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# Visible-Light Photocatalytic Decarboxylation of α,β-Unsaturated Carboxylic Acids: Facile Access to Stereoselective Difluoromethylated Styrenes in Batch and Flow

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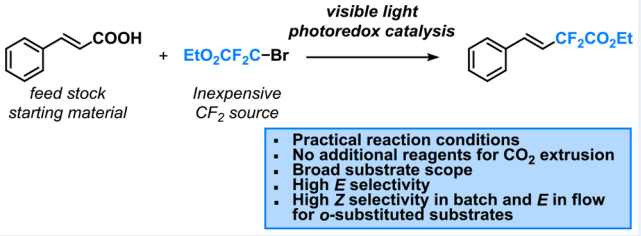
Supporting Information

**ABSTRACT:** The development of synthetic methodologies which provide access to both stereoisomers of α,β-disubstituted olefins is a challenging undertaking. Herein, we describe the development of an operationally simple and stereoselective synthesis of difluoromethylated styrenes via a visible-light photocatalytic decarboxylation strategy using *fac*-Ir(ppy)$_3$ as the photocatalyst. Meta- and para-substituted cinnamic acids provide the expected *E*-isomer. In contrast, *ortho*-substituted cinnamic acids yield selectively the less stable *Z*-product, whereas the *E*-isomer can be obtained via continuous-flow processing through accurate control of the reaction time. Furthermore, our protocol is amenable to the decarboxylative difluoromethylation of aryl propiolic acids.




**KEYWORDS:** *E/Z selectivity, flow chemistry, TTET, difluoromethylation, decarboxylation, photoredox catalysis*

The introduction of fluorinated moieties into organic compounds has resulted in a dramatic enhancement of their physical, chemical, and biological properties, rendering medicinal and agrochemical compounds to be more potent.[1] Consequently, in recent years, a tremendous amount of research effort has been devoted to develop new methods to enable the efficient incorporation of fluorinated moieties into parent molecules.[2] Among these, the $CF_2$ motif plays an increasingly important role, since the hydrogen bond donor properties of the difluoromethyl group increases acidity of its neighboring group, which enhances dipole moments and conformational changes in the molecules.[3] In recent years, great progress has been made with regard to radical difluoroalkylation reactions, especially via visible-light photoredox catalysis.[4] Visible light photoredox catalysis has become one of the most powerful tools in organic synthesis wherein both single electron transfer (SET) and triplet−triplet energy transfer (TTET) processes with organic substrates can be facilitated.[5]

With biomass feedstocks of vinyl carboxylic acids abundantly available, these inexpensive and stable compounds have attracted a great deal of attention as substrates for a wide variety of synthetic transformations.[6] Perhaps the most widely used decarboxylative fluoroalkylation strategy involves transition-metal coordination in combination with high temperatures or strong oxidants to facilitate the $CO_2$ extrusion process (Scheme 1A).[7] It is evident that such harsh reaction conditions have repercussions on the substrate scope. Photocatalytic strategies have allowed the decarboxylative functionalization process to proceed at room temperature but still require stoichiometric amounts of strong oxidants or transition metals (Scheme 1B).[8,9] In addition, all these methods give access to the thermodynamically more stable *E*-alkenes,[10] while methods delivering selectively the *Z*-isomers are far less common.[11]

The strategy we describe here involves a photocatalytic decarboxylation methodology to access difluoroalkenes, which is operationally simple, mild and requires no additional transition metals or oxidants to enable $CO_2$ extrusion (Scheme 1C). Moreover, with *ortho*-substituted cinnamic acid substrates, *Z*-isomers could be obtained in high selectivity. The corresponding *E*-isomer could be accessed as well via continuous-flow processing through accurate control of the reaction time. To the best of our knowledge, having access to both stereoisomers simply by changing the reactor has never been reported before and constitutes a powerful approach to tune reaction selectivity for photoredox catalysis.

Building on our recent experience with the direct trifluoromethylation of styrenes,[10a] we commenced our investigations by using *fac*-Ir(ppy)$_3$ as the photocatalyst (Table 1). The targeted product could be obtained in a 31% yield and with an *E*/*Z* ratio of 52:48 using 3 equiv of ethyl bromodifluoroacetate **2** and KOAc as a base (Table 1, entry 1). Interestingly, no metal cocatalyst or hypervalent iodine reagent (HIR) was required to facilitate the $CO_2$ extrusion. The rather poor *E*/*Z* selectivity can be explained due to the high triplet energy level of the *fac*-Ir(ppy)$_3$ photocatalyst ($E_T$ = 2.41 eV).[12] Consequently, a triplet−triplet energy transfer occurs leading to

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**Scheme 1. (A) Classical Decarboxylative Cross-Coupling Strategies. (B) Recent Photocatalytic Approaches Still Require the Use of Metals or Hypervalent Iodine Reagents (HIR) to Enable the Decarboxylation Step. (C) Our Strategy for the Photocatalytic Radical Difluoromethylation of Cinnamic Acids**

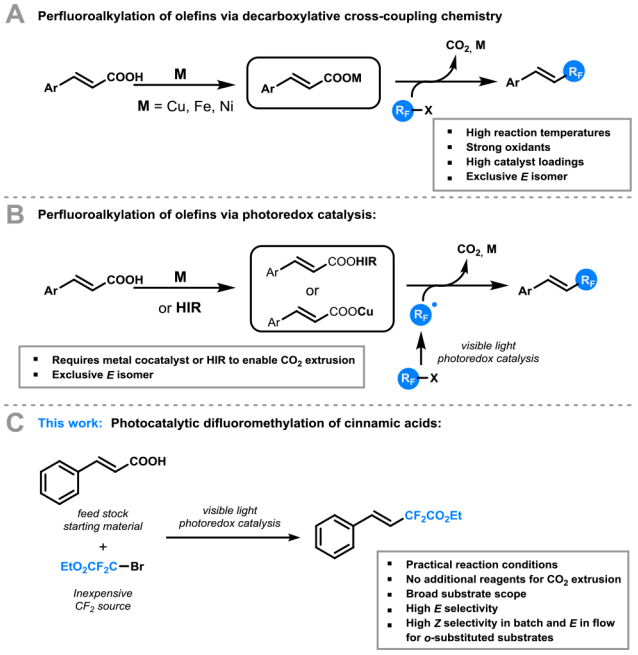
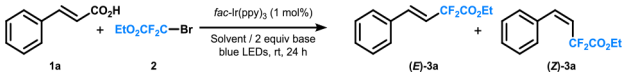



**Table 1. Reaction Discovery and Optimization Studies for the Photocatalytic Difluoromethylation of Cinnamic Acids[a]**



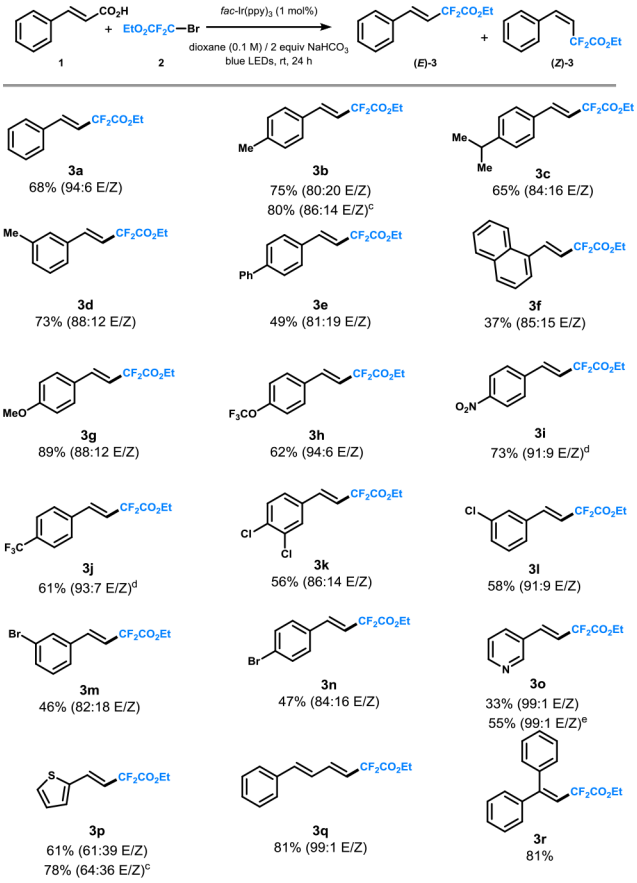

| entry | base | solvent | yield[b] (%) | $E/Z$[b] |
|---|---|---|---|---|
| 1[d] | KOAc | 0.2 M $CH_3CN$ | 31 | 52:48 |
| 2 | KOAc | 0.2 M EtOH | 44 | 57:43 |
| 3 | KOAc | 0.2 M 1,4-dioxane | 60 | 51:49 |
| 4 | $Cs_2CO_3$ | 0.2 M 1,4-dioxane | 46 | 71:29 |
| 5 | 2,6-lutidine | 0.2 M 1,4-dioxane | 70 | 46:54 |
| 6 | $NaHCO_3$ | 0.2 M 1,4-dioxane | 75 | 75:25 |
| 7[c,d] | $NaHCO_3$ | 0.2 M 1,4-dioxane | 83 | 50:50 |
| 8[d] | $NaHCO_3$ | 0.1 M 1,4-dioxane | 68 | 94:6 |
| entry | change from best conditions (entry 5) | | yield[b] (%) | $E/Z$[b] |
| 9 | no light | | 0 | |
| 10 | no photocatalyst | | 0 | |

[a]Reaction conditions: *fac*-Ir(ppy)$_3$ (1 mol %), cinnamic acid **1** (0.2 mmol), $NaHCO_3$ (0.4 mmol), ethyl bromodifluoroacetate **2** (0.6 mmol), solvent (2 mL, 0.1 M), blue LEDs (3.12 W), room temperature, argon atmosphere, stirred for 24 h. [b]Yield and $E/Z$ values are determined with $^{19}F$ NMR using $\alpha,\alpha,\alpha$-trifluorotoluene as internal standard. [c]10 equiv of $H_2O$ was added. [d]Reported yields are those of isolated compounds; $E/Z$ values are determined by $^1H$ NMR of isolated products.

an erosion of the stereoselectivity.[11] Various solvents and bases were subsequently screened (Table 1, entries 1−6); the best results were obtained using 1,4 dioxane as a solvent and $NaHCO_3$ as the base. Addition of water provided an improved yield but a decreased selectivity (Table 1, entry 7). Optimal results were obtained when the concentration was reduced to 0.1 M leading to a 68% yield and an excellent $E/Z$ selectivity (94:6) (Table 1, entry 8). Lastly, control experiments confirmed the photocatalytic nature of our transformation, as no reaction was observed in the absence of photocatalyst and/or light (Table 1, entries 9 and 10).

Having identified the optimal reaction conditions for the photocatalytic difluoromethylation of cinnamic acid, we aimed to define the reaction scope (Table 2). Our protocol was found

**Table 2. Decarboxylative Difluoromethylation: Scope of Meta- and Para-Substituted Cinnamic Acids[a,b]**




[a]Reaction conditions: cinnamic acid **1** (0.2 mmol, 1.0 equiv), ethyl bromodifluoroacetate **2** (0.6 mmol, 3.0 equiv), *fac*-Ir(ppy)$_3$ (1 mol %), $NaHCO_3$ (0.4 mmol, 2.0 equiv), 1,4-dioxane (2.0 mL), argon, blue LEDs (3.12 W), 24 h. [b]Reported yields are those of isolated compounds; $E/Z$ values are determined by $^1H$ NMR of isolated products. [c]*fac*-Ir(*t*Buppy)$_3$ was used as the photocatalyst. [d]Reaction time, 30 h. [e]Due to the limited solubility of the substrate, the yield is lower for compound **3o**. However, the yield could be increased by recycling the unreacted starting material.

to readily accommodate a variety of *para*- and *meta*-substituted cinnamic acids, including electron-neutral (**3a−d**), electron-donating (**3e−g**), and electron-withdrawing substituents (**3h−n**). Overall, the $E/Z$ ratio was good to excellent for all these examples. In addition, the presence of halogens was well tolerated, providing opportunities for further decoration of the molecule, e.g., via cross coupling (**3k−n**). In addition, heterocyclic substrates, such as pyridine (**3o**) and thiophene (**3p**), were found to be competent substrates. The pyridine analogue displayed an excellent $E/Z$ selectivity (99:1), while the thiophene one was obtained with a lower stereoselectivity (61:39). Extended conjugation, e.g., for (2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid, was tolerated as well, delivering the



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corresponding product (**3q**) in good yield and excellent selectivity (81%, 99:1). Also, β-substituted cinnamic acids, e.g., 1,1-diphenylethylene (**3r**), could be successfully subjected to our reaction conditions resulting in a good isolated yield (81% yield). The lower *E*/*Z* selectivity in some cases prompted us to evaluate the efficacy of *fac*-Ir(*t*Buppy)$_3$. This photocatalyst was recently reported by Weaver et al. and was shown to lower the energy transfer rate due to the increased steric bulk.[11a] However, while an increase in yield was observed, the *E*/*Z* selectivity only marginally improved (Table 2, **3b** and **3p**).

However, when *ortho*-substituted cinnamic acids were evaluated, a selectivity switch was observed toward the *Z* product (Table 3, entry 1). Interestingly, the use of *fac*-Ir(*t*Buppy)$_3$ completely altered the selectivity (Table 3, entry 2), confirming the observations of Weaver et al.[11a] We were delighted to find that an increase in concentration resulted in an improvement in both yield and selectivity (Table 3, entry 1 and 3). A further increase in catalyst loading and concentration contributed to an enhancement of the selectivity toward the *Z* isomer (Table 3, entries 4−6). Kinetic experiments revealed that the thermodynamically more stable *E*-isomer was formed first, after which the *Z*-isomer was obtained via a triplet−triplet energy transfer mechanism (TTET) (see the Supporting Information).[11b] Consequently, it should theoretically be possible to stop the reaction before *E*/*Z* isomerization occurs. In order to obtain high conversions in a short amount of time, we turned our attention to the use of continuous-flow microreactors which allow to accelerate photocatalytic reactions due to an improved irradiation profile and enhanced mass transfer characteristics (Table 3, entries 7−11).[13,14] In flow, the reaction time could be reduced significantly resulting in a reversed *E*/*Z* selectivity (Table 3, entry 7). An increase in catalyst loading and concentration could further reduce the reaction time to 15 min resulting in an excellent *E* selectivity (62%, 92:8) (Table 3, entry 11).[15] Longer residence times lead to an increase in yield but an erosion of the selectivity (Table 3, entries 8 and 9). However, it should be noted that it was possible to recover the starting material quantitatively, which can be subsequently reintroduced into the flow reactor obtaining higher overall conversions while maintaining a high stereoselectivity (see Table 4, **5g** and **3p**).

**Table 3. Optimization Studies for the Photocatalytic Difluoromethylation of Ortho-Substituted Cinnamic Acids in Batch[a] or Continuous-Flow[b]**


| entry | conc (M) | *fac*-Ir(ppy)$_3$ (mol %) | reaction time (h) | Yield[c] (%) | *E*/*Z*[c] |
|---|---|---|---|---|---|
| | | Batch Conditions[a] | | | |
| 1 | 0.1 | 1 | 24 | 67 | 21:79 |
| 2[d] | 0.1 | 1 | 24 | 60 | 79:21 |
| 3 | 0.2 | 1 | 24 | 86 | 15:85 |
| 4 | 0.2 | 3 | 24 | 88 | 10:90 |
| 5[e] | 0.5 | 3 | 24 | 77 | 6:94 |
| 6[e] | 1.0 | 2 | 24 | 57 | 5:95 |
| | | Continuous-Flow Conditions[b] | | | |
| 7 | 0.05 | 0.5 | 2 | 51 | 75:25 |
| 8 | 0.1 | 0.5 | 2 | 68 | 68:32 |
| 9 | 0.1 | 1.0 | 2 | 46 | 26:74 |
| 10 | 0.1 | 1.5 | 0.5 | 55 | 78:22 |
| 11[e] | 0.15 | 1.0 | 0.25 | 62 | 92:8 |

[a]Reaction conditions in batch: *fac*-Ir(ppy)$_3$ (1 mol %), (*E*)-3-(*o*-tolyl)acrylic acid **4a** (0.2 mmol), ethyl bromodifluoroacetate **2** (0.6 mmol), $NaHCO_3$ (0.4 mmol), $H_2O$ (3.0 mmol), 1,4-dioxane (0.4 mL), blue LEDs (3.12 W), room temperature, argon atmosphere, stirred for 24 h. [b]Reaction conditions in continuous flow: *fac*-Ir(ppy)$_3$ (1 mol %), (*E*)-3-(*o*-tolyl)acrylic acid **4a**(1.0 mmol), ethyl bromodifluoroacetate **2** (3.0 mmol), 2,6-lutidine (2.0 mmol), 1,4-dioxane/EtOH (v/v 5:1, 6.7 mL, 0.15 M), blue LEDs (3.12 W), room temperature, argon atmosphere. [c]Yield and *E*/*Z* values are determined with $^{19}$F-NMR using α,α,α-trifluorotoluene as internal standard. [d]*fac*-Ir(*t*Buppy)$_3$ was used as the photocatalyst. [e]Reported yields are those of isolated compounds; *E*/*Z* values are determined by $^1$H NMR of isolated products.

Next, a diverse set of *ortho*-substituted cinnamic acids were examined in both batch and flow (Table 4). Cinnamic acids bearing electron-neutral (**5a**), electron-donating (**5b−d**) and electron-withdrawing substituents (**5e**) could be difluoromethylated in high *Z*-selectivity in batch, while the corresponding *E*-isomer could be readily accessed via continuous-flow processing. Also, *o*-halogenated cinnamic acids were competent substrates (**5f−i**). Enhanced selectivity for the *Z*-isomer was observed with increasing steric bulk (F < Cl < Br). Interestingly, when both *ortho* positions were occupied with bulky groups (e.g., **5k,l**), a high *Z*-selectivity was observed which could not be revoked via continuous-flow processing. This observation highlights the need for sterical bulk in the *ortho*-position to access the *Z*-stereoisomer. Furthermore, in the case of β-methyl-substituted cinnamic acids, a similar trend in the selectivity was observed due to the steric effect of the β-substituent (**5m−o**). Finally, substrates with a low *E*-selectivity in batch (e.g., substrate **3p**) could be obtained in flow with an improved stereoselectivity.

To further demonstrate the utility of our protocol, we sought to demonstrate its potential for the decarboxylative difluoromethylation of aryl propiolic acids. A small tweak of the reaction conditions (i.e., CsOAc as a base) resulted in the formation of the desired compounds in modest but synthetically useful yields (Table 5). Our protocol was successfully applied to *ortho*-, *meta*-, and *para*-substituted aryl propiolic acids (**7a−l**). These findings are noteworthy because, to the best of our knowledge, this is the first time that propiolic acids are used as substrates for photocatalytic decarboxylation chemistry.[6a,b]

Based on the above results, we suggest a plausible mechanism for the developed transformation as outlined in Scheme 2. Photoexcitation of *fac*-Ir(ppy)$_3$ upon blue irradiation results in a metal-to-ligand charge transfer (MLCT) excited state. Photoluminescence quenching experiments showed that the photoexcited *fac*-[$Ir^{3+}$(ppy)$_3$]* ($E_{1/2}^{red}$ [*$Ir^{3+}$/$Ir^{4+}$] = −1.72 V vs SCE) can be quenched by **2** ($E^{red}$ = −0.57 V vs SCE)[12c] at a rate constant of 1.84 × $10^8$ $M^{-1}$ $s^{-1}$. Our investigations also showed that the excited photocatalyst can be quenched by cinnamate **A** though at a lower rate constant of 1.24 × $10^8$ $M^{-1}$ $s^{-1}$. However, radical trapping experiments showed that only the key intermediate $^{\bullet}CF_2CO_2Et$ could be captured by BHT (2,6-di-*tert*-butyl-4-methylphenol) suggesting the feasibility of this oxidative quenching pathway. Next, intermolecular π-addition of the radical to **A** produces the benzylic radical **B**. Single-electron transfer from radical **B** to *fac*-[Ir(ppy)$_3$]$^+$ affords carbocation **C** and facilitates subsequent $CO_2$ extrusion to yield the *E* stereoisomer. The formation of *E* isomer as both the thermodynamically and kinetically preferred isomer is sup-


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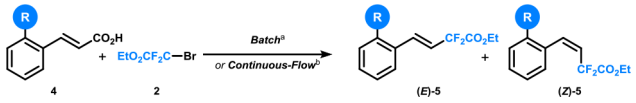
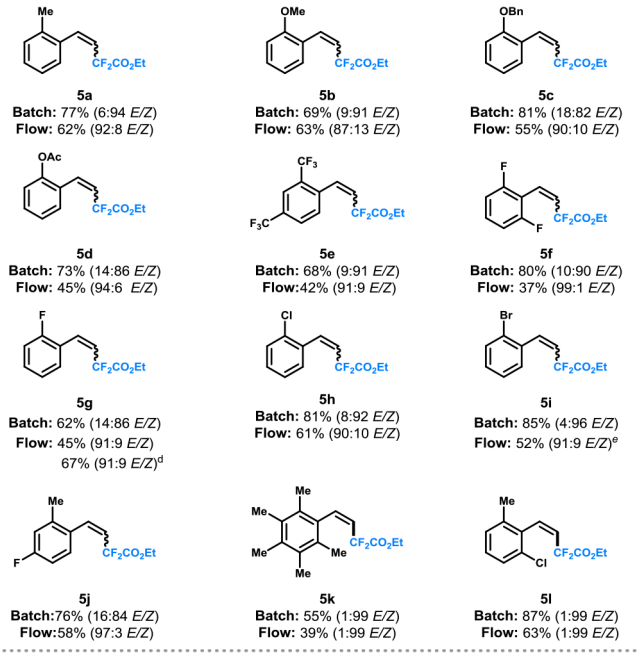
**Table 4. Decarboxylative difluoromethylation: Scope of *Ortho*- and *β*-Substituted Cinnamic Acids in Batch[a] or Continuous-Flow[b,c]**




*ortho-substituted cinnamic acids*




**5a** Batch: 77% (6:94 *E/Z*) Flow: 62% (92:8 *E/Z*)

**5b** Batch: 69% (9:91 *E/Z*) Flow: 63% (87:13 *E/Z*)

**5c** Batch: 81% (18:82 *E/Z*) Flow: 55% (90:10 *E/Z*)

**5d** Batch: 73% (14:86 *E/Z*) Flow: 45% (94:6 *E/Z*)

**5e** Batch: 68% (9:91 *E/Z*) Flow:42% (91:9 *E/Z*)

**5f** Batch: 80% (10:90 *E/Z*) Flow: 37% (99:1 *E/Z*)

**5g** Batch: 62% (14:86 *E/Z*) Flow: 45% (91:9 *E/Z*) 67% (91:9 *E/Z*)[d]

**5h** Batch: 81% (8:92 *E/Z*) Flow: 61% (90:10 *E/Z*)

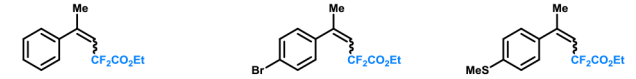
**5i** Batch: 85% (4:96 *E/Z*) Flow: 52% (91:9 *E/Z*)[e]

**5j** Batch:76% (16:84 *E/Z*) Flow:58% (97:3 *E/Z*)

**5k** Batch: 55% (1:99 *E/Z*) Flow: 39% (1:99 *E/Z*)

**5l** Batch: 87% (1:99 *E/Z*) Flow: 63% (1:99 *E/Z*)

*β-substituted cinnamic acids*




**5m** Batch: 71% (10:90 *E/Z*) Flow:51% (90:10 *E/Z*)

**5n** Batch: 88% (18:82 *E/Z*) Flow: 43% (90:10 *E/Z*)

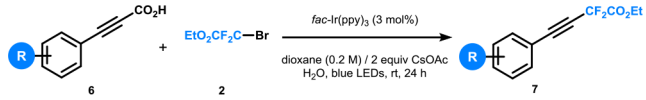
**5o** Batch: 77% (1:99 *E/Z*) Flow: 53% (80:20 *E/Z*)[e]

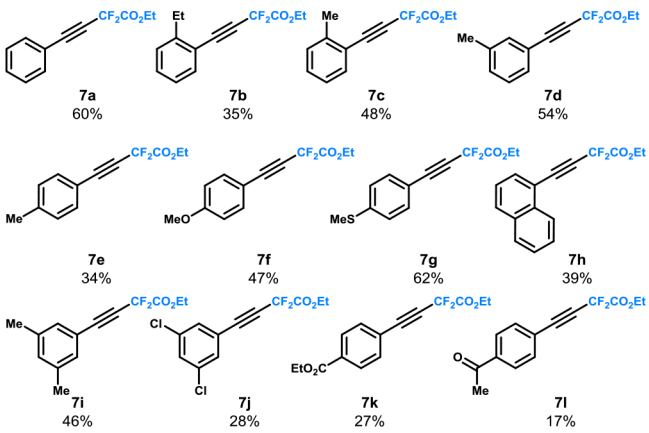
*non-substituted cinnamic acids*


**3p** Batch: 61% (61:39 *E/Z*) Flow: 40% (91:9 *E/Z*) 65% (91:9 *E/Z*)[d]

[a]Reaction conditions in batch: *fac*-Ir(ppy)$_3$ (3 mol %), *o*-cinnamic acid **4** (0.2 mmol), ethyl bromodifluoroacetate **2** (0.6 mmol), $NaHCO_3$ (0.4 mmol), $H_2O$(3.0 mmol), 1,4-dioxane (0.4 mL, 0.5 M), blue LEDs (3.12 W), room temperature, argon atmosphere, stirred for 24 h. [b]Reaction conditions in continuous flow: *fac*-Ir(ppy)$_3$ (1 mol %), *o*-cinnamic acid **4** (1.0 mmol), ethyl bromodifluoroacetate **2** (3.0 mmol), 2,6-lutidine (2.0 mmol), 1,4-dioxane/EtOH (v/v 5:1, 6.7 mL, 0.15 M), blue LEDs (3.12 W), room temperature, argon atmosphere, residence time: 15 min. [c]Reported yields are those of isolated compounds; *E*/*Z* values are determined by $^1$H NMR of isolated products. [d]Yield based on one time starting material recycle. [e]10 min residence time.

**Table 5. Decarboxylative Difluoromethylation of Aryl Propiolic Acids[a,b]**




**7a** 60%

**7b** 35%

**7c** 48%

**7d** 54%

**7e** 34%

**7f** 47%

**7g** 62%

**7h** 39%

**7i** 46%

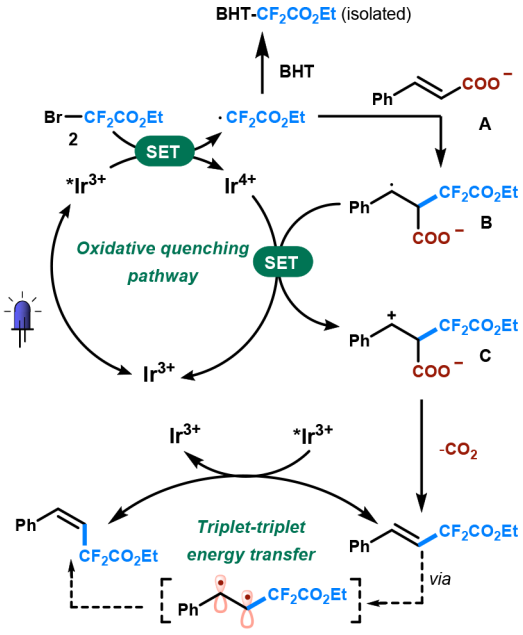
**7j** 28%

**7k** 27%

**7l** 17%

[a]Reaction conditions: aryl propiolic acid **6** (0.2 mmol, 1.0 equiv), ethyl bromodifluoroacetate **2** (0.6 mmol, 3.0 equiv), *fac*-Ir(ppy)$_3$ (3 mol %), CsOAc (0.4 mmol, 2.0 equiv), $H_2O$(2 mmol, 10 equiv), 1,4-dioxane (1.0 mL), argon, blue LEDs (3.12 W), 24 h. [b]Reported yields are those of isolated compounds.

**Scheme 2. Proposed Catalytic Cycle for the Decarboxylative Difluoromethylation**




ported by kinetic experiments (see the Supporting Information). The *Z* isomer is subsequently formed due to a triplet−triplet energy transfer process with *fac*-[Ir$^{3+}$(ppy)$_3$]* ($\tau_0$ = 1.9 $\mu$s[5a] and $E_T$ = 2.41 eV[12a,b]).

In this work, we have introduced a simple yet effective photocatalytic decarboxylative protocol to prepare difluoromethylated styrenes and phenylacetylenes. In contrast to previously described methods, this procedure does not require additional metal catalysts or hypervalent iodine reagents to facilitate $CO_2$ extrusion. The generality of our protocol is demonstrated by the broad substrate scope (difluoromethylated styrenes, 31 *E*-selective examples and 15 *Z*-selective; difluoromethylated phenylacetylenes, 12 examples). *Ortho*-substituted cinnamic acids give the less stable *Z*-selective products. The thermodynamically favored *E*-stereoisomer could be readily obtained in continuous-flow through accurate control of the reaction time. Having access to both stereoisomers simply by changing the reactor is a unique and powerful approach and provides opportunities for other photocatalytic transformations.



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## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b03019.

Experimental procedures, mechanistic studies, and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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