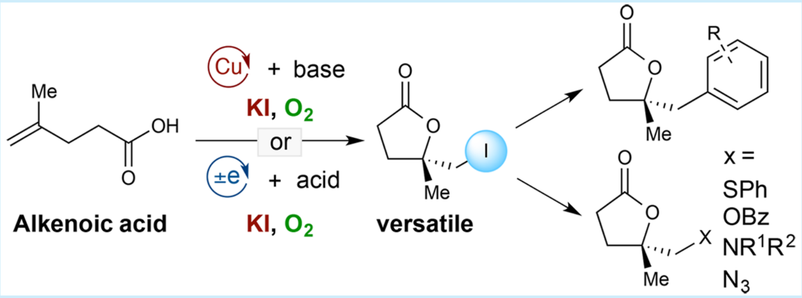
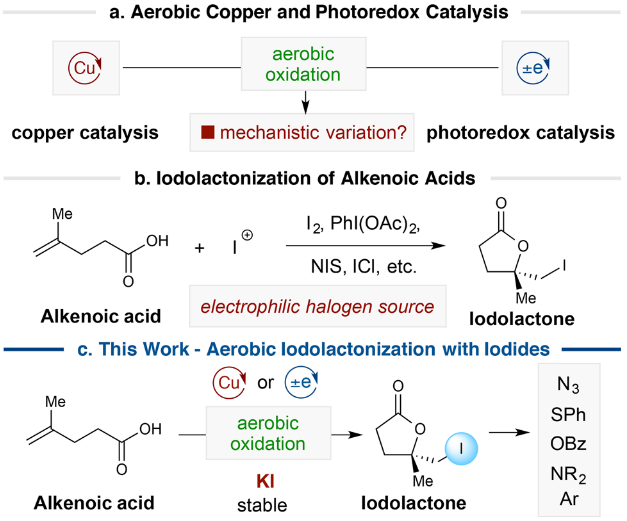
Supporting Information



ABSTRACT: Mechanistic evaluations and comparison of two important aerobic catalytic oxidation processes, aerobic copper catalysis and photoredox catalysis, are performed. Interesting and distinct catalytic behaviors were observed for a common reaction of iodolactonization of alkenoic acids. Namely, the aerobic copper catalysis requires the formation of a copper carboxylate, whereas the aerobic photoredox catalysis requires the addition of proton sources to proceed to completion. Furthermore, the iodolactone products obtained from these catalytic processes are extensively derivatized to a number of functionalized lactones, including aryl lactones generated from the nickel-catalyzed reductive coupling with aryl halides.

The utilization of molecular oxygen as a terminal oxidant in chemical transformations, often referred to as aerobic oxidation, is an attractive feature that has been widely studied and applied in many important catalytic processes.[1] For example, aerobic copper catalysis has long been utilized in the Glaser−Hay couplings,[2] the Chan−Lam couplings,[3] and C−H functionalizations.[4] On the other hand, photoredox catalysis, with its ability to engage organic substrates in single electron transfer (SET) processes, has recently emerged as a powerful catalytic platform to engineer novel chemical transformations.[5] Not surprisingly, aerobic oxidation has made its way into photoredox catalysis through the efforts of several groups.[6] As part of our interest in the development of catalytic halogenation, the oxidation of halide salts with a benign terminal oxidant is crucial for the overall conditions.[7] In this regard, copper and photoredox catalysis are ideal catalytic avenues for the aerobic oxidation of halides. More importantly, discovery and understanding of new mechanistic features in different oxidation processes is pivotal for the development of practical aerobic oxidation procedures (Scheme 1a).

Scheme 1. Background and Reaction of Interest



The reaction of interest for our study is the iodolactonization of alkenoic acids. This is a well-known strategy for the generation of iodolactones, highly versatile synthetic intermediates amenable to access a range of functionalized products.[8] This strategy has demonstrated proven applications for the synthesis of complex natural products and medicinally relevant molecules.[9] A significant drawback for this strategy is the frequent usage of a stoichiometric amount of highly electrophilic halogen sources, such as I_2, $PhI(OAc)_2$, NIS, $NaIO_4$, ICl, etc., often resulting in limited functional group compatibility

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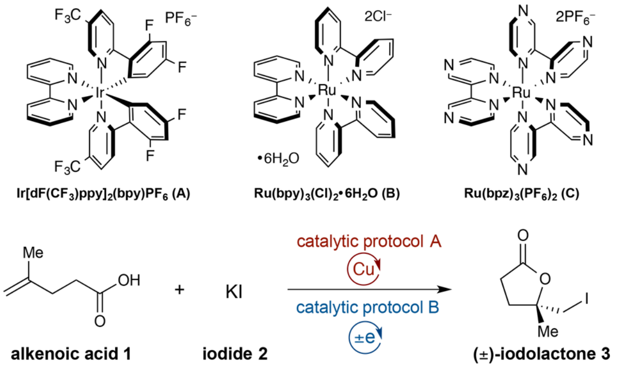
(Scheme 1b).[10] The adoption of a stable halide salt as a halogen precursor via in situ aerobic oxidation is a useful and practical alternative.[11] The reason we are interested in the use of iodide salt is because it is easily oxidized and versatile for functional group interconversion. Intrigued by the different facets of mechanistic features that various aerobic oxidation processes may possess, we decided to utilize the iodolactonization reaction as a standard template to study and compare aerobic copper and photoredox catalysis. Herein, we report our findings of distinct catalytic behaviors from these two aerobic catalyses in the iodolactonization reaction (Scheme 1c). We have fully explored the synthetic versatility of the iodolactone product through extensive derivatizations and, most notably, the nickel-catalyzed reductive couplings of iodolactones and aryl iodides to furnish useful aryl lactone structures.

With these goals in mind, we began our study with the alkenoic acid **1** and potassium iodide **2** as our standard substrates. For the copper-catalyzed variant (catalytic protocol A), initial screening of copper catalysts revealed that the utilization of copper(II) triflate [$Cu(OTf)_2$] afforded only a 3% yield, suggesting no catalytic turnover (Table 1, entry 1). Copper(II) acetate monohydrate [$Cu(OAc)_2 \cdot H_2O$], on the other hand, afforded a 64% yield. Interestingly, the addition of diisopropylamine (DIPA) as a base with $Cu(OTf)_2$ afforded the desired product in 55% yield (Table 1, entries 2−4). With $Cu(OAc)_2$ as the catalyst, we further examined the addition of a mild inorganic base and discovered that KH_2PO_4 was the optimal base to give the iodolactone product in 91% yield (Table 1, entries 5−8). Satisfied with this condition, we then focused our attention on the development of the photoredox-catalyzed protocol (catalytic protocol B). Screening a number of photocatalysts revealed $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ **A** as the best catalyst, providing a 40% yield (Table 1, entries 9−12). In addition, solvent screening identified methanol as the optimal solvent. However, regardless of how we changed our conditions, we were never able to increase the yield beyond 50%. In particular, addition of base additives often resulted in lower yields. By contrast, the addition of an acid additive improved the reaction yield to 64% (Table 1, entries 13 and 14). Furthermore, a slight increase of the reaction time to 24 h eventually led to reaction completion with a 93% yield (Table 1, entry 15).

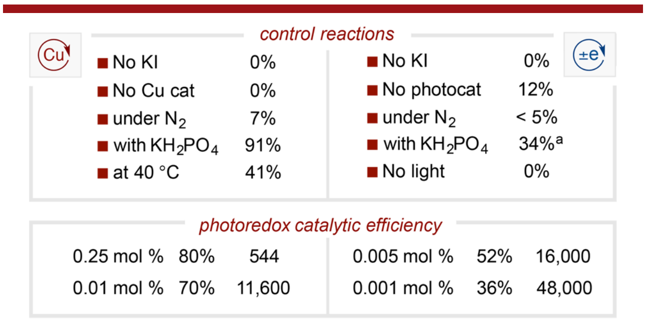
Table 1. Reaction Optimization[a]



entry	catalyst (%)	solvent (M)	additive	time (h)	yield (%)[b]
1	$Cu(OTf)_2$ (10)	MeCN (0.5)	-	16	3
2	$Cu(OAc)_2 \cdot H_2O$ (10)	MeCN (0.5)	-	36	53
3	$Cu(OAc)_2 \cdot H_2O$ (15)	MeCN (0.5)	-	36	64
4	$Cu(OTf)_2$ (10)	MeCN (0.5)	DIPA	16	55
5	$Cu(OAc)_2 \cdot H_2O$ (15)	MeCN (0.5)	K_2HPO_4	36	61
6	$Cu(OAc)_2 \cdot H_2O$ (15)	MeCN (0.5)	K_2CO_3	36	21
7	$Cu(OAc)_2 \cdot H_2O$ (15)	MeCN (0.5)	HOAc	36	18
8	$Cu(OAc)_2 \cdot H_2O$ (15)	MeCN (0.5)	KH_2PO_4	36	91
9	photocat **A** (0.5)	MeCN (0.25)	-	16	27
10	photocat **A** (0.5)	MeOH (0.25)	-	16	40
11	photocat **B** (0.5)	MeOH (0.25)	-	16	15
12	photocat **C** (0.5)	MeOH (0.25)	-	16	4
13	photocat **A** (0.5)	MeOH (0.25)	TFA	16	3
14	photocat **A** (0.5)	MeOH (0.25)	AcOH	16	64
15	photocat **A** (0.5)	MeOH (0.25)	AcOH	24	93(90)

[a] Reaction conditions for photoredox catalysis: alkenoic acid **1** (0.25 mmol), photocatalyst (0.5 mol %), KI (0.275 mmol), solvent (1 mL), 40 °C. Reaction conditions for copper catalysis: alkenoic acid **1** (0.5 mmol), copper catalyst (15 mol %), KI (0.5 mmol), KH_2PO_4 (0.5 mmol), solvent (1 mL), 60 °C. [b] Yields were determined by crude ^1H NMR using 1,3-benzodioxole as the internal standard. Yield shown in parentheses was isolated yield.

With the optimal conditions in hand, we conducted and evaluated a series of control reactions for each catalytic protocol (Figure 1). For the copper-catalyzed reaction, the exclusion of the catalyst completely inhibited the reaction. Under a nitrogen environment, the reaction produced a 7% yield. To compare directly with the photocatalytic condition, running the reaction at 40 °C afforded a 41% yield. For the photoredox process, removing the photocatalyst still afforded the iodolactone in 12% yield, suggesting that oxygen under blue LED light can function for iodide oxidation to a certain extent. Similar to the copper catalysis, a nitrogen environment led to catalyst inhibition with a less than 5% yield. The addition of base was detrimental to the reaction yield. Furthermore, running the reaction in the absence of light completely inhibited the reaction. Finally, we also evaluated the catalytic efficiency of the photoredox procedure by measuring the turnover numbers.[12] In this case, the catalyst loading can be lowered to 0.001 mol % to afford a 36% yield. Excluding the background reaction, the turnover number was calculated to be 48 000, suggesting that the photocatalytic process is incredibly efficient.



control reactions

Cu		±e	
■ No KI	0%	■ No KI	0%
■ No Cu cat	0%	■ No photocat	12%
■ under N_2	7%	■ under N_2	< 5%
■ with KH_2PO_4	91%	■ with KH_2PO_4	34%[a]
■ at 40 °C	41%	■ No light	0%

photoredox catalytic efficiency

0.25 mol %	80%	544	0.005 mol %	52%	16,000
0.01 mol %	70%	11,600	0.001 mol %	36%	48,000

Figure 1. Control experiments and catalyst turnover. [a] Ring opening product with methanol.

We also performed time studies for both reactions (Figure 2). A number of features were notable here. First, the photoredox conditions had an induction time of approximately 30 min prior to the product formation. Careful UV−vis studies indicated that the immediate formation of trioiodide I_3^- species, followed by a slow equilibrium to iodine was most likely to be responsible for the initial induction time.[13] For the copper-catalyzed process, an initial burst of product formation was followed by a steady increase in product formation. UV−vis studies of mixing stoichiometric $Cu(OAc)_2$ and potassium iodide also revealed the formation of I_3^-. As the reaction progressed, consumption of

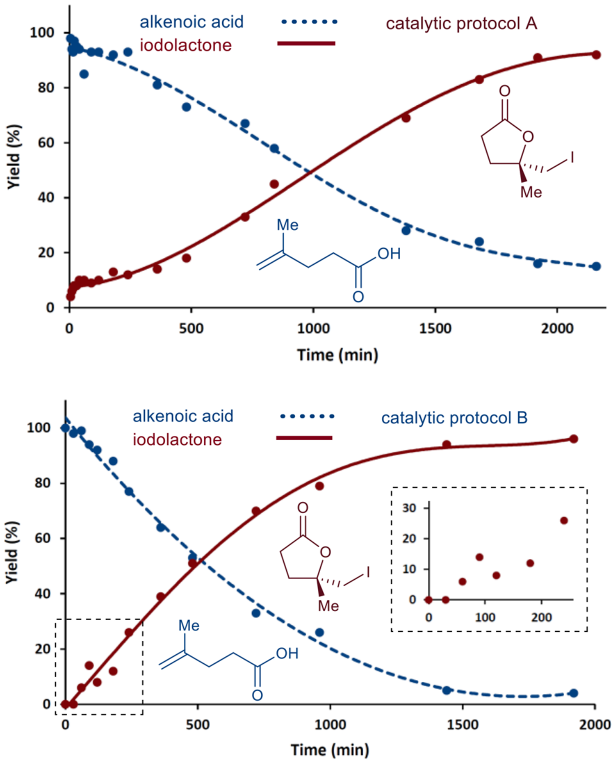


Figure 2. Time studies of both aerobic processes.

the starting material was commensurate with the product formation.

Based on these studies, we have extracted useful information about both aerobic oxidation processes. In the copper-catalyzed process, the formation of the copper carboxylates **D** is critical for the catalytic turnover (Figure 3).[15] This is supported by the fact that when $Cu(OTf)_2$ is used as the catalyst, only 3% of the desired product is obtained. With the addition of diisopropylamine as an exogenous base, the iodolactone formation can be increased to 55%. When $Cu(OAc)_2$ is used as the catalyst, the ligand exchange is much more thermodynamically favorable; hence, base additives are not required to achieve catalytic turnovers. However, the addition of certain base additives such as KH_2PO_4 can facilitate the ligand exchange and catalyst turnover. The formation of product **3** can occur with iodination of **1**, **D**, or **E**.[16] In addition, the presence of copper carboxylate **D** or **E** may facilitate the equilibrium shift of I_3^- to iodine with no induction time observed initially.[17] On the other hand, the photoredox protocol requires no such ligand exchange process. Instead, accumulation of the oxygen radical anion **F** may inhibit the reaction. This is primarily the reason why, without an appropriate acid additive, the reaction never afforded yields greater than 50% and, with the acid additive, the yield was increased to 93%. These mechanistic insights suggest that, for the reaction of interest, aerobic copper catalysis proceeds smoothly under basic conditions, whereas photoredox catalysis can be facilitated under acidic conditions. The mechanistically distinct behaviors observed here will be further explored in other aerobic catalytic conditions.

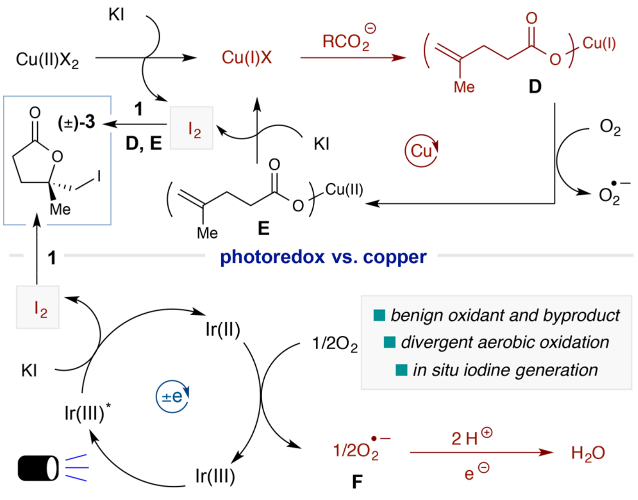
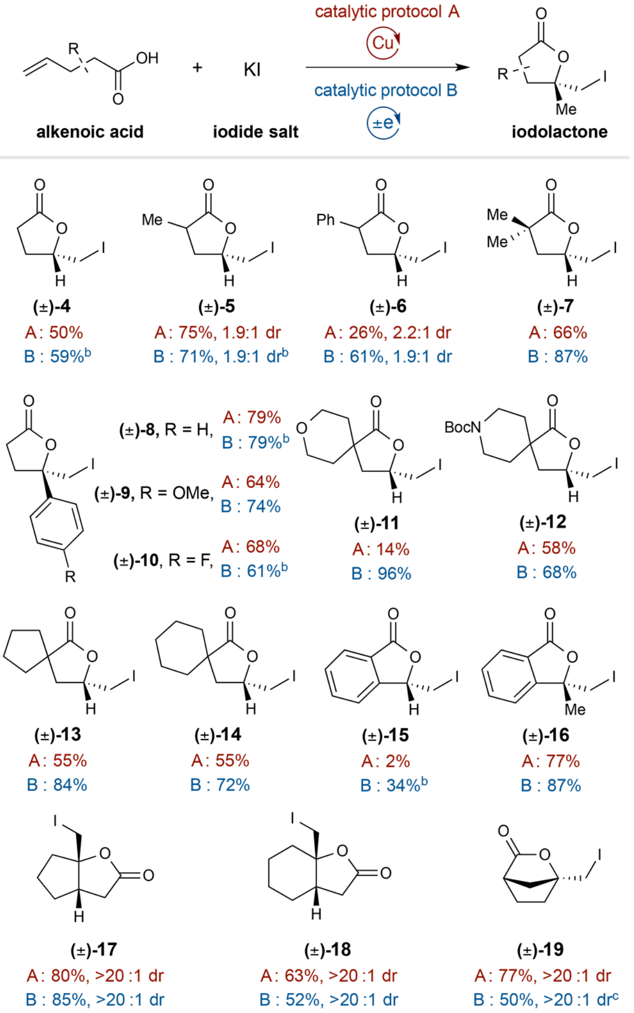


Figure 3. Proposed mechanisms and features.

With the mechanistic picture being elucidated, we decided to turn our attention to the scope of the alkenoic acid substrates.[18] In this case, both catalytic processes worked efficiently for a range of α-substituted and 4,4-disubstituted pentenoic acids (Scheme 2, products **4**−**10**). An exception in this case is

Scheme 2. Iodolactonization Substrate Scope[a]



(±)-4 A: 50% B: 59%[b]

(±)-5 A: 75%, 1.9:1 dr B: 71%, 1.9:1 dr[b]

(±)-6 A: 26%, 2.2:1 dr B: 61%, 1.9:1 dr

(±)-7 A: 66% B: 87%

(±)-8, R = H, A: 79% B: 79%[b]

(±)-9, R = OMe, A: 64% B: 74%

(±)-10, R = F, A: 68% B: 61%[b]

(±)-11 A: 14% B: 96%

(±)-12 A: 58% B: 68%

(±)-13 A: 55% B: 84%

(±)-14 A: 55% B: 72%

(±)-15 A: 2% B: 34%[b]

(±)-16 A: 77% B: 87%

(±)-17 A: 80%, >20:1 dr B: 85%, >20:1 dr

(±)-18 A: 63%, >20:1 dr B: 52%, >20:1 dr

(±)-19 A: 77%, >20:1 dr B: 50%, >20:1 dr[c]

[a] Standard reaction conditions. Yields for catalytic protocol B were isolated yields. Yields for catalytic protocol A were determined by crude ^{1}H NMR using 1,3-benzodioxole as the internal standard. [b] Reaction time was 36 h. [c] An additional 25% of ring opening product by methanol was also observed.

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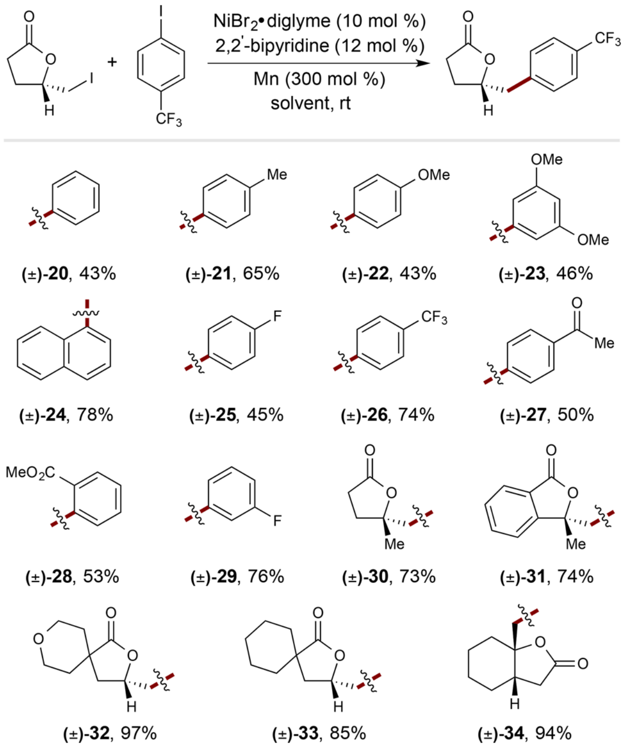
compound **6**, with which the copper-catalyzed protocol afforded a much lower yield due to the acidic α-carbonyl proton being problematic under more basic conditions. Spirocyclic iodolactones could also be obtained with good yields (Scheme 2, products **11**−**14**). Moreover, benzene backbones could be tolerated under both catalytic conditions (Scheme 2, products **15** and **16**). Finally, fused and bridge iodolactone structures also proceeded smoothly in good yields (Scheme 2, products **17**−**19**). Notably, these bicyclic structures were also produced with exceptional diastereoselectivity.

An exceptional feature of the iodolactone product from these reactions is its versatility in accessing a range of derivatized products. In particular, we wondered about the capacity of incorporating these molecules in the nickel-catalyzed reductive cross electrophile coupling reactions. With that in mind, we followed a modified coupling protocol based on the elegant work of Weix,[19] Gong,[20] and Reisman.[21] Gratifyingly, a range of aryl iodides, with varying electronic properties, all participated readily to afford the desired aryl lactones in reasonable yields (Scheme 3, products **20**−**29**). Compared to the electron-rich aryl iodides, the electron-deficient substrates generally performed better. In addition, sterically demanding substrates also reacted effectively to form the desired products in reasonable yields (Scheme 3, products **24** and **28**). Interestingly, different classes of iodolactone structures all participated in this reductive coupling reaction with exceptional efficiencies (Scheme 3, products **30**−**34**).

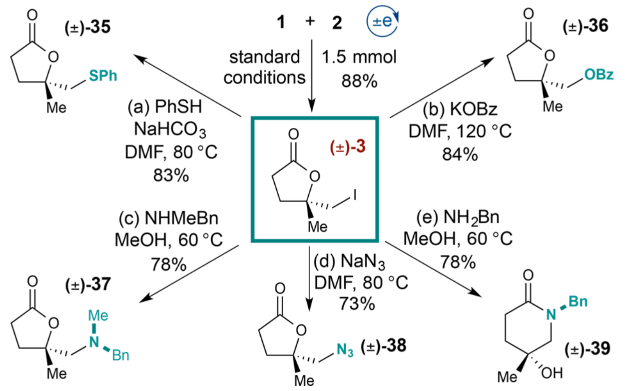
Scheme 3. Dielectrophile Coupling Reactions



[a] Reaction conditions: iodolactone (0.375 mmol), aryl iodide (0.25 mmol), NiBr$_2$·diglyme (10 mol %), 2,2′-bipyridine (12 mol %), Mn (300 mol %), DMA (0.25 M), rt, 16 h.

To explore the versatility of the iodolactone product further, we examined a range of other nucleophiles (Scheme 4). For example, reactions of the iodolactone **3** with thiolate, carboxylate,[22] secondary amine, and azide nucleophiles all afforded the respective functionalized lactone products **35**−**38** in good yields.[23] In the case of a primary amine as the nucleophile, a lactam structure was obtained. In this case, the primary amine initially produced the amino lactone product, followed by a subsequent intramolecular lactam formation to produce **39** in great yield. These nucleophilic derivatizations demonstrated the synthetic versatility of the iodolactone.

Scheme 4. Iodolactone Derivatizations



In summary, we have conducted mechanistic investigations on two widely used aerobic oxidation processes. We have observed very interesting and distinct oxidative features of the aerobic copper and photoredox catalysis. Specifically, the copper catalysis requires the generation of a copper carboxylate for catalytic turnover. In contrast, the aerobic photoredox protocol requires an infusion of a proton source to drive the reaction to completion. Additionally, we have demonstrated the synthetic utility of the iodolactone product in the nickel-catalyzed reductive coupling reactions with aryl iodides. Finally, we have also extended the utility of these iodolactones to access a range of functionalized lactone structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02771.

Experimental procedure and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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