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Visible-Light-Driven, Metal-Free Divergent Difunctionalization of Alkenes Using Alkyl Formates

Ming Zheng, Jing Hou,* Le-Wu Zhan, Yan Huang, Ling Chen, Li-Li Hua, Yan Li, Wan-Ying Tang, and Bin-Dong Li*

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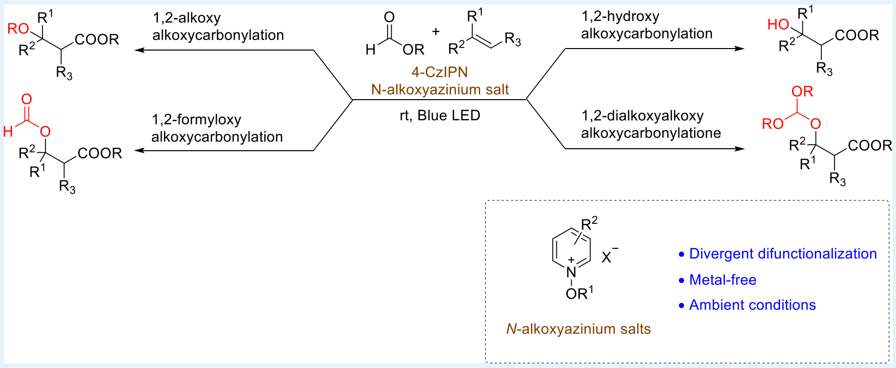

ABSTRACT: In recent decades, difunctionalization of alkenes has received considerable attention as an efficient and straightforward way to increase molecular complexity. However, examples of the difunctionalization of alkenes initiated by the intermolecular addition of alkoxycarbonyl radicals providing substituted alkanoates are still rare. Herein, we present the visible light-driven metal-free divergent difunctionalization of alkenes triggered by the intermolecular addition of alkoxycarbonyl radicals under ambient conditions. Employing alkyl formates as precursors of alkoxycarbonyl radicals and 4CzIPN as the photocatalyst, a variety of substituted alkanoates, including β-alkoxy, β-hydroxy, β-dimethoxymethoxy, and β-formyloxy alkanoates, could be facilely accessed with high functional group tolerance and high efficiency. Moreover, the mechanism study revealed that β-hydroxy alkanoates were generated by a selective decomposition of orthoformates promoted by the *N*-alkoxyazinium salt.

KEYWORDS: *difunctionalization, alkoxycarbonyl radicals, visible light-driven, alkyl formats, alkanoates, N-alkoxyazinium salt*

■ INTRODUCTION

Difunctionalization of alkenes represents an efficient and straightforward strategy that allows for the rapid buildup of molecular complexity.[1] Alkene difunctionalization initiated by the addition of alkoxycarbonyl radicals is a particularly intriguing transformation that simultaneously introduces an ester group and constructs another C−C or C−X bond.[1b] Although alkene functionalization through the intramolecular addition of alkoxycarbonyl radicals to alkenes is relatively well known,[2] examples of the alkene difunctionalization triggered in an intermolecular fashion are still limited because of the rapid decarboxylation of alkoxycarbonyl radicals.[3] In 2010, 1,2-hydroxy alkoxycarbonylation of alkenes was disclosed by Taniguchi and co-workers using an iron catalyst and carbazates as precursors of alkoxycarbonyl radicals (Figure 1a).[4] Later, several other groups reported studies on the generation of alkoxycarbonyl radicals using the same strategy.[5] Nevertheless, more readily available precursors and efficient activation patterns are highly desirable.

Methyl formate, an important commodity chemical that can be generated from the hydrogenation of carbon dioxide,[6] is an ideal and green C1 source.[7] Abstracting the hydrogen from methyl formate [bond dissociation energy of MeOC(O)−H, 97.2 kcal/mol][8] using an alkoxy radical to provide the methoxycarbonyl radical (bond dissociation energy of RO−H bonds, 105 kcal/mol)[9] was admirably achieved by the Urry group in 1953.[10] Recently, Zhu and co-workers demonstrated an elegant copper-catalyzed 1,2-alkoxy methoxycarbonylation of styrenes employing methyl formate as the methoxycarbonyl radical precursor via the oxygen radical derived from di-*tert*-butylperoxide-promoted hydrogen atom transfer (HAT) (Figure 1b).[11] However, the transition-metal catalyst and

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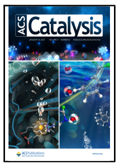

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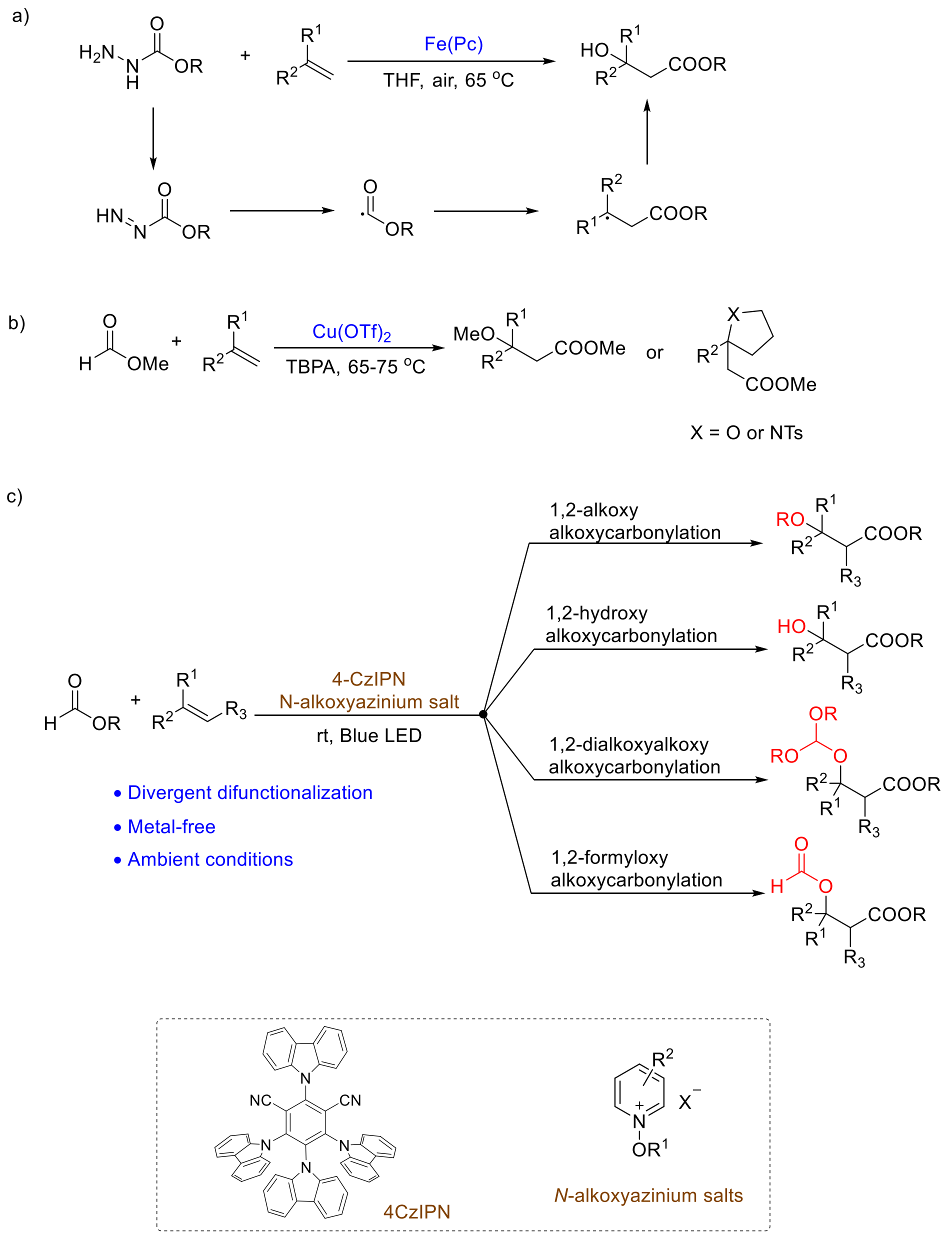
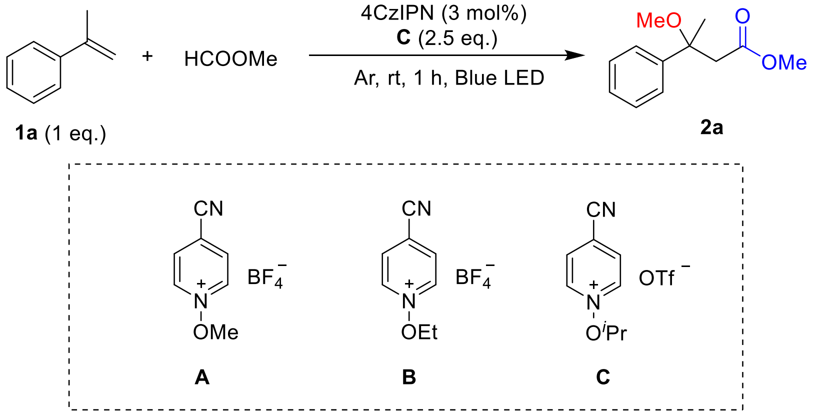


Figure 1. Difunctionalization of alkenes initiated by the intermolecular addition of alkoxycarbonyl radicals. (a) Iron-catalyzed alkene 1,2-hydroxy alkoxycarbonylation with carbazates (ref 4). (b) Copper-catalyzed alkene 1,2-alkoxy methoxycarbonylation with methyl formate (ref 11). (c) Visible-light-driven metal-free alkene difunctionalization with alkyl formate (this work).

elevated temperature were necessary. Moreover, molecular motifs accessible by the reported protocol are limited, and only terminal alkenes afforded the desired products. Thus, the development of a metal-free divergent difunctionalization of alkene approach using alkyl formates as the alkoxycarbonyl radical precursors under ambient conditions would present an unprecedented opportunity for the rapid construction of a variety of substituted alkanoates.

Recently, the light-driven generation of highly reactive alkoxy radical intermediates has received considerable attention.[12] Photocatalytic reduction of *N*-alkoxyazinium salts is a facile way to generate alkoxy radicals, and this strategy has been recently used in synthetic applications.[13] Lakhdar group[14] reported a P−H functionalization reaction of secondary phosphine oxides, Zhu group[15] reported remoted C(sp^3)−H functionalization, and Hong group[16] demonstrated the pyridylation of C(sp^3)−H bonds and alkenes with *N*-alkoxyazinium salts as alkoxy radical precursors. The direct addition of alkoxy radicals to alkenes was disclosed by Dagousset and co-workers.[17] Inspired by these advances, we envisioned that alkoxy radicals from the photocatalytic reduction of *N*-alkoxyazinium salts could be used for the generation of alkoxycarbonyl radicals from alkyl formates. This strategy may provide opportunities to realize the difunctionalization of alkenes to access carbonylation products under ambient conditions. Herein, we describe a visible light-driven divergent difunctionalization of alkenes with alkyl formates and *N*-alkoxyazinium salts, affording a series of *β*-alkoxy, *β*-hydroxy, *β*-dialkoxyalkoxy, and *β*-formyloxy alkanoates (Figure 1c).

Table 1. Optimization of 1,2-Methoxy Methoxycarbonylation of α-Methyl Styrene[a]



entry	deviation	yield[b] (%)
1	none	80
2	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4CzIPN	62
3	$Ru(bpy)_3Cl_2$ instead of 4CzIPN	72
4	**A** instead of **C**	53
5	**B** instead of **C**	72
6	using 1.5 equiv **C**	66
7	0.05 M instead of 0.017 M	68
8	10 equiv CH_3OH as the additive	79
9	1 mL CH_3OH as the additive	36
10	TBHP or oxone instead of **C**	N.D.
11	without **C**	N.D.
12	without light or 4CzIPN	N.D.

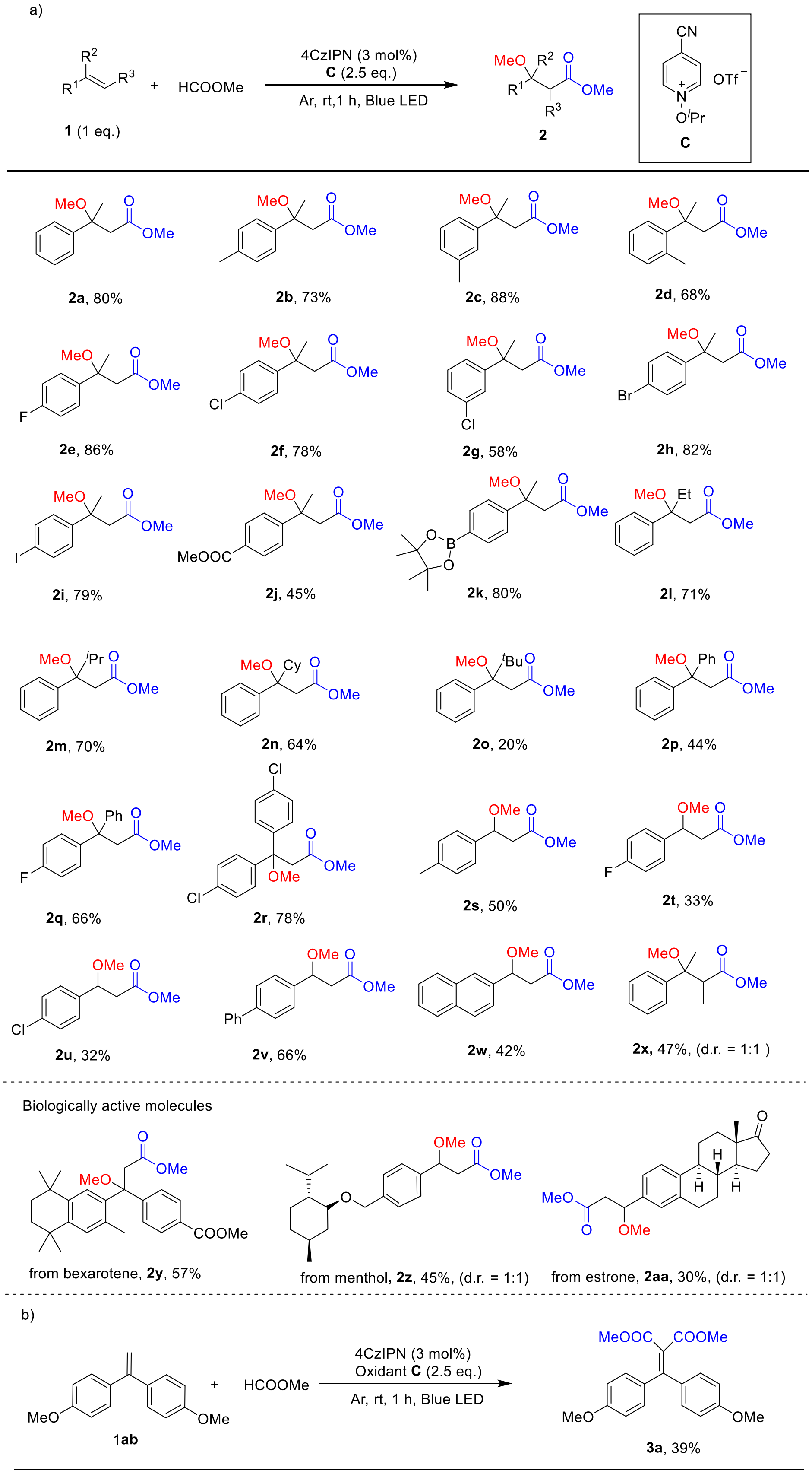
[a] Reaction conditions: **1a** (0.1 mmol), 4CzIPN (3 mol %), HCOOMe (6 mL), C (0.25 mmol), blue LED, and Ar, rt, 1 h. [b] Isolated yield. N.D. = not detected.

■ RESULTS AND DISCUSSION

Optimization of Reaction Conditions. We initially investigated alkene difunctionalization employing α-methyl styrene **1a** as the model substrate and methyl formate as the solvent in the presence of a photocatalyst, 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene), and an *N*-alkoxyazinium salt under blue LED irradiation (Table 1). To our delight, the 1,2-methoxy methoxycarbonylation product, methyl 3-methoxy-3-phenylbutanoate (**2a**), was obtained under the initial conditions. After extensive evaluation, we found that the treatment of substrate **1a** with 2.5 equiv **C** as the oxidant in the presence of 3 mol % 4CzIPN at room temperature provided the best result, affording **2a** in 80% yield. Using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ or $Ru(bpy)_3Cl_2$ instead of 4CzIPN as the photocatalyst gave lower yields (entries 2 and 3). Compared with the *N*-alkoxyazinium salt **C**, reactions with salts **A** and **B** suffered decreased yields with significant amounts of byproducts from direct alkoxy radical addition to **1a**, indicating that the use of a salt with a sterically bulky isopropyl group inhibits the side reaction (entries 4 and 5). Decreasing the amount of **C** also led to a lower yield because of the decrease in the corresponding isopropoxy radical that initiates the generation of the methoxycarbonyl radical (entry 6). The alkene concentration had a significant effect on reactivity, as the yield of product **2a** decreased when the concentration of **1a** was increased from 0.017 to 0.05 M (entry 7). To investigate the origin of the methoxy group, we analyzed the purchased methyl formate by NMR, which revealed the presence of 6 mol % MeOH as a potential nucleophile. Adding external MeOH (10 equiv) to the system had no effect to the reaction (entry 8). However, increasing the amount of external MeOH to 1 mL, the desired product was detected in only 36% yield, and the $C(sp^3)$−H activation of MeOH was observed (entry 9). No desired product was obtained when TBHP or oxone was used as the oxidant (entry 10). Finally, no difunctionalization product was detected in the absence of the oxidant (**C**), photocatalyst (4CzIPN), or light, demonstrating that all these components were essential (entries 11 and 12).

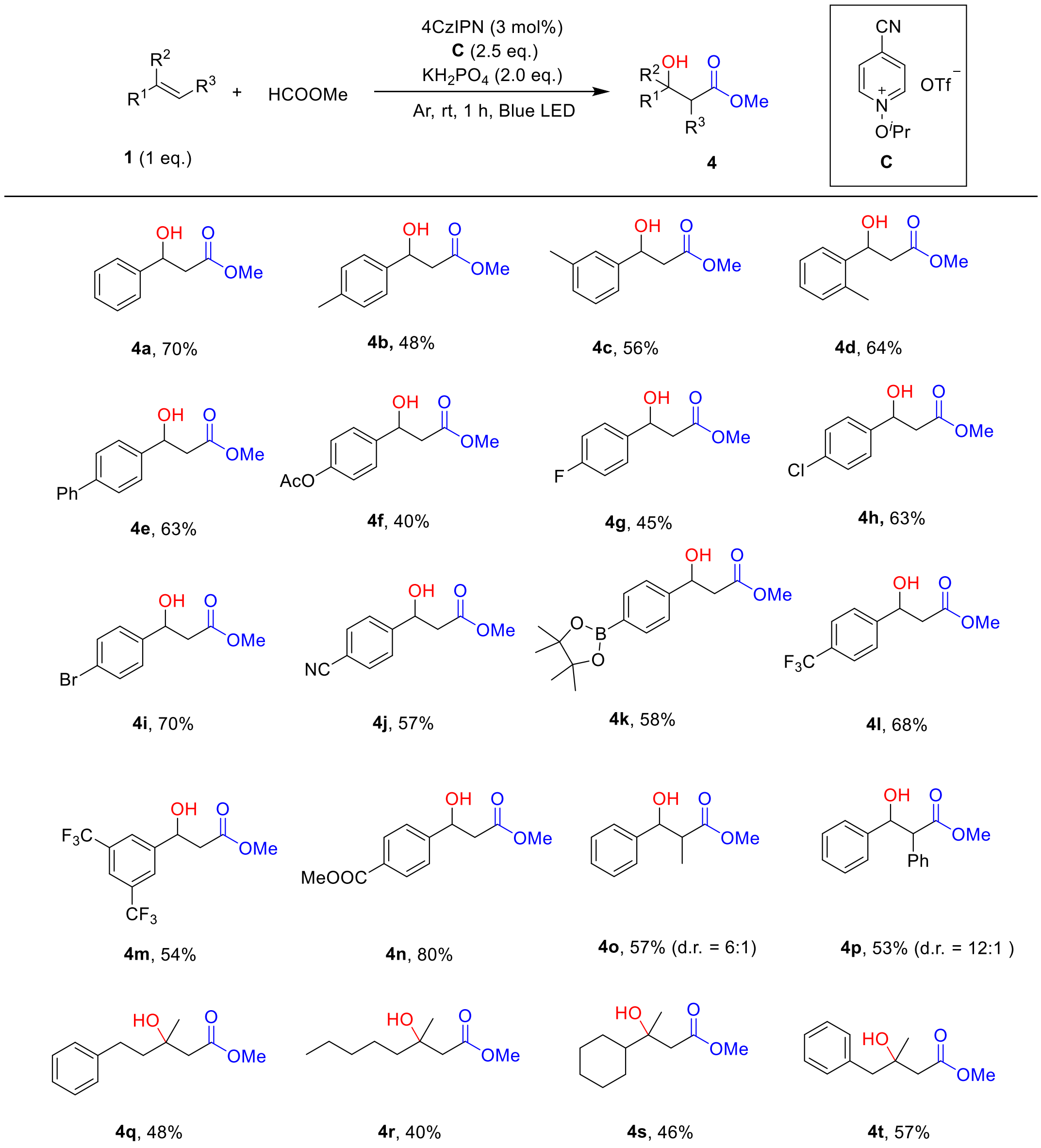
Scope of Visible Light-Driven 1,2-Methoxy Methoxycarbonylation of Alkenes. With the optimized conditions in hand, we explored the scope of the alkene substrates. As shown in Scheme 1a, α-methyl styrenes with a weakly electron-donating group (Me−) at different positions of the benzene ring delivered the expected products in good yields (**2b**−**2d**). Electron-withdrawing groups such as halogens and esters were also well tolerated (**2e**−**2j**). It is worth noting that product **2i**, bearing an aryl iodide moiety, that was incompatible with the previous Cu-catalyzed approach,[11] was smoothly produced under our standard protocol. A boronic ester substituent was also compatible (**2k**). Substituting the methyl group in **1a** with ethyl, isopropyl, and cyclo-hexyl groups led to products **2l**, **2m**, and **2n**, respectively, in satisfactory yields. A lower yield was obtained for **2o** when a-*tert*-butyl styrene was applied as the substrate because of steric hinderance. 1,1-Diarylsubstituted ethylenes furnished the corresponding products in moderate to good yields (**2p**−**2r**). Moreover, our catalytic protocol was successfully applied to monosubstituted aryl alkenes, giving products **2s**−**2w** in moderate yields. Gratifyingly, the synthetic method could be expanded effectively to trisubstituted alkenes, providing **2x** in 47% yield. To demonstrate the applicability of

Scheme 1. Visible Light-Driven 1,2-Methoxy Methoxycarbonylation of Alkenes[a,b][a]



[a] [a]The standard reaction conditions (Table 1, entry 1). [b]Isolated yield.

Scheme 2. Visible Light-Driven 1,2-Hydroxy Methoxycarbonylation of Alkenes[a][a,b]

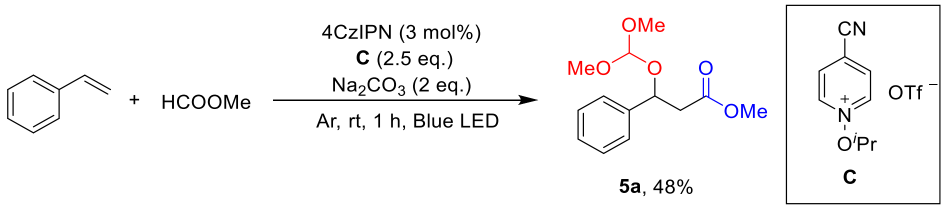


[a][a]1 (0.1 mmol), 4CzIPN (3 mol %), HCOOMe (6 mL), C (0.25 mmol), KH_2PO_4 (0.2 mmol), blue LED, and Ar, rt, 1 h. [b]Isolated yield.

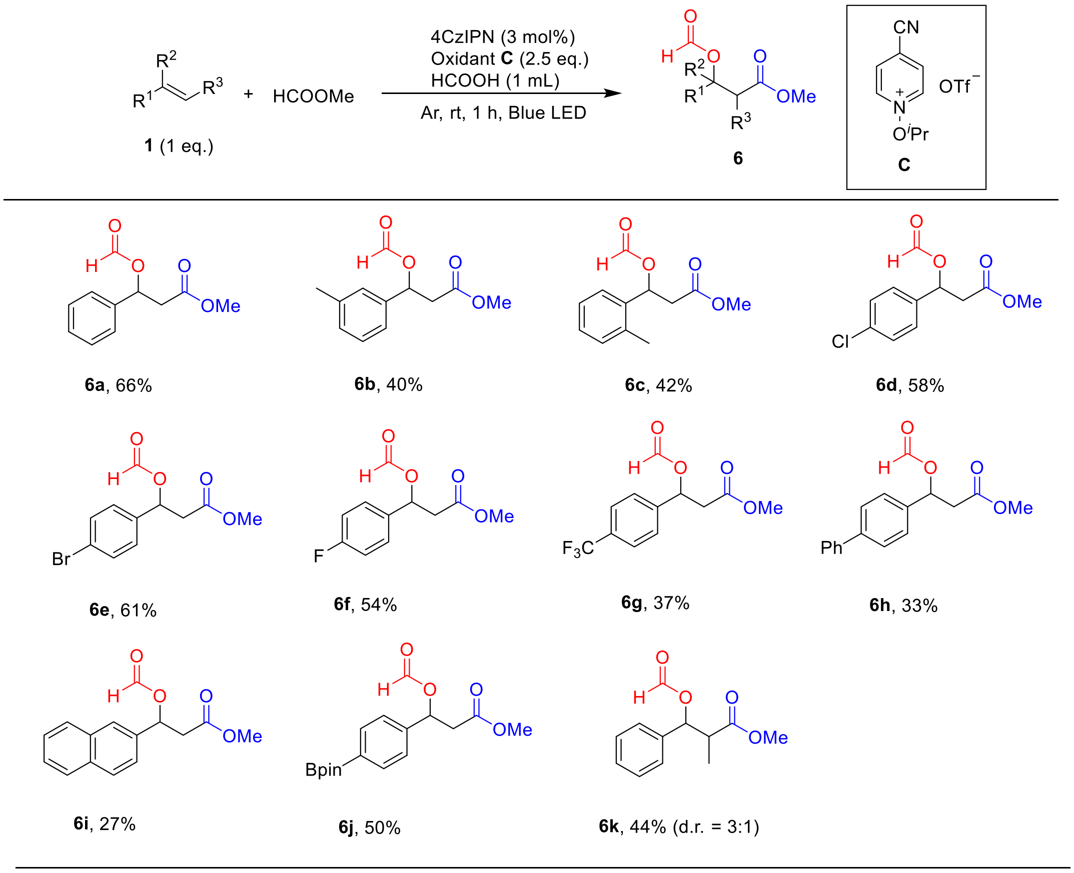
the method to the late-stage synthetic elaboration of biologically relevant complex molecules, several drug candidates were tested in the current transformation and the desired products were successfully obtained (**2y**−**2aa**). Notably, employing **1ab** [4,4′-(ethene-1,1-diyl)bis(methoxybenzene)] as the substrate afforded *α*,*β*-unsaturated ester **3a** (Scheme 1b). We reasoned that the *para*-quinone methide intermediate which could isomerize to give the *α*,*β*-unsaturated ester may be generated from the carbocation intermediate because of the presence of 4-methoxyphenyl groups. This *α*,*β*-unsaturated ester with one ester group would again react with the methoxycarbonyl radical to provide **3a**.

Development and Scope of 1,2-Hydroxy Methoxycarbonylation of Alkenes. *β*-Hydroxy esters are important structural motifs for polymeric materials and fine chemicals.[18] Of particular note, poly(*β*-hydroxy alkanoates) are ideal candidates for biomedical applications because of their biocompatibility.[19] The rapid and effective synthesis of *β*-hydroxy esters, especially from nontoxic and inexpensive feedstock methyl formate, would be of considerable importance for synthetic chemistry.[20] We were delighted to find that the 1,2-hydroxy methoxycarbonylation of alkenes could occur, with *β*-hydroxy esters obtained as the major products from mono- or 1,2-disubstituted aryl alkene substrates, with KH_2PO_4 as an additive. As shown in Scheme 2, the 1,2-hydroxy methoxycarbonylation of styrene led to product **4a** in 70% yield under these conditions. A variety of monosubstituted alkenes with electron-donating and electron-withdrawing aryl substituents were efficiently converted to *β*-hydroxy esters in moderate to good yields (**4b**−**4n**). Notably, a boronic ester substituent was compatible with the reaction conditions, providing a handle for further transformation. 1,2-Disubstituted alkenes were well tolerated, affording access to *α*-substituted *β*-hydroxy esters (**4o**, **4p**). Simple aliphatic alkenes were also suitable for the transformation (**4q**−**4t**).

Scheme 3. Visible Light-Driven 1,2-Dimethoxymethoxy Methoxycarbonylation of Styrene



Scheme 4. Visible Light-Driven 1,2-Formyloxy Methoxycarbonylation of Alkenes[a,b][a]



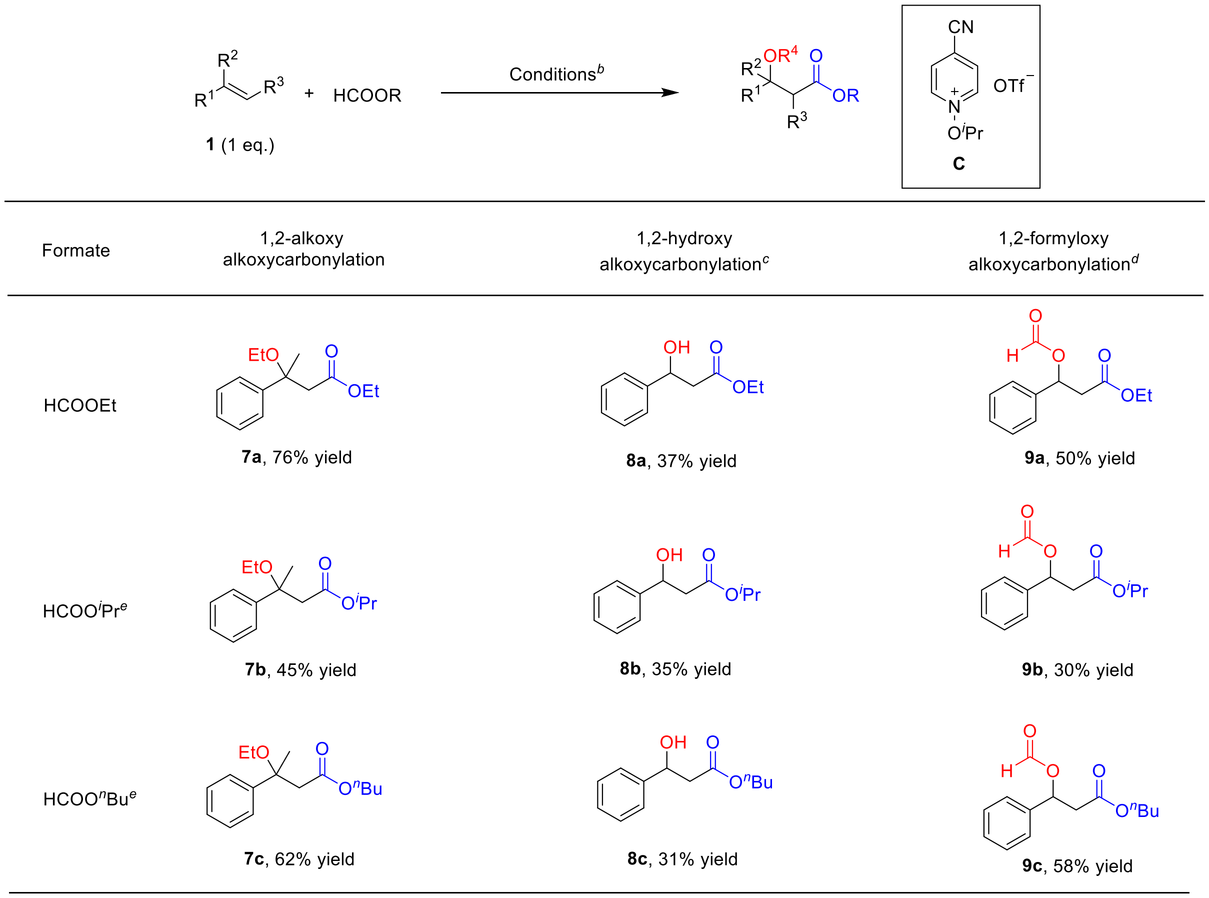
[a][a]1 (0.1 mmol), 4CzIPN (3 mol %), HCOOMe (6 mL), C (0.25 mmol), HCOOH (1 mL), blue LED, and Ar, rt, 1 h. [b]Isolated yield.

Development and Scope of 1,2-Dimethoxymethoxy Methoxycarbonylation of Alkenes. Orthoformates are widely used reagents in organic transformations such as alkylations, acylations, and Claisen rearrangements.[21] We were pleased to find that 1,2-dimethoxymethoxy methoxycarbonylation product **5a** [methyl 3-(dimethoxymethoxy)-3-phenylpropanoate] was obtained after changing KH_2PO_4 to Na_2CO_3 based on the 1,2-hydroxy methoxycarbonylation conditions (Scheme 3). In addition, a broad range of aryl substituents, such as methyl, fluoro, chloro, bromo, and trifluoromethyl groups, were compatible with the conditions (Scheme S1). Nevertheless, the desired orthoformates were sensitive to acid conditions and rapidly converted to the corresponding β-hydroxy esters and β-formyloxy esters.

Development and Scope of 1,2-Formyloxy Methoxycarbonylation of Alkenes. Based on the formation of β-methoxy esters, we speculated that carbocation intermediates derived from the oxidation of benzylic radicals might be involved. Therefore, we investigated other nucleophiles for the attack of the carbocation intermediates. We found that 2-formyloxy methoxycarbonylation was achieved using formic acid as the nucleophile-affording β-formyloxy esters. As shown in Scheme 4, the reaction of styrene-bearing methyl, halogen (F, Cl, and Br), trifluoromethyl, phenyl, naphthyl, and boronic ester groups proceeded well to deliver the desired products (**6b**−**6j**). Moreover, 1,2-disubstituted alkenes also participated in the reaction, giving product **6k** in moderate yields.

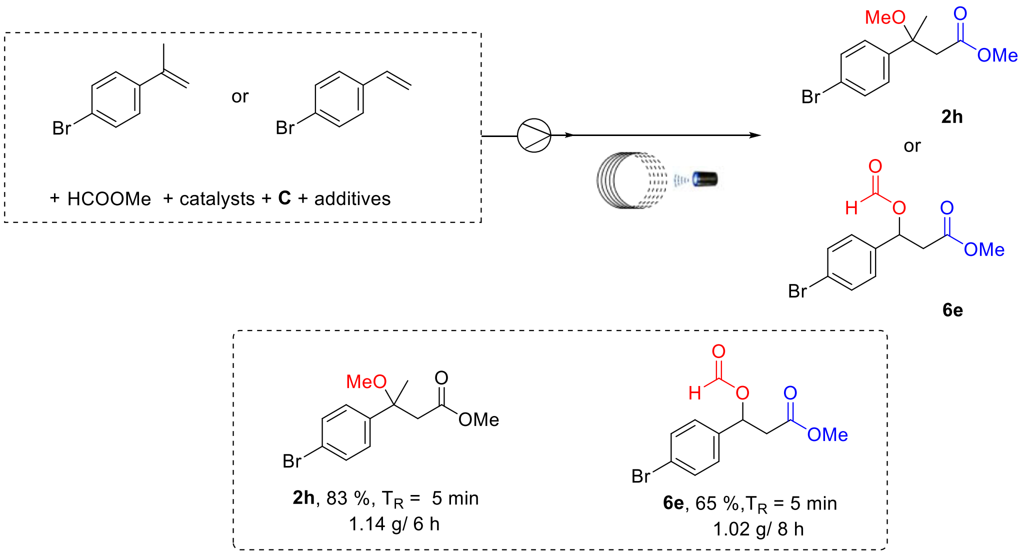
Scope of Alkyl Formates. To further extend the scope of the protocol, we examined other alkyl formates as precursors of alkoxycarbonyl radicals (Scheme 5). Gratifyingly, 1,2-alkoxy, 1,2-hydroxy, and 1,2-formyloxy alkoxycarbonylations occurred with ethyl, isopropyl, and ^n^butyl formates to generate the corresponding esters. ^n^Octyl, 2,2,2-trifluoroethyl, and 2-phenylethyl formates were also investigated, giving β-methoxy and β-formyloxy ester in moderate yields (Scheme S2). However, orthoesters could not be obtained in these cases and only decomposition products were observed, suggesting the instability of the desired products.

Scheme 5. Visible Light-Driven Difunctionalization of Alkenes with other Formates[a][a]



[a][a]Isolated yield; [b]alkene (0.1 mmol), 4CzIPN (3 mol %), HCOOEt or HCOOiPr (6 mL), EtOH (0.4 mL) C (0.25 mmol), blue LED, and Ar, rt, 1 h; [c]KH_2PO_4 (0.2 mmol) as the additive; [d]HCOOH (1 mL) as the additive; and [e]CH_3CN (1 mL) as the co-solvent.

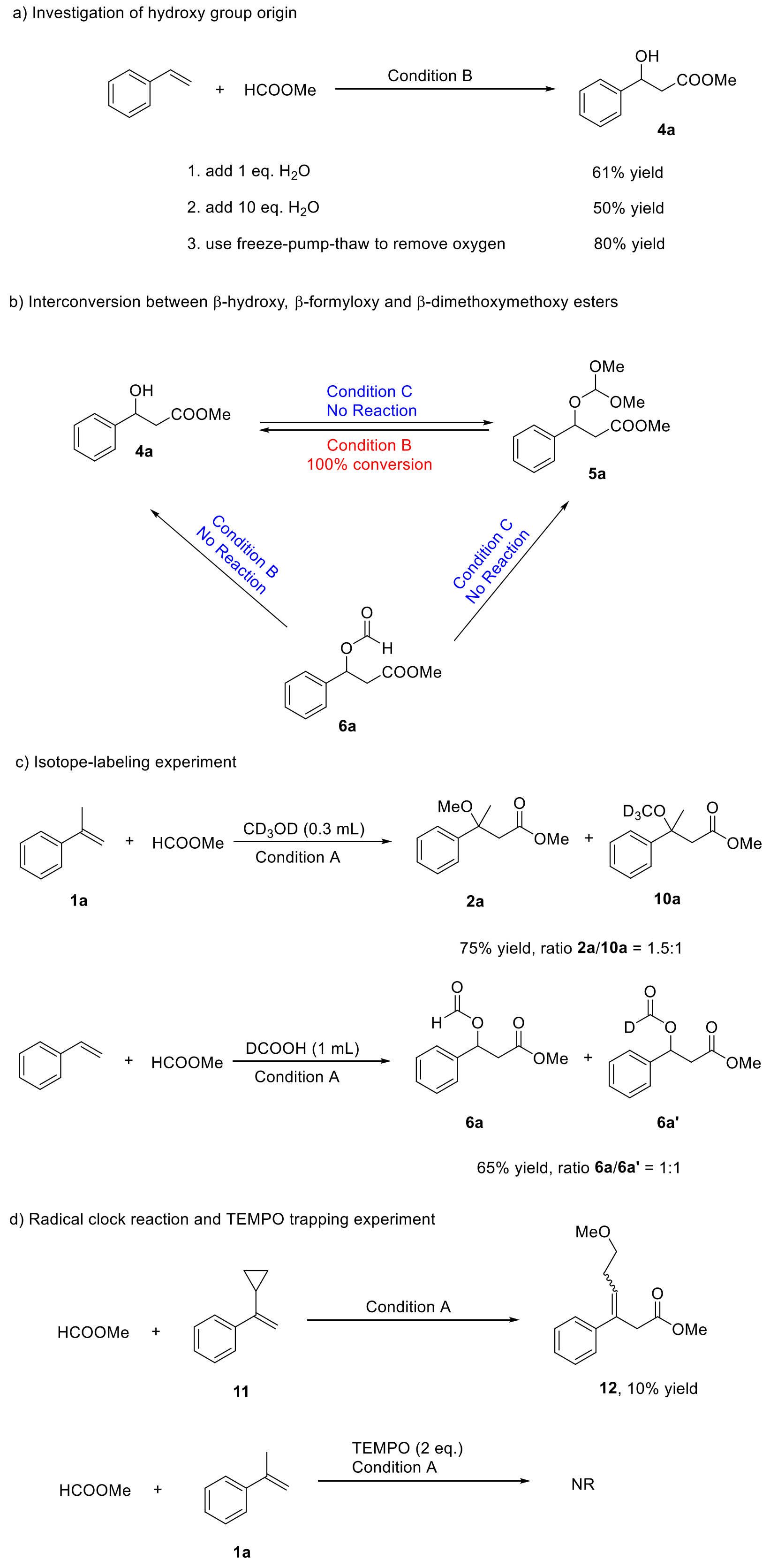
Scheme 6. Gram-Scale Continuous-Flow Synthesis



Gram-Scale Continuous-Flow Synthesis. To demonstrate the synthetic value of the protocol, the 1,2-hydroxy methoxycarbonylation and 1,2-formyloxy methoxycarbonylation of alkenes were scaled up to gram quantities using continuous-flow technology (Scheme 6). Of particular note, both reactions could finish within a 5 min residence time.

Mechanistic Study of Alkene Difunctionalization. Various control experiments were conducted to gain insights into the mechanisms for these divergent transformations. According to the results of Stern−Volmer quenching studies, the excited photocatalyst $[E_{1/2}(P^+/{}^*P) = -1.04\text{ V vs SCE in MeCN}]$[22] could be quenched by **C** $[E_{1/2} = -0.15$ V vs SCE in

Scheme 7. Control Experiments[a][a]



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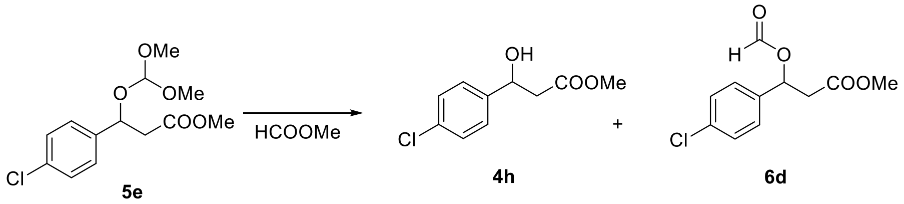
[a][a] Condition A: alkene (0.1 mmol), 4CzIPN (3 mol %), HCOOMe (6 mL), C (0.25 mmol), blue LED, and Ar, rt, 1 h; condition B: alkene or **5a** or **6a** (0.1 mmol), 4CzIPN (3 mol %), HCOOMe (6 mL), C (0.25 mmol), KH_2PO_4 (0.2 mmol), blue LED, and Ar, rt, 1 h; and condition C: alkene or **4a** or **6a** (0.1 mmol), 4CzIPN (3 mol %), HCOOMe (6 mL), C (0.25 mmol), Na_2CO_3 (0.2 mmol), blue LED, and Ar, rt, 1 h.

Scheme 8. Investigation of the Role of Additives

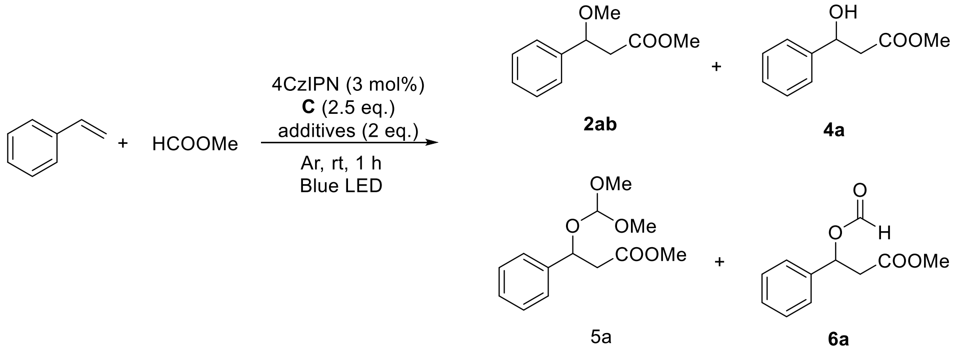
a) Decomposition of β-dimethoxymethoxy esters[a]



entry	conditions	result
1	KH_2PO_4 (2 eq.), rt, 2 h	No Reaction
2	KH_2PO_4 (2 eq.), **C** (1 eq.), rt, 2 h	**4h** 95% yield
3	Na_2CO_3 (2 eq.), **C** (1 eq.), rt, 2 h	**4h** trace (decomposition of **C** was observed)

[a] Procedure: The additive and **C** stir for 30 min and then add **5e**

b) Transformation of styrene with different additives



entry	additive	**2ab** (%)	**4a** (%)	**5a** (%)	**6a** (%)
1	none	31	21	0	14
2	KH_2PO_4	14	70	0	0
3	K_2HPO_4	10	63	0	0
4	NaOH	23	59	0	0
5	Na_2CO_3	15	18	48	0
6	K_2CO_3	17	14	38	0

MeCN, Figure S2] (Figure S3). To probe the origins of the hydroxy group, we initially postulated H_2O or O_2 as likely sources. However, the 1,2-hydroxy methoxycarbonylation of styrene in the presence of 1 or 10 equiv H_2O led to lower yields of the product (Scheme 7a). After removing O_2 via the freeze−pump−thaw method, the transformation proceeded well. According to these results, neither H_2O nor O_2 could be the source of the hydroxy group. Then, we resubjected *β*-hydroxy (**4a**), *β*-dimethoxymethoxy (**5a**), and *β*-formyloxy esters (**6a**) to the transformation conditions. Compounds **4a** and **6a** were stable under the 1,2-hydroxy methoxycarbonylation and 1,2-dimethoxymethoxy methoxycarbonylation conditions, respectively (Scheme 7b). In contrast, **5a** decomposed rapidly under the conditions for 1,2-hydroxy methoxycarbonylation, converting to **4a**. This indicates that the *β*-dimethoxymethoxy ester is an intermediate in the formation of the *β*-hydroxyester.

The addition of CD_3OD (0.3 mL) to the 1,2-methoxy methoxycarbonylation reaction of **1a** afforded **2a** and **10a** in a 1.5:1 ratio (Scheme 7c). Based on the results of the control experiments of **1a** with ethyl formate without external ethanol (Scheme S3), the *N*-alkoxyazinium salt (**C**) could also promote the transesterification of the methyl formate to give free methanol in situ under the reaction conditions. Thus, the methoxy group may derive either from methyl formate or from external methanol in the formate solution (6 mol %). Compounds **6a** and **6a′** were obtained in a 1:1 ratio using DCOOH (1 mL) instead of HCOOH in the 1,2-formyloxy methoxycarbonylation system, suggesting that *β*-formyloxy esters were generated from two pathways (Scheme 7c). One

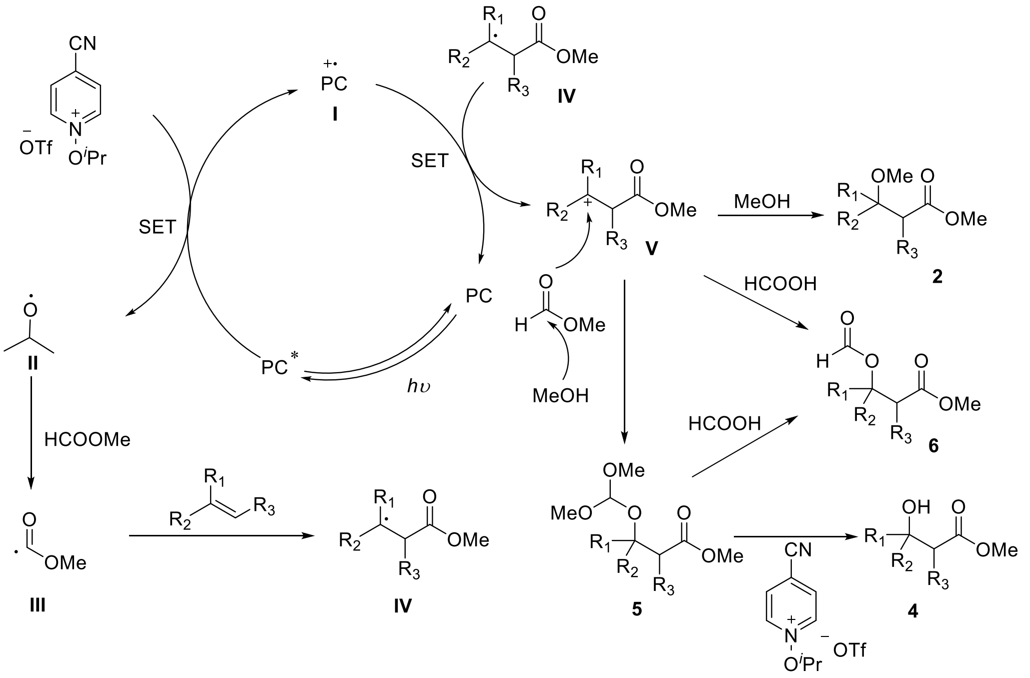


Figure 2. Proposed mechanism.

was the decomposition of the β-dimethoxymethoxy esters and another way was the reaction of formic acid with carbocation intermediates. The results of the radical clock experiment and 1,2-methoxy methoxycarbonylation in the presence of the radical scavenger, TEMPO (2 equiv), confirm the formation of radical intermediates (Scheme 7d).

To investigate the role of additives, we performed control experiments of the decomposition of β-dimethoxymethoxy esters (**5e**) (Scheme 8a). As shown in Scheme 8a, the orthoformate was stable in the HCOOMe solution in the presence of KH_2PO_4. While we added the *N*-alkoxyazinium salt (**C**) to the system, β-hydroxy ester **4h** could be obtained in 95% yield as the sole product, suggesting that **C** may promote the selective decomposition of **5e** as the Lewis acid.[23] We proposed that the interaction between the *N*-alkoxyazinium salt and oxygen at the benzylic position may be stronger than the other two oxygen atoms. When the additive was changed to Na_2CO_3, the transformation could not occur and the decomposition of **C** was observed. Accordingly, in the 1,2-dimethoxymethoxy methoxycarbonylation system, β-dimethoxymethoxy esters could be obtained because of the decomposition of **C** facilitated by Na_2CO_3. Then, we conducted the transformation of styrene with different additives (Scheme 8b). Without any additives, **2ab** was obtained as the major product. Interestingly, **6a** was also produced and we reasoned that **6a** may have come from the acidic decomposition of **5a**. In contrast, when we used KH_2PO_4 or other bases as the additive, the acidic decomposition of **5a** was suppressed and **4a**, derived from the selective decomposition of **5a** promoted by **C**, became the major product (entry 2−4). These results indicate that the addition of KH_2PO_4 may increase the selective decomposition rate of β-dimethoxymethoxy esters to give β-hydroxy esters. Using carbonate salts as the additive, only part of **5a** decomposed that was consistent with the result of the control experiment shown in Scheme 8a.

A plausible mechanism was proposed based on these control experiments (Figure 2). Photoactivated 4CzIPN could be oxidized by **C** to afford oxidized 4CzIPN **I** and isopropoxy radical **II**. Radical **II** then abstracts a hydrogen atom from methyl formate via HAT to deliver methoxycarbonyl radical **III**, which can undergo addition to alkene to afford **IV**. Adduct **IV** ($E^{\text{ox}}_{1/2}$ = +0.73 V vs SCE for benzyl radical)[24] can be oxidized by **I** [$E_{1/2}(P^+/P)$ = +1.52 V vs SCE in MeCN][22] to give rise to carbocation intermediate **V**. The subsequent nucleophilic addition of MeOH to **V** can produce β-methoxy ester **2**. Using monosubstituted aryl alkene as substrates, the three-component reaction of MeOH, methyl formate, and **V** occurs to give β-dimethoxymethoxy ester **5**. When excess formic acid exists as the nucleophile in the reaction system, β-formyloxy ester **6** can be generated. In addition, the decomposition of **5** under the acidic conditions can also produce **6**. β-Hydroxy ester **4** is generated from the decomposition of **5** promoted by the *N*-alkoxyazinium salt. Using α-alkyl-substituted styrenes as substrates, the three-component reaction may be inhibited by steric effects. Therefore, 1,2-hydroxy methoxycarbonylation does not proceed for this type of substrate.

CONCLUSIONS

In summary, we have demonstrated the efficient metal-free difunctionalization of alkenes with alkyl formates and *N*-alkoxyazinium salts, affording a series of value-added β-alkoxy, β-hydroxy, β-formyloxy, and β-dimethoxymethoxy alkanoates under mild conditions. The 1,2-hydroxy methoxycarbonylation and 1,2-formyloxy methoxycarbonylation of alkenes can be easily scaled to gram quantities. Comprehensive mechanistic studies revealed that β-hydroxy alkanoates were generated by an unprecedented selective decomposition of orthoformates promoted by the *N*-alkoxyazinium salt. This work is a rare example of the catalytic carbonylation of alkenes initiated by the intermolecular addition of alkoxycarbonyl radicals. We expect that this strategy could be used to enable the carbonylation of other unsaturated compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c04332.

Experimental details, characterization data of compounds, NMR spectra, and mechanistic discussion (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Jing Hou − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China;* orcid.org/0000-0002-1892-2025; Email: chmhouj@njust.edu.cn

Bin-Dong Li − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China;* orcid.org/0000-0003-3771-7649; Email: libindong@njust.edu.cn

Authors

Ming Zheng − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*

Le-Wu Zhan − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*

Yan Huang − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*

Ling Chen − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*

Li-Li Hua − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*

Yan Li − *School of Physics and Electronic-Electrical Engineering, Ningxia University, Yinchuan 750021, China*

Wan-Ying Tang − *College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c04332

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