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# Direct $\beta$ -Selective Hydrocarboxylation of Styrenes with $\text{CO}_2$ Enabled by Continuous Flow Photoredox Catalysis

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Supporting Information Placeholder

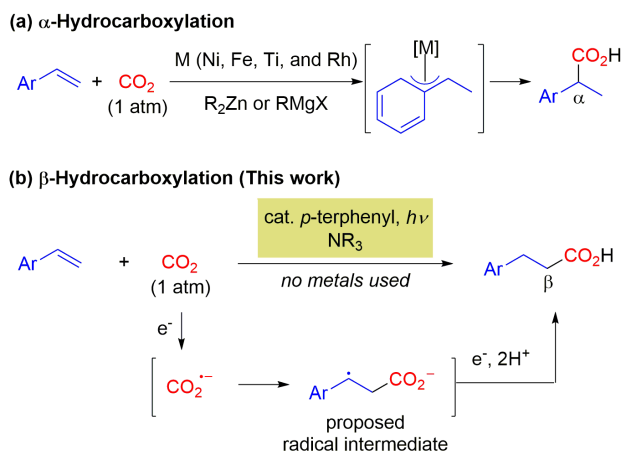
**ABSTRACT:** The direct  $\beta$ -selective hydrocarboxylation of styrenes under atmospheric pressure of  $\text{CO}_2$  has been developed using photoredox catalysis in continuous flow. The scope of this methodology was demonstrated with a range of functionalized terminal styrenes, as well as  $\alpha$ -substituted and  $\beta$ -substituted styrenes.

Carboxylation using  $\text{CO}_2$  offers direct access to valuable carboxylic acids that are traditionally prepared by multi-step formylation/oxidation processes.<sup>1</sup> However, the high kinetic and thermodynamic stability of  $\text{CO}_2$  has generally demanded the use of nucleophilic organometallic substrates or harsh reaction conditions.<sup>2</sup> There have been efforts to develop methods for the direct catalytic hydrocarboxylation of unsaturated hydrocarbons<sup>3</sup> such as styrenes<sup>4,5</sup> via transition metal catalysis. Despite these advances, high-energy reductants are required in most cases. In this regard, a single electron pathway via photoredox catalysis would be an ideal method to obviate the use of high-energy reagents.<sup>6</sup>

Another challenge with the direct catalytic hydrocarboxylation using  $\text{CO}_2$  is the limited number of methods to obtain the anti-Markovnikov product.<sup>3m</sup> Transition metal catalyzed strategies, for example, provide access to  $\alpha$ -functionalized acids (*i.e.*, Markovnikov product) due to the formation of the more stable  $\eta^3$  benzylic metal species. [Scheme 1(a)]<sup>4a-d</sup>

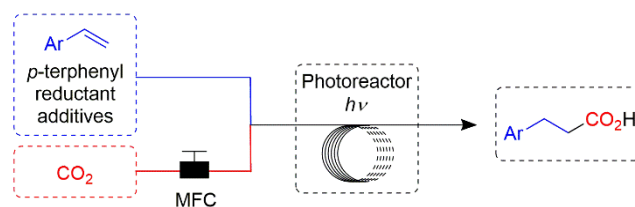
Herein we present an alternative approach for the  $\beta$ -selective hydrocarboxylation of styrenes via continuous flow, photoredox catalysis, in the presence of a tertiary amine reductant and atmospheric pressure of  $\text{CO}_2$  [Scheme 1(b)]. We envisioned that photoredox catalytic conditions would involve a stable benzylic radical anion intermediate.

**Scheme 1. Direct hydrocarboxylation of styrenes with  $\text{CO}_2$ .**



As shown in Scheme 2, the continuous flow setup featured a DMF solution (0.15 M) containing the styrene substrate, photoredox catalyst, reductant, and additives mixed in line with  $\text{CO}_2$  under atmospheric pressure that was metered using a mass flow controller (MFC). Each reaction used the *p*-terphenyl (20 mol%, absorption  $\lambda_{\text{max}} = 283 \text{ nm}$ )<sup>7</sup> photoredox catalyst due to its success in our previously reported synthesis of  $\alpha$ -amino acids.<sup>8</sup> The resulting segmented flow was then introduced into the UV photoreactor (500 W Hg(Xe) lamp) equipped with a longpass filter ( $\lambda > 280 \text{ nm}$ ).<sup>9</sup> Notably, biphasic reactions and photochemical transformations have been proven to be more efficient in continuous flow than in the traditional batch system due to superior mixing and the short path length.<sup>10</sup>

**Scheme 2. Schematic diagram of the continuous flow photochemical system for the  $\beta$ -selective hydrocarboxylation of styrenes.**



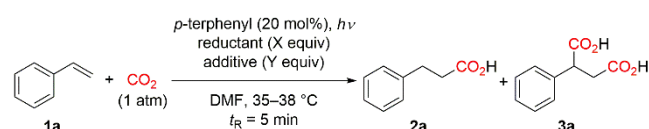
MFC, mass flow controller. See Supporting Information for details.

Initially we explored the hydrocarboxylation of styrene in the continuous flow setup using triethylamine (1 equiv) as a reductant in the absence of any additives and for a residence time of 5 min. As shown in Table 1, entry 1, the desired hydro-

cinnamic acid (**2a**) was obtained in 12% yield with the detection of coupling products between triethylamine and styrene by GC-MS. The use of triphenylamine in place of triethylamine in order to suppress the undesired couplings nevertheless did not improve the yield of the desired **2a** (Table 1, entry 2). However, a survey of various reductants (Table S1) revealed that one equivalent of 1,2,2,6,6-pentamethylpiperidine (PMP) furnished 31% of **2a** (Table 1, entry 3) along with 29% of a dicarboxylic acid (**3a**, see Figure S11 for proposed pathway for the formation of **3a**). Despite the poor selectivity observed, the combined yield of **2a** and **3a** was greatly improved compared to entries 1 and 2.

We next investigated the effect of additives such as thiophenol, triphenylsilane, and water with the hypothesis in mind that these may terminate the reaction through a hydrogen atom transfer or by protonation of a reduced benzylic radical intermediate. Neither thiophenol nor triphenylsilane improved the outcome of the reaction (Table 1, entries 4-5). However, in the presence of 1 equivalent of water and 2 equivalents of PMP, the ratio and combined

**Table 1. Optimization of the  $\beta$ -selective hydrocarboxylation.<sup>a</sup>**



entry	reductant (equiv)	additive (equiv)	yield <b>2a</b> <sup>b</sup> (%)	yield <b>3a</b> <sup>b</sup> (%)	<b>2a/3a</b> <sup>b</sup>
1	NEt <sub>3</sub> (1)	-	12	4.9	2.4:1
2	NPh <sub>3</sub> (1)	-	0	0	-
3	PMP (1)	-	31	29	1.1:1
4	PMP (2)	PhSH (1)	0	0	-
5	PMP (2)	Ph <sub>3</sub> SiH (1)	29	19	1.5:1
6	PMP (2)	H <sub>2</sub> O (1)	41	25	1.6:1
7	PMP (2)	H <sub>2</sub> O (19)	87	3	29:1

<sup>a</sup>Reactions were carried out using a continuous flow photochemical system developed by Beeler.<sup>9</sup> 1 atm of CO<sub>2</sub> is equivalent to 1.1 equiv. CO<sub>2</sub> <sup>b</sup>Calculated by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

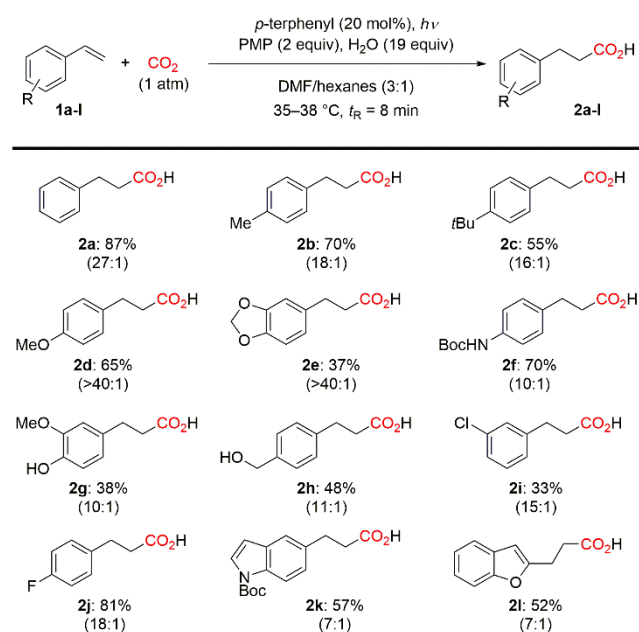
yield of **2a** and **3a** improved to 1.6:1 and 66% respectively (Table 1, entry 6). Upon increasing the stoichiometry of water to 19 equivalents (Table S2), **2a** was obtained in 87% yield and with a 29:1 ratio of mono- to dicarboxylation (Table 1, entry 7). Notably, the use of more water (>19 equiv) proved detrimental to the homogeneity of the reaction mixture. Finally, the addition of hexanes as a co-solvent (DMF:hexanes = 3:1 v/v) was found to be critical in preventing reactor clogging by precipitation of a product resulting from coupling of 2 PMP and formal loss of 2 H atoms (compound **S2**, see Supporting Information for the structure), particularly on larger scale. Although the added hexanes did not affect yield or selectivity, some minor modifications to the flow setup and an increased residence time of 8 min were required. (See Supporting Information for details.) In a comparable batch experiment, wherein the same stoichiometry and concentration described in Table 1, entry 7, were used but continuous bubbling CO<sub>2</sub> through the reaction mixture was employed, the desired product **2a** was obtained in a reduced yield of 36% yield, but

with an excellent mono/di carboxylation selectivity (see Supporting Information for details).

We subsequently utilized the conditions that had emerged as superior for styrene for a collection of derivatives. As shown in Table 2, the reaction provided exclusive formation of the corresponding  $\beta$ -carboxylated products with good to excellent mono/di carboxylation selectivity. A range of electron-rich and electron-neutral substituents on styrene (**1a-1i**) were tolerated in moderate to good yields. Notably, phenol (**1g**) and benzylic alcohol **1h** provided moderate yields of the desired products without additional protection/deprotection steps. Electron-deficient styrene **1j** was also transformed to the corresponding product in good yield. Alkene-substituted heterocycles, including an indole and benzofuran, furnished the respective hydrocarboxylated compounds in moderate yields (**2k** and **2l**).

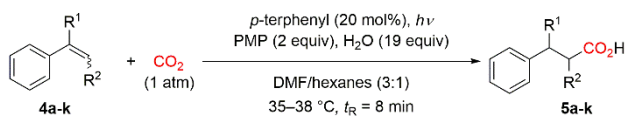
This reaction also tolerates more substituted  $\alpha$ -substituted and  $\beta$ -substituted styrenes, providing  $\beta$ -selective hydrocarboxylated products (Table 3). In the case of  $\alpha$ -substituted styrenes **4a-e**, the corresponding monocarboxylated products **5a-e** were produced exclusively. The reaction also performed well with both *trans*- and *cis*- $\beta$ -substituted styrenes (**5f-k**). Notably, allylic alcohol and Boc-protected allylic amine were likewise tolerated to provide  $\beta$ -hydroxy acid **5g** and protected  $\beta$ -amino acid **5h**, respectively. However, more sterically demanding  $\beta,\beta$ -disubstituted

**Table 2. Scope of terminal styrenes.<sup>a</sup>**

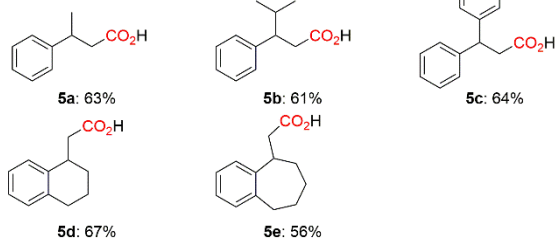


<sup>a</sup>Isolated yield of the monocarboxylated product. Ratio of mono/di carboxylated product determined by <sup>1</sup>H NMR. See Supporting Information for details.

**Table 3. Scope of  $\alpha$ -substituted and  $\beta$ -substituted styrenes.<sup>a</sup>**

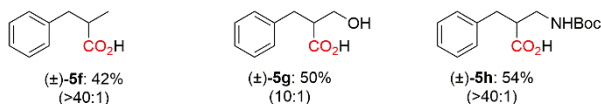


From  $\alpha$ -substituted styrenes ( $R^2 = H$ )

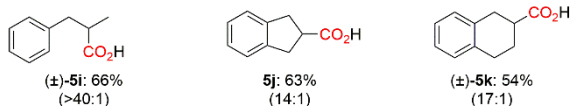


From  $\beta$ -substituted styrenes ( $R^1 = H$ )

Trans:



Cis:



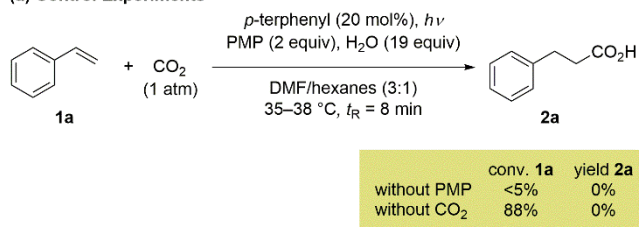
<sup>a</sup>Isolated yield of the monocarboxylated product. Ratio of mono/di carboxylated product determined by <sup>1</sup>H NMR. See Supporting Information for details.

styrenes were not reactive under these conditions.

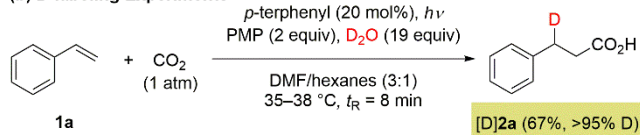
Preliminary studies provide some insight into the mechanism of the reaction. First, control experiments conducted in the absence of PMP did not provide any product, emphasizing its crucial role in the reaction [Scheme 3(a)]. Second, in the absence of CO<sub>2</sub> under otherwise optimized conditions, styrene conversion was 88% and ethylbenzene was detected. Given that the reduction potential of styrene is  $E_{1/2} = -2.58$  V vs SCE in DMF,<sup>11</sup> its direct reduction by the radical anion of *p*-terphenyl ( $E^0 = -2.63$  V vs SCE in DMF)<sup>10</sup> is reasonable. Alternatively, when CO<sub>2</sub> ( $E^0 = -2.21$  V vs SCE in DMF)<sup>12</sup> was present in the reaction, ethylbenzene was not observed. Although further studies are warranted, a mechanism involving the initial formation of a CO<sub>2</sub> radical anion remains feasible.<sup>13, 14</sup> Third, replacing H<sub>2</sub>O with D<sub>2</sub>O led to the near exclusive formation of the deuterated product [D]2a [Scheme 3(b)] as determined by <sup>1</sup>H NMR spectroscopy. This suggests that the reaction involves the reduction and then protonation of a benzylic radical intermediate by water.

### Scheme 3. Preliminary mechanistic investigations.

#### (a) Control Experiments



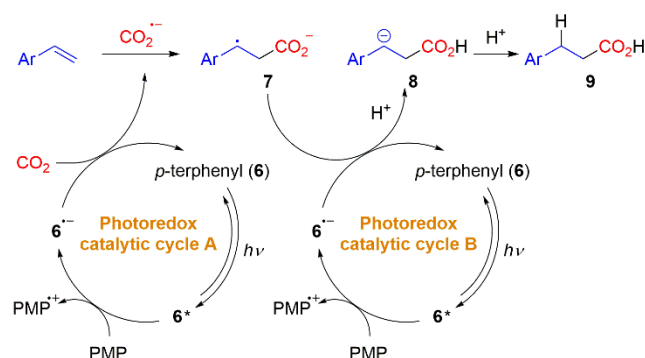
#### (b) D-labeling Experiments



Based on these results, we propose a mechanism summarized in Scheme 4. Photoexcitation of the organic photoredox catalyst, *p*-terphenyl (**6**), produces the excited singlet state of *p*-terphenyl (**6**<sup>\*</sup>), which undergoes single electron transfer (SET) with PMP to provide the strong reductant *p*-terphenyl radical anion (**6**<sup>•-</sup>) and the PMP radical cation (Photoredox catalytic cycle A).<sup>8</sup> This SET step is supported by Stern-Volmer luminescence quenching experiments (see Supporting Information). The *p*-terphenyl radical anion (**6**<sup>•-</sup>) would reduce CO<sub>2</sub> to its radical anion. The CO<sub>2</sub> radical anion then adds to the  $\beta$ -position of styrene and produces a stable benzylic radical intermediate **7**. As the reduction potentials of benzylic radicals with various substituents on the aromatic ring have been reported in range of  $-1.82$  V to  $-0.71$  V vs SCE in acetonitrile,<sup>15</sup> the benzylic radical **7** would be further reduced to the benzylic anion **8** by photoredox catalytic cycle B. Since the benzylic radical **7** can be reduced to the anion **8**, the hydrocarboxylation of styrenes was successful without the competing polymerization.<sup>16</sup> Finally, the hydrocarboxylated product **9** is formed by a protonation of the benzylic anion **8**. The formation of the dicarboxylated byproduct **3a** is explained by the trapping of CO<sub>2</sub> by anion **8** (Figure S11). The sterically hindered PMP radical cation is then quenched by dimerization after the deprotonation.

In summary, the direct  $\beta$ -selective hydrocarboxylation of styrenes under atmospheric pressure of CO<sub>2</sub> with PMP as a reductant was developed using photoredox catalysis in continuous flow. This method has been shown to be compatible with a range of styrene derivatives with a variety of functional groups, along with  $\alpha$ -substituted and  $\beta$ -substituted styrenes.

#### Scheme 4. Proposed mechanism.



#### ASSOCIATED CONTENT

##### Supporting Information

The Supporting information is available free of charge on the ACS Publications website at DOI:

Experimental details and compound characterizations (PDF)

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##### Notes

The authors declare no competing financial interest.

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(14) Although the experimental observations are consistent with a mechanism that proceeds through the initial formation of CO<sub>2</sub> radical anion, we cannot rule out the possibility of involving a styrene radical anion and homogeneous charge transfer to CO<sub>2</sub> at this time. For discussions on mechanisms of electrochemical carboxylation of styrene, See: (a) Gambino, S.; Gennaro, A.; Filardo, G.; Silvestri, G.; Vianello, E. *J. Electrochem. Soc.* **1987**, *134*, 2172. (b) Matthesen, R.; Fransær, J.; Binnemans, K.; De Vos, D. E. *Beilstein J. Org. Chem.* **2014**, *10*, 2484.

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