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Decarboxylative Alkylcarboxylation of α,β-Unsaturated Acids Enabled by Copper-Catalyzed Oxidative Coupling

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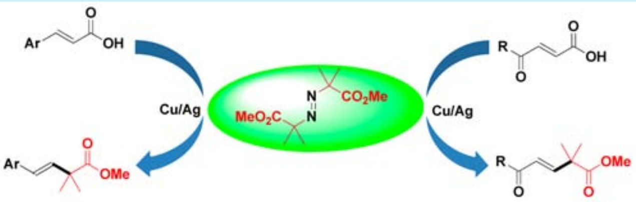
Ⓢ *Supporting Information*



ABSTRACT: A facile and general method for copper-catalyzed decarboxylative alkylcarboxylation of cinnamic acids with dimethyl 2,2′-azobis(2-methylpropionate) has been developed. The scope and versatility of the reaction was demonstrated, and a broad range of substrates bearing electron-donating and -withdrawing groups on the aromatic rings were all compatible with this reaction to provide desired β,γ-unsaturated esters in moderate to good yields. Moreover, α,β-unsaturated acids with a carbonyl group on the γ-position of acrylic acids also smoothly proceeded to furnish the desired products in good yields.

The carboxylic group (COOR) prevails in natural products, pharmaceuticals, agrochemical compounds, and synthetic functional materials.[1] As a result, the incorporation of the carboxylic group into a simple starting material for the synthesis of carboxylic acids and their derivatives has attracted considerable attention.[2] Carbonylation with CO as the carbonyl source has been well developed and successfully utilized for the synthesis of carboxylic acids in the past several decades.[3] However, the high toxicity and odorless and flammable character of CO gas restrict its application in both laboratory and industry, especially when high pressure CO is required.

Consequently, HCHO, HCOOR, and some other C1 sources have been explored as alternative carbonyl sources.[4] Dimethyl 2,2′-azobis(2-methylpropionate) (AIBME) is probably one of the most popular commercially available radical initiators in polymer chemistry and radical-mediated organic synthesis and is capable of generating 2 equiv of a carboxymethyl radical on heating. The carboxymethyl moiety could be viewed and utilized as a kind of useful carboxylic source once an efficient catalytic protocol was developed to incorporate this moiety into simple starting materials.

The β,γ-unsaturated carboxylic acids and their derivatives, possessing one additional carbon between the double bond and carboxylic group, are not only a class of important building blocks for many organic transformations but also frequently exist in pharmaceuticals (Figure 1).[5] Although many efficient methods, such as carbonylation with CO (Scheme 1a), are available for synthesis of α,β-unsaturated carboxylic acids, few methods are available for the efficient synthesis of β,γ-unsaturated carboxylic acids.[6] In this context, transition-metal-catalyzed C−C coupling between a vinyl carbon and an α-carbon of carboxylic acids or their derivatives has been developed as a promising method toward to β,γ-unsaturated carboxylic acids (Scheme 1b).[7] Optimal use of this strategy requires the identification of an alkenyl partner and a suitable carboxymethyl moiety. Cinnamic acids and their derivatives could be recognized as alkenyl coupling partners since the carboxylic group could be removed in the presence of metal catalysts. The elegant work on the transition-metal-catalyzed decarboxylation coupling reactions pioneered by Nilsson, Tsuji, and Myers[8] disclosed that cinnamic acids could be utilized

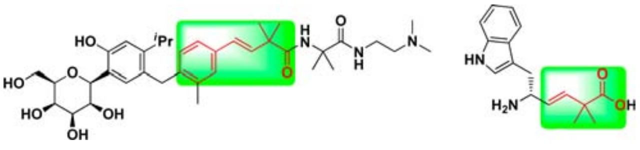
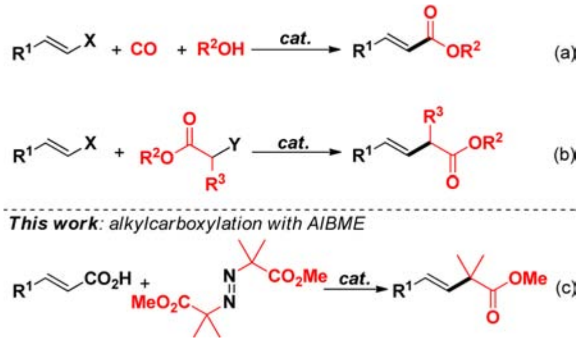


Figure 1. Biologically active β,γ-unsaturated carboxylic acids.

Scheme 1. Strategies for the Synthesis of β,γ-Unsaturated Carboxylic Esters



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widely in organic synthesis as alkenyl coupling partners.[9] A prominent feature of this approach is that the radical could act as an effective coupling partner to react with cinnamic acid via decarboxylation to furnish the construction of C–C bond. Inspired by these results and in line with studies by our group and others regarding the use of AIBN as a reactant,[10] we envisioned that AIBME could act as a coupling partner to effectively couple with cinnamic acids to furnish β,γ-unsaturated esters via decarboxylation. To the best of our knowledge, the reaction reported herein represents the first example of the synthesis of a β,γ-unsaturated ester using AIBME as a carboxylic source.

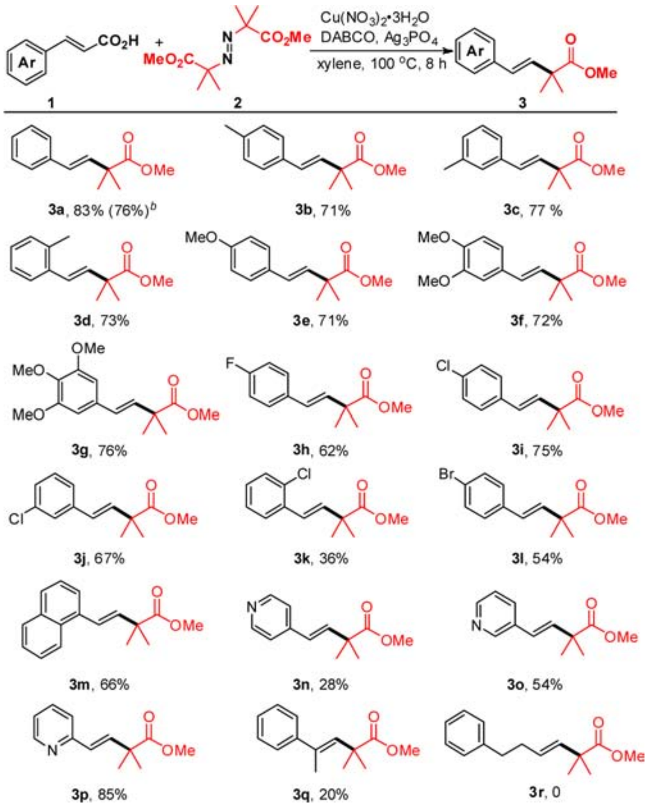
We commenced our studies by attempting the proposed decarboxylative coupling of cinnamic acid **1a** with dimethyl 2,2′-azobis(2-methylpropionate) (AIBME) **2** in xylene at 100 °C under copper catalysis. To our delight, the reaction took place under the catalysis of $Cu(NO_3)_2 \cdot 3H_2O$, and a 60% yield of the desired product **3a** was obtained when Ag_2CO_3 (2.0 equiv) served as an oxidant and DABCO (2.0 equiv) was used as a base (Table 1, entry 1). Inspired by this preliminary result, other copper salts were then tested, but no better yield was observed (see Supporting Information (SI)). A further control experiment demonstrated that no desired reaction occurred in the absence of the copper catalyst. The desired product **3a** could be obtained in 37% yield when the reaction was conducted in the absence of Ag_2CO_3, but only a trace amount of product was obtained in the absence of DABCO. These results indicated that copper salt is essential for this reaction. Variation of the silver salts revealed that Ag_3PO_4 demonstrated the best oxidative efficiency in delivering the desired product **3a** in 62% yield (Table 1, entry 7). Further studies revealed that only an organic base could promote the reaction and DABCO is superior to other bases used here. The reaction was inhibited when K_2CO_3 was used as a base. The yield of **3a** could dramatically increase to 85% when the loadings of AIBME and DABCO were increased (Table 1, entry 12). We were pleased to find that the reaction time could be shortened to 8 h, giving the desired product in 83% isolated yield (Table 1, entry 13). Furthermore, only the *E*-isomer could be obtained when *Z*-cinnamic acid was used as a substrate, which revealed that the *E*/*Z* selectivity of this reaction was not affected by the configuration of the cinnamic acid (see SI).

Table 1. Optimization of the Reaction Conditions[a]

entry	variation from the initial conditions	yield (%)[b]
1	none	60
2	no $Cu(NO_3)_2 \cdot 3H_2O$	0
3	no Ag_2CO_3	37
4	no DABCO	trace
5	AgOAc as oxidant	27
6	$AgNO_3$ as oxidant	55
7	Ag_3PO_4 as oxidant	62
8	Ag_3PO_4 as oxidant, DBU as base	53
9	Ag_3PO_4 as oxidant, Et_3N as base	44
10	Ag_3PO_4 as oxidant, K_2CO_3 as base	trace
11	Ag_3PO_4 as oxidant, 2.5 equiv of DABCO	65
12	Ag_3PO_4 as oxidant, 2.5 equiv of DABCO, 2.5 mmol AIBME	85
13	Ag_3PO_4 as oxidant, 2.5 equiv of DABCO, 2.5 mmol AIBME, 8 h	85 (83)[c]

[a]Reaction conditions: cinnamic acid **1a** (0.5 mmol), AIBME **2** (1.0 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (10 mol %), Ag_2CO_3 (1.0 mmol), DABCO (1.0 mmol), xylene (2 mL), 100 °C, 12 h. [b]Yield determined by GC using *n*-hexadecane as internal standard. [c]Isolated yield.

Scheme 2. Scope of the Cinnamic Acids[a]



[a]Reaction conditions: **1** (0.5 mmol), AIMBE **2** (2.5 mmol), DABCO (1.25 mmol), Ag_3PO_4 (0.67 mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (10 mol %), xylene (2 mL), 100 °C, 8 h. Isolated yield. Only *E*-isomer was observed. [b]*Z*-cinnamic acid was used.

Having identified the optimum reaction conditions, we explored the substrate scope of this new reaction with a variety of substituted cinnamic acids (Scheme 2). In all cases, cinnamic acids bearing both electron-donating and -withdrawing groups on the aromatic rings were all smoothly converted to the corresponding β,γ-unsaturated esters in moderate to good yields (36–83%, **3a**–**3l**). Obviously, cinnamic acids with electron-donating groups provided the desired products with good yields (71–83%, **3a**–**3g**). In contrast, cinnamic acids substituted by electron-withdrawing groups such as fluorine, chlorine, and bromine gave the corresponding products with relatively lower yields (36–75%, **3h**–**3l**). Moving the chlorine atom from the *para* to the *meta* and *ortho* position decreased the yield from 75% to 36%, suggesting that steric crowding affected the reactivity. In addition to the cinnamic acid derivatives, the naphthyl-substituted acrylic acid was also compatible with this reaction, affording the corresponding adduct **3m** in 66% yield. Furthermore, the methodology was equally effective for heteroaryl-substituted acrylic acids to give the corresponding products in 28–85% yields (**3n**–**3p**) under the optimized conditions. The distinguished different reactivity was observed for the pyridine-derived substrates (**1n**−**1p**). Changing the N-atom of the pyridine ring from the *ortho*- to *meta*- and *para*-position decreased the reactivity, suggesting that a strong electron-withdrawing group decreased the reactivity. The substrate **1q** with a methyl group on the *β*-position of the double bond could react with AIBME under standard reaction conditions, giving product **3q** in 20% yield. Unfortunately, the aliphatic acrylic acid **1r** failed to produce any of the desired ester **3r** and the starting material **1r** was intact. A detailed reason is not clear yet, which might be ascribed to the lower reactivity of the substrate to react with the radical. It is worth mentioning that the reaction is highly selective and only the *E*-isomer was observed in all cases. The solid state structure of **3g** was unambiguously determined by single-crystal X-ray crystallographic analysis (Figure 2) (see SI).[11]

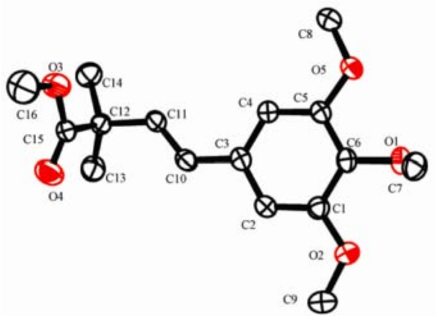
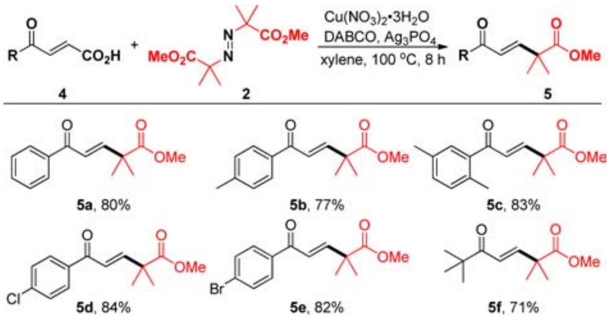


Figure 2. ORTEP drawing of product **3g**.

Once we had identified that the cinnamic acids are adequate substrates for this reaction system, we aimed to expand the substrate scope to more complex *α*,*β*-unsaturated acids. As such, substrates containing two carbonyl groups were synthesized and investigated under the optimized reaction conditions. As summarized in Scheme 3, all substrates examined here bearing both electron-wihdrawing and -donating groups in the aromatic rings could afford the desired products in good yields (77−84%) with high selectivity (only the *E*-isomer was observed by NMR). No obvious steric hindrance effect was observed in these reactions. Moreover, aliphatic unsaturated ketoacid **4f** proceeded well to furnish the corresponding product **5f** in 71% yield.

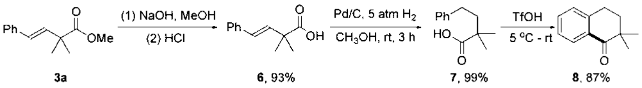
Scheme 3. Scope of Unsaturated Ketoacids[a]



[a]Reaction conditions: **4** (0.5 mmol), AIBME **2** (2.5 mmol), DABCO (1.25 mmol), Ag_3PO_4 (0.67 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (10 mol %), xylene (2 mL), 100 °C, 8 h. Isolated yield, only *E*-isomer was observed.

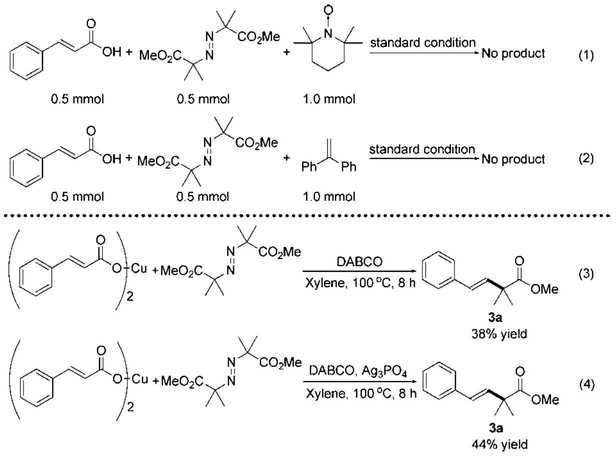
The synthetic versatility of the present catalytic system was next demonstrated through the conversion of product **3a** (Scheme 4). The base hydrolysis of substrate **3a** provided *β*,*γ*-unsaturated carboxylic acid **6**. The hydrogenation of **6** quickly proceeds to afford **7** in the presence of a catalytic amount of $Pd(OH)_2/C$. Subsequently, intermediate **7** could be directly converted into 1-tetralone derivate **8**, which is an important building block for the synthesis of chiral diol.[12]

Scheme 4. Conversion of Substrate 3a for the Synthesis of the 1-Tetralone Derivates



To gain some insight into the mechanism of the present decarboxylation coupling reaction, some control experiments were conducted (Scheme 5). Radical scavengers, such as TEMPO and 1,1-diphenylethylene, were employed in the standard reaction, and no desired coupling product was detected. This result suggested that a free radical process was involved in the present coupling reaction. Meanwhile, by using bis(cinnamoyloxy)copper instead of cinnamic acid as a substrate, the product **3a** could be afforded in either the presence or absence of Ag_3PO_4, which indicates that a copper cinnamate might be a key intermediate for this reaction and the silver salt just acts as an oxidant.

Scheme 5. Control Experiments for Mechanistic Studies



On the basis of the above results and previous report,[9] a plausible reaction mechanism is depicted in Figure 3. Initially,

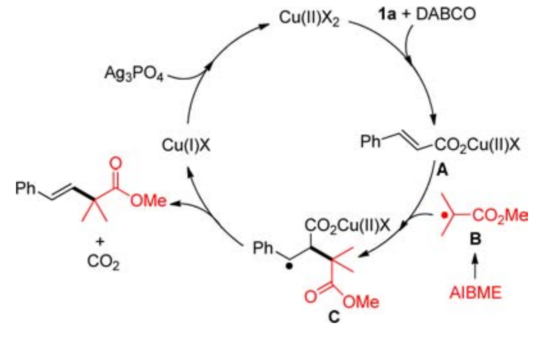


Figure 3. Plausible reaction mechanism.

(cinnamoyloxy)copper **A** was formed in the presence of DABCO and at the same time radical **B** would be generated by heating AIBME. Addition of the radical **B** at the α-position of the double bond in **A** would give the benzylic radical **C**, which then proceeds via an elimination of carbon dioxide and Cu(I) to generate the product. The Cu(I) was oxidized by Ag_3PO_4 to regenerate Cu(II) species.

In summary, we have successfully developed an efficient copper-catalyzed oxidative decarboxylation coupling with cinnamic acids, unsaturated ketoacids, and dimethyl 2,2′-azobis(2-methylpropionate) (AIBME) to give the corresponding β,γ-unsaturated carboxylic esters with high selectivity, in which AIBME has been identified as a useful alkylcarboxylic source. The reaction proceeded well to give the desired products in moderate to good yields with complete stereoselectivity, which provided an easy access to β,γ-unsaturated esters. Further studies to apply this strategy are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02382.

X-ray crystallographic data (CIF)
Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1419100 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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