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Merging Photoredox and Nickel Catalysis: The Direct Synthesis of Ketones by the Decarboxylative Arylation of α-Oxo Acids**

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Abstract: *The direct decarboxylative arylation of α-oxo acids has been achieved by synergistic visible-light-mediated photoredox and nickel catalysis. This method offers rapid entry to aryl and alkyl ketone architectures from simple α-oxo acid precursors via an acyl radical intermediate. Significant substrate scope is observed with respect to both the oxo acid and arene coupling partners. This mild decarboxylative arylation can also be utilized to efficiently access medicinal agents, as demonstrated by the rapid synthesis of fenofibrate.*

Photoredox catalysis employing visible light has recently emerged as a valuable platform for the design of unique one-electron-transfer pathways that allow the invention of valuable new chemical reactions.[1] In this vein, our laboratory has described the decarboxylative coupling of α-amino, α-oxy, and alkyl carboxylic acids with aryl halides, a method that enables broad access to C_{sp^3}–C_{sp^2} bonds using abundant and inexpensive starting materials.[2] This new fragment coupling relies on the capacity of photoredox catalysts to simultaneously modulate the oxidation states of organometallic intermediates while generating open-shell organic species that can interface with transition-metal catalysts (e.g., Pd, Ni, Cu).[2,3] Recently, we questioned whether this synergistic catalysis pathway might provide a direct and mild route to ketones by the radical decarboxylative coupling of simple α-oxo acids and aryl halides, a transformation that to our knowledge has not previously been described.[4] Herein, we detail the successful execution of these ideals, and present a new mechanism for the production of diaryl, alkyl–aryl, and dialkyl carbonyl compounds at room temperature without the requirement for CO, strong bases, or organometallic reagents.

Ketones have long been established as a linchpin functional group in organic chemistry owing to their innate capacity to function as electrophiles across a tremendous array of bond-forming reactions (e.g., to form C–C, C=C, C–N, and RO–C=O bonds). Moreover, ketones are a common structural element found in a wide range of agrochemicals, bioactive natural products, pharmaceuticals, and electronic materials (including photovoltaics).[5] Common methods for ketone synthesis currently include 1) organometallic additions to Weinreb amides,[6] 2) Stille couplings between acyl chlorides and stannanes,[7] 3) metal-catalyzed carbonylations between aryl halides and prefunctionalized transmetalation reagents (e.g., boronic acids),[8] and 4) alkene hydroacylations (Figure 1).[9] Whereas the synthetic value of these coupling strategies is self-evident, the development of new catalytic transformations that provide access to structurally diverse ketones using simple, inexpensive substrates would be welcomed by synthetic chemists.

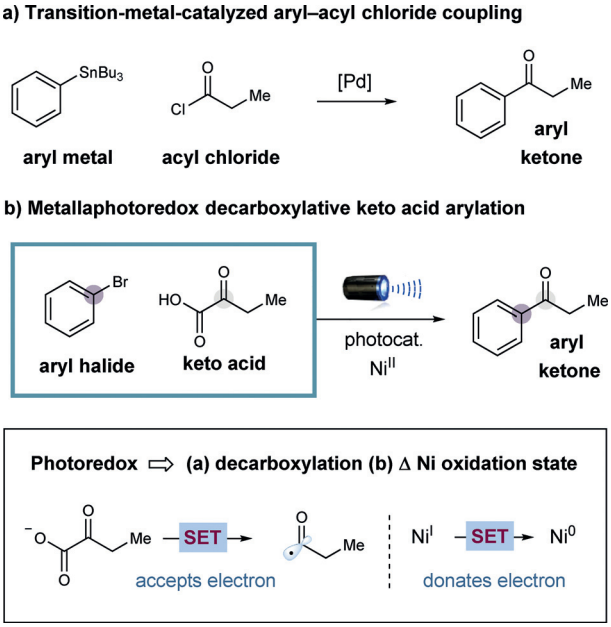

Figure 1. Metallaphotoredox decarboxylative arylation of α-oxo acids.

Within the realm of open-shell chemistry, acyl radicals derived from acyl selenides and tellurides have long been used to initiate cyclization cascades to generate complex ketones in formal hydroacylation reactions.[10] However, the synthetic utility of acyl radicals has been somewhat limited owing to their innate nucleophilicity[11] along with the immoderate conditions required for their generation (typically entailing high temperatures, UV light, or stoichiometric amounts of tin reagents). As a critical advantage, we postulated that the implementation of photoredox-mediated decarboxylation[2,12] would allow for a broad range of acyl radicals to be accessed from α-oxo acids, such as pyruvic acid, thereby allowing ketone production from an abundant, non-

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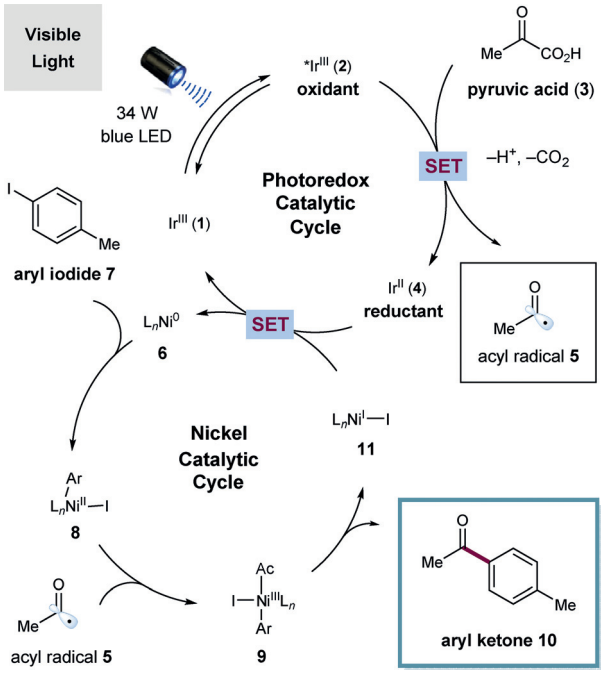
metal-based source. As a key design element, this photoredox approach to nickel acyl complex formation would allow facile generation of a series of carbonyl products using mild conditions (room temperature) without the need for toxic reagents or stoichiometric oxidants.[13]

A detailed mechanism for the proposed metallaphotoredox aryl cross-coupling with α-oxo acids is shown in Scheme 1. It is well established that photoredox catalyst

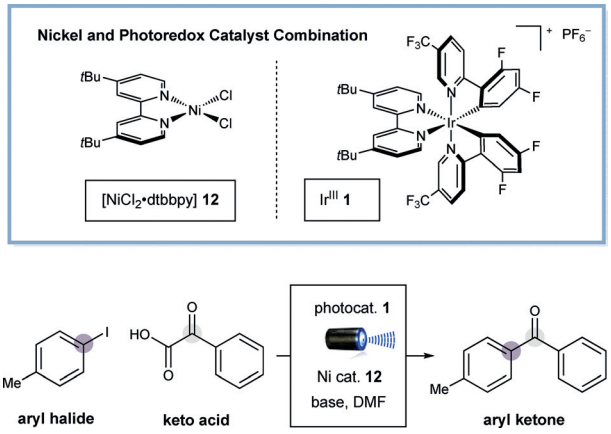


Scheme 1. Merged photoredox and nickel catalytic cycles.

$[Ir\{dF(CF_3)ppy\}_2\{dtbbpy\}]^+$ **1**[14] readily absorbs photons upon visible-light irradiation to generate the oxidizing excited state $*[Ir\{dF(CF_3)ppy\}_2\{dtbbpy\}]^+$ **2** ($E_{1/2}^{III*/II} = +1.21$ V vs. saturated calomel electrode (SCE) in CH_3CN].[15] Base-mediated deprotonation of an α-oxo acid substrate [such as pyruvic acid (**3**), see Scheme] and subsequent single-electron oxidation of the resulting carboxylate functional group ($E_{1/2}^{red} = +1.03$ V vs. SCE in DMSO)[13d] by the excited photocatalyst **2** should generate the reduced photocatalyst **4** and a corresponding carboxyl radical species. At this stage, we presumed that this open-shell dicarbonyl intermediate would rapidly extrude CO_2 to deliver the critical acyl radical species **5**. Within the same time frame, the second catalytic cycle would be initiated by oxidative addition of the Ni^0 catalyst **6**[16] into the aryl halide (e.g., 4-iodotoluene (**7**), as shown) to generate Ni^{II} aryl complex **8**. The resulting electrophilic metal species **8** would then rapidly trap the nucleophilic acyl radical **5** to produce nickel acyl complex **9**. At this stage, reductive elimination from this Ni^{III} complex would be expected to forge the requisite C_{sp^2}–C_{sp^2} bond of compound **10**, while expelling the corresponding Ni^I complex **11**. Finally, single-electron transfer (SET) from the photocatalyst, Ir^{II} species **4**, to the Ni^I–dtbbpy complex **11** would return the metal catalyst to the required Ni^0 oxidation state in an exergonic process. Indeed, the thermodynamic requirements of the two-electron reduction of Ni^{II} to Ni^0 are favorable ($E_{1/2}^{II/0} = -1.2$ V vs. SCE in DMF),[17] given the corresponding reduction potential of Ir^{II} complex **4** ($E_{1/2}^{III/II} = -1.37$ V vs. SCE in CH_3CN).[15] It should be noted that this second photoredox-mediated SET event regenerates the ground-state Ir^{III} catalyst **1** while reconstituting the requisite Ni^0 complex **6**, completing the photoredox and nickel cycles simultaneously.

We began our investigations into this new acyl cross-coupling method using phenylglyoxylic acid and *para*-iodotoluene in the presence of $[Ir\{dF(CF_3)ppy\}_2\{dtbbpy\}]^+$ **1**, Ni complex **12**, Cs_2CO_3, and DMF. Given the findings from our previous studies into the decarboxylative nickel-catalyzed arylation of amino acids, we presumed that a strongly oxidizing photocatalyst (e.g., **1**) would be required to oxidize the carboxylate and initiate the CO_2 extrusion step. Indeed, we were delighted to achieve proof of concept using the optimized catalytic conditions from our earlier studies; however, the efficiency of ketone product formation was poor (Table 1, entry 1, 13% yield). Pleasingly, changing from

Table 1: Optimization of the decarboxylative α-oxo acid arylation.[a]



Entry	Base	Light source	H_2O [equiv]	Yield [%]
1	Cs_2CO_3	blue LED strips	0	13
2	Li_2CO_3	blue LED strips	0	38
3	Li_2CO_3	34 W blue LED	0	60
4[b]	Li_2CO_3	34 W blue LED	0	74
5[b]	Li_2CO_3	34 W blue LED	2	84
6[b]	Li_2CO_3	34 W blue LED	8	54
7[b,c]	Li_2CO_3	34 W blue LED	2	88

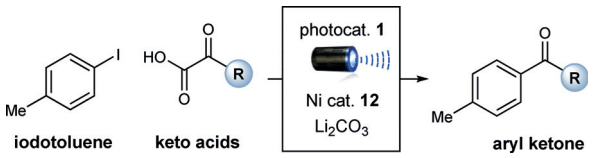
[a] Yield determined by ^1H NMR spectroscopy using 1,3-bis(trifluoromethyl)-5-bromobenzene as an internal standard. [b] Reaction time: 72 h. [c] 2 mol% of the photocatalyst.

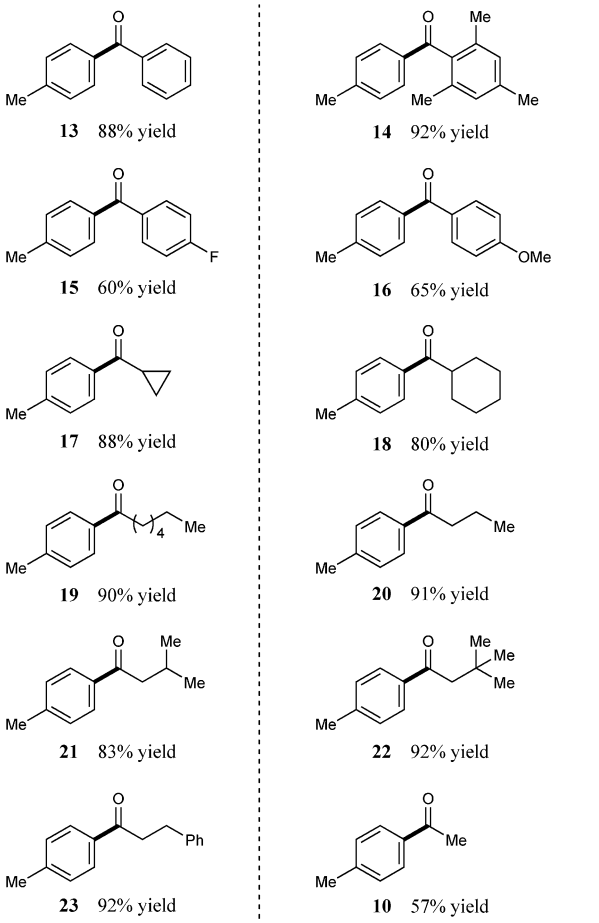
Cs_2CO_3 to Li_2CO_3 led to a notable increase in reaction efficiency (entry 2, 38% yield). Moreover, implementation of a more powerful 34 W blue LED lamp in lieu of the standard blue LED strips provided further improvement (entry 3, 60% yield), highlighting that the reaction is likely photon-limited. The addition of two equivalents of water produced a modest boost in yield while adding further equivalents was detrimental, presumably owing to protonolysis of the putative Ni^{II} aryl

complex at high H_2O concentration (entries 5 and 6).[18] Ultimately, increasing the photocatalyst loading to 2 mol% provided superior conditions, delivering the desired diaryl ketone adduct in excellent yield (entry 7, 88%).

With optimized conditions in hand, we next examined the scope of the α-oxo acid component in this new cross-coupling method. As described in Table 2, a wide range of α-keto acids bearing aromatic and aliphatic substituents were amenable to this CO_2 extrusion mechanism. Pleasingly, this open-shell pathway allows for the ready implementation of an *ortho*-substituted aryl ring on the keto acid component (product **14**, 92% yield), a significant limitation for many previous cross-coupling systems owing to the accompanying steric demands.[4] Surprisingly, electron-deficient arenes were tolerated on the keto acid, despite the inherent difficulty of the carboxylate oxidation step (product **15**, 60% yield). Electron-rich aryl glyoxylic acids readily served as efficient nucleophiles, generating the product ketones in good yields (products **14** and **16**, 92% and 65% yield).

Table 2: Decarboxylative coupling: scope of the α-oxo acid.[a]





[a] Reactions performed using the optimized conditions from Table 1 (see the Supporting Information for details). Yields of isolated products are given.

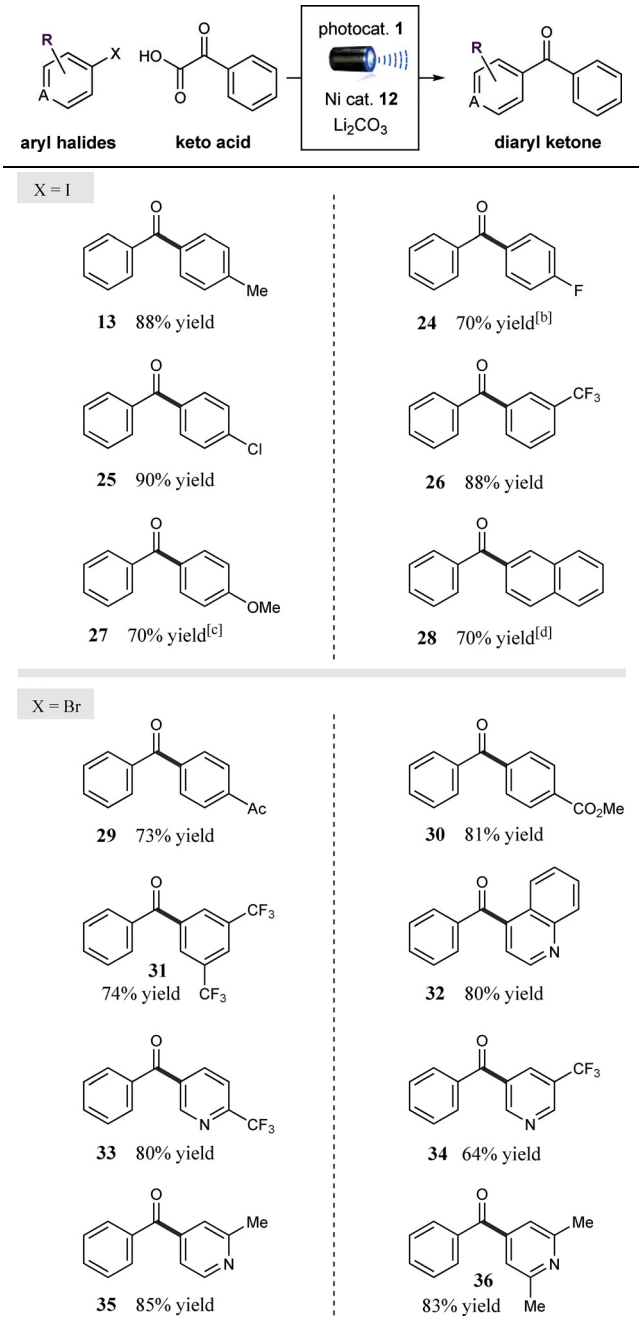
As further detailed in Table 2, a range of aliphatic keto acids can also serve as efficient coupling partners. Particularly notable are cyclic systems, such as cyclopropyl and cyclohexyl glyoxylic acids (products **17** and **18**, 88% and 80% yield). Moreover, a variety of acyclic alkyl-substituted ketones were readily accessible using the appropriate α-oxo acids (products **19**–**23**, 83–92% yield). Perhaps most pleasingly, pyruvic acid, which is available from biomass, can be readily harnessed to generate aryl acylation adducts directly (product **10**, 57% yield).

With respect to the electrophilic coupling partner, the mild conditions employed with this photoredox/nickel method allow for a wide range of aryl halides to be employed (Table 3). For example, iodoarenes bearing fluoride and chloride substituents could be used to generate halogenated ketones without the formation of dehalogenated adducts (products **24** and **25**, 70% and 90% yield). The enhanced rate of oxidative addition to aryl iodides relative to aryl chlorides allows for chemoselectivity in the cross-coupling of 1-chloro-4-iodobenzene, which allows the chloride group to be retained as a handle for further synthetic manipulations or as a structural element for medicinal chemistry. In this context, it is important to note that a trifluoromethyl group can also be incorporated on the arene ring (product **26**, 88% yield). Electron-rich arenes can also serve as electrophiles, albeit with increased reaction times (products **27** and **28**, both 70% yield). Not surprisingly, electron-deficient arenes are highly competent in this cross-coupling reaction, enabling the use of bromoarenes as electrophiles in these cases (products **29**–**36**, 64–85% yield). As a critical requirement for the broad-scale implementation of this transformation, heteroarenes could be successfully employed to rapidly build nitrogen-containing aryl ketone adducts (products **32**–**36**, 64–85% yield). Specifically, 3-bromopyridines could be coupled effectively (products **33** and **34**, 80% and 64% yield). Last, we have further determined that 4-bromopyridines are valuable coupling partners, and that the steric environment around the nitrogen atom is inconsequential with respect to reaction yield (products **32**, **35**, and **36**, 80–85% yield).

To further demonstrate the utility and generality of this novel cross-coupling reaction, we sought to employ electrophiles beyond the realm of aromatic halides. As shown in Scheme 2a, hindered vinyl halides can be readily utilized in the procedure to build α,β-unsaturated ketones directly. Perhaps more importantly, alkyl halides, such as bromocyclopentane, were successfully utilized in this new transformation to generate dialkyl ketones (Scheme 2b). This latter example highlights the use of nickel catalysis to enable oxidative insertion into C_{sp^3}–halogen bonds without the intervention of detrimental β-hydride elimination pathways.

Finally, we sought to highlight the value of this new method for medicinal chemistry by the rapid production of a biologically active small molecule incorporating a diaryl ketone. Within this context, fenofibrate, a cholesterol-modulating pharmaceutical of the fibrate class, currently ranked

Table 3: Decarboxylative coupling: scope of the aryl halide.[a]



[a] Reactions performed using the optimized conditions from Table 1 (see the Supporting Information for details). Yields of isolated products are given. [b] Reaction performed using 5.0 equiv of the acid and Li_2CO_3. [c] 84 h. [d] 90 h.

47th in American retail sales,[5c] was synthesized in a single decarboxylation step (3 steps overall) in 71% yield (Scheme 2c).

Keywords: arylation · decarboxylation · nickel catalysis · photoredox catalysis · α-oxo acids

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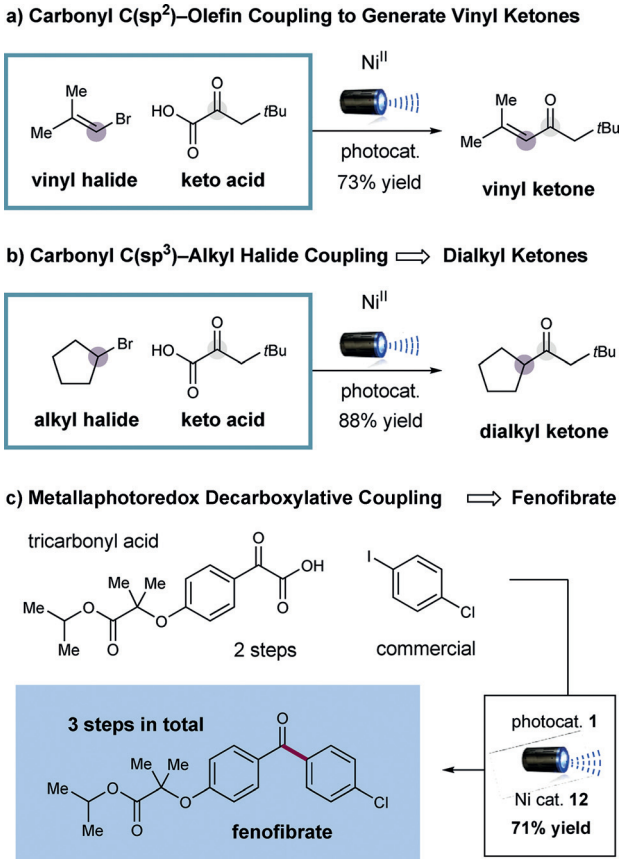

Scheme 2. Metallaphotoredox decarboxylation and its application.

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