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Cu-Catalyzed highly regioselective 1,2-hydrocarboxylation of 1,3-dienes with CO₂†

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A practical copper-catalyzed highly regioselective 1,2-hydrocarboxylation of terminal 1,3-diene with carbon dioxide has been developed. Under mild reaction conditions, this chemistry afforded 2-benzyl- β , γ -unsaturated acid derivatives as products, which are a kind of important unit for bio-active molecules and versatile precursors for organic synthesis, with good functional group tolerance. The key intermediate in this transformation is illustrated by control experiments.

2-Benzyl- β , γ -unsaturated acid derivatives are important motifs in biologically active molecules, synthetic drugs or drug candidates (for some examples, see Fig. 1).¹ Furthermore, they are used as useful precursors to obtain various meaningful functional groups.² Therefore, numerous efforts have been made to construct 2-benzyl- β , γ -unsaturated acid derivatives.² To date, the prevalent strategy employs the reaction of active metal reagent intermediates with β , γ -unsaturated acid derivatives or α , β -unsaturated acid derivatives (A, Fig. 2).³ Usually, by the above methods, the branch and linear selectivity is difficult to control. Furthermore, the necessary metal intermediate might induce a limited substrate scope. So, despite numerous efforts for the synthesis of 2-benzyl- β , γ -unsaturated acid derivatives, the development of mild and efficient methods is still desired. Herein, we present a mild and practical one pot reaction to synthesize 2-benzyl- β , γ -unsaturated acid derivatives from easily available starting materials with good functional group tolerance.

Since it can afford multiple complex isomeric products from simple precursors, functionalization of conjugated dienes with high selectivity is an important strategy in organic synthesis.^{4,5} In recent years, a lot of breakthroughs focused on the 1,4-or 3,4-functionalization of terminal 1,3-dienes have provided

powerful methods for the synthesis of drugs, natural products and functional materials.⁵ In comparison with the above work, the methods for the 1,2-functionalization of terminal 1,3-dienes are rare, but useful and challenging.⁶ Recently, considering environmental protection and the increasing quest for fossil resources, the use of carbon dioxide (CO₂) as an abundant, nontoxic and sustainable one-carbon building block attracts much attention from synthetic communities.^{7,8} So the highly selective reaction of 1,3-dienes with CO_2 is a fantastic strategy to construct a complex compound. In this field, Yu's group developed an elegant research about the highly selective function of 1,3-dienes to obtain valuable hydroxyl compounds (1, B, Fig. 2).⁹ The catalytic carboxylation with CO_2 could construct carboxylic acid, which is a kind of important unit for natural products and pharmaceuticals. Martin's group reported an amazing highly selective 1,4-dicarboxylation of 1,3-dienes with CO₂ (2, B, Fig. 2).¹⁰ Herein, based on our previous studies about Cu-catalyzed highly selective 1,2-functionalization of 1,3-dienes in a one pot reaction,^{6a} and the research on copper-catalyzed carboxylation of allylic pinacol boronates with CO_{2} ¹¹ we developed a mild and practical one pot method for highly selective functionalization of 1,3-diene with CO2 to





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(A) Previous work



synthesise 2-benzyl- β , γ -unsaturated acid derivatives, which exist extensively in bio-active molecules (C, Fig. 2).

Our study commenced with a one pot copper-catalyzed reaction of *trans*-buta-1,3-dien-1-ylbenzene, B_2Pin_2 and CO_2 (1 atm). At the beginning, this practical protocol afforded 2-benzyl- β , γ -unsaturated acid (2a) with 4% yield (entry 1, Table 1). We then surveyed the effect of different bases (entries 2 and 3, Table 1). Among them, KO^tBu was selected as the best

Table 1 Effect of different reaction conditions ^a					
Ph + CO ₂ - trans-1a		[Cu] (10 mol%), Ligand (11 mol%) B ₂ Pin ₂ (2.0 equiv), Base (2.0 equiv) MeOH (1.25 equiv), Solvent, rt, 1.5 h then CO ₂ (1 atm), KO ^f Bu (2.0 equiv) 70 °C, 24 h; HCl (aq)			Ph HO 2a
Entry	[Cu]	Ligand	Base	Solvent	Yield ^b (%)
1	CuCI ₂	IMesHCI	LiO ^t Bu	NMP	4
2	CuCI ₂	IMesHCI	NaO ^t Bu	NMP	8
3	CuCl ₂	IMesHCI	KO ^t Bu	NMP	50
4	CuCl ₂	IMesHCI	KO ^t Bu	THF	7
5	CuCl ₂	IMesHCI	KO ^t Bu	DMF	41
6	CuCl ₂	IMesHCI	KO ^t Bu	DMA	43
7	$Cu(OTf)_2$	IMesHCI	KO ^t Bu	NMP	24
8	CuCI	IMesHCI	KO ^t Bu	NMP	46
9	CuCI ₂	ICyHCI	KO ^t Bu	NMP	39
10	$CuCI_2$	IPrHCI	KO ^t Bu	NMP	26
11	$CuCI_2$	PCy ₃	KO ^t Bu	NMP	24
12	$CuCI_2$	PPh_3	KO ^t Bu	NMP	$68 (63)^c$
13	None	PPh ₃	KO ^t Bu	NMP	Ó
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^{*a*} trans-**1a** (0.2 mmol), B₂Pin₂ (0.4 mmol), KO^tBu (0.4 mmol), [Cat] (10 mol%), PPh₃ (11 mol%), MeOH (0.25 mmol), NMP (1.5 ml), after 1.5 h; then CO₂ (1 atm), KO^tBu (0.4 mmol) 70 °C, 24 h then HCl (aq.) was added, r.t. ^{*b*} Yields were determined by GC using 2-methoxynaphthalene as an internal standard. Based on the data of raw ¹H-NMR and GC-Ms, there is no 5-phenylpent-3-enoic acid (1,4-selective product) in the reaction system. ^{*c*} Isolated yields.

one (entry 3, Table 1). The efficiency of this transformation decreased when using other kinds of solvents, such as tetrahydrofuran, *N*,*N*-dimethylformamide, or *N*,*N*-dimethylacetamide (entries 4–6, Table 1 and the ESI†). Then the effect of different copper catalysts was studied. Compared with CuCl₂, Cu(OTf)₂ and CuCl resulted in low yields (entries 1, 7 and 8, Table 1). Further studies indicated that different kinds of ligands could affect the results of this reaction (entries 9–12, Table 1). Under the same conditions, ICyCl, IPrCl and PCy₃ resulted in low yields. Interestingly, PPh₃, which is a kind of easily available ligand, afforded the best result. Moreover, the 2-benzyl- β , γ -unsaturated acid product could not be detected from the reaction without the copper catalyst (entry 13, Table 1).

Once the optimized reaction conditions were established, the substrate scope for this Cu-catalyzed highly regioselective carboxylation of 1,3-diene with CO2 was investigated (Table 2). To demonstrate that this chemistry could employ the readily available 1,3-diene to produce 2-benzyl- β , γ -unsaturated acid derivatives, trans-version and cis-version mixed starting materials were selected, because, compared with absolute trans-1,3-dienes, they are much more easily prepared, and could afford nearly the same yield (see the ESI[†]). In general, modest to good yields using either electron-rich or electron-deficient aryl substituted 1,3diene were obtained (3a to 3v, Table 2). Notably, the orthosubstituents did not affect the efficiency of this transformation (3d and 3e, Table 2). Interestingly, when chloric-substituted aromatic 1,3-diene was employed as a starting material, the corresponding product could be afforded, which could be used for further transformation (30, Table 2). To our delight, the methylthio group, which widely exists in bio-active molecules, could survive under these reaction conditions (3p, Table 2). Importantly, this method could be used to obtain boron ester groups containing the product, which is a kind of versatile intermediate for a lot of well-established C-C and C-heteroatom bond forming reactions (3q, Table 2). As expected, heterocyclic substrates worked well under this reaction condition, such as oxygen-containing heterocyclic-, thienyl- and indole-groups (3r to 3v, Table 2). The potentiality for pharmaceutical molecule modification of this reaction was well demonstrated by these results. We then tried to extend the application range to alkyl 1,3-dienes. The data suggested that the corresponding product could be obtained from an alkyl starting material, but the efficiency needed further improvement (3w, Table 2).

2-Benzyl- β , γ -unsaturated acid, which could be obtained by this method at a 1 mmol-scale (eqn (1), Scheme 1), is a kind of versatile intermediate for chemical synthesis. As shown in Scheme 1, the product **2a** could undergo a reductive reaction to yield a homo-allylic alcohol compound with 88% yield (a, Scheme 1). Furthermore, an iodo-lactone compound could be synthesized from **2a** with good efficiency (b, Scheme 1). Importantly, 2-benzyl- β , γ -unsaturated acid was reported as the starting material to synthesise a novel type of irreversible inhibitor for carboxypeptidase A (c, Scheme 1).¹²

Control experiments were designed to understand the mechanism of this transformation. First, this transformation did not work without B_2Pin_2 (eqn (1), Scheme 2). Furthermore,

Table 2 Cu-catalyzed highly regioselective 1,2-hydrocarboxylation of 1,3-dienes with $\mathrm{CO_2}^\vartheta$



 a 1 (0.2 mmol), B₂Pin₂ (0.4 mmol), KO'Bu (0.4 mmol), CuCl₂ (10 mol%), PPh₃ (11 mol%), MeOH (0.25 mmol), NMP (1.5 ml), after 1.5 h; CO₂ (1 atm), KO'Bu (0.4 mmol) 70 °C, 24 h, then MeI (0.6 mmol) was added, r.t., 3 h. ^b Isolated yields.

boron ester **6** could be detected in the reaction system without carbon dioxide with 90% GC-yield (eqn (2), Scheme 2 and the ESI†). Without the copper catalyst, the intermediate **6** could not be detected, which suggested that the step to generate **6** is a copper-catalyzed process (eqn (3), Scheme 2).¹³ Further study revealed that the boron ester **6** could be used as a starting material to obtain the product **3a** under standard conditions with good efficiency (eqn (4), Scheme 2). These results suggested that the boron ester **6** should be one of the key intermediates in this chemistry. However, the above reaction, which converted **6** into the product, did not work without CuCl₂, and this result suggested that copper-salt plays a key role as a catalyst in this step (eqn (5), Scheme 2).



Scheme 1 Further transformation of the product: (a) 2a (0.40 mmol), LiAlH₄ (1.2 mmol), THF (2.0 mL), isolated yield. (b) 2a (0.32 mmol), oxone (0.64 mmol) and KI (0.64 mmol), CH₃CN : H₂O = 1:1 (4.0 mL), the isolated yield.



Based on the above results, the proposed mechanism for this carboxylate reaction is illustrated in Scheme 3. The active copper catalyst was generated in the first step of this transformation. It reacted with B_2Pin_2 to form Cu–B complex 8, which could react with 1,3-diene to afford the key intermediate boron ester 6.¹³ After the above steps, the transmetalation reaction of copper salt and boron ester 6 could afford intermediate 9,¹³ which reacted with carbon dioxide to produce the desired product 2a.^{11,14} Furthermore, in this reaction system, compound 11 could be detected by GC-MS and HRMS. It was generated from the reaction of B_2Pin_2 with CO₂, and it could consume and deactivate the copper catalyst to induce a negative effect on the result of the desired reaction path.¹⁵

In conclusion, we have demonstrated a novel Cu-catalyzed highly regioselective carboxylation of 1,3-diene with CO₂. This chemistry could realize the synthesis of 2-benzyl- β , γ -unsaturated acid derivatives, which are versatile precursors for a lot of transformations and are important motifs for bioactive molecules, from easily available starting materials with good functional group tolerance. The key boron ester intermediate of this



transformation was proved by control experiments. Further studies on synthetic applications are on-going in our laboratory.

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Conflicts of interest

The authors declare no competing financial interest.

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