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Photocatalyzed, β -Selective Hydrocarboxylation of α , β -Unsaturated Esters with CO₂ under Flow for β -Lactone Synthesis

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employing CO₂ radical anion generated under flow conditions was developed. A range of substrates bearing a variety of functional groups were tolerated, demonstrating chemoselectivity. A series of quaternary carboxylic acids were obtained from sterically demanding $\beta_{j}\beta_{j}$ -disubstituted alkenes including those derived from natural products. Mechanistic studies support a Giese-type CO₂ radical anion conjugate addition followed by hydrogen atom transfer from (TMS)₃SiH as the principal reaction pathway. Finally, a telescoped process involving the described β -carboxylation followed by a α -bromination/ β -lactonization sequence provides a strategy for β -lactone synthesis.



KEYWORDS: photocatalysis, CO_{2} , β -lactonization, flow chemistry, natural product derivatization, Giese-type radical addition

1. INTRODUCTION

 β -Lactones are versatile synthetic intermediates¹ and useful probes for activity-based proteome profiling.² Furthermore, covalent modifiers of proteins, including β -lactones (e.g., tetrahydrolipstatin), are an enduring source of drug leads and have recently experienced a resurgence.³ Our group's continued interest in β -lactone synthesis,⁴ led us to consider what arguably might be the ideal and possibly most versatile synthesis of β -lactones, namely addition of CO₂ to alkenes. Despite the obvious unfavorable thermodynamics of the direct process, we reasoned that a stepwise strategy might be feasible. Specifically, we considered a β -selective hydrocarboxylation of electron-deficient alkenes (EWG = electron-withdrawing group, e.g., ester) followed by an α -bromination/ β -lactonization sequence leading to β -lactones that has now been put into practice as described herein (Scheme 1).

Scheme 1. Stepwise Synthesis of β -Lactones from Alkenes Involving Alkene Hydrocarboxylation



The hydrocarboxylation of alkenes was first described by Lapidus in 1978, leading to a remarkable synthesis of propionic acid from ethylene and CO₂ employing heterogeneous Rh and Pd catalysts.⁵ Subsequently, Hoberg employed stoichiometric Ni(0) for this transformation.⁶ More recently, several methods for transition-metal-catalyzed hydrocarboxylation of terminal alkenes and disubstituted alkenes were described. Most frequently, these methods employed styrene and derivatives as substrates and included use of Ni(II),⁷ Fe(III),⁸ Fe(III),⁸

Rh(I),¹⁰ Ru(0),¹¹ Ti(IV),¹² and Co(II)¹³ catalysts, leading to varying degrees of linear versus branched selectivities. Electron-deficient alkene substrates gave almost exclusively α carboxylated products, presumably because of the stability of the α -metalated (enolate) intermediate (Scheme 2a).^{16a,13} Electrochemical hydrocarboxylation of electron-deficient alkenes were also recently described employing cinnamate esters,¹⁵ cinnamonitriles,¹⁶ flavones,¹⁷ and bicycloalkylidene derivatives¹⁸ as substrates. The proposed mechanism for the majority of these hydrocarboxylations involve alkene reduction followed by electrophilic addition of CO₂ to ultimately generate either mono-carboxylated products or a mixture of mono- and di-carboxylated adducts (Scheme 2b). Very recently, a synergistic photo- and electrochemical catalytic strategy was developed for the β -selective hydrocarboxylation of enones; however, the substrates were restricted to chalcones.¹⁹ Additionally, a Mg-promoted hydrocarboxylation of ethyl cinnamates was reported, providing a mixture of β carboxylated and α_{β} -dicarboxylated products, which following α -decarboxylation and esterification delivered succinate esters.²⁰

In 2017, Iwasawa described the first photochemical hydrocarboxylation of α_{β} -unsaturated carbonyl compounds through the combination of a Rh(I) catalyst and a photocatalyst, leading exclusively to α -carboxylated products (Scheme 2c).²¹ Within a short time, successful methods for

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Scheme 2. Hydrocarboxylation of Electron-Deficient Alkenes



the hydrocarboxylation of alkenes were developed by König,²² Martin,²³ Jamison,²⁴ Yu,²⁵ and Wu.²⁶ Inspired by the use of *p*-terphenyl (1,4-diphenyl benzene) for the reduction of CO₂ to the corresponding radical anion²⁷ under flow conditions,²⁴ we now report the first photocatalyzed, β -selective hydrocarboxylation of α , β -unsaturated esters employing CO₂ under flow conditions. We envisioned the development of a Giese-type addition of the radical anion of CO₂ to an electron-deficient alkene followed by quenching of the resultant α -radical with a hydrogen atom or protonation of the resultant enolate following further reduction. Furthermore, we sought to utilize this process in a telescoped synthesis of β -lactones through a subsequent halogenation- β -lactonization sequence (Scheme 2d).

2. DISCUSSION

We utilized a photochemical flow reactor since increased surface area enables more efficient irradiation of catalyst compared to a batch reactor, leading to shorter reaction times and facile scale-up (Figure 1).²⁸ A tube-in-tube reactor was employed to more efficiently deliver CO_2 (6 bar) to the liquid



Figure 1. Schematic of flow hydrocarboxylation reaction set up including CO_2 (6 bar) inlet, a tube-in-tube reactor with Teflon AF-2400 inner tube and polytetrafluoroethylene (PTFE) outer tube (gastropod), a 10 mL photoreactor maintained at 35 °C, a backpressure regulator set to 4 bar, and a final acidic quench (3 M HCl).

flow stream (substrate in DMF, 0.1M) and form a homogeneous reaction solution in a controlled manner.²⁹ A 10 mL photoreactor was employed for UV excitation (220–400 nM, 105 W). The reaction temperature was maintained at 35 °C during photoexcitation with a total resident time (t_R) of 10 min (Table 1). A back-pressure regulator maintained the flow reactor pressure to 4 bar.

Table 1. Optimization of the Hydrocarboxylation of α_{β} -Unsaturated Esters^{*a*}

Ph	★ CO ₂ Me + CO ₂ 1a	<i>p</i> -terphenyl (20 2 (2.0 equiv) H• source (2.0 e DMF, t _R = 10 Flow rate: 1.0 e	mol %) hv equiv) min nL/min CO ₂ H CO ₂ H CO ₂ H Sa 3a	CO ₂ Me
entry	R (2)	conc. 1a [M]	H^{\bullet} or H^{+} source	yield 3a (%) ^b
1	methyl(2a)	0.1	H ₂ O	ND ^c
2	ethyl (2b)	0.1	H ₂ O	19
3	"	0.1	BHT	16
4	"	0.1	Ph ₃ SiH	17
5	"	0.1	(TMS) ₃ SiH	61
6	<i>i</i> -butyl (2c)	0.1	"	40
7	hexyl (2d)	0.1	"	58
8	ethyl	0.05	"	66
9 ^d	"	0.05	ű	71
10 ^{<i>d,e</i>}	**	0.05	ű	73
$11^{d,e,f}$	<i>cc</i>	0.05	ű	66

"Unless otherwise noted, all reactions were performed with alkene **1a** (1.0 equiv), *p*-terphenyl (20 mol %), amine **2** (2.0 equiv) in DMF (0.05 M, initial alkene concentration) with 105 W UV light, a flow rate of 1.0 mL/min, and the reaction mixture was degassed by several freeze–pump–thaw cycles prior to initiation. ^bYields refer to isolated, purified carboxylic acid **3a**. ^cReaction led to clogged tubing. ^dFreeze–pump thaw was not applied. ^eFlow rate was decreased to 0.5 mL/min. ^JSubstoichiometric amount (0.3 equiv) of amine **2b** was employed. (ND = not determined).

Our hydrocarboxylation studies were initiated with a simple α_{β} -unsaturated ester 1a (Table 1). Building on studies by Jamison,²⁴ we used *p*-terphenyl as photocatalyst and 1-methyl-2,2,6,6-tetramethylpiperidine (PMP, 2a) as electron donor and water as a proton source. Our first reaction under these conditions did not provide any product as it led to clogging of the line likely because of formation of PMP-dimer as previously noted by Jamison²⁴ (entry 1). We reasoned that a bulkier N-alkyl group may prevent dimerization, thus we explored the *N*-Et piperidine analogue,³⁰ and this indeed led to 19% yield of the desired carboxylic acid 3a. Different hydrogen atom sources including Ph₃SiH and 2,6-di-t-butyl-4-methyl phenol (BHT) did not lead to improvements (entries 3, 4); however, use of the bulky hydrogen atom donor, (TMS)₃SiH, led to a significant increase in yield (61%, Table 1, entry 5). To determine if larger N-alkyl groups provided any further improvement, we also synthesized N-i-butyl piperidine 2c and N-hexyl piperidine 2d;³⁰ however, this led to no further improvements (entries 6, 7). Reducing the substrate concentration to 0.05 M led to a slight increase in yield (66%, entry 8). Control experiments indicated that freezepump-thaw cycles were unnecessary, leading to comparable yields (entry 9). Decreasing the flow rate to 0.5 mL/min furnished the carboxylic acid in 73% yield (entry 10). Interestingly, substoichiometric amounts of amine 2b gave 66% yield (see Table S1 for additional optimization studies).

With optimized conditions in hand, we explored several $\alpha_{,\beta}$ unsaturated ester substrates along with nitriles and ketones (Table 2). Substrates **1a**-**x** for hydrocarboxylation were

Table 2. Photocatalyzed, β -Selective Hydrocarboxylation of Electron-Deficient Alkenes with CO₂ under Flow Conditions^{*a*}



^{*a*}Unless otherwise noted, all reactions were performed with alkene (1.0 equiv, 0.05 M), *p*-terphenyl (20 mol %), amine **2** (2.0 equiv) in DMF under 105 W UV light. If diastereomers were produced, only the major diastereomer is shown. Yields refer to purified, isolated products (as mixtures of diastereomers when produced). ^{*b*}Substoichiometric amounts (0.3 equiv) of amine **2b** was employed. ^{*c*}More intense UV light (148.5W) was used. ^{*d*}Flow rate was reduced to 0.2 mL/min. ^{*e*}(TMS)₃SiH was omitted. ^{*f*}The reaction mixture was degassed by a freeze–pump–thaw, and 1.0 equiv of MgBr₂·Et₂O was added at a flow rate of 1.0 mL/min. ^{*g*}0.025[M] concentration was applied.

prepared by standard methods from aldehydes or ketones (see SI for details). Use of β -substituted and $\alpha_{\beta}\beta$ -disubstituted unsaturated esters provided the β -carboxylated adducts 3a-3cin 68-73% yields. In the case of 1-carbomethoxy cyclohexene (1c), carboxylic acid 3c was obtained as a 5:1 mixture of diastereomers with the major diastereomer possessing *syn* relative stereochemistry. Sterically demanding β , β -disubstituted alkenes are recalcitrant substrates for regioselective hydrocarboxylation, and most methods are limited to terminal or disubstituted alkenes.³¹ This transformation would deliver α -quaternary carboxylic acids; however, to our knowledge, there are no reports of photocatalyzed hydrocarboxylation of β , β -disubstituted alkenes. Under the optimized conditions, exocyclic enoates on carbocyclic rings ranging in size from 4 to 12 reacted efficiently to deliver guaternary carboxylic acids 3e-3h in yields ranging from 53 to 87%. In the case of carboxylic acid 3f (dr 2:1), the relative stereochemistry of the major diastereomer was verified to be syn by X-ray analysis (see SI for details). Acyclic $\beta_{,\beta}$ -disubstituted alkenes also participated, including one bearing a bulky γ -adamantyl group, to furnish the quaternary carboxylic acids 3d and 3i in 43-49% vield. Notably, by extending the irradiation time through reducing the flow rate to 0.2 mL/min and increasing light intensity (148.5 W), a tetra-substituted alkene 1i also delivered quarternary carboxylic acid 3j in 50% yield. $\alpha_{,\beta}$ -Unsaturated nitriles and enones also gave the desired β -carboxylated products 3l-n albeit in moderate yield with the ketone requiring addition of MgBr₂·OEt₂. We also studied the compatibility of this reaction with several functional groups, and several were found to be compatible with the reaction, including carbamates, cyanide, chloride, hydroxyl, silylether, ketone, alkene, cyclopropane, and an additional ethyl ester, providing the corresponding carboxylic acids 30-3v in 38-84% yield (aqua, Table 2). Moreover, β , β -disubstituted alkene substrates derived from the natural products aromadendrene and cholestanol afforded quaternary carboxylic acids 3w and 3x in 53% and 84% yield, respectively, with moderate diastereoselectivity. Finally, we verified that substoichiometric amounts of amine 2 (0.3 equiv) in conjunction with a slower flow rate (0.2 mL/min) could be employed with minor impact on yield in the case of carboxylic acids 3a, 3c, 3f, 3t (57-86% vields).

Toward our primary and overall goal of synthesizing β lactones from alkenes, we investigated the α -halogenation β lactonization with carboxylic acid **3g** as the model substrate. We began with conditions previously employed in a synthesis of belactosin A.³² However, only 36% of the corresponding β lactone was obtained (Table 3, entry 1). Building on

Table 3. Optimization of the α -Halogenation- β -Lactonization

но	3g	iHMDS (2.1 equiv) en source X (1.5 equiv) THF, T °C 4f	-CO ₂ Me	Br 3g'
entry	х	additives	$T(^{\circ}C)$	4f (yield%)
1 ^{<i>a</i>}	CCl_4	Et ₂ O/5% NaHCO ₃	-78→23	36
2	Br₂·dioxane	sat Na ₂ S ₂ O ₃	23	38
3 ^b	Br₂·dioxane	sat Na ₂ S ₂ O ₃	23	53
4 ⁶	Br ₂ ·dioxane	sat Na ₂ S ₂ O ₃	$-78 \rightarrow 23$	65
5 ^b	Br ₂ ·dioxane	Et ₂ O/1% NaHCO ₃	$-78 \rightarrow 23$	80

^{*a*}2.4 equiv of LiHMDS and 1.2 equiv of CCl₄ were used following the reported procedure. ^{*b*}The *in situ* generated enolate mixture was added to the halogen source in THF.

conditions reported for α -bromination of alkyl sulfones with Br_2 ·dioxane,³³ we studied the α -bromination of the dianion with this brominating agent initially under batch conditions. Direct β -lactonization was attempted with the crude α -bromoacid obtained following hydroxycarboxylation. Thus, bromination followed by addition of sat. $Na_2S_2O_3$ to the crude reaction mixture to reduce excess bromine while also enabling ion exchange from Na^+ to Li^+ in intermediate 3g' in order to facilitate β -lactone formation, gave 38% yield of the β -lactone.

Next, the bromination was attempted with an in situ generated enolate and addition to a bromine/THF solution (inverse addition), in efforts to minimize the reaction between the enolate and α -bromo ester.³⁴ This delivered the β -lactone with a significant increase in yield (Table 3, entry 3). Lowering the temperature for both enolate formation and bromination steps further increased the yield to 65%. Using a biphasic ether/ NaHCO₃ solvent mixture as described by Barlaam³⁵ to remove bromide ion from the ether phase which presumably avoids β lactone ring cleavage gave the best yield (80%) (Table 3, entry 5). Next, we studied a telescoped process involving the described hydrocarboxylation and direct α -bromination/ β lactonization without purification of the intermediate carboxylic acid. After extensive experimentation, optimal conditions involved addition of an aqueous HCl solution to the crude hydroxcarboxylation product and vigorous extraction with EtOAc (see SI for details). The latter was found to be the key for the success of this telescoped sequence since it ensured complete recovery of the carboxylic acid product and also removed byproducts. Without extraction, no β -lactone was generated. An *in situ* IR experiment verified that significant β lactonization did not occur directly upon α -bromination by the pendant lithium carboxylate but rather only after addition of 1% aq. NaHCO₃ solution enabling ion exchange (see Figure S1 for further details). This suggests the importance of the carboxylate counterion and the faster rate of β -lactonization with a sodium carboxylate versus a lithium carboxylate.

Utilizing the optimized conditions, a series of β -lactones, including bicyclic β -lactones and spiro β -lactones **4a**-**f** were prepared without purification of intermediates through this telescoped β -selective hydrocarboxylation/ α -bromination/ β -lactonization sequence (Table 4). A trisubstituted alkene

Table 4. Synthesis of β -Lactones 4 via a Telescoped Hydrocarboxylation $-\alpha$ -Bromination $-\beta$ -Lactonization Sequence



^{*a*}Overall yield for stepwise process involving purification of the intermediate β -carboxy ester.

derived from cholestanol provided spiro β -lactone **4h** as a 1:1 mixture of diastereomers. In this case, and also with substrates leading to β -lactones **4d** and **4h** (major diastereomer verified by X-ray analysis, see SI), higher yields were obtained through a stepwise process wherein the intermediate hydrocarboxylation product was isolated and subjected to α -bromination/ β -lactonization. However, in other cases, higher or comparable yields (e.g., β -lactone **4f**) were obtained through the telescoped process.

A series of experiments were performed to shed light on a possible mechanism for the described hydrocarboxylation

focused on providing evidence for the expected initial Giesetype radical addition of CO₂ radical anion. However, several mechanistic pathways were considered on the basis of related reactions^{17a,24,36} and the reaction conditions utilized in the current method. Considering the reduction potential of β substituted unsaturated esters (e.g., methyl crotonate $E_{1/2}$ = -2.33 V vs SCE in DMF)³⁷ and CO₂ ($E^0 = -2.21$ V vs SCE in DMF),³⁸ both species can be reduced by the utilized pterphenyl catalytic system ($E^0 = -2.63$ V vs SCE in DMF). However, on the basis of these reduction potentials, CO₂ is expected to be reduced faster. Pathway A involves initial reduction of the unsaturated ester to radical enolate II and further reduction to deliver the dianion III. This highly nucleophilic intermediate could capture CO₂ and deliver the carboxylate enolate IV which can be protonated to provide carboxylate VII (Scheme 3a). Alternatively, reduction of CO₂

Scheme 3. Possible Mechanistic Pathways for the Hydrocarboxylation



to the radical anion V followed by a Giese-type conjugate addition⁴⁰ leads to the radical carboxylate VI that is either reduced to an enolate and then protonated or captured by a hydrogen atom to more directly arrive at the carboxylated adduct VII (Scheme 3b).

Several control experiments were conducted to verify the importance of each reagent (Table 5). Omitting the addition

Table 5. Control Experiments for the Hydrocarboxylation^a

Ph 1a	SCO2Me	p-terphen 2b (2.0 d (TMS) ₃ Sil DMF, (<i>hv</i> , 20 min	VI (20 mol%) equiv), CO2 H (2.0 equiv) D.05 [M] I, 0.5 mL/min	Ph	CO ₂ H CO ₂ H 3a Ph	Me + Ph-	Si(TMS) ₃ CO ₂ Me 5 D ₂ Me
entry	omitted	reagent	3a (% yi	eld) ^b	5 (% yi	eld) ^b	6 (% yield) ^b
1	UV light		0		0		0
2	p-terphenyl		0		0		0
3	amine		0	0 0			0
4	CO_2		0		28		21
5	(TMS) ₃ SiH		23	23			0
ar-	c. 1:a.			l no o oti		a manf	

^aExcept for differences noted, all reactions were performed under optimized conditions. ^bRefers to isolated, purified yields.

of UV light, *p*-terphenyl, and the amine led to no products (Table 5, entries 1–3). In the absence of CO_2 , silane 5 was isolated in 28% yield, suggesting an operative background hydrosilylation presumably proceeding through Giese-type addition of tris-trimethylsilane radical (Table 5, entry 4). In addition, 21% of the reduced unsaturated ester, methyl-5-phenyl pentanoate (6), was also isolated indicating a competitive reduction through electron transfer. On the other hand, omitting (TMS)₃SiH led exclusively to carboxylic acid 3a, albeit in greatly reduced yield (23% vs 73%, Table 5, entry 5), indicating the importance of the silane as a hydrogen

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atom donor for conversion of radical VI to carboxylate VII or alternatively, other proton sources for conversion to the same intermediate VII following reduction to carboxylate dianion IV (Scheme 3).

To ascertain the possibility of initial reduction of the α , β unsaturated ester, a radical clock experiment⁴¹ employing methyl (*E*)-3-cyclopropyl acrylate (**1**y) was conducted, resulting in 49% of the cyclopropyl β -carboxylated adduct **3**y with no evidence of cyclopropane ring opening (Scheme 4).

Scheme 4. A Radical-Clock Reaction



This result and the aforementioned reduction potentials of β substituted unsaturated esters compared with CO₂,^{36,37} coupled with the high concentration of CO₂ in the reaction mixture achieved by use of the tube-in-tube reactor and flow reactor, leads us to propose initial CO₂ reduction to the radical anion (**V**, Scheme 3b, pathway B). Furthermore, erosion of diastereoselectivity (from 1:2 to 1:1 dr) during the hydrocarboxylation leading to acid **3f** in the absence of silane (see SI for details) and the complete lack of diastereoselectivity observed in formation of acid **3u** (Table 2) both support an initial, reversible Giese-type addition of CO₂ radical anion (Scheme 3b).

Toward understanding the origin of hydrogen atoms or protons in the hydrocarboxylation products, a series of deuterium trapping experiments were performed with unsaturated ester 1g (Table 6). Use of $(TMS)_3SiD^{42}$ led to a 64%

Table 6. Det	uterium Tr	apping E	xperiments
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ζ	CO ₂ Me + CC	p-terphenyl (20 amine 2t (TMS) ₃ SiH DMF, 0.05 hυ, 20 min, 0.5	mol %) HO ₂ (H(D) [M] mL/min	H 2 CO ₂ Me 3g	D(H) D(H) D ₂ -2b	
entry	2b (equiv) ^a	(TMS)3SiH (equiv)	D_2 - 2b (equiv)	(TMS) ₃ SiD (equiv)	yield (%)	%D
1	2.0	0	0	2.0	64	56
2	0	0	2.0	0	35	17
3	0	0	2.0	2.0	55	65
4 ^{<i>a</i>}	2.0	0	0	0	35	55
5	0	2.0	2.0	0	64	4
6	0.3	0	0	2.0	37	72
^{<i>a</i>} 2.0 e	quiv of D ₂	O was added.				

yield of the β -carboxylated product with 56% deuterium incorporation at C2 of adduct **3g** as determined by ¹H NMR integration (Table 6, entry 1). This provides evidence that (TMS)₃SiH is the principal source of hydrogen atoms and furthermore suggests the intermediacy of the α -radical **VI** (Scheme 3). When the deuterated amine D₂-**2b** was employed without (TMS)₃SiH, 17% deuterium incorporation was observed at C2 suggesting the role of amine **2b** as a secondary proton source (Table 6, entry 2). If both deuterated amine D₂-**2b** and (TMS)₃SiD were employed, 65% D-incorporation was observed at C2 in adduct **3g** as expected. However, this result suggests the presence of other proton and hydrogen sources including adventitious H_2O (Table 6, entry 3). To address the possibility that enolate IV could be an intermediate, we next studied the impact of adding D_2O . If (TMS)₃SiH was replaced with D_2O , this indeed led to 55% deuterium incorporation at C2 of acid 3g (Table 6, entry 4). This result suggests that H_2O can serve as a proton source and supports the intermediacy of enolate IV, which likely results from competitive reduction of radical intermediate VI. Finally, use of deuterated amine D_2 -2b with (TMS)₃SiH led to only 4% D-incorporation at C2 suggesting that, under our optimized conditions, (TMS)₃SiH is the major source of C2-hydrogen atoms (Table 6, entry 5). Once again, substoichiometric amounts of amine (0.3 equiv) could be employed with 2.0 equiv of (TMS)₃SiD, leading to 72% deuterium incorporation and importantly indicating turnover of the amine (Table 6, entry 6).

Taking into account all our observations to date, we propose that the hydrocarboxylation does indeed primarily proceed through a Giese-type addition of CO_2 radical anion requiring only substoichiometric amounts of the amine, *p*-terphenyl (Scheme 5). Photoexcitation of the photocatalyst, *p*-terphenyl

Scheme 5. Proposed Mechanisms for the Hydrocarboxylation



(X), generates the excited singlet state of p-terphenyl* (XI), which undergoes single electron transfer with amine 2b to afford the reduced *p*-terphenyl radical anion XII^{24} and the radical cation IX. The p-terphenyl radical anion XII then reduces CO₂ to CO₂ radical anion V, initiating a Giese-type addition to the α , β -unsaturated ester to produce radical anion VI. Subsequent trapping with a hydrogen atom from (TMS)₃SiH affords the carboxylate VII (Scheme 5, route a). Since radical anion VI has a lower reduction potential than the starting unsaturated ester I,³⁶ it can also be reduced to dianion IV, which can be protonated to also deliver carboxylate VII (Scheme 5, route b). A comparison of the deuterium trapping experiments of entries 1, 2, and 5 in Table 6 indicates that "route a" is the dominant pathway. The amine radical cation IX could also serve as a proton source, as indicated by deuterium studies, to form the carbon radical VIII, which then regenerates the amine by abstracting a hydrogen atom from $(TMS)_3SiH.$

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3. CONCLUSIONS

In summary, the first photocatalyzed, β -selective hydrocarboxylation of α_{β} -unsaturated esters is reported employing CO₂ under flow conditions. A range of unsaturated esters bearing various functional groups are compatible with this methodology. Notably, sterically demanding β , β -disubstituted alkenes also participate in this reaction, providing a series of quaternary carboxylic acids with serviceable yields. Furthermore, a telescoped synthesis of β -lactones was realized from α,β -unsaturated esters involving the hydrocarboxylation as a key step followed by α -bromination and β -lactonization. Mechanistic studies point to a Giese-type addition of CO₂ radical anion followed by capture with (TMS)₃SiH as the principal reaction pathway. Alternatively, reduction of the incipient radical leads to an enolate which can be captured by various proton sources present in the reaction mixture; however, this appears to be a minor pathway because of rapid capture of the radical by (TMS)₃SiH. Further applications of the described telescoped route to β -lactones and extension to additional alkenes is underway in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05050.

Experimental procedures including further optimization studies of the hydrocarboxylation (Table S2), control experiments (Table S3), X-ray diffraction, and compound characterization (PDF)

Crystallographic data for 3f (CIF)

Crystallographic data for 3p (CIF)

Crystallographic data for 4h (CIF)

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Notes

The authors declare no competing financial interest.

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