

Generation of Phosphoranyl Radicals via Photoredox Catalysis Enables Voltage–Independent Activation of Strong C–O Bonds

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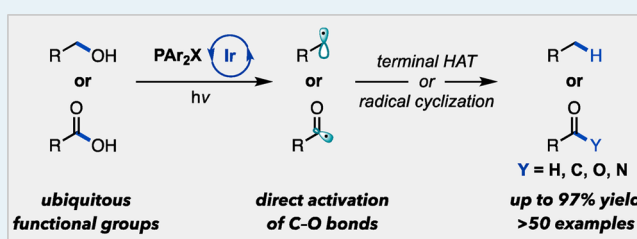
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S Supporting Information

ABSTRACT: Despite the prevalence of alcohols and carboxylic acids as functional groups in organic molecules and the potential to serve as radical precursors, C–O bonds remain difficult to activate. We report a synthetic strategy for direct access to both alkyl and acyl radicals from these ubiquitous functional groups via photoredox catalysis. This method exploits the unique reactivity of phosphoranyl radicals, generated from a polar/SET crossover between a phosphine radical cation and an oxygen-centered nucleophile.

We show the desired reactivity in the reduction of benzylic alcohols to the corresponding benzyl radicals with terminal H atom trapping to afford the deoxygenated products. Using the same method, we demonstrate access to synthetically versatile acyl radicals, which enables the reduction of aromatic and aliphatic carboxylic acids to the corresponding aldehydes with exceptional chemoselectivity. This protocol also transforms carboxylic acids to heterocycles and cyclic ketones via intramolecular acyl radical cyclizations to forge C–O, C–N, and C–C bonds in a single step.

KEYWORDS: photoredox catalysis, C–O Bond activation, phosphoranyl radical, β -scission, radical cyclization, carboxylic acid



Over the past decade, photoredox catalysis has witnessed rapid development as a mechanism to address long-standing challenges in synthetic chemistry. This transformative synthetic tool often utilizes direct single-electron transfer (SET) between an excited photoredox catalyst and an organic substrate to access highly reactive radical intermediates.^{1–3} Because of the abundance of aliphatic alcohols and carboxylic acids as feedstock chemicals and complex molecules, direct activation of the C–O bonds of these functional groups to generate new C–H, C–C, and C–X bonds has been a long-sought goal in the fields of organic synthesis and organometallic catalysis. However, the high redox potentials as well as the strength of C–O bonds have deterred the identification of general solutions in these fields as well as in the area of photoredox catalysis (Figure 1A).⁴ Methods to access radicals from C–O bonds via photoredox catalysis have instead relied on conversion of the precursor alcohol or acid into a new functional group that is amenable to SET.^{5,6} For example, alcohols may be converted to alkyl oxalates, which upon single-electron oxidation, generate an alkyl radical after two successive decarboxylations with heating.⁵ However, primary and secondary alcohols are generally not amenable to this strategy and require an alternative approach via multistep conversion to an organotrifluoroborate, for example.⁷ Similarly, carboxylic acids, which represent potential precursors to valuable acyl radicals, must be converted to a new functional

group in order to activate the C–O bond.^{8–11} In situ generation of a mixed anhydride from an aromatic acid and subsequent single-electron reduction with a highly reducing photocatalyst can afford the acyl radical.^{9,12} However, this approach is highly substrate-specific and is not amenable to aliphatic carboxylic acids, which retain even higher reduction potentials, and necessitate a distinct strategy.¹³ Thus, despite advances to access these diverse and exceptionally valuable radical species, each functional group class requires distinct prefunctionalization strategies; activation methods vary from strongly oxidizing to strongly reducing; and within the functional group class, voltage-gating limits the generality according to substrate identity. As such, the identification of a single, tunable strategy to access these diverse radicals that is not reliant on substrate redox potentials would be incredibly valuable.

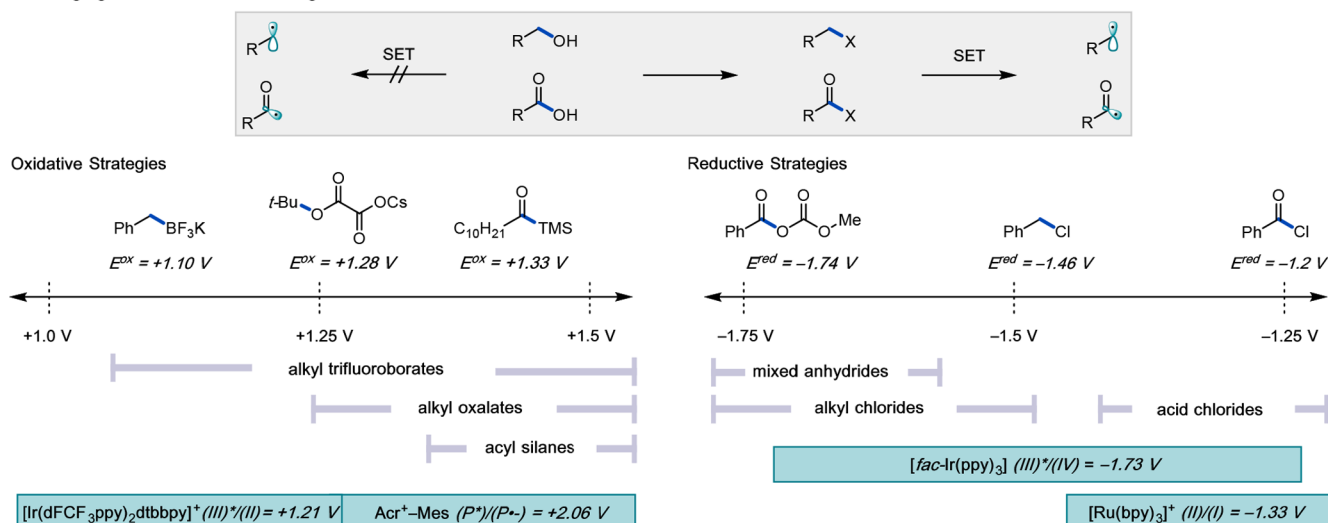
Here we describe a catalytic strategy for direct C–O bond activation via photoredox catalysis inspired by the studies of Bentrude and others on C–O bond activation with phosphoranyl radicals, which are tetravalent phosphine-centered radicals.¹⁴ Bentrude has demonstrated that, dependent on the phosphorus substitution pattern, phosphoranyl

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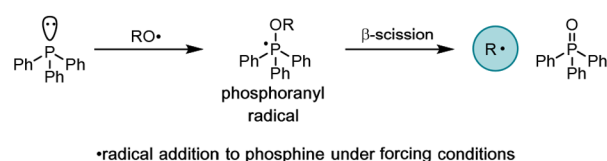
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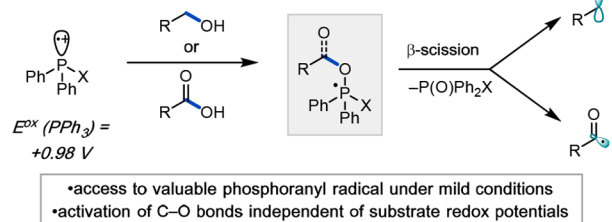
A. Voltage-gated SET activation strategies for functionalization of C–O bonds



B. Reactivity of phosphoranyl radicals



C. This Work – phosphine radical mediator (X = Ph or OEt)



D. Mechanistic proposal

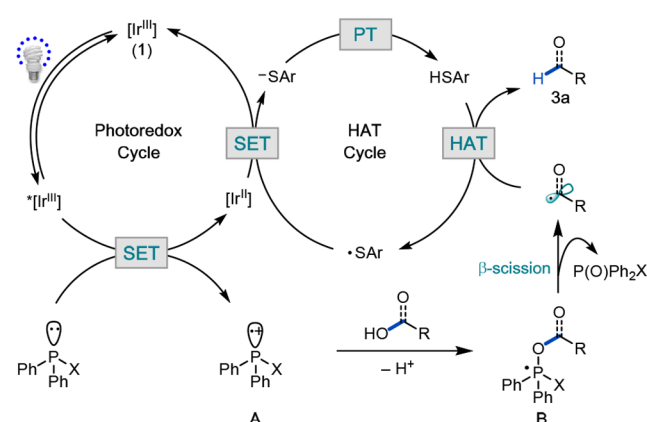


Figure 1. (A) Common functional group interconversions with corresponding redox windows of substrates and photocatalysts for accessing alkyl and acyl radicals. (B) Reactivity of phosphoranyl radicals. (C) New activation pathway to access phosphoranyl radicals and cleave C–O bonds. (D) Mechanistic proposal. Stern–Volmer quenching studies are consistent with this mechanistic hypothesis. See SI for full experimental details.

radicals can undergo β -scission to form a strong phosphorus–oxygen double bond (130 kcal/mol) and a new carbon-centered radical species (Figure 1B). Despite the intriguing possibilities of this fragmentation pathway, the phosphoranyl radicals are generated stoichiometrically via addition of oxygen-centered radicals to phosphines.^{15–22} Typically, these high-energy radicals are formed from peroxides under forcing conditions which limit functional group tolerance. Since phosphines, like tertiary amines, can undergo single electron oxidation to form a phosphine radical cation, we questioned whether phosphoranyl radicals could be accessed via nucleophilic addition of an alcohol or acid to a phosphine radical cation generated by photoinduced SET.^{23–25} While existing reports demonstrate that nucleophilic addition to a phosphine radical cation is feasible under stoichiometric conditions, the intermediate phosphoranyl radical is oxidized before C–O activation via β -scission can occur. Thus, the combination of these three elementary steps has not been exploited to effect catalytic C–O activation.^{26,27}

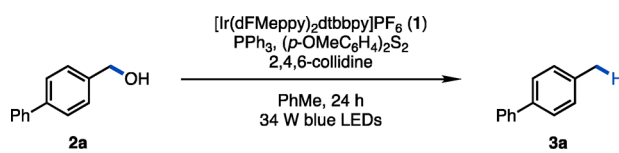
From a synthetic perspective, we envisioned application of this polar/SET crossover reaction platform to the direct

deoxygenation of alcohols and carboxylic acids (Figure 1C).^{28–30} By employing tunable phosphine mediators, we would circumvent functional group interconversion or preactivation of C–O bonds to render them susceptible to single electron oxidation or reduction. Additionally, we expected that the strategy would accomplish direct conversion to the corresponding radical species, independent of functional group identity and substrate-dependent redox potentials. Here we describe the development of catalytic conditions for the deoxygenation of benzylic alcohols to toluenes via trapping of benzyl radicals with terminal H atom sources. Furthermore, we show that the same conditions can be used for the reduction of aromatic carboxylic acids to the corresponding aldehydes with unprecedented functional group orthogonality,¹² featuring the selective reduction of carboxylic acids preferentially in the presence of other reactive carbonyl compounds. Ultimately, this strategy can be generalized to both aromatic and aliphatic acids, a major limitation of traditional approaches, and to reactions beyond terminal hydrogen atom transfer (HAT), including intramolecular hydroacylation of olefins and carbonyl derivatives.³¹

Mechanistically, we envisioned that $[\text{Ir}(\text{dFMeppy})_2\text{dtbbpy}]\text{PF}_6$ (**1**) [dFMeppy = 2-(2,4-difluorophenyl)-5-methylpyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] when irradiated with light $\{E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +0.97 \text{ V}$ versus saturated calomel electrode (SCE) $\}^{32}$ would undergo SET with triphenylphosphine $\{E_{1/2} = +0.98 \text{ V}$ versus SCE $\}^{23}$ to afford catalytic amounts of a phosphine radical cation (**A**, Figure 1D). Polar nucleophilic addition to the cation with an alcohol or carboxylic acid would generate a phosphoranyl radical (**B**), which upon β -scission would generate the corresponding alkyl or acyl radical and triphenylphosphine oxide. Terminal HAT from an aryl thiol would afford the desired product. A final reduction of the thiyl radical and a proton transfer (PT) to the thiolate would close both catalytic cycles.

To evaluate the reaction platform, we began our studies by examining the deoxygenation of benzylic alcohols, a transformation of value in a complex molecule as well as commodity chemical synthesis from biomass.²⁸ We were gratified to find that, upon optimization, toluene **3a** is afforded in quantitative yield (Table 1, entry 1). Control reactions clearly demonstrate

Table 1. Reaction Evaluation of Benzylic Alcohols

		
entry	deviation from standard conditions ^a	% yield ^b
1	none	>99%
2	no PPh ₃	0%
3	no light	0%
4	no [Ir] 1	0%
5	no (p-OMeC ₆ H ₄) ₂ S ₂	4%
6	ACN (0.1M), no (p-OMeC ₆ H ₄) ₂ S ₂	80%
7	2,6-lutidine (1.0 equiv)	79%
8	no base	32%
9	Ph ₂ POEt (1.2 equiv)	91%
10	TRIP-SH (20 mol %)	59%
11	TRIP ₂ S ₂ (10 mol %)	93%
12	$[\text{Ir}(\text{dFCF}_3\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ (2 mol %)	75%

^aStandard conditions: PPh₃ (1.2 equiv), [Ir] (**1**) (2 mol %), (p-OMeC₆H₄)₂S₂ (10 mol %), 2,4,6-collidine (1.0 equiv), PhMe (0.1M).

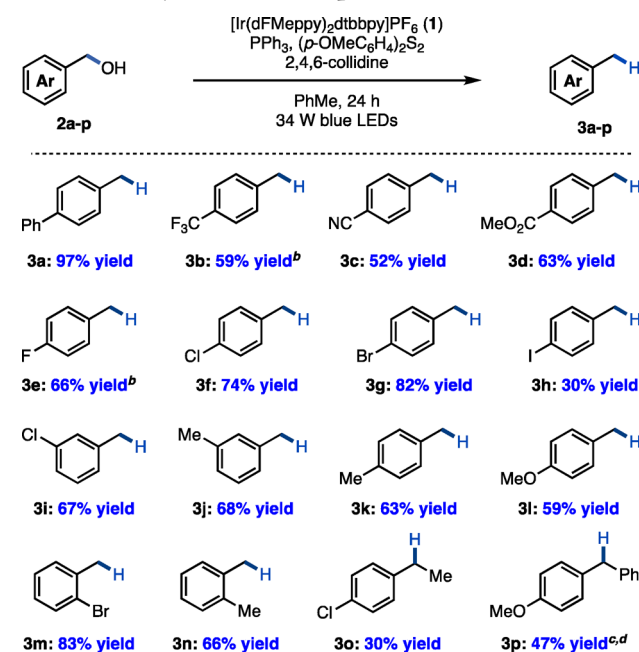
^bYields based on GC analysis using dodecane as an external standard. Disulfides can also quench the excited state of the photocatalyst to form Ir(IV), which is also capable of oxidizing PPh₃ to the phosphine radical cation. It is likely that both catalytic cycles are operative, depending on whether disulfide is present. See SI for Stern–Volmer quenching studies.

that phosphine, photoredox catalyst, and light are all necessary for reactivity (entry 2–4). Toluene **3a** is formed in trace yield in the absence of disulfide, presumably with the solvent or base acting as an H atom source (entry 5). Use of acetonitrile (ACN) as the solvent in the absence of additional H atom source affords the product in 80% yield (entry 6). Use of 2,6-lutidine as the base in place of 2,4,6-collidine results in a less efficient reaction and in the absence of base, the reaction proceeds to only 32% yield (entry 7–8). Ethyl diphenylphosphinite also affords the product in comparable yield to PPh₃ (entry 9). Use of TRIP-SH (2,4,6-triisopropylbenzenethiol) as an H atom source results in 59% yield, while TRIP₂S₂ affords the product in 93% yield (entry 10–11). Use of the

commercially available photocatalyst $[\text{Ir}(\text{dFCF}_3\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ gives a slightly less efficient reaction, with the product observed in 75% yield (entry 12).

With the optimized conditions, we sought to examine the scope of benzylic alcohol deoxygenation (Table 2). Toluene **3a**

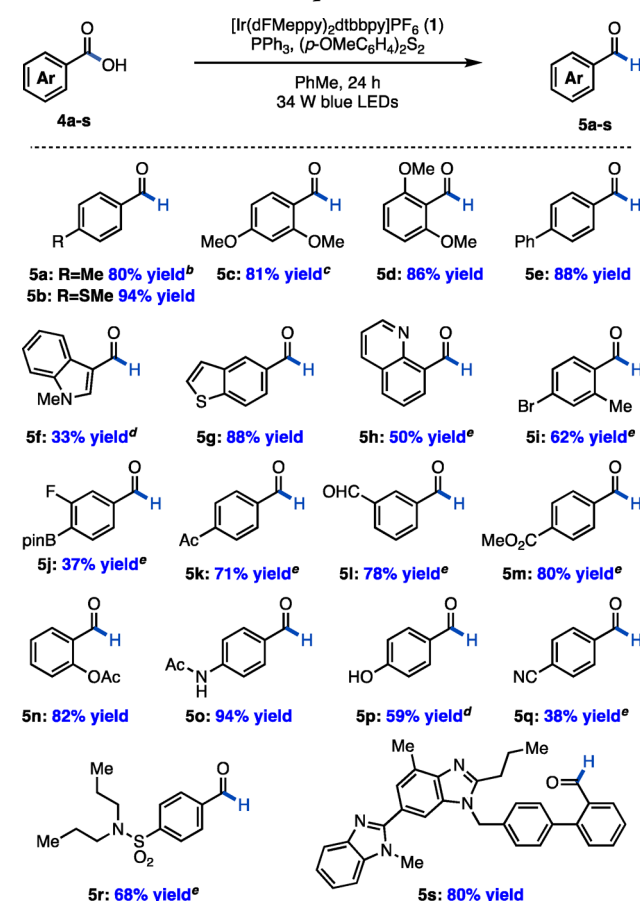
Table 2. Benzylic Alcohol Scope^a



^aYields based on an average of two runs on 0.5 mmol scale using standard conditions from Table 1, entry 1, based on GC analysis using dodecane as an external standard. ^bYields based on ¹⁹F NMR using 1-fluoronaphthalene as an external standard. ^cReaction run under conditions according to Table 1, entry 6. ^dYield determined by ¹H NMR.

was observed in 97% yield upon scale-up. Alcohols bearing more electron-deficient arenes afforded product in slightly reduced yield (**3b–3d**), likely due to the lower nucleophilicity of the alcohol. *p*-Halogen substitution is well tolerated, with the deoxygenated products observed in 30% to 82% yield (**3e–3h**). *m*-Substitution is also well tolerated, with **3i** and **3j** formed in 67% and 68% yield, respectively. Interestingly, when a more electron-rich benzylic alcohol is employed, the product is observed in reduced yield relative to **3a** (**3k–3l**). In these cases, the reduced yields may be due to formation of electron-rich phosphoranyl radicals that are more susceptible to oxidation prior to β -scission. In general, *ortho*-substitution is well tolerated: *o*-bromo benzyl alcohol (**2m**) is efficiently reduced to the corresponding toluene in excellent yield (83%) and more sterically encumbered 2-methylbenzyl alcohol is reduced with similar efficiencies as its isomeric derivatives. Secondary alcohols such as 4-chlorophenethyl alcohol **2o** are also competent under the reaction conditions, albeit the deoxygenation proceeds in reduced yields, consistent with a slower addition of a more sterically hindered alcohol to a phosphine radical cation. In the case of benzhydrol **2p**, improved yields of diaryl methane **3p** could be obtained in acetonitrile as solvent, suggesting that additional reaction optimization could lead to high-yielding conditions for deoxygenation of more substituted alcohols.

We next sought to evaluate our reaction platform for direct and selective reduction of carboxylic acids to aldehydes, broadly useful intermediates in organic synthesis. Despite many advances in synthetic methodology development, methods for the conversion of carboxylic acids to aldehydes still exhibit poor chemoselectivity, limited functional group tolerance, and often require harsh reaction conditions.^{33–35} Employing the optimal conditions for benzylic alcohol reduction, we evaluated *p*-toluic acid for reduction to *p*-tolualdehyde (**5a**) and found that base was not necessary for this transformation and that reduced catalyst loadings could be used, with the product afforded in 80% yield. Electron-neutral and electron-rich aromatic acids are efficiently converted to the corresponding aldehydes under the reaction conditions (Table 3, **5b–5e**). A reaction setup on the benchtop affords comparable reaction efficiency to that obtained with reactions setup in a glovebox. Electron-rich heteroaromatics are also competent substrates, with indole substrate **5f** and benzothio-
 phene **5g** giving product in 33% and 88% yield, respectively, although indole **5f** can be isolated in 45% yield when 2,6-

Table 3. Aromatic Acid Scope^a

^aStandard conditions: PPh₃ (1.2 equiv), (p-OMeC₆H₄)₂S₂ (5 mol %), [Ir] (**1**) (1 mol %), PhMe (0.1M). Isolated yields based on an average of two runs. See SI for more optimization details. ^bYield determined by GC analysis using dodecane as an external standard. ^cReaction setup on the benchtop. ^dNMP (0.1M) used. ^e2,6-lutidine (1.0 equiv) and (p-OMeC₆H₄)₂S₂ (10 mol %) used. Over-reduction of the aldehyde to alcohol does not involve phosphine, and likely occurs through single-electron reduction of the aldehyde to the ketyl radical, followed by H atom transfer. See SI for further optimization details.

Me₂C₆H₃SH is used as the H atom source (see SI for more details). Electron-deficient acids require the addition of 2,6-lutidine to avoid over-reduction, but with base, they afford the desired aldehydes (**5h–5j**) in good yield. Notably, ketones, esters, and aldehydes are not reactive under these conditions, providing an orthogonal method for selective carboxylic acid reduction (**5k–5n**). The full chemoselectivity of the method is highlighted with substrates bearing secondary acetamide, phenol and cyano groups, which provide the desired aldehydes (**5o–5q**) in good to excellent yields. Finally, Probenecid (**5r**) and Telmisartan (**5s**) are efficiently converted to the corresponding aldehydes in 68% and 80% yield, respectively (Table 3).

We next turned our attention to the reduction of aliphatic carboxylic acids (Table 4). Unfortunately, we observed

Table 4. Aliphatic Acid Optimization

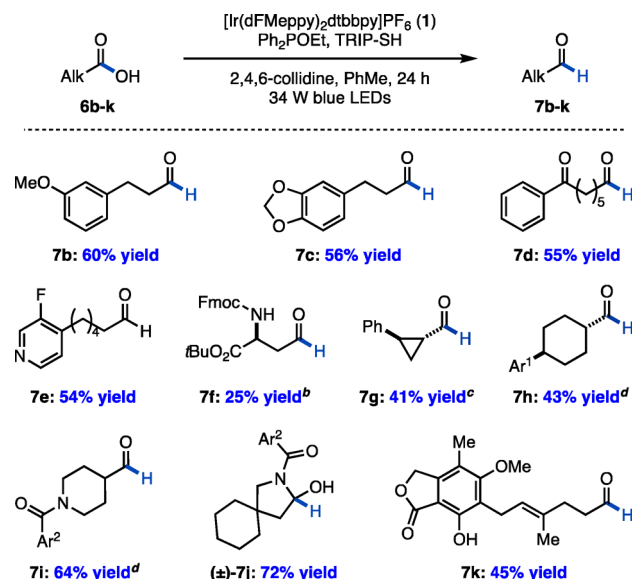
Reaction scheme for Table 4: Aliphatic Acid Optimization. **6a** (2-phenylacetic acid) + [Ir(dFMeppy)₂dtbbpy]PF₆ (**1**) + Ph₂PX, TRIP-SH, 2,4,6-collidine in PhMe, 24 h, 34 W blue LEDs yields **7a** (2-phenylacetaldehyde).

entry	Ph ₂ PX, [M] ^a	% yield ^b
1	PPh ₃ , 0.1M	4%
2	Ph ₂ POEt, 0.1M	43%
3	Ph ₂ POEt, 0.02M	60%
4	Ph ₂ POEt, 0.0133M	68%
5	PPh ₃ , 0.0133M	8%

^aStandard conditions: Ph₂PX (1.2 equiv), TRIP-SH (50 mol %), 2,4,6-collidine (1.0 equiv), [Ir] (**1**) (2 mol %), PhMe. ^bYields based on GC analysis using dodecane as an internal standard. During optimization, we observed formation of the corresponding thioester, as well as the ethyl ester when using Ph₂POEt. See SI for further optimization details.

diminished reactivity relative to aryl carboxylic acids under our standard reaction conditions (<5% yield). We attribute this change in reactivity to the formation of a more electron-rich phosphoranyl radical, which is susceptible to oxidation and would afford a phosphonium intermediate capable of rapid acyl transfer. Consistent with this hypothesis, exchanging triphenylphosphine for a more electron-deficient phosphinite leads to improved yields for the reduction of **6a** (entry 2). Ultimately, when the reaction is conducted under dilute conditions, hydrocinnamaldehyde is afforded in 68% yield (entry 4). We hypothesize that decreasing the concentration of the reaction decreases the rate of the proposed counterproductive bimolecular oxidation events relative to unimolecular β -scission. Use of PPh₃ under identical conditions, however, does not afford the same result, highlighting the importance of the phosphinite, Ph₂POEt. Access to aliphatic and aromatic acyl radicals from carboxylic acids under nearly identical in situ conditions has not been achieved before and underscores the potential of our approach for nonredox-gated C–O bond activation.

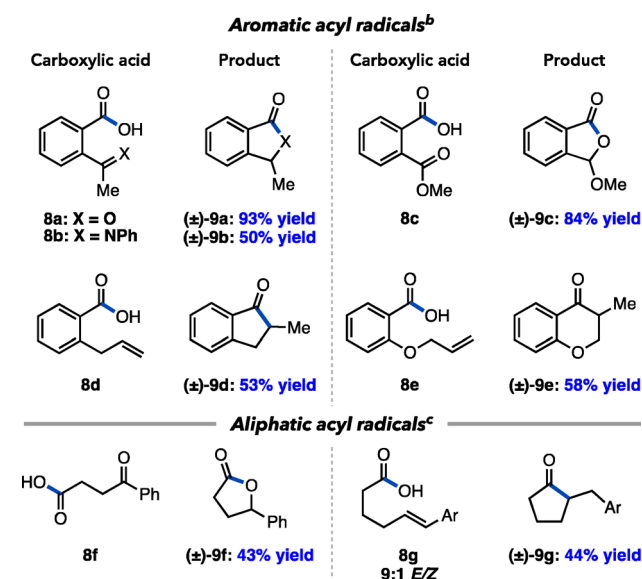
With the new optimized conditions, we examined the scope of aliphatic acids (Table 5). Hydrocinnamaldehyde derivatives **7b** and **7c** are formed in 60% and 56% yield, respectively. Longer-chain aliphatic acid **6d** affords the corresponding aldehyde in 55% yield without competitive ketone reduction. Additionally, Lewis basic heteroaromatic substituents are compatible with the reduction conditions, with pyridine **6e** affording the desired aldehyde in 54% yield. The method is

Table 5. Aliphatic Acid Scope^a

^aIsolated yields based on an average of two runs using standard conditions in Table 3. ^bACN as the solvent. Yield based on ¹H NMR analysis with dodecane as an internal standard. ^cWe observed ~5% yield of the linear aldehyde product, consistent with radical ring opening of the cyclopropane. ^dPhMe (0.02M). Ar¹ = 4-ClC₆H₄, Ar² = 4-FC₆H₄.

also applicable to the reduction of the side-chain acid of protected aspartic acid derivative **6f**, a notable result given the utility of aldehydes for bioconjugation chemistry. α -Branched aldehydes **7g** – **7i** are generated in 41%, 43% and 64% yield from alkyl carboxylic acids **6g** – **6i** with no loss of stereochemical information. For these secondary alkyl carboxylic acids, we observed a minimal amount of the alkane arising from decarboxylation under standard reaction conditions. The excellent chemoselectivity of these conditions was also highlighted using secondary benzamide **6j**, which, upon reduction, is isolated as the *N,O* hemiacetal. Furthermore, electron-rich Mycophenolic acid (**6k**), is converted to the corresponding aldehyde in 45% yield, with retention of the lactone.

The generation of the intermediate acyl radical offers an important synthetic opportunity beyond terminal hydrogen atom transfer. By intercepting the intermediate radical with an acceptor, new C–C and C–X bonds may be generated. Historically, these cyclizations have been achieved using acyl selenides, tellurides, or via HAT from aldehydes.³¹ Gratifyingly, when 2-acetylbenzoic acid is subjected to the standard reaction conditions, lactone **9a** is formed in excellent yield (Scheme 1). Similarly, lactam **9b** and acetal **9c** are afforded when benzoic acids **8b** and **8c** are subjected to the reaction conditions. C–C bond formation is also accomplished via cyclization onto pendant olefins with 2-allylbenzoic acid and 2-allyloxybenzoic acid to afford 5- and 6-membered ketones **9d** and **9e**, respectively. Additionally, C–O and C–C bond formation via intramolecular cyclization is also achieved with aliphatic carboxylic acids, providing lactone **9f** and ketone **9g**. These constitute valuable bond disconnections that can be achieved from simple, inexpensive starting materials. Furthermore, these examples suggest the intermediacy of an acyl radical as these nucleophilic cyclizations have been well demonstrated in the literature.³¹

Scheme 1. Intramolecular Cyclizations^a

^aIsolated yields based on an average of two runs. ^bConditions: PPh_3 , H atom source, PhMe:DMF, **1**. ^cConditions: Ph_2POEt , $TRIP-SH$, 2,4,6-collidine, PhMe, **1**; Ar = 4-FC₆H₄. See SI for full experimental details.

In summary, we have described a unique C–O bond activation pathway employing phosphines and photoredox catalysis to access distinct radical species from alcohols and carboxylic acids using a unified approach. Benzylic radicals can be accessed from the corresponding alcohol and with terminal H atom transfer, reduced to toluenes. By tuning the conditions, aromatic acids are efficiently reduced to the corresponding aldehydes with terminal HAT, and by modifying the phosphine component, we have expanded this reactivity to alkyl carboxylic acid activation. Furthermore, we have exploited the reactivity of acyl radicals to afford valuable C–O, C–N, and C–C bond-forming reactions. This approach avoids a voltage-gated restriction to appropriately functionalized starting materials and enables orthogonal bond-activation. Given the broad utility of radical intermediates, we anticipate that this pathway will open numerous new avenues for research in synthesis and synthetic methodology development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b03592.

Procedures, additional experimental data, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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