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Research Article

Copper-Catalyzed Decarboxylative Functionalization of Conjugated β,γ-Unsaturated Carboxylic Acids

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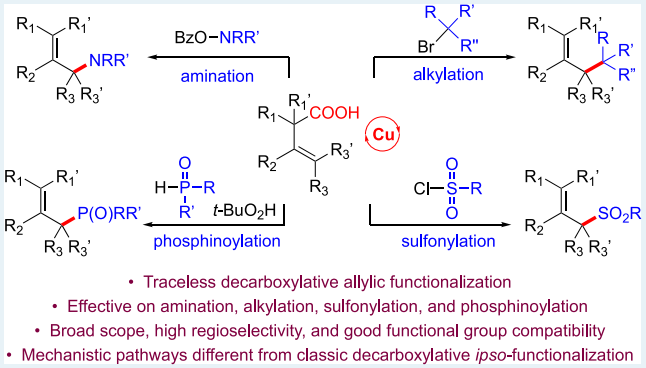
ABSTRACT: Copper-catalyzed decarboxylative coupling reactions of conjugated β,γ-unsaturated carboxylic acids have been achieved for allylic amination, alkylation, sulfonylation, and phosphinoylation. This approach was effective for a broad scope of amino, alkyl, sulfonyl, and phosphinoyl radical precursors as well as various conjugated β,γ-unsaturated carboxylic acids. These reactions also feature high regioselectivity, good functional group tolerance, and simple operation procedure. Mechanistic studies show that the reaction proceeds via copper-catalyzed electrophilic addition onto an olefin followed by decarboxylation, with radical intermediates involved. These insights present a modular and powerful strategy to access versatilely functionalized allyl-containing skeletons from readily available and stable carboxylic acids.



KEYWORDS: *decarboxylation, amination, alkylation, sulfonylation, radical reaction, copper catalysis*

Carboxylic acids represent an important class of building blocks in organic synthesis.[1] Developing decarboxylative functionalization strategies that utilize carboxylic acids as stable and highly prevalent starting materials has received great attention, offering an attractive approach to introduce versatile functionalities and to assemble complex skeletons.[2] In comparison to numerous examples in sp- and sp^2-decarboxylative functionalization,[3] fewer have been reported on sp^3-decarboxylative functionalization and usually required the use of a stoichiometric strong oxidant (e.g., Hunsdiecker reaction).[4] Not until recently, remarkable advances in sp^3-decarboxylative functionalization have been achieved with different transition-metal catalysts such as silver, copper, nickel, palladium, and even visible-light catalysis systems under environmentally friendly conditions.[5]

Decarboxylative coupling reactions of β,γ-unsaturated carboxylic acids under mild conditions will offer an appealing approach to construct allylic functionalized skeletons that are of great value in organic synthesis. Among various decarboxylative functionalizations, the Hu group reported copper-catalyzed decarboxylative fluoroalkylations using Togni-type fluoroalkylating agents (Scheme 1a).[6] The Minakata group reported decarboxylative amidation and oxygenation using hypervalent iodine reagents or *N*-iodo-*N*-chloroamides generated *in situ* from chloramine salts and I_2 (Scheme 1b).[7] Interestingly, the reactions reported by the Hu and Minakata groups were mechanistically distinct from classic decarboxylative *ipso*-functionalization as they were initiated by the addition to the olefin by an electrophile followed by decarboxylation. Such an unusual decarboxylation pathway presents an efficient strategy for regiospecific γ-functionalization (Scheme 1). So far, only hypervalent iodine(III) agents have been used as the precursors to introduce the functional groups, while greater potential remains to be explored to enable the installation of different functionalities. Herein, we report the development of copper-catalyzed decarboxylative coupling reactions of conjugated β,γ-unsaturated carboxylic acids with different precursors to achieve regioselective allylic amination, alkylation, sulfonylation, and phosphinoylation (Scheme 1c). These transformations offer a direct approach to access a diverse range of allyl-containing skeletons.

Our group has recently demonstrated that *O*-acyl-*N*-hydroxylamines are effective in engaging in the copper-catalyzed electrophilic amination onto an olefin.[8] Thus, we envisioned that *O*-acylzoyl-*N*-hydroxylamines could be used as the amino precursors for developing a decarboxylative allylic amination reaction of conjugated β,γ-unsaturated carboxylic acids. Such an allylic amination transformation will greatly expand beyond the use of chloramine salts as the nitrogen precursors in previous work.[7b] With allylic amines as highly

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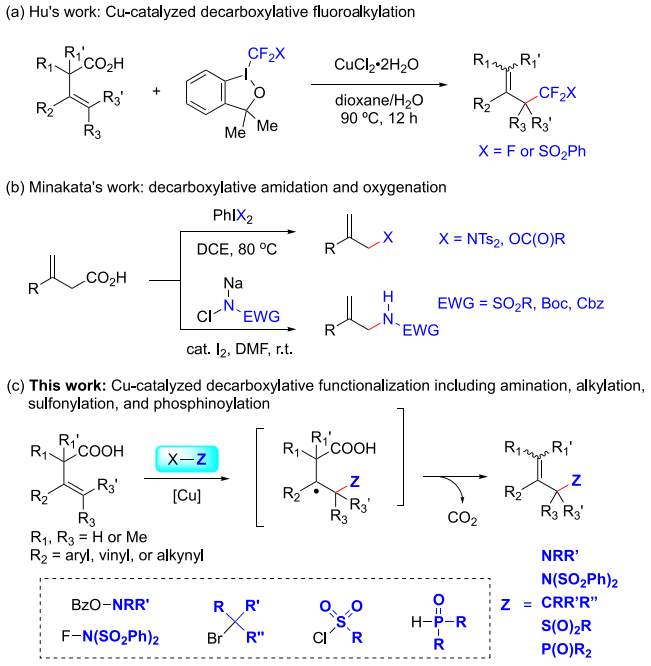
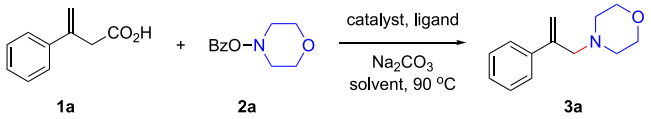
Scheme 1. Decarboxylation-Assisted γ-Functionalization of Conjugated β,γ-Unsaturated Carboxylic Acids



valuable building blocks in organic synthesis,[9] the development of such a direct and regioselective synthesis of allylic amines is desired. Our studies began with the decarboxylative amination of 3-phenylbut-3-enoic acid **1a** and *O*-benzoyl-*N*-hydroxylmorpholine **2a** (Table 1). With $Cu(OTf)_2$ as the catalyst and Na_2CO_3 as the base, the reaction in DCE afforded 4-(2-phenylallyl)morpholine **3a** in 62% yield (Table 1, entry 1). In comparison, **3a** was not formed without a copper catalyst (entry 2). The absence of Na_2CO_3 decreased the formation of **3a** to 52% yield, suggesting that the carboxylate form may facilitate the decarboxylation (entry 3). Various solvents (entries 4−6) and ligands (entries 7−9) were examined, none of which gave further improvement. Among the copper catalysts tested, $Cu(OTf)_2$ was the most effective one (entries 10−14). Finally, the yield of **3a** was increased to 76% when the reaction was run with **2a** as the limiting reagent and reversing the ratio of **1a**:**2a** (entry 15), which was subsequently chosen as standard conditions to examine the generality of the decarboxylative allylic amination reaction.

Table 1. Optimization for Decarboxylative Amination[a]



1a 2a 3a

entry	catalyst	solvent	ligand	yield (%)[b]
1	$Cu(OTf)_2$	DCE	none	60 (62)[c]
2	none	DCE	none	ND
3[d]	$Cu(OTf)_2$	DCE	none	52
4	$Cu(OTf)_2$	dioxane	none	53
5	$Cu(OTf)_2$	toluene	none	47
6	$Cu(OTf)_2$	MeCN	none	43
7	$Cu(OTf)_2$	DCE	bpy	43
8	$Cu(OTf)_2$	DCE	BINAP	55
9	$Cu(OTf)_2$	DCE	diamine	53
10	$Cu(OAc)_2$	DCE	none	56[c]
11	CuI	DCE	none	47
12	$Cu(MeCN)_4BF_4$	DCE	none	45
13	CuTC	DCE	none	52
14	$Cu(acac)_2$	DCE	none	55
15[e]	$Cu(OTf)_2$	DCE	none	76[c]

[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.02 mmol), ligand (0.02 mmol), Na_2CO_3 (0.24 mmol), solvent (3.0 mL). [b]Yields determined by ^{1}H-NMR with dibromomethane as an internal standard. [c]Isolation yield. [d]Without Na_2CO_3. [e]Reaction using **1a** (0.4 mmol), **2a** (0.2 mmol) instead of **1a** (0.2 mmol), **2a** (0.4 mmol). bpy = 1,1′-dipyridine. BINAP = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene. Diamine = *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine. ND = Not detected.

With established decarboxylative amination conditions, we studied the scope of both hydroxylamines and carboxylic acids in this reaction (Table 2). A diverse range of piperidine and piperazine-derived allylic amines were all formed in good yields (**3b**−**3f**). Besides six-membered cyclic amines, five-membered pyrrolidine **3g** and seven-membered azepane derivatives **3h** were also obtained, albeit in lower yields. Acyclic *O*-benzoyl-*N*-hydroxylamines were compatible in the formation of **3i** and **3j**. The scope of carboxylic acids was also examined. Substrates bearing a methyl group at the *ortho*-, *meta*-, and *para*-positions on the phenyl ring effectively produced allylic amines **3k**−**3m**, respectively. Both electron-donating (**3n**, **3o**) and electron-withdrawing (**3p**−**3r**) substitutions were well tolerated, with no significant impact on the outcomes. Even the free hydroxyl group was compatible (**3s**). The formation of thienyl-substituted product **3t** showed the applicability of this reaction with heteroarenes. Yet, aliphatic-substituted substrates did not participate in the reaction, with **3u** undetected. Encouragingly, γ-methyl- and γ,γ-dimethyl-substituted carboxylic acids afforded **3v** and **3w**, with lower yields resulting from the increased steric hindrance, respectively. The cyclic dialin-containing substrate also delivered **3x**. Furthermore, α-methyl-, α,α-dimethyl- and even α,α,γ-trimethyl-substituted substrates afforded **3y**, **3z**, and **3aa** successfully, respectively. Results from α- and γ-substituted carboxylic acids suggested that the formation of the allylic amine products was initiated by Cu-catalyzed amination of the olefin at the γ-position of carboxylic acid followed by the decarboxylation step to regenerate the double bond in the products. Correspondingly, the steric bulkiness at the γ-position hindered the efficiency of the reactions, as seen in the poor formation of **3w**. Excitingly, when β-alkynyl- and β-vinyl-substituted carboxylic acids were tested for this reaction, all led to the selective formation of desired allylic amine products **3ab**−**3ad** while other unsaturated carbon−carbon bonds remained intact.

We next explored the decarboxylation-assisted allylic functionalization by using other radical species besides *O*-acyl-*N*-hydroxylamines. Under modified copper-catalyzed conditions,[10] we have established a decarboxylative alkylation by using alkyl radicals derived from α-bromocarbonyl derivatives or α-bromonitrile.[11] We evaluated the scope in a diverse range of alkyl bromides and carboxylic acids (Table 3). When different alkyl bromides were examined in this reaction, all successfully formed allylic alkylation products, demonstrating the generality of this decarboxylative alkylation reaction from various α-carbonyl alkyl radical precursors, ranging from tertiary and secondary α-bromoacetates (**5a**−**5g**), primary α-bromonitrile (**5h**), α-bromoacetamide (**5i**), and even α-bromoketone (**5j**). A range of carboxylic acids bearing different

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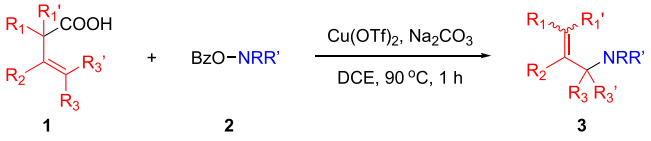
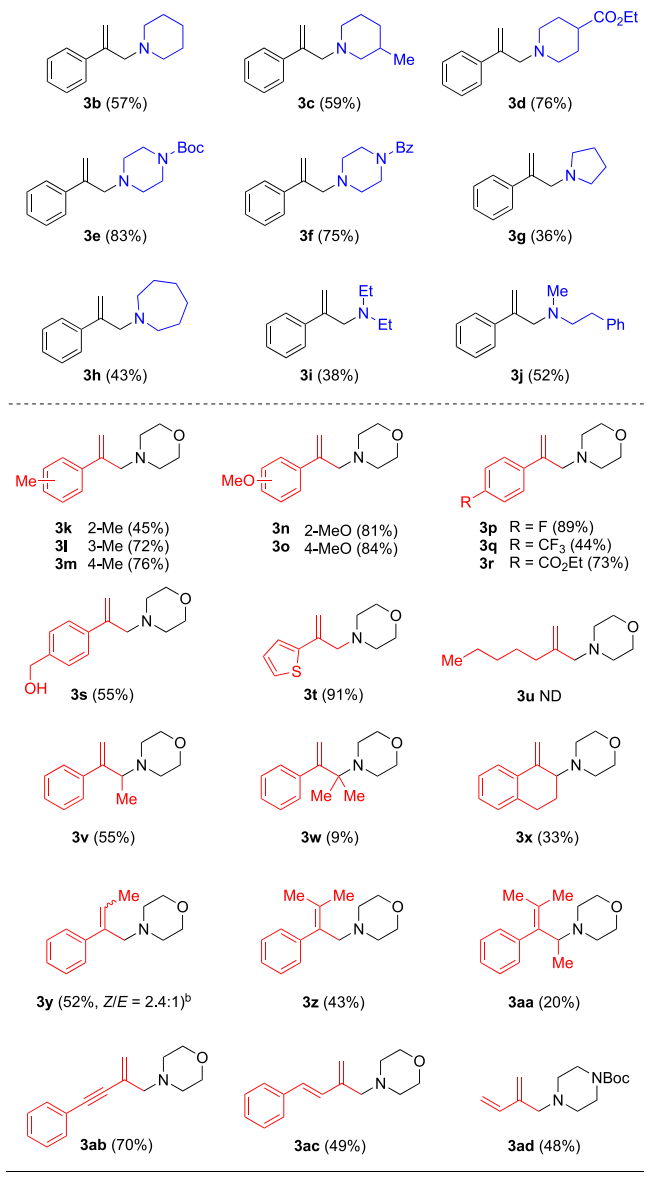
Table 2. Decarboxylative Amination of Conjugated β,γ-Unsaturated Carboxylic Acids[a]

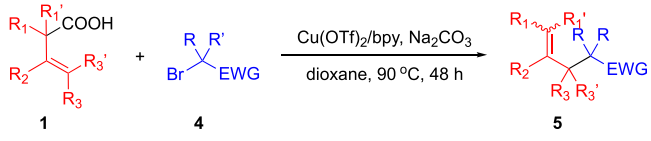


1 2 3

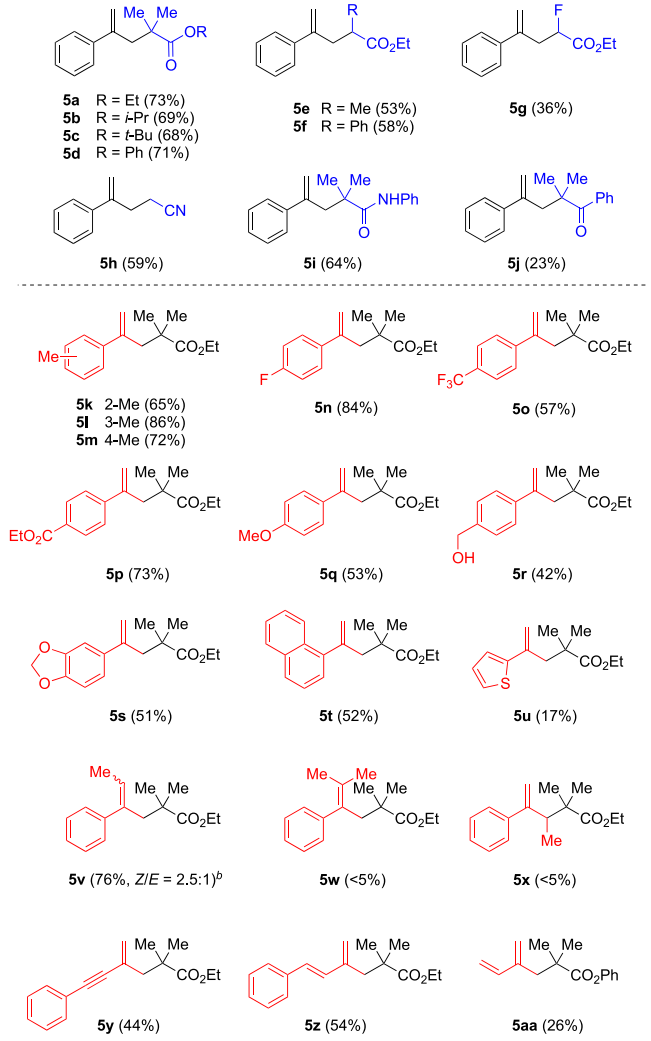


[a]Condition A: **1** (2.0 equiv.), **2** (0.2 mmol, 1.0 equiv.), $Cu(OTf)_2$ (10 mol %), Na_2CO_3 (1.2 equiv.), DCE, 90 °C. Isolation yields. [b]*Z*/*E* ratio determined by ^{1}H-NMR of the crude reaction.

Table 3. Decarboxylative Alkylation of Conjugated β,γ-Unsaturated Carboxylic Acids[a]



1 4 5



[a]Condition B: **1** (1.5 equiv.), **4** (0.3 mmol, 1.0 equiv.), $Cu(OTf)_2$ (10 mol %), bpy (10 mol %), Na_2CO_3 (1.1 equiv.), dioxane, 90 °C. Isolation yields. [b]*Z*/*E* ratio determined by ^{1}H-NMR of the crude reaction mixture.

substitutions on the phenyl ring were also investigated, including *ortho*-, *meta*-, and *para*-methyl groups (**5k**−**5m**), various electron-withdrawing groups (**5n**−**5p**), and electron-donating groups (**5q**−**5s**). Naphthyl-substituted carboxylic acid afforded product **5t** in 52% yield, while thienyl-containing carboxylic acid formed **5u** in only 17% yield. Substitution effects on the α- and γ-positions were also investigated in the reactions. Although α-monomethyl-substituted acid provided **5v** in 76% yield, both α,α-dimethyl-substituted acid and γ-methyl-substituted substrates failed to deliver **5w** and **5x** effectively, respectively, suggesting that steric bulkiness significantly hampered the decarboxylative alkylation. Finally, the reactions of β-alkynyl and β-vinyl substitutions successfully afforded the alkylation products **5y**−**5aa**.

We have also developed an analogous sulfur radical-initiated decarboxylative sulfonylation reaction of conjugated β,γ-unsaturated carboxylic acid (Table 4). The copper-catalyzed decarboxylative conditions were found to be effective,[10] promoting the formation of aromatic and aliphatic allylic sulfone products **7a**−**7e** using different sulfonyl chlorides.[12] Carboxylic acids bearing various functional groups on the phenyl ring all gave the desired allylic sulfones (**7f**−**7l**). Thienyl-substituted acid gave sulfone **7m** in only 29% yield. An α-monomethyl-substituted acid smoothly formed **7n**, while a γ-

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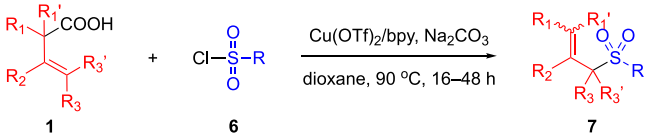
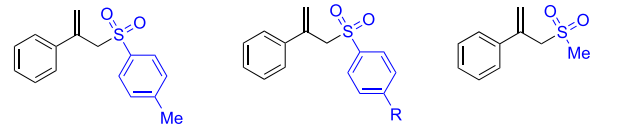
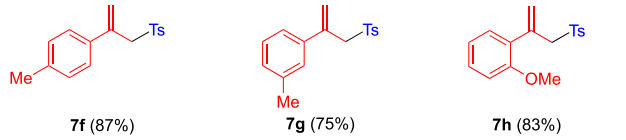
Table 4. Decarboxylative Sulfonylation of Conjugated β,γ-Unsaturated Carboxylic Acids[a]



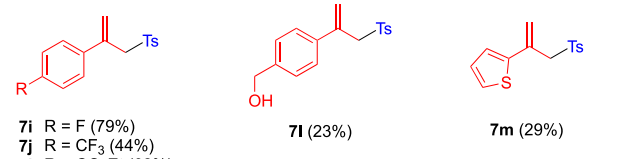
1 6 7



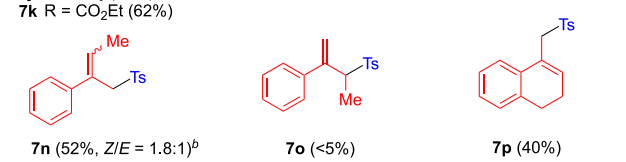
7a (71%) 7b R = H (67%) 7c R = OMe (73%) 7d R = NO2 (33%) 7e (51%)



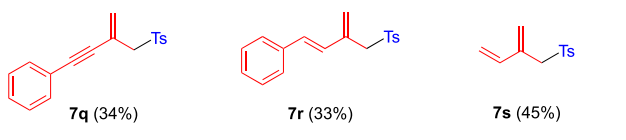
7f (87%) 7g (75%) 7h (83%)



7i R = F (79%) 7j R = CF3 (44%) 7k R = CO2Et (62%) 7l (23%) 7m (29%)



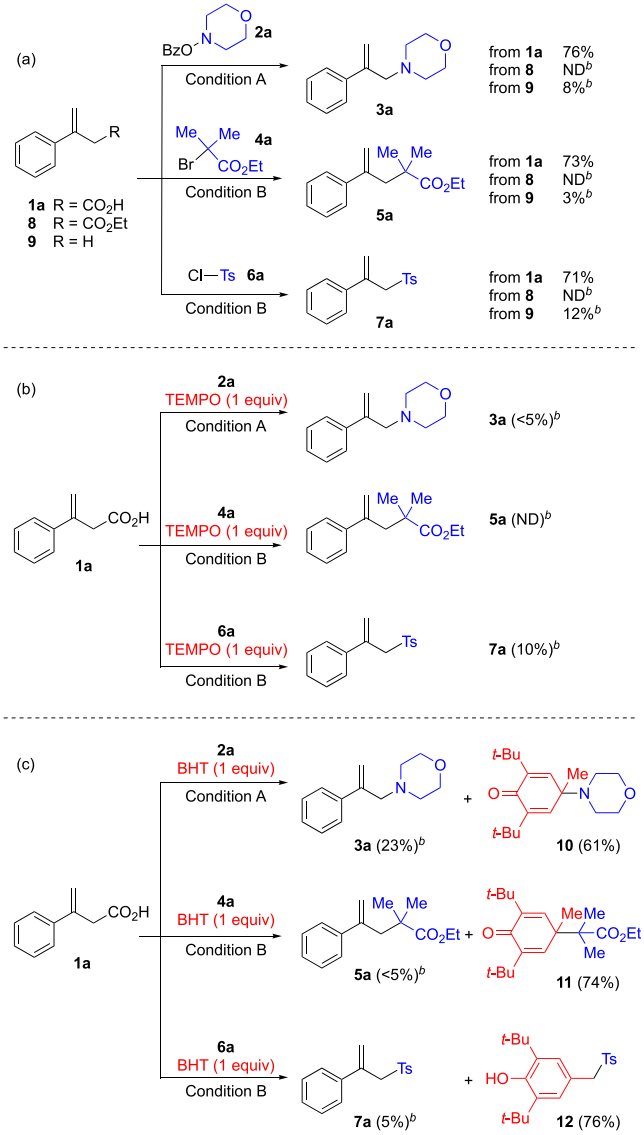
7n (52%, Z/E = 1.8:1)[b] 7o (<5%) 7p (40%)



7q (34%) 7r (33%) 7s (45%)

[a]Condition B: **1** (1.5 equiv.), **6** (0.3 mmol, 1.0 equiv.), $Cu(OTf)_2$ (10 mol %), bpy (10 mol %), Na_2CO_3 (1.1 equiv.), dioxane, 90 °C. Isolation yields. [b]Z/E ratio determined by ^{1}H-NMR of the crude reaction mixture.

Scheme 2. Control Experiments and Radical Capture Experiments[a]



[a]Isolation yields. Condition A shown in Table 2. Condition B shown in Tables 3 and 4. ND = Not detected. [b]Yields determined by ^{1}H-NMR with dibromomethane as an internal standard.

monomethyl-substituted acid failed to deliver the desired product **7o**. Interestingly, the dialin substrate formed **7p**, with the opposite regioselectivity to the amination product **3x**, possibly resulting from a direct decarboxylation pathway.[13] Carboxylic acids bearing β-alkynyl and β-vinyl groups worked effectively, generating desired allylic sulfones **7q**–**7s**.

Our development of the copper-catalyzed decarboxylative functionalization began with the hypothesis that the reactions would be initiated by electrophile addition to the olefin followed by subsequent decarboxylation. To examine this hypothesis, we ran a series of control experiments (Scheme 2). First, comparative experiments were performed using β,γ-unsaturated carboxylic acid **1a**, ester **8**, and simple olefin **9** under the standard conditions for decarboxylative amination, alkylation, and sulfonylation (Scheme 2a). The results from these experiments demonstrated that the free carboxyl group is critical in the decarboxylation step. To probe the presence of radical intermediates, control experiments were run with the addition of radical inhibitors, such as TEMPO (Scheme 2b) and butylated hydroxytoluene (BHT) (Scheme 2c). In all cases, the presence of a radical scavenger suppressed the formation of desired products. The observation of BHT-trapped products **10**–**12** further supports the formation of radical intermediates, which initiate the reaction by adding onto the double bond in these copper-catalyzed reactions. Note that the stereochemical outcomes observed in these decarboxylative transformations also indicated the involvement of radical intermediates. For example, when α-methyl-substituted β,γ-unsaturated carboxylic acid was used, allylic amine **3y** was obtained as a mixture of E/Z isomers. Similarly, allylic alkylation product **5v** and allylic sulfone **7n** were also formed as a mixture of E/Z isomers.

Based on these experimental observations and related studies,[8,11,12] we propose that the decarboxylation-assisted amination, sulfonylation, and alkylation of conjugated β,γ-unsaturated carboxylic acids may involve a similar pathway as shown in Scheme 3. First, the Cu(II) precatalyst would generate the active Cu(I) catalyst via disproportionation. Then

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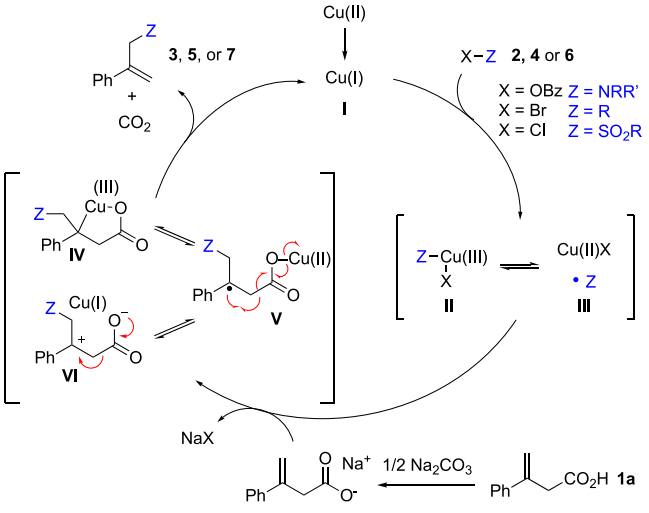
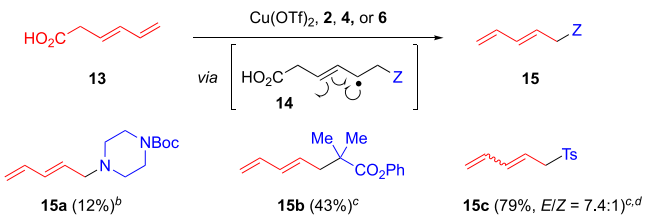
Scheme 3. Proposed Reaction Pathways for Decarboxylative Amination, Alkylation, and Sulfonylation



the oxidative addition of radical precursors X−Z (i.e., **2**, **4**, or **6**) to Cu(I) would generate a copper complex **II**, which possibly exists in an equilibrium with a Cu(II) species **III**. The resultant radical intermediates can be trapped by BHT, as shown in Scheme 2c. Subsequent addition to olefin would occur at the γ-position of β,γ-unsaturated carboxylic acid **1a**. The resulting intermediates **IV**−**VI** would undergo decarboxylation by either a one-electron or two-electron pathway to regenerate the Cu(I) catalyst and afford the allylic-functionalized product (i.e., **3**, **5**, or **7**). The control experiments with compound **9** in Scheme 2a suggest that C−H allylic functionalization pathways unlikely contribute to the formation of products (i.e., **3**, **5**, or **7**) under our reaction conditions, although allylic functionalization of α-methyl styrene has been reported for allylic alkylation using α-bromoesters[11f−g] or allylic sulfonylation using sulfonyl chlorides.[12]

With these mechanistic insights, we examined the potential of this decarboxylative functionalization pathway further on the diene system (Scheme 4). Encouragingly, the reactions of **13**

Scheme 4. Decarboxylative Functionalization of (*E*)-Hexa-3,5-dienoic Acid[a]

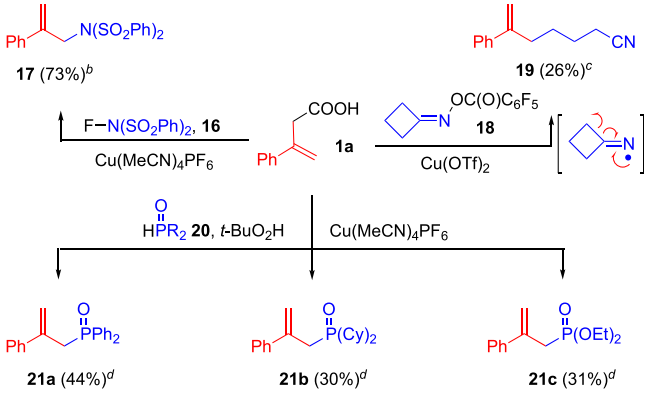


[a]Isolation yields. [b]Run under condition A shown in Table 2, see the Supporting Information for by-products. [c]Run under condition B shown in Tables 3 and 4. [d]*E*/*Z* ratio determined by 1H-NMR of the crude reaction mixture.

successfully delivered products **15**, under standard conditions for the decarboxylative amination, alkylation, and sulfonylation, presumably through the intermediate **14** via selective addition onto the terminal double bond. The poor yield of **15a** resulted in part from the competing amino lactonization pathway (see the Supporting Information).

Finally, we examined the applicability of this decarboxylation-assisted functionalization strategy on other radical precursors (Scheme 5). Using *N*-fluorobenzenesulfonimide

Scheme 5. Decarboxylative Sulfonimidation, Alkylation, Phosphinoylation, and Phosphonylation[a]



[a]Isolation yields. [b]Conditions: **1a** (2.0 equiv.), **16** (0.1 mmol, 1.0 equiv.), $Cu(MeCN)_4PF_6$ (10 mol %), DCE, 60 °C, 3 h. [c]Conditions: **1a** (2.0 equiv.), **2** (0.1 mmol, 1.0 equiv.), $Cu(OTf)_2$ (10 mol%), Na_2CO_3 (1.2 equiv.), DCE, 90 °C. [d]Conditions: **1a** (2.0 equiv.), **20** (0.1 mmol, 1.0 equiv.), $Cu(MeCN)_4PF_6$ (10 mol %), *t*-BuO_2H (2.0 equiv.), MeCN, 90 °C, 1 h.

(NFSI) **16** as a different type of nitrogen precursor, the reaction of carboxylic acid **1a** readily formed the allylic sulfonimide product **17** in 73% yield under modified conditions. The reaction of cyclobutanone *O*-acyloxime **18** led to the decarboxylative alkylation product **19** via a ring-opening generation of a primary alkyl radical. We also investigated a phosphine-centered radical generated under copper-catalyzed oxidative conditions in this decarboxylative approach.[14] Excitingly, the decarboxylative allylic phosphinoylation and phosphonylation of **1a** were viable, affording allylphosphine oxides **21a** and **21b** and allylphosphonate product **21c**.

In conclusion, we have developed a copper-catalyzed decarboxylative redox-neutral and traceless approach for the preparation of allylic amines, homoallylic carbonyl derivatives, and allylic sulfones from conjugated β,γ-unsaturated carboxylic acids. Decarboxylative allylic phosphinoylation and phosphonylation have also been achieved under oxidative conditions. These reactions feature high regioselectivity, good functional group tolerance, and simple operation procedure. Mechanistic studies suggest that the reaction is initiated by copper-catalyzed addition of radicals onto the olefin followed by decarboxylation. These insights support a general allylic functionalization strategy to rapidly construct diverse allyl-containing skeletons.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03621.

Condition optimizations, experimental procedures, compound characterization, and NMR spectra (PDF)

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Author Contributions

§W.Z. and C.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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