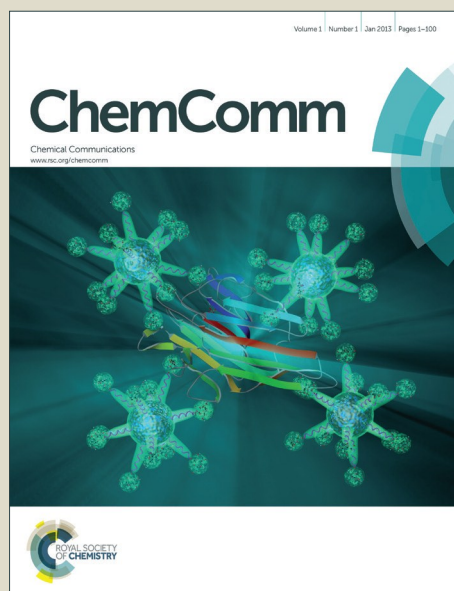


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## COMMUNICATION

## Zirconocene-catalyzed sequential ethylcarboxylation of alkenes using ethylmagnesium chloride and carbon dioxide†

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2015,  
Accepted 00th January 2015

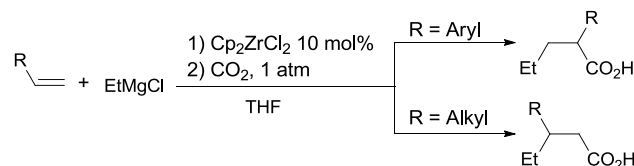
DOI: 10.1039/x0xx00000x

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**The zirconocene-catalyzed sequential ethylcarboxylation of alkenes using ethylmagnesium chloride and carbon dioxide has been developed. A range of alkenes were transformed to the corresponding carboxylic acids in high yields.**

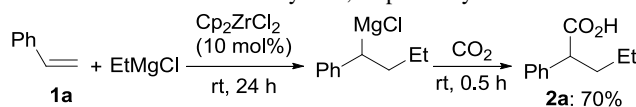
Carbon dioxide is an extremely attractive carbon source that is readily available, inexpensive, nonflammable, and inherently renewable. Its utilization as a C1 feedstock has seen considerable growth in recent years.<sup>1</sup> Among them, its utilization in carboxylation of carbon nucleophiles is a straightforward method for the synthesis of carboxylic acids. Grignard and organolithium reagents are strong nucleophiles which react with CO<sub>2</sub> directly to form valuable carboxylic acids; however, their sensitivity to moisture and poor functional group compatibility ultimately limits their use.<sup>2</sup> Less reactive organoboranes,<sup>3</sup> organozincs<sup>4</sup> and organotin<sup>5</sup> were found to react with CO<sub>2</sub> with good functional group tolerance in the presence of a transition-metal catalyst. However, all these carboxylation reaction required preformed organometallic reagents to react with CO<sub>2</sub>. Thus, catalytic generation of nucleophilic organometallic species *in situ* from easily available unsaturated hydrocarbons would be highly desirable from the point of view of the atom economical synthetic methodology. Carboxylation of styrenes<sup>6</sup> and allenes<sup>7</sup> with CO<sub>2</sub> in the presence of transition metal catalysts such as Ni, Fe, Pd and Cu have been reported. The carboxylation of styrenes with CO<sub>2</sub> proceeded with good selectivity to afford phenylacetic acids. The catalytic carboxylation of allenes with CO<sub>2</sub> provided a method for the synthesis of allyl carboxylic acids. All these reactions proceeded in hydrocarboxylation of unsaturated substrates. Very recently, Tsuji reported a regiodivergent silacarboxylation of allenes with silylborane and CO<sub>2</sub> in the presence of a copper catalyst and the regioselectivity can be highly controlled.<sup>8</sup> As part of an ongoing program in our laboratory to study zirconocene chemistry, we herein describe a zirconocene-catalyzed ethylcarboxylation of alkenes with ethylmagnesium chloride and carbon dioxide (Scheme 1). When styrene derivatives were used and  $\alpha$ -aryl carboxylic acids were formed. When alkyl-substituted alkenes were used and alkanolic acids were formed.



**Scheme 1** Zr-catalyzed ethylcarboxylation of alkenes with ethylmagnesium chloride and carbon dioxide

Zirconocene complexes have been found extensive application as stoichiometric reagents in organic synthesis.<sup>9</sup> Needless to say, catalytic process is much more expected. Cp<sub>2</sub>ZrCl<sub>2</sub>-catalyzed addition of ethylmagnesium halides to alkenes has been reported.<sup>10</sup> This reaction accomplishes a formation of carbon-carbon bond by addition of an alkyl Grignard reagent to an alkene with high regioselectivity. Furthermore, the resulting product would be employed in further bond-forming processes. Herein we report details of Cp<sub>2</sub>ZrCl<sub>2</sub>-catalyzed ethylcarboxylation of alkenes with ethylmagnesium chloride and CO<sub>2</sub>.

A typical procedure is as follows (Scheme 2). To a solution of zirconocene dichloride (0.1 mmol) in THF (2 mL) was added EtMgCl (3 mmol) at -78 °C. The solution was stirred at room temperature for 1 h, followed by the addition of alkene **1a** (1 mmol) at -78 °C and stirred for 1 h. Then the reaction mixture was warmed to room temperature and stirred for 24 h.<sup>10c</sup> Subsequently, the reaction mixture was bubbled with CO<sub>2</sub> for 0.5 h at room temperature. Hydrolytic workup afforded carboxylic acid **2a** in 70% isolated yield (based on **1a**) with high regioselectivity. When EtMgCl employed in 1.5 mmol and 2.0 mmol and the product **2a** was obtained in 50% and 57% yields, respectively.



**Scheme 2** Typical procedure of ethyl carboxylated styrene.

The scope of the reaction was investigated and the representative results are summarized in Table 1. Pleasingly, it was found that styrene derivatives bearing electron-donating groups worked well to afford  $\alpha$ -carboxylic acids. Alkyl substitution in all positions on the aromatic ring was well tolerated (entries 2-5), giving the  $\alpha$ -

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carboxylic acids **2b–2e** in high yields. The electron-rich *para*-, *meta*- and *ortho*-methoxystyrene derivatives gave the  $\alpha$ -carboxylic acids **2f**, **2g** and **2h** in satisfied yields, respectively. 2,5-Bismethoxystyrene **1i** gave  $\alpha$ -carboxylic acid **2i** in 59% yield (entry 9). However, 3,4-bismethoxystyrene **1j** gave a reduced yield (entry 10), possibly due to Grignard-mediated demethylation which was enhanced by coordination to the adjacent methoxy group. In addition, when *para*-fluorostyrene, *para*-chlorostyrene, *ortho*-methylstyrene, and 2-vinylpyridine were used and carboxylic acids formed in trace. As example, the reaction mixture was treated with allylic bromide instead of hydrolysis to afford allyl 2-(4-isopropylphenyl)pentanoate **3d** in 67% isolated yield (entry 11).

Table 1. Zirconocene-catalyzed ethylcarboxylation of various styrenes<sup>a</sup>

Entry	Styrenes	Product	Yield (%) <sup>b</sup>
1			70%
2			75%
3			60%
4			79%
5			84%
6			90%
7			64%
8			54%
9			59%
10			10%
11 <sup>c</sup>			67%

<sup>a</sup>Reaction conditions: Cp<sub>2</sub>ZrCl<sub>2</sub> (0.1 mmol, 10 mol%), EtMgCl (3.0 mmol, 3 equiv), styrene **1** (1.0 mmol) in THF (2 mL), CO<sub>2</sub> (1 atm). <sup>b</sup>Isolated yield based on alkene. <sup>c</sup>The reaction mixture was treated with allylic bromide (4 mmol) at room temperature for 3 h in the presence of CuCl.

Notably, under this catalytic system, alkyl alkenes could also work smoothly and the corresponding aliphatic carboxylic acids were produced in high efficiency. The examples are shown in Table 2. The terminal alkene could bear different alkyl substituents with functional groups. In all cases, the products are formed in high yields. In contrast to Ni- and Fe-catalyzed carboxylation of alkenes,<sup>6</sup> this approach enables carboxylation of compatible aliphatic alkenes. Again, esterification of the reaction mixture by allylic bromide afforded allyl 3-ethyl-5-(4-fluorophenyl)pentanoate **3n** in 62% isolated yield (entry 10).

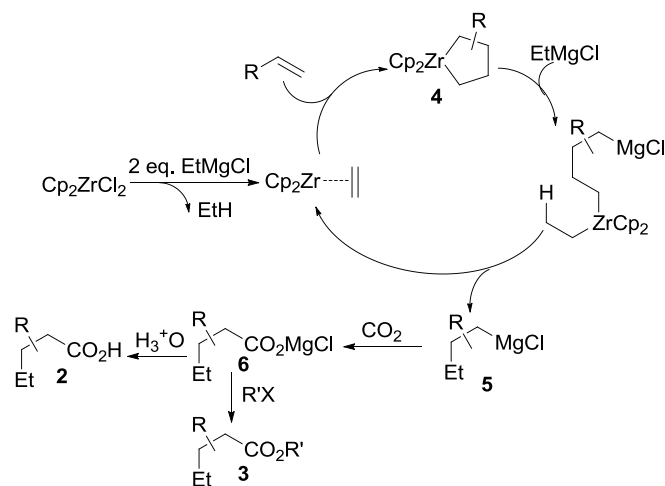
Table 2. Zirconocene-catalyzed ethylcarboxylation of terminal alkenes<sup>a</sup>

Entry	Alkene	Product	Yield (%) <sup>b</sup>
1			66%
2			74%
3			52%
4			73%
5			55%
6			60%
7			78%
8			53%
9			82%
10 <sup>c</sup>			62%

<sup>a</sup>Reaction conditions: Cp<sub>2</sub>ZrCl<sub>2</sub> (0.1 mmol, 10 mol%), EtMgCl (3.0 mmol, 3 equiv), alkene **1** (1.0 mmol) in THF (2 mL), CO<sub>2</sub> (1 atm). <sup>b</sup>Isolated yield based on alkene. <sup>c</sup>The reaction mixture was treated with allylic bromide (4 mmol) at room temperature for 3 h in the presence of CuCl.

The zirconocene-catalyzed ethylmagnesiation reaction of simple monosubstituted alkenes by ethylmagnesium chloride has been reported.<sup>10a-c</sup> In combination with known facts, a plausible mechanism is shown in Scheme 3. The reaction of Cp<sub>2</sub>ZrCl<sub>2</sub> with two molar amounts of EtMgCl and one equimolar amount of alkene (RCH=CH<sub>2</sub>) produces zirconacyclopentane **4**. The third molar amount of EtMgCl reacts with zirconacyclopentane **4** to undergo transmetalation followed by  $\beta$ -H abstraction to afford ethylmagnesiated product **5** and regenerated Cp<sub>2</sub>Zr(ethylene). The resulting intermediate **5** reacts with CO<sub>2</sub> to afford magnesium acetate **6<sup>6a</sup>** which undergoes hydrolysis or esterification to form carboxylic acid **2** or ester **3**. To further confirm the reaction mechanism, we

monitored the reaction by IR. For example, the IR spectra absorption in the carboxylate of **6f** appeared in 1647 cm<sup>-1</sup>, which moved to 1704 cm<sup>-1</sup> after workup to form product **2f**. The result indicated that the intermediate **6** is the most like intermediate.



**Scheme 3** Plausible reaction mechanism

In summary, we have developed a zirconocene-catalyzed sequential ethylcarboxylation of alkenes using ethylmagnesium chloride and carbon dioxide. The reaction proceeds under mild conditions in high yields with a wide range of alkenes. Styrene and its derivatives were used to afford  $\alpha$ -aryl carboxylic acids and aliphatic alkenes were used to form alkanolic acids.

This work was supported by the National Natural Science Foundation of China (21272132 and 21472106) and the National Key Basic Research Program of China (973 program) (2012CB933402).

## Notes and references

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† Dedicated to Professor Tamotsu Takahashi on the occasion of his 60th birthday.

† Electronic Supplementary Information (ESI) available: Experimental procedures, full characterization including <sup>1</sup>H NMR and <sup>13</sup>C NMR data and spectra for all compounds. See DOI: 10.1039/c000000x/

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