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

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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 product. 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

Main Text

Over the last decade, photoredox catalysis has witnessed rapid development as a mechanism to address longstanding 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] Due to 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 multi-step 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.

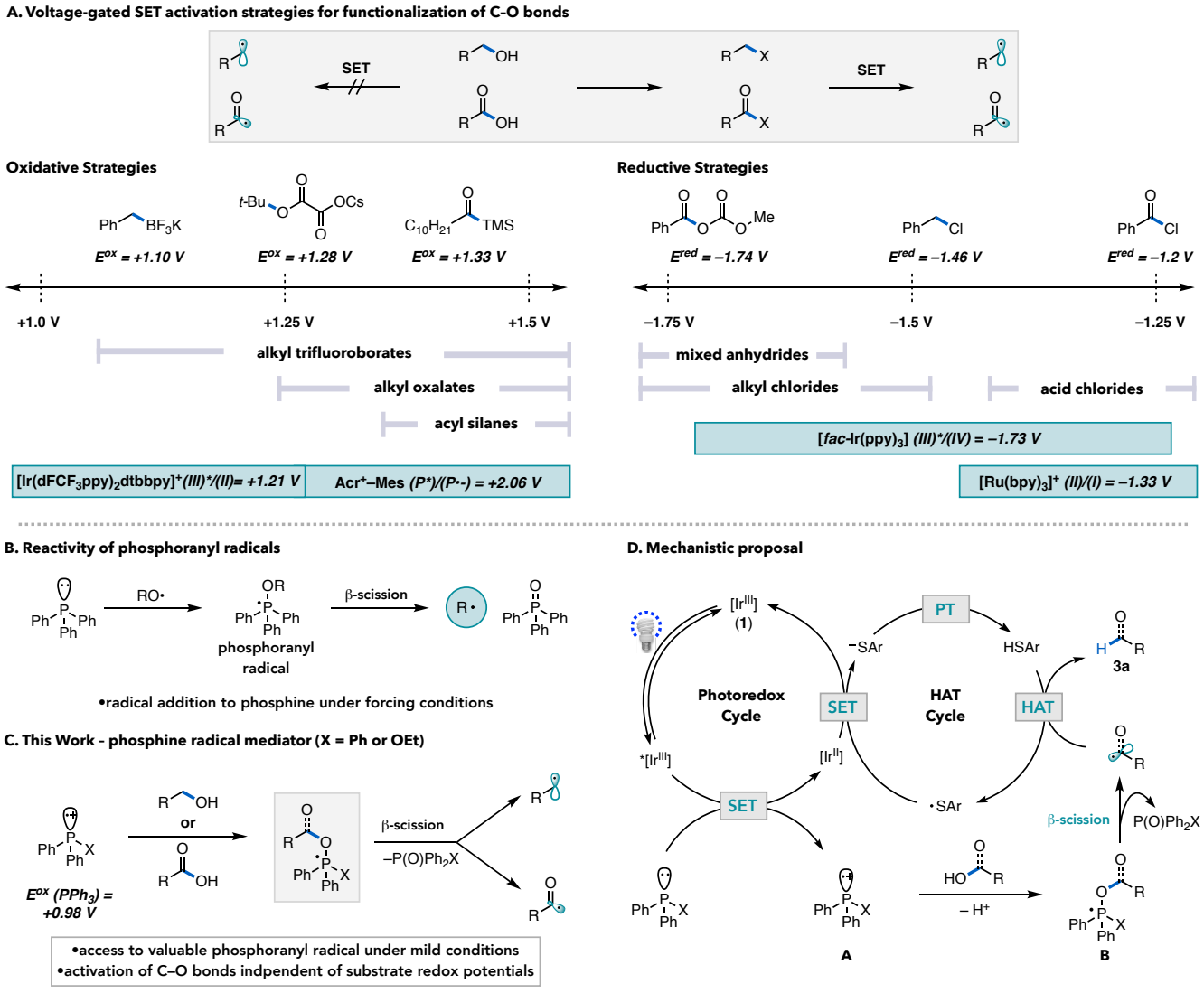


Figure 1. A) Common functional group interconversions with corresponding redox windows of substrates and photocatalysts for accessing alkyl and acyl radicals. B) Reactivity of phosphoranyl radicals. C) New activation pathway to access phosphoranyl

radicals and activate C–O bonds. D) Mechanistic proposal. Stern-Volmer quenching studies are consistent with this mechanistic hypothesis. See SI for full experimental details.

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 activation with phosphoranyl radicals, tetravalent phosphine centered radicals.[14] Bentrude has demonstrated that, dependent on the phosphorus substitution pattern, phosphoranyl 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 offer poor 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]

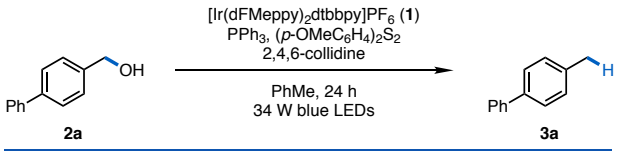
From a synthetic perspective, we envisioned application of this polar/SET crossover reaction platform to the direct deoxygenation of alcohols and carboxylic acids (Figure 1C).[28-30] By employing tunable phosphine mediators, we could circumvent functional group interconversion or pre-activation of C–O 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 is generalizable across 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 $[Ir(dFMeppy)_2dtbppy]PF_6$ (**1**) [dFMeppy = 2-(2,4-difluorophenyl)-5-methylpyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] when irradiated with light $\{E_{1/2}^{red}[^*Ir^{III}/Ir^{II}] = +0.99$ V versus saturated calomel electrode (SCE)$\}$[32] would undergo SET with triphenylphosphine $\{E_{1/2} = +0.98$ 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 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 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 PPh_3 (entry 9). Use of TRIP-SH (2,4,6-triisopropylbenzene thiol) as an H-atom source results in 59% yield, while $TRIP_2S_2$ affords the product in 93% yield (entry 10-11). Use of the commercially available photocatalyst $[Ir(dFCF_3)_2dtbbpy]PF_6$ gives a slightly less efficient reaction, with the product observed in 75% yield (entry 12).

Table 1. Reaction evaluation of benzylic alcohols



2a **3a**

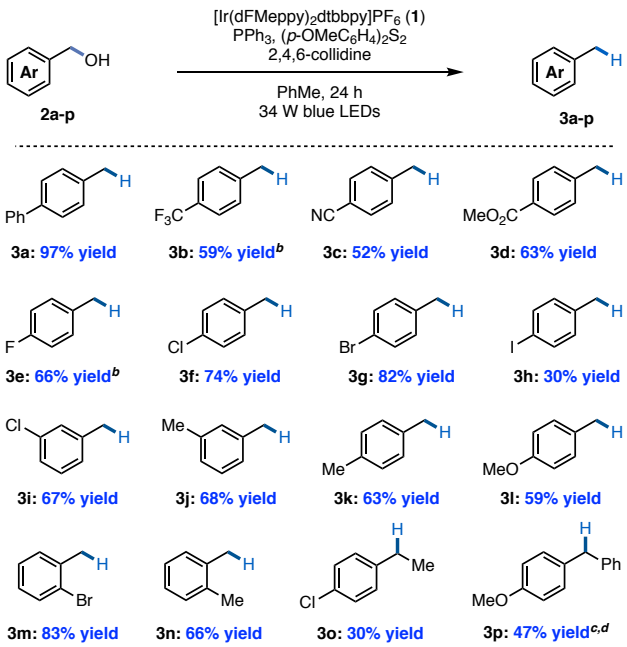
entry	deviation from standard conditions[a]	% yield[b]
1	none	>99%
2	no PPh_3	0%
3	no light	0%
4	no [Ir] **1**	0%
5	no $(p\text{-}OMeC_6H_4)_2S_2$	4%
6	ACN (0.1M), no $(p\text{-}OMeC_6H_4)_2S_2$	80%
7	2,6-lutidine (1.0 equiv)	79%
8	no base	32%
9	Ph_2POEt (1.2 equiv)	91%
10	TRIP-SH (20 mol%)	59%
11	$TRIP_2S_2$ (10 mol%)	93%
12	$[Ir(dFCF_3ppy)_2dtbbpy)]PF_6$ (2 mol%)	75%

[a] Standard conditions: PPh_3 (1.2 equiv), [Ir] (**1**) (2 mol%), $(p\text{-}OMeC_6H_4)_2S_2$ (10 mol%), 2,4,6-collidine (1.0 equiv), PhMe (0.1M). [b] Yields based on GC analysis using dodecane as an external standard on 0.1 mmol scale. Disulfides can also quench the excited state of the photocatalyst to form Ir(IV), which is also capable of oxidizing PPh_3 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.

With the optimized conditions, we sought to examine the scope of benzylic alcohol deoxygenation (Table 1). Toluene **3a** 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.

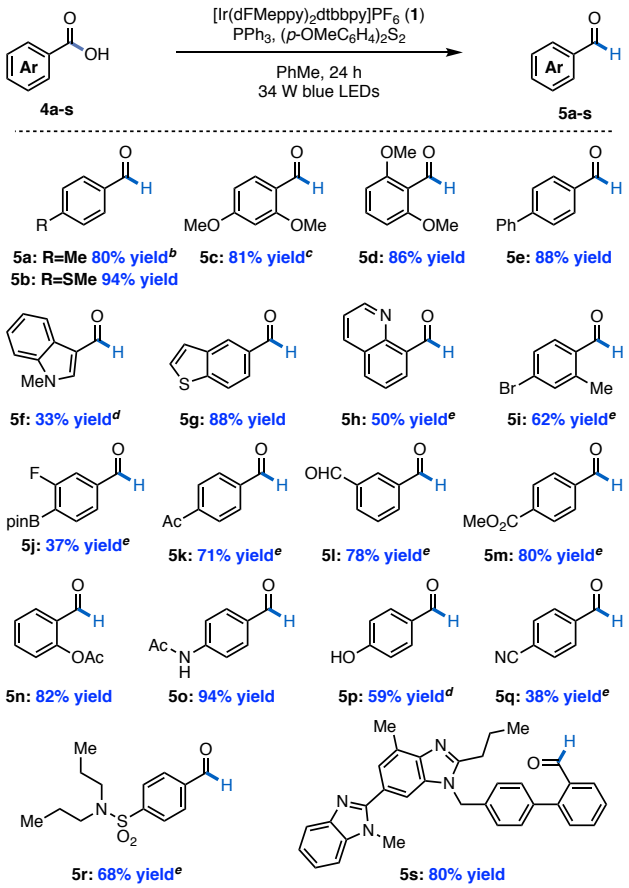
Table 2. Benzylic alcohol scope[a]



[a] Yields 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. [b] yields based on ^{19}F NMR using 1-fluoronaphthalene as an external standard. [c] Reaction run under conditions according to Table 1, entry 6. [d] yield determined by ^{1}H NMR.

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.[33,34,35] 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 2, **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 benzothiophene **5g** giving product in 33% and 88% yield, respectively, although indole **5f** can be isolated in 45% yield when 2,6-$Me_2C_6H_3SH$ 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, 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. Aromatic acid evaluation[a]

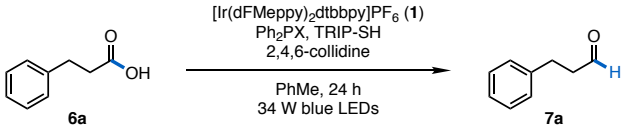


[a] Standard conditions: PPh_3 (1.2 equiv), $(p\text{-}OMeC_6H_4)_2S_2$ (5 mol%), [Ir] (**1**) (1 mol%), PhMe (0.1M). Isolated yields based on an average of two runs. See SI for more optimization details. [b] Yield determined by GC analysis using dodecane as an external standard. [c] Reaction set up on the benchtop. [d] NMP (0.1M) used. [e] 2,6-lutidine (1.0 equiv) and $(p\text{-}OMeC_6H_4)_2S_2$ (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.

We next turned our attention to the reduction of aliphatic carboxylic acids. Unfortunately, we observed diminished reactivity relative to aryl carboxylic acids under our standard reaction conditions (<5% yield). After additional optimization, we found that TRIP-SH was the optimal H-atom source, with hydrocinnamic acid delivering 8% yield of the corresponding aldehyde **7a** (Table 4, entry 1, see SI for more optimization details). 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 PPh_3 under identical conditions, however, does not afford the same result, highlighting the importance of the phosphinite,

Ph_2POEt. 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 non-redox gated C–O bond activation.

Table 4. Aliphatic acid optimization

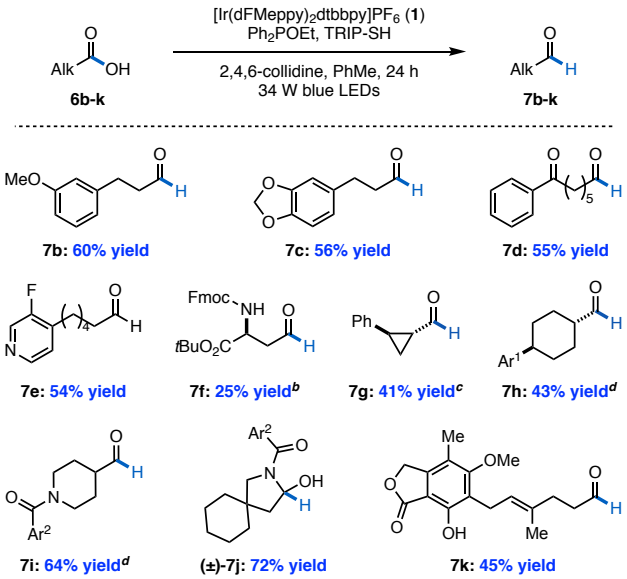


entry	Ph_2PX, [M][a]	% yield[b]
1	PPh_3, 0.1M	4%
2	Ph_2POEt, 0.1M	43%
3	Ph_2POEt, 0.02M	60%
4	**Ph_2POEt, 0.0133M**	**68%**
5	PPh_3, 0.0133M	8%

[a] standard conditions: Ph_2PX (1.2 equiv), TRIP-SH (50 mol%), 2,4,6-collidine (1.0 equiv), [Ir] **1** (2 mol%), PhMe. [b] yields 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 Ph_2POEt. See SI for further optimization details.

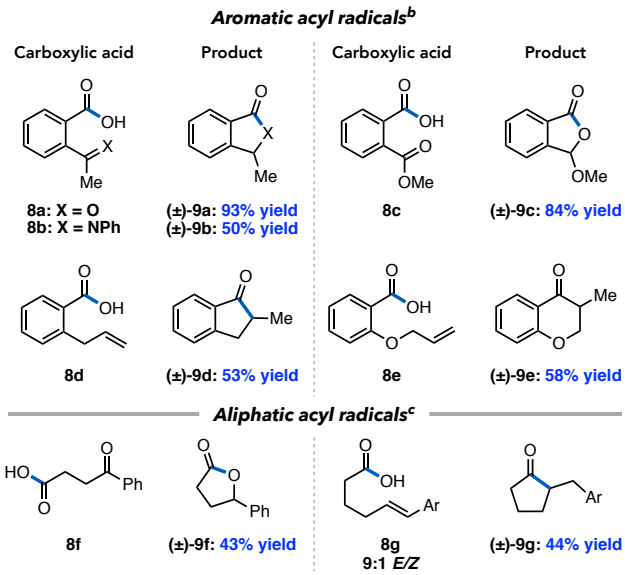
With the new optimized conditions, we examined the scope of aliphatic acids (Table 5). Hydrocinnamaldehyde derivatives **7b** and **7c** are formed in 60% and 56% yield, respectively. Longer chain aliphatic acid **6d** affords the corresponding aldehyde in 55% yield without competitive ketone reduction.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

Table 5. Aliphatic acid scope[a]



[a] Isolated yields based on an average of two runs using standard conditions in Table 3. [b] CH_3CN as the solvent. Yield based on ^1H NMR analysis with dodecane as an internal standard. [c] We observed ~5% yield of the linear aldehyde product, consistent with radical ring opening of the cyclopropane. [d] PhMe (0.02M). $Ar^1 = 4\text{-}ClC_6H_4$, $Ar^2 = 4\text{-}FC_6H_4$.

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.[29]



Scheme 1. Intramolecular Cyclizations[a] [a] Isolated yields based on an average of two runs. [b] conditions: PPh_3, H-atom source, PhMe:DMF, **1**. [c] conditions: Ph_2POEt, TRIP-SH, 2,4,6-collidine, PhMe, **1**; Ar = 4-FC_6H_4. 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 toluene. 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.

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Associated Content

Procedures, additional experimental data, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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