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Merging Photoredox and Nickel Catalysis: The Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides

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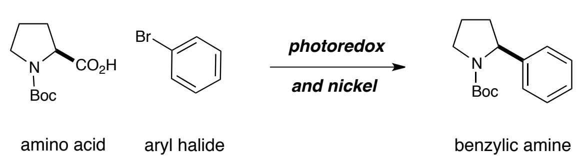
Abstract. The decarboxylative cross-coupling of alkyl carboxylic acids with vinyl halides has been accomplished through the synergistic merger of photoredox and nickel catalysis. This new methodology has been successfully applied to a variety of α-oxy and α-amino acids, as well as simple hydrocarbon-substituted acids. Structurally diverse vinyl iodides and bromides give rise to vinylation products in high efficiency under mild, operationally simple reaction conditions.

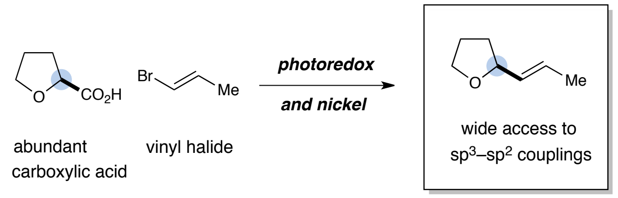
Arguably one of the most important developments in synthetic chemistry has been the advent of transition metal-catalyzed cross-coupling reactions.[1,2] Such processes have had a profound impact on almost all areas of chemical synthesis, stemming from their ability to form C–C, C–N, and C–O bonds in a highly predictable and chemoselective fashion. At the present time, the majority of transition metal-mediated carbon–carbon couplings rely on the use of nucleophilic substrates that are pre-functionalized with organometallic traceless activation groups (TAGs, e.g. boronic acids, stannanes, zincates, and Grignards). However, an ever-increasing impetus to improve the versatility, cost, and operational utility of transition metal-based methods has led to the development of elegant protocols that employ organic, native functionality as activation handles for complex fragment coupling reactions.[3]

One complementary approach to the use of organometallic TAGs has been the implementation of simple carboxylic acids, an organic activation group that is (i) widely available from abundant biomass feedstocks, (ii) generally inexpensive, and (iii) compatible with multi-step reaction sequences in native or latent form (e.g. one step from esters, amides, and olefins).[3b] Indeed, since the pioneering work of Gooβen *et al.*,[4] the decarboxylative cross-coupling between carboxylic acids and aryl halides has found application in the construction of C_{sp^2}–C_{sp^2} and C_{sp}–C_{sp^2} bonds.[5] More elusive, however, is the successful implementation of alkyl carboxylic acids for the production of C_{sp^3}–C_{sp^2} bonds in complex fragment couplings. This deficiency can be readily appreciated given the diminished reactivity of C_{sp^3} carboxylic acids towards decarboxylative transmetalation in the presence of commonly employed metal catalysts. Indeed, most examples to date of decarboxylative C_{sp^3}–C_{sp^2} bond formations rely on the use of activated substrates, such as electron-deficient benzylic,[6] cyclohexadienyl,[7] α-cyano,[8] or β-ester carboxylic acids.[9,10] Clearly, a modern strategy enabling simple alkyl carboxylic acids to function broadly as generic nucleophiles in conventional cross-coupling reactions would be of substantial utility to synthetic chemists operating within both academic and industrial settings.

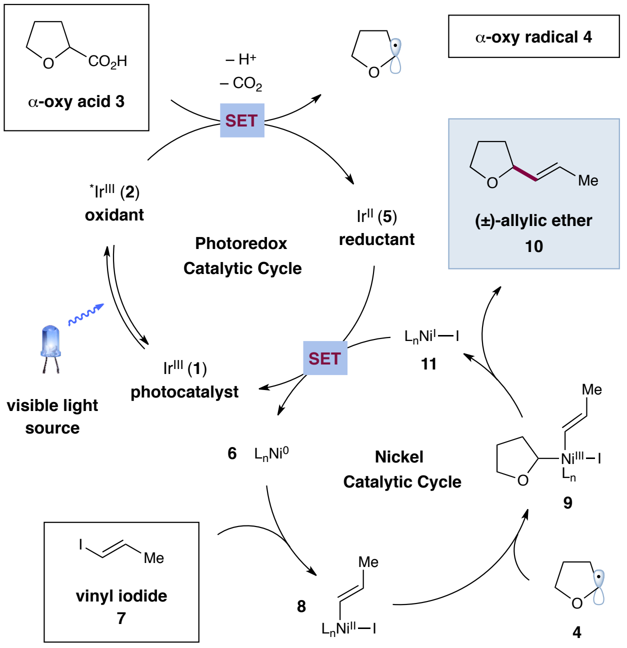
Decarboxylative Arylation with Nickel and Photoredox Catalysis (Eq 1)



Expanding this New sp^3–sp^2 Coupling: Decarboxylative Olefination (Eq 2)

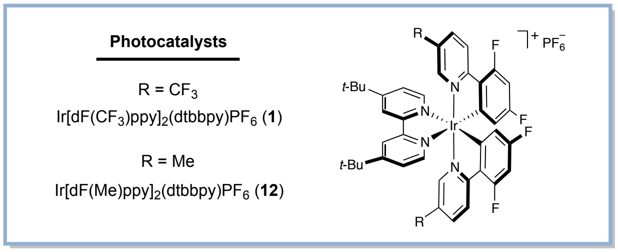


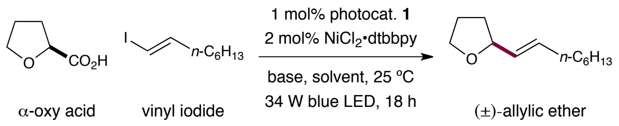
Scheme 1. Proposed Mechanism of Decarboxylative Olefination.



In recent years, synergistic or dual catalysis has come to the fore as a valuable mechanistic paradigm for the invention of novel chemical transformations that are currently not possible via the action of a single catalyst.[11] The successful application of synergistic catalysis typically requires the simultaneous activation and engagement of two distinct coupling partners with two separate catalysts (wherein each catalyst independently operates on a respective substrate). Recently, our laboratory introduced a new dual catalysis platform that allows the decarboxylative coupling of C_{sp^3} carboxylic acids with aryl halides under the combined action of visible-light photoredox catalysis and Ni^{II} catalysis.[12–16] Importantly, this new synergistic

Table 1. Optimization of the Decarboxylative Olefination.[a]

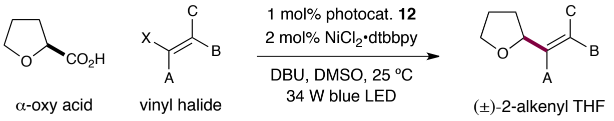


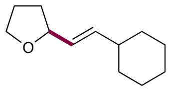
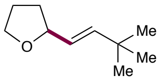
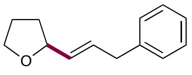
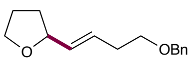
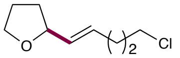
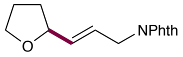
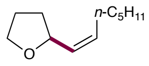
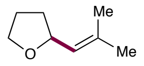
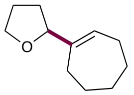
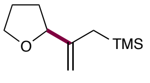


entry	conditions	base	solvent	yield
1[b]	10 mol% $NiCl_2$•dtbbpy	Cs_2CO_3	DMF	83%
2[b]	No photocatalyst	Cs_2CO_3	DMF	0%
3[b]	No $NiCl_2$•dtbbpy	Cs_2CO_3	DMF	<5%
4[b]	No base	--	DMF	0%
5[b]	No light	Cs_2CO_3	DMF	0%
6[c]	As shown	Cs_2CO_3	DMF	22%
7[c]	As shown	Cs_2CO_3	DMSO	52%
8[c]	As shown	DBU	DMSO	61%
9[c]	1 mol% photocat. **12**	DBU	DMSO	92%

[a] Reactions performed using (*E*)-1-iodo-1-octene (0.1 mmol) and tetrahydrofuran-2-carboxylic acid (1.7 equiv.), dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. Yields determined by ^{1}H NMR analysis using an internal standard. [b] Reactions performed at 0.025 M for 72 h. [c] Reactions performed at 0.1 M.

Table 2. Decarboxylative Olefination: Vinyl Halide Scope.[a]



entry	product, % yield	entry	product, % yield
1	 **(±)-13** 90%	2	 **(±)-14** 78%
3[b]	 **(±)-15** 74%	4	 **(±)-16** 77%
5	 **(±)-17** 68%	6[b]	 **(±)-18** 67%
7[b]	 **(±)-19** 84%	8[c]	 **(±)-20** 71%
9[c]	 **(±)-21** 73%	10[c]	 **(±)-22** 60%

[a] All reaction yields are of isolated products. Reactions performed with the corresponding vinyl iodide. [b] Reactions performed using conditions from Table 1, entry 1. [c] Reaction performed using the corresponding vinyl bromide. For detailed experimental procedures, see Supporting Information.

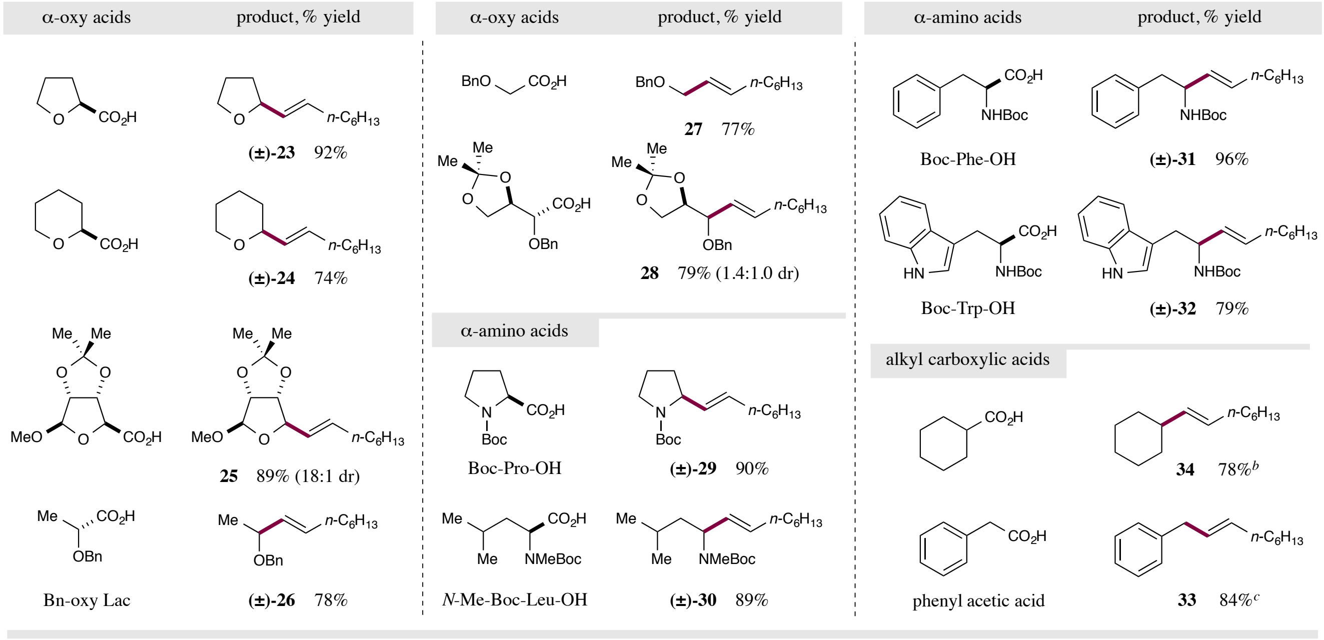
protocol represents a general approach towards the coupling of alkyl, α-amino, and α-oxy acids with a wide range of aryl and heteroaryl halides (Eq 1).[17]

In an effort to demonstrate the wide-ranging applications of this new photoredox–nickel dual catalysis activation mode, we recently sought to explore the feasibility of a decarboxylative coupling between vinyl halides with a broad array of commercial C_{sp^3} carboxylic acids. We recognized that the successful realization of these ideals would enable a new carbon–carbon bond forming reaction that would allow direct access to complex alkyl vinyl, allylic amino, and allylic oxy products in only one step from simple, abundant, and inexpensive starting materials (Eq 2). Perhaps most important, to our knowledge this transformation has not previously been accomplished in a generic format.

Design Plan. As shown in Scheme 1, our proposed olefination mechanism begins with photoexcitation of iridium(III) photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ [$dF(CF_3)ppy$ = 2-(2, 4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] (**1**) to produce the long-lived (τ = 2.3 μs)[18] excited state Ir^{III} species **2**. This photoexcited complex is a strong oxidant ($E_{1/2}^{\mathrm{red}}$ $[{}^*\mathrm{Ir}^{\mathrm{III}}/\mathrm{Ir}^{\mathrm{II}}]$ = +1.21 V vs. SCE in MeCN)[18] and should undergo a thermodynamically favorable single electron transfer (SET) with the carboxylate formed by deprotonation of α-oxy acid **3** (e.g. for THF-2-CO_2Cs, $E_{1/2}^{\mathrm{red}}$ = +1.08 V vs. SCE in MeCN).[19] This results in the formation of a carboxyl radical, which are known to rapidly undergo CO_2-extrusion,[20] to generate α-oxy radical **4** along with reduced Ir^{II} species **5**. Concurrent with this photoredox mechanism, the nickel catalytic cycle will initiate with oxidative addition of L_nNi^0 species **6** into vinyl iodide **7** to generate vinyl Ni^{II} intermediate **8**. Interception of α-oxy radical **4** by **8** would then generate organometallic Ni^{III} adduct **9**, which upon reductive elimination would deliver allylic ether product **10** and Ni^{I} species **11**. Completion of the two catalytic cycles is then achieved by reduction of Ni^{I} species **11** ($E_{1/2}^{\mathrm{red}}$ $[\mathrm{Ni}^{\mathrm{II}}/\mathrm{Ni}^{0}]$ = –1.2 V vs. SCE in DMF)[21] by the reduced state of the photocatalyst **5** ($E_{1/2}^{\mathrm{red}}$ $[\mathrm{Ir}^{\mathrm{III}}/\mathrm{Ir}^{\mathrm{II}}]$ = –1.37 V vs. SCE in MeCN)[18] to regenerate photocatalyst **1** and Ni^0 catalyst **6**.

Initial investigations into the proposed decarboxylative cross-coupling focused on the reaction of tetrahydrofuran-2-carboxylic acid with (*E*)-1-iodo-1-octene (Table 1). We were delighted to find that irradiation of the carboxylic acid and vinyl iodide in the presence of photocatalyst **1**, $NiCl_2$·glyme (10 mol%), dtbbpy (10 mol%), and Cs_2CO_3 provided the desired allylic ether product in excellent yield (entry 1, 83% yield). Control experiments highlighted the essential roles of the photocatalyst, nickel catalyst, base, and light in this transformation (entries 2–5, <5% yield). While the vinylation product was obtained in high yield under the conditions described in entry 1, we recognized early on that the implementation of high dilution and nickel loadings would not be operationally optimal. However, conducting the same experiment with only 2 mol% $NiCl_2$·glyme and at 0.1 M in DMF led to a significant reduction in reaction efficiency (entry 6, 22% yield). An evaluation of solvents revealed that DMSO

Table 3. Decarboxylative Olefination: Carboxylic Acid Scope.[a]



[a] Reactions performed using the optimized conditions from Table 1 with 0.5 mmol (*E*)-1-iodo-1-octene or (*E*)-1-bromo-1-octene. Yields are of isolated products. Ratios of diastereomers determined by ^{1}H NMR analysis. For detailed experimental procedures, see Supporting Information. [b] Primary alkyl and fully substituted carboxylic acids provided encouraging levels of efficiency, see Supporting Information for experimental results. [c] Good yields were obtained for phenyl acetic acid derivatives *p*-OMe (96% yield) and *m*-Cl (68% yield). For experimental procedures, see Supporting Information.

provided a significant improvement in yield (entry 7, 52% yield), and changing the base from insoluble Cs$_2$CO$_3$ to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) also proved to be beneficial (entry 8, 61% yield). Finally, the identification of Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ [dF(Me)ppy = 2-(2,4-difluorophenyl)-5-methylpyridine] (**12**) as the optimal photocatalyst provided a significant enhancement in yield, furnishing the desired cross-coupled product in 92% yield (entry 9) while retaining higher reaction concentrations and low catalyst loadings.[22] Time studies have revealed that the use of photocatalyst **1** under similar reaction molarities (0.1 M) leads to catalyst decomposition prior to full conversion of the starting materials, resulting in diminished yields (entry 8, 61% yield). We believe the dramatic enhancement in reaction efficiency in changing to photocatalyst **12** from **1** (entry 9, 92% yield) directly correlates to the improved stability of catalyst **12** towards organic radical-mediated decomposition under concentrated reaction conditions.[23]

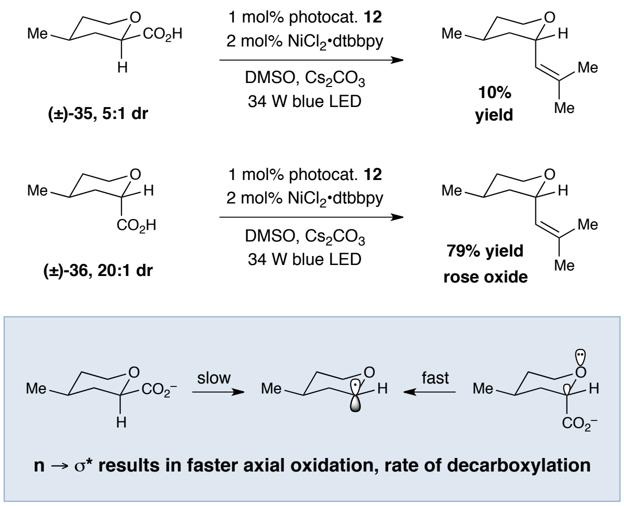
With the optimal dual catalysis conditions in hand, we next sought to examine the scope of the vinyl halide component in this new C$_{sp^3}$–C$_{sp^2}$ carbon–carbon bond forming protocol. As shown in Table 2, a range of structurally diverse vinyl halides undergo efficient cross-coupling with tetrahydrofuran-2-carboxylic acid (as the representative nucleophile). These include β-alkyl-substituted (*E*)-vinyl iodides, which provide cross-coupled products in high yield regardless of the size of the β-substituent (entries 1 and 2, 90% and 78% yield, respectively). Vinyl iodides possessing various functional groups, including aromatic rings, benzyl ethers, alkyl chlorides, and phthalimidoyl-protected amines also delivered the corresponding allyl ether products in good yield (entries 3–6, 67–77% yield). In addition to *E*-vinyl iodides, those with *Z*-geometry could be readily incorporated to generate *cis*-olefin containing products in excellent yield and with no observable geometrical isomerization (entry 7, 84% yield).[24] Notably, for vinyl halides possessing α-substitution or β,β-disubstitution, the use of the corresponding vinyl bromide provided higher yields of the cross-coupled adduct. Under these conditions, vinyl bromides allowed the generation of trisubstituted olefin products **20** and **21** with excellent efficiency (entries 8 and 9, 71% and 73% yield, respectively). Finally, the synthesis of allyl silane **22** demonstrates the ability of this decarboxylative cross-coupling protocol to generate olefin products containing synthetically useful functional handles that might be readily exploited in subsequent transformations (entry 10, 60% yield). It is important to note that throughout all of our investigations into this new vinylation protocol, the stereochemical information present in the vinyl halides was translated directly to the olefin-bearing products, with no observed erosion in *E*:*Z* ratio.[24]

We next turned our attention to examining the scope of the carboxylic acid component. As revealed in Table 3, we were delighted to find that a broad range of substrates bearing C$_{sp^3}$ carboxylates readily participate as coupling partners in this CO$_2$-extrusion/vinylation protocol. For example, five- and six-membered cyclic α-oxy carboxylic acids readily undergo cross-coupling to form the allyl ethers in excellent yields (products **23** and **24**, 92% and 74% yield, respectively). Pleasingly, a highly functionalized ribose-derived cyclic α-oxy acid was also found to be a competent coupling partner, providing **25** in excellent yield and diastereoselectivity (89% yield, 18:1 dr). This result clearly demonstrates the potential utility of this new coupling protocol for late-stage and orthogonal nucleoside functionalization (an area of significant interest among pharmaceutical agencies developing anti-viral agents).[25] The decarboxylative olefination could also be extended to acyclic primary and secondary α-oxy acids, including benzyl-protected lactic and glycolic acids, generating the allylic ether products in high yields (products **26** and **27**, 78% and 77% yield, respectively). Furthermore, an erythronic acid derivative was readily functionalized to generate olefin **28** in high yield albeit with low diastereoselectivity (79% yield, 1.4:1.0 dr).

In addition to α-oxy acids, α-amino acids readily undergo decarboxylative vinylation. A broad array of cyclic and acyclic *N-tert*-butoxycarbonyl (Boc)-protected amino acids were found to be highly efficient coupling partners, generating synthetically versatile allylic amine products in excellent yields (products **29**–**32**, 79–96% yield) from biomass derivatives.

Most importantly, simple hydrocarbon-substituted carboxylic acids that lack radical stabilizing α-heteroatoms can also be readily employed in this new coupling protocol. For example, phenylacetic acid proved to be a valuable coupling partner, presumably due to the formation of a stabilized benzyl radical intermediate, furnishing allyl benzene **33** in 84% yield. Last, cyclohexanecarboxylic acid readily undergoes efficient cross-coupling to provide 1-cyclohexyloct-1-ene (**34**) with excellent efficiency (78% yield). This result is of particular note as it demonstrates the potential value of this cross-coupling methodology to functionalize simple alkyl carboxylic acids, without the requirement of a radical-stabilizing α-substituent.[26] Moreover, this result highlights the potential breadth of simple, hydrocarbon-based nucleophile partners that may be employed in this C_{sp^3}–C_{sp^2} coupling.

Synthesis of *trans*-Rose Oxide via Decarboxylative Vinylation (Eqs 3, 4)



In order to further demonstrate the utility of this decarboxylative vinylation method, we applied it to the racemic synthesis of *trans*-rose oxide, a natural product and widely used fragrance (Eq 3). As shown above, exposure of *trans*-tetrahydropyran carboxylic acid **36** to this photoredox-Ni coupling provided *trans*-rose oxide in high yield and with useful levels of diastereoselectivity. Intriguingly, however, when the corresponding *cis*-tetrahydropyran carboxylic acid **35** was employed, high coupling efficiencies were not observed, instead leading to recovery of **35** enriched in the *cis*-diastereomer. This result is rationalized by the change in bond strength and oxidation potential of the C–CO_2 moiety as it exists in either the anomeric axial or the non-anomeric equatorial topography. We assume that the axial C–CO_2 bond is weaker, and the rate of decarboxylation is faster (in competition with back electron transfer) due to the hyperconjugative stabilization by the ring oxygen lone pair in the case of the *trans*-tetrahydropyran carboxylic acid system.

In summary, we have demonstrated the successful merger of photoredox and nickel catalysis to enable the decarboxylative vinylation of alkyl carboxylic acids. This C_{sp^2}–C_{sp^3} coupling protocol enables the union of structurally diverse vinyl iodides and bromides with α-oxy, α-amino, and simple hydrocarbon-substituted carboxylic acids. The olefin bearing products are formed in high yields under mild, operationally simple reaction conditions. Due to the ready availability of both alkyl carboxylic acids and vinyl halides, we expect this methodology to find widespread application in both academic and industrial settings. Studies to elucidate the mechanistic details of this transformation are ongoing and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Graphical Abstract