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Cis-Selective Decarboxylative Alkenylation of Aliphatic Carboxylic Acids with Vinyl Arenes Enabled by Photoredox/Palladium/Uphill Triple Catalysis

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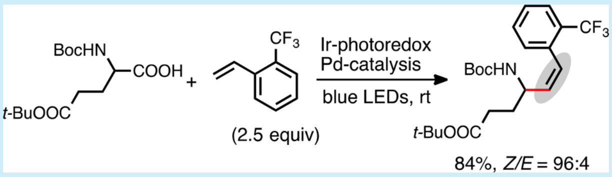
Supporting Information

ABSTRACT: An iridium photoredox catalyst in combination with phenanthroline-supported palladium catalyst catalyzes decarboxylative alkenylation of tertiary and secondary aliphatic carboxylic acids with vinyl arenes to deliver *β*-alkylated styrenes with *Z*-selectivity. A broad scope of aliphatic carboxylic acids, including amino acids, exhibit as amenable substrates, and external oxidant is not required. The reaction proceeds by synergistic utilization of both energy-transfer and electron-transfer reactivity of iridium photoredox catalyst merging with palladium-catalyzed hydride elimination and insertion.



Photoredox catalysis has experienced an increase in use in organic synthesis by utilizing either its electron-transfer or energy-transfer reactivity.[1] The recent development of transition-metal-catalyzed cross-coupling reactions[2] also significantly benefited from merging transition-metal-catalyst with photoredox catalyst. Among various types of cross-couplings, the methodology of transition-metal-catalyzed decarboxylative cross-couplings[3] is arguably most significantly improved by judicious merging with photoredox catalyst to work synergistically.[4] As elegantly developed by MacMillan and co-workers,[5] nickel catalysis merging with photoredox catalysis by using either its electron-transfer or energy-transfer properties enables a series of unachievable cross-coupling reactions[6] (e.g., decarboxylative alkylation,[7] challenging nickel-catalyzed C−O, C−N formation[8]) to take place under very mild conditions. As part of our continuous interest in utilizing biomass-derived carboxylic acids as feedstock in cross-coupling reactions,[9] we wondered whether free aliphatic carboxylic acids could be utilized in a Heck process[10] to deliver alkylated styrene derivatives with *Z*-selectivity. This unprecedented process is very challenging by using transition-metal catalysis in its ground state, because of the high energy-barrier for redox neutral decarboxylation[11] and the thermodynamically favored *E*-selectivity of olefin products. We conceived a palladium/iridium dual catalytic system[12] to address this challenging issue as depicted in Figure 1.

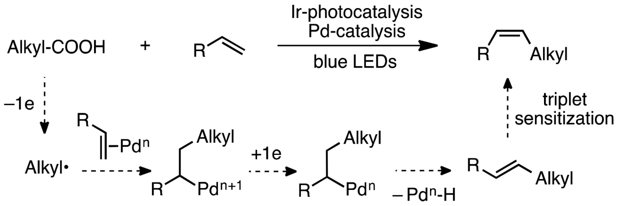


Figure 1. Hypothetical mechanism for *Z*-selective decarboxylative Heck reaction of free aliphatic carboxylic acids with vinyl arenes by merging Ir photocatalysis and palladium catalysis.

Figure 1 demonstrates our working hypothesis. A photoredox catalyst with suitable oxidation potential can catalyze radical decarboxylation of aliphatic carboxylic acid to deliver alkyl radical. The photoredox catalyst is hypothesized to work in concert with a palladium catalyst, which traps the photoredox-generated alkyl radical and alkene to generate a benzylic palladium species, followed by oxidative regeneration of photoredox catalyst to complete a photoredox cycle. Then, *β*-H elimination on benzylic palladium species may proceed to deliver *E*-alkene and generates a palladium hydride species. If the same photoredox catalyst can work as a triplet sensitizer to sensitize *E*-alkene to the triplet state, inducing uphill catalysis to isomerize *E*-alkene to *Z*-alkene,[13] this process can be used to directly achieve decarboxylative *cis*-alkyl Heck reaction in one catalytic system. However, to balance all these processes together to work synergistically in one catalytic system is of considerable challenge. Here, we show that by judicious selection of palladium catalyst, ligand, and photoredox catalyst, *Z*-selective decarboxylative alkyl Heck reaction between free aliphatic carboxylic acid and vinyl arene proceeds smoothly at

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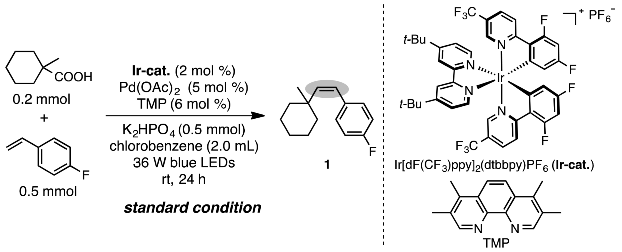
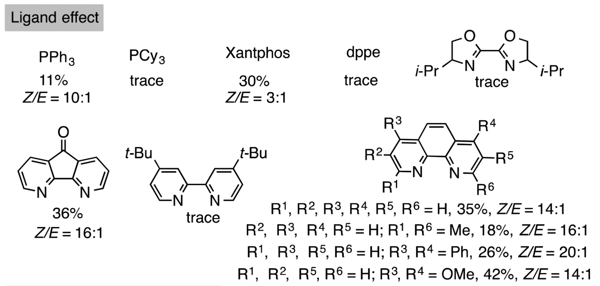
room temperature. This reaction not only presents a novel example of decarboxylative Heck reaction using free aliphatic carboxylic acids as alkyl donor, demonstrating a general case of intermolecular alkyl Heck process with high *Z*-selectivity, but also demonstrates the potential of merging photoredox catalysis with palladium catalysis for solving challenges in ground-state palladium-catalyzed cross-coupling reactions.

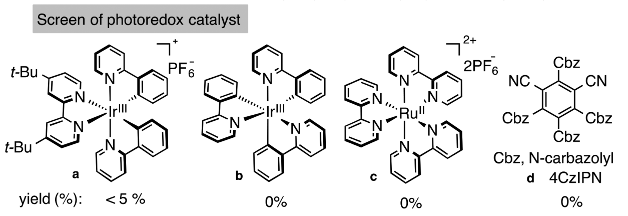
We demonstrated the optimized reaction condition and structures of the optimal catalysts in the top equation in Scheme 1. A transparent Schlenk tube charged with Ir[dF-$(CF_3)ppy]_2(dtbbpy)PF_6$ (Ir-cat.) (2 mol %), $Pd(OAc)_2$ (5 mol %), 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP, 6 mol %), 1-methylcyclohexane-1-carboxylic acid (0.2 mmol), 4-fluorostyrene (0.5 mmol, 2.5 equiv), and K_2HPO_4 (0.5 mmol) in chlorobenzene solvent was exposed under irradiation of 36 W blue LEDs at room temperature (1−2 cm distance from the LED source). After irradiation for 24 h at room temperature, the desired decarboxylative Heck product was detected in 80% yield with a high *Z*/*E* ratio of 96/4 (Scheme 1, entry 1). The key parameters that control the reaction outcomes are listed in Scheme 1.

Scheme 1. Parameters Controlling *Z*-Selective Decarboxylative Heck Reaction



entry	variations from standard condition	yield (%)[a]	*Z*/*E* ratio[a]
1	none	80	96:4
2	without blue LEDs	n.r.	/
3	without **Ir-cat.**	n.r.	/
4	without $Pd(OAc)_2$	n.r.	/
5	without TMP	trace	/
6	$PdCl_2$ instead of $Pd(OAc)_2$	65	92:8
7	$Pd(OTFA)_2$ instead of $Pd(OAc)_2$	63	93:7
8	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	25	66:34
9[b]	under O_2	trace	/
10[b]	addition of 0.4 mmol $K_2S_2O_8$ as oxidant	53	95:5
11[b]	addition of 0.4 mmol $PhI(OAc)_2$ as oxidant	trace	/



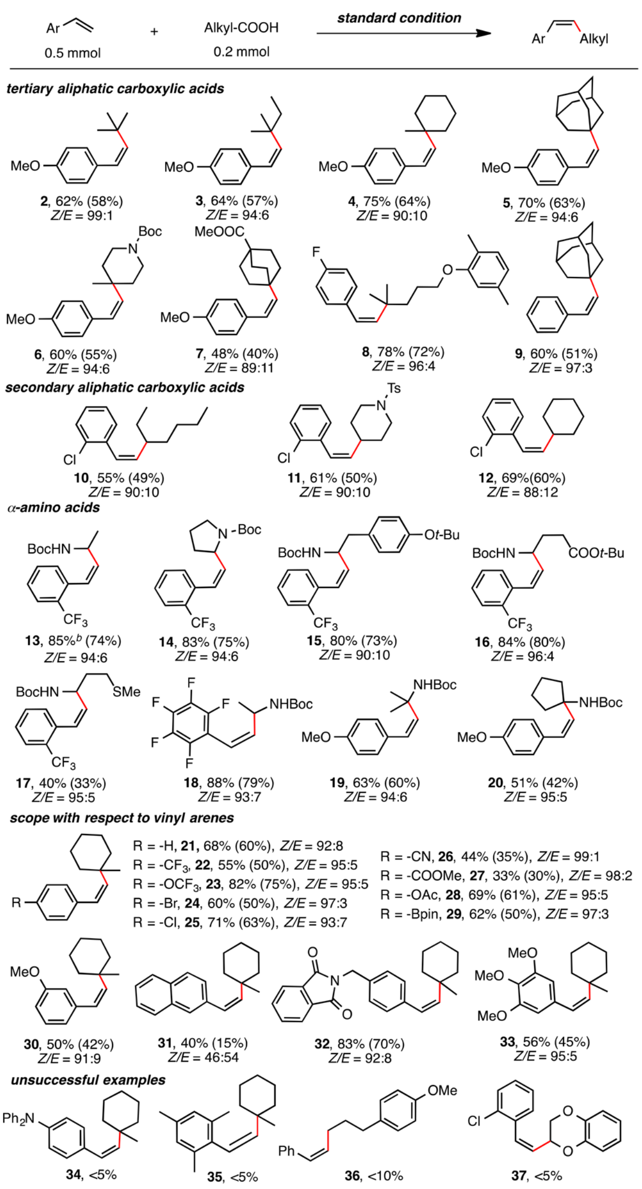


[a]The *Z*/*E* ratio determined by ^1H NMR analysis. Isolated yield of *Z*-**1** was 75%. [b]0.3 mmol of 4-fluorostyrene was used.

The reaction did not proceed at all in the absence of irradiation (Scheme 1, entry 2). Control experiments also revealed that iridium photoredox catalyst, palladium salts, and TMP ligand are all essential for the reaction to proceed (entries 3−5). Screening the palladium catalysts revealed that $Pd(OAc)_2$ was the optimal catalyst and other palladium salts such as $PdCl_2$, $Pd(OTFA)_2$, and $Pd_2(dba)_3$ were less effective, delivering alkene product in lower *Z*/*E* ratio (entries 6−8), probably due to the isomerization of *Z*- alkene to *E*- alkene catalyzed by palladium catalyst.[16] Exposure to oxygen entirely killed this reaction, probably due the reaction of triplet oxygen with the excited photoredox catalyst or a reactive intermediate (such as alkylpalladium species) (entry 9). It should be noted that this reaction requires oxidant, but there is no external oxidant in the reaction mixture. It was revealed a 1 equiv excess of vinyl arene worked as hydrogen acceptor to generate ethyl arene. Testing other chemical oxidants together with a reduced amount of vinyl arene either showed reduced efficiency or was entirely unproductive (entries 10 and 11). Judicious selection of supporting ligand for palladium catalyst and the selection of photoredox catalyst are key for the successful development of this reaction. The results of the ligand effect and screen of different photoredox catalysts are demonstrated at the bottom of Scheme 1. Among various ligands tested, phosphine ligands were all much less effective compared with 1,10-phenanthroline. Testing other bidentate nitrogen ligands revealed the backbone structure heavily affects the catalyst efficacy, as evidenced by the entire ineffectiveness of bisoxazoline ligands and bipyridine ligand. The substituent on 1,10-phenanthroline also significantly influenced the catalyst efficacy. Substitution at the 2,9-position to increase the steric hindrance on palladium catalyst is not beneficial for this reaction. TMP was proved to be the optimal ligand. As for the photoredox catalyst, based on our working hypothesis in Figure 1, we believe that suitable redox potential, singlet−triplet energy level (E_T), and excitation-state lifetime are all important factors to determine its efficiency. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (Ir-cat.) worked as the best photocatalyst due to its suitable redox potential ($E_{1/2}{}^{*III/II}$ = +1.21 V, $E_{1/2}{}^{III/II}$ = −1.37 V),[1b] matched triplet energy level with styrene (61 kcal/mol, and $E_T \sim 60$ kcal/mol for styrene),[14] and long excitation-state lifetime (τ = 2300 ns).[1b] Other photoredox catalysts such as $Ir(ppy)_2(dtbbpy)PF_6$ (**a**), *fac*-$Ir(ppy)_3$ (**b**), and $Ru(bpy)_3(PF_6)_2$ (**c**) were totally ineffective to give the decarboxylative Heck type product, probably because of their weak oxidation potentials that are ineffective to oxidize carboxylate anion [$E_{1/2}(^*M/M^-)$ = +0.66 V, +0.31 V, and +0.77 V, respectively].[1b] An organophotoredox catalyst, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-Cz-IPN), of suitable redox potential [$E_{1/2}$(*4Cz-IPN/4Cz-IPN$^-$) = +1.35 V, $E_{1/2}$(4CzIPN$^-$/4Cz-IPN) = −1.21 V] and excitation-state lifetime (τ = 5.1 μs),[15] was, however, ineffective, probably due to its incompatibility to merge with palladium catalyst under the reaction conditions.

The substrate scope of this reaction is demonstrated in Scheme 2. A variety of tertiary and secondary carboxylic acids were amenable substrates to give *Z*-type alkene products in good yield with high *Z*/*E* selectivity. α-Amino acids were also tolerable to deliver *Z*-type allylic amine derivatives as valuable synthetic intermediates. Various functional groups such as ether (**2**, **8**), amide (**6**), aryl halide (**10**, **12**, **24**), ester (**7**, **16**),

Scheme 2. Substrate Scope of Ir/Pd-Catalyzed *Z*-Selective Decarboxylative Heck Reaction[a]

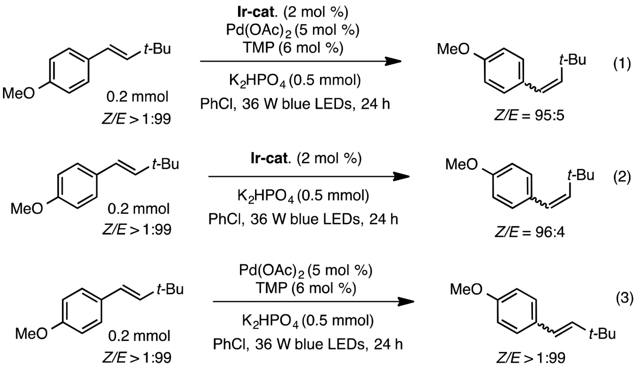


[a]Reaction conditions: aliphatic carboxylic acids (0.2 mmol), alkene (0.5 mmol), **Ir-cat.** (2.0 mol %), Pd(OAc)$_2$ (5.0 mol %), TMP (6.0 mol %), K_2HPO_4 (0.5 mmol), PhCl (2.0 mL), irradiated by 36 W blue LEDs for 24 h under Ar. Yields of isolated *Z*/*E* mixtures, *Z*/*E* ratio determined by ^{1}H NMR analysis. Yields of isolated *Z*-isomer are shown in parentheses. [b]Reaction performed on a 1.0 mmol scale.

sulfonamide (**11**), trifluoromethyl (**13**), trifluoromethoxy (**23**), cyano (**26**), and boronate (**29**) were all well tolerated. Testing the scope of vinyl arenes revealed various electron-rich and electron-deficient styrene substrates were all amenable to generate alkene product in moderate to good yields with *Z*-selectivity ranging from 92/8 to 99/1. Pentafluorostyrene was also suitable substrate to deliver *Z*-product in high yield (**18**). However, for 2-vinyl naphthalene, the *Z*/*E* ratio of the product was much deteriorated (**31**). This low *Z*/*E* selectivity (46:54) of 2-vinyl naphthalene can be explained by the triplet energy (E_T) of naphthalene (60.5 kcal/mol), which is almost the same compared with 2-alkyl styrene.[14] Thus, the naphthalene ring will affect the triplet sensitization step, which is proposed to be crucial for the *Z*/*E* selectivity. Several unsuccessful examples are also listed at the bottom of Scheme 2. A triarylamine moiety was not tolerated in this reaction, due the high reducing ability of triarylamine that may quench the excited triplet photoredox catalyst (**34**). Vinyl mesitylene was unreactive due to the large steric hindrance that prevents coordination with palladium catalyst (**35**). Primary aliphatic carboxylic acids and *α*-alkoxy aliphatic carboxylic acids were poorly reactive under the optimized reaction conditions (**36**, **37**), recovering large amount of alkenes and carboxylic acids after the reaction, probably due to the low efficiency of decarboxylation.

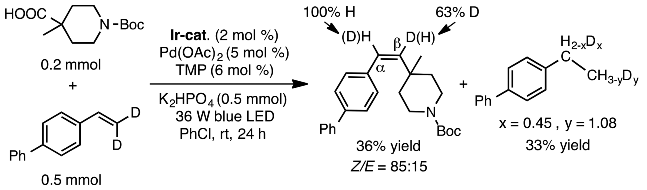
Control experiments to confirm the origin of the *Z*-selectivity are shown in Scheme 3. As demonstrated in Scheme 3, eq 1, the *E*-styrene derivative successfully isomerized under the optimal reaction conditions in the presence of iridium photoredox catalyst and palladium catalyst. The iridium photocatalyst alone can also catalyze the *E* to *Z* isomerization with comparable efficiency[13] (Scheme 3, eq 2). However, the palladium catalyst alone showed no effect on isomerization of the *E*-alkene (Scheme 3, eq 3). This set of control experiments unambiguously proved the iridium photosensitizer is the key catalyst to determine the *Z*/*E* selectivity. Although the literature reported that a palladium(II) catalyst can catalyze the *Z* to *E* isomerization of alkenes,[16] the palladium catalyst under our optimized condition did not cause any deterioration of the *Z*/*E* selectivity under irradiation.

Scheme 3. Control Experiments Confirming the Origin of *Z*-Selectivity



One of the intriguing factors of this reaction is that oxidant is not required in this oxidative coupling type reaction and ethyl arene was generated as side product, suggesting vinyl arene works as both coupling partner and hydrogen acceptor. We performed a deuterium-labeling experiment using 4-(vinyl-2,2-d_2)-1,1′-biphenyl as substrate (Scheme 4). An almost equally molar amount of 4-ethylbiphenyl was generated with desired coupling product. ^{1}H NMR analysis of the isolated product and byproduct revealed the deuterium distribution. In the alkene

Scheme 4. Isotope-Labeling Experiment Revealing Pd−H Insertion



product, the deuterium was not incorporated in the α-position of the double bond, while only 63% of deuterium remained on the β-position. The reduced deuterium percentage on the β-position of alkene product may be related to palladium-catalyzed C−H activation of terminal olefin that leads to H/D scrambling.[17] However, we found deuterium was incorporated into the benzylic position of the 4-ethylbiphenyl side product (23% D incorporation), while only 36% of D remained on the terminal methyl. The deuterium incorporation suggests that a process of Pd−H insertion to styrene generating phenethyl palladium species followed by protonation to deliver ethylbenzene is involved in the use of styrene as H-acceptor to regenerate palladium(II) catalyst.

On the basis of the above studies, a proposed mechanism is demonstrated in Figure 2 to rationalize this novel reaction.

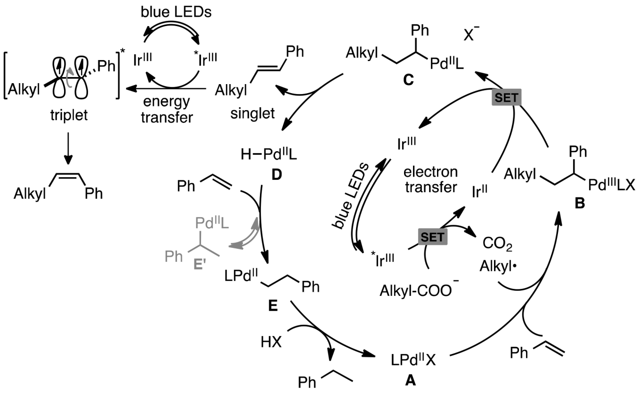


Figure 2. Proposed mechanism.

First, the Ir-photoredox catalyst in its excited triplet state is reductively quenched by carboxylate anion to generate alkyl radical.[4a] The alkyl radical is intercepted by styrene and phenathroline-supported Pd(II) catalyst to generate a benzylic Pd(III) species (**B**). The benzylic Pd(III) species oxidizes the Ir(II) to regenerate Ir(III) and to complete the photoredox cycle.[12a] β-H elimination proceeds on the benzylic Pd(II) species (**C**) to deliver *E*-olefin product and Pd(II)−H species (**D**). The Pd−H species inserts into styrene to generate phenethyl Pd(II) (**E**) followed by protonation to give ethylbenzene and regenerated Pd(II) catalyst (**A**). Simultaneously, the excited Ir-photoredox catalyst in its triplet state sensitizes *E*-olefin product to its triplet state through energy transfer. This uphill catalysis isomerizes *E*-olefin to its thermodynamically less favored *Z*-isomer. We mention in the catalytic cycle that Pd−H species (**D**) reacts with styrene to generate phenethyl Pd(II) intermediate (**E**) followed by protonation. This step is supported by the substantial deuterium incorporation into the benzylic position of the generated ethyl arene byproduct (Scheme 4). We cannot rule out the possibility of Pd−H insertion to form a more stable benzyl-Pd species (**E′**, arrow in gray). However, Pd−H insertion steps (from **D** to **E** and **E′**) are reversible. Phenethyl Pd(II) intermediate (**E**) of lower stability undergoes irreversible protonation to deliver ethyl arene to complete the catalytic cycle. We did not detect a significant amount of alkyl arene generated from protonation of intermediate **C**, suggesting benzylic palladium intermediate of higher stability does not undergo protonation. This further supports the fact that ethyl arene byproduct is formed through protonation of phenethyl Pd(II) intermediate (**E**). It is notable although not mentioned in the catalytic cycle in Figure 2 that recent studies by Gevorgyan and our group revealed that palladium species can also be excited by irradiation of blue LEDs,[18] so that we should notice the palladium complexes mentioned in this mechanism are excited by irradiation to be distinct in reactivity from its ground state under thermal conditions.[18b,e]

In summary, unprecedented *Z*-selective decarboxylative Heck reactions of secondary and tertiary aliphatic carboxylic acids with vinyl arenes are achieved by merging palladium/phenathroline catalyst with iridium photocatalyst under irradiation. The amenable substrates of this reaction encompass a broad scope of tertiary and secondary aliphatic carboxylic acids as well as natural and unnatural α-amino acids. The catalyst system enabling this unprecedented transformation features its unique property that merges a palladium catalyst with iridium photoredox catalyst, where both electron-transfer and energy-transfer properties of the photoredox catalyst are utilized synergistically.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00712.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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