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Cp_2TiCl_2-Catalyzed Regioselective Hydrocarboxylation of Alkenes with CO_2

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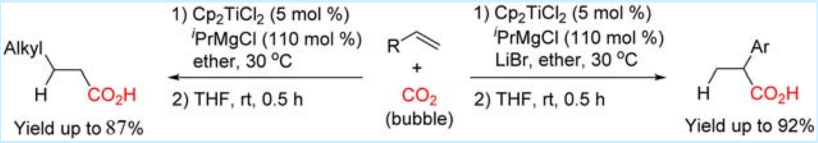
Supporting Information



ABSTRACT: Cp_2TiCl_2-catalyzed regioselective hydrocarboxylation of alkenes with CO_2 to give carboxylic acids in high yields has been developed in the presence of ^iPrMgCl. The reaction proceeds with a wide range of alkenes under mild conditions. Styrene and its derivatives can transform to α-aryl carboxylic acids, and aliphatic alkenes can transform to form alkanoic acids.

Carbon dioxide (CO_2) is an environmentally friendly carbon source that is readily available, inexpensive, nonflammable, and inherently renewable. Utilization of CO_2 as a chemical feedstock has seen considerable growth in recent years.[1,2] One of the uses developed for CO_2 has been as a C1 source to synthesize carboxylic acids and their derivatives,[2c−e,i,j] which are an important class of organic compounds used in medicinal chemistry and fine chemicals synthesis.[3] Direct reaction of strong nucleophiles such as Grignard and organolithium reagents with CO_2 presented a straightforward method for synthesis of carboxylic acids; however, poor functional group compatibility limits their use.[4] This protocol has been expanded to transition-metal-catalyzed carboxylation of less reactive organometallic reagents such as organoboranes,[5] organozincs,[6] organotins,[7] organoaluminums,[8] and organozirconium,[9] which provided a useful method for preparing a variety of carboxylic acids bearing functional groups. For all this, the carboxylation reaction required preformed organometallic reagents to react with CO_2. Therefore, catalytic generation of organometallic species in situ from readily available unsaturated hydrocarbons is more straightforward and uses more efficient routes. Recently, several groups have reported transition-metal-catalyzed direct carboxylation of alkenes with CO_2 to afford alkyl carboxylic acids.[10] Rovis and co-workers first realized nickel-catalyzed hydrocarboxylation of electron-deficient styrene derivatives with CO_2 in the presence of Et_2Zn to afford α-carboxylated acids.[10a] More recently, Thomas and co-workers used low-cost and readily available $FeCl_2$ as a precatalyst to achieve a hydrocarboxylation of electron-rich styrene derivatives with CO_2 in the presence of Grignard reagents to obtain α-carboxylic acids.[10b] All of the suggested mechanism of these reactions involved a "metal hydride" species.

It has been reported that titanium-catalyzed exchange of alkenes with Grignard reagents leads to new Grignard reagents.[11,12] In this reaction, a highly active "titanium hydride" species was generated from $TiCl_4$ or Cp_2TiCl_2 and Grignard reagent, followed by insertion of alkene and transmetalation to yield a new Grignard reagent. Encouraged by these results and as part of our ongoing projects on group IV metal complexes in organic synthesis,[13,14] we herein report a Cp_2TiCl_2-catalyzed regioselective hydrocarboxylation of variously substituted alkenes with CO_2 in the presence of isopropylmagnesium chloride (Scheme 1). Aryl-substituted alkenes afforded α-carboxylic acids and alkyl-substituted alkenes afforded alkanoic acids.

In the initial study, the reaction using *p*-*tert*-butylstyrene **1a** as a model substrate and 5 mol % of Cp_2TiCl_2 as a catalyst in the presence of isopropylmagnesium chloride (^iPrMgCl) in diethyl ether at 30 °C for 24 h proceeded smoothly to form the hydromagnesation intermediate. Subsequently, CO_2 was added to the reaction system at room temperature for 0.5 h to give α-carboxylated acid **2a** in 60% yield with β-carboxylated acid **2a′** in 20% yield (Table 1, entry 1). During the CO_2 gas bubbling, the reaction mixture became a slurry and often blocked the syringe needle for CO_2 gas flow. Therefore, we tried to remove the diethyl ether and add THF in the vessel to improve the solubility of magnesium salts. As we expected, the CO_2 gas flowed smoothly in the THF solution. We then examined some Grignard reagents, such as *n*-propylmagnesium chloride (^nPrMgCl), isobutylmagnesium chloride (^iBuMgCl), cyclopentylmagnesium chloride (C_5H_9MgCl), and cyclohexylmagnesium chloride ($C_6H_{11}MgCl$). In all cases, the products were formed as a mixture of two isomers (entries 2−5). It is noteworthy that when ^iPrMgBr was used the reaction proceeded well and afforded the α-carboxylated product **2a** in 63% yield with high regioselectivity (entry 6). ^nPrMgBr and

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Scheme 1. Hydrocarboxylation of Aryl and Alkyl Terminal Alkenes

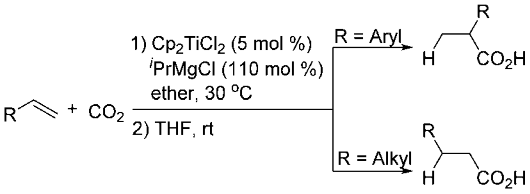
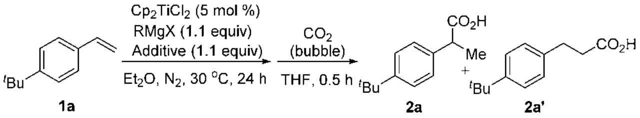


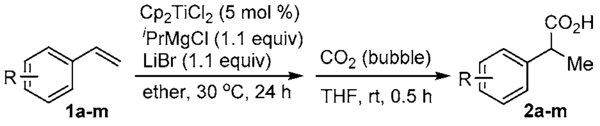
Table 1. Optimization of the Reaction Conditions[a]

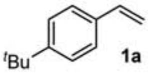
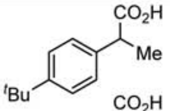
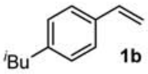
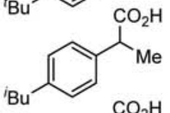
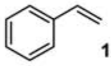
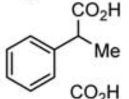
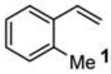
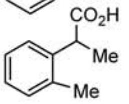
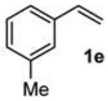
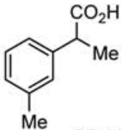
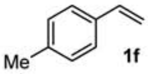
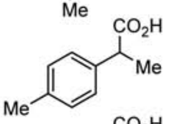
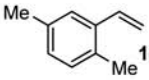
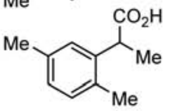
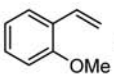
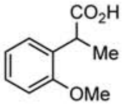
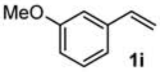
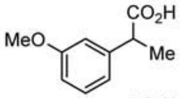
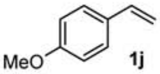
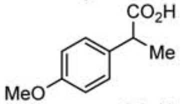
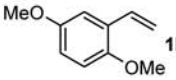
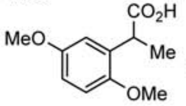
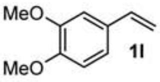
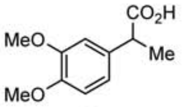
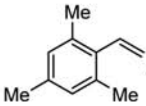
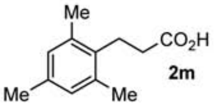


entry	RMgX	additive	yield of product **2a**/**2a′**[b] (%)
1	^{i}PrMgCl		60/20
2	^{n}PrMgCl		57/23
3	^{i}BuMgCl		40/35
4	C_5H_9MgCl		51/20
5	$C_6H_{11}MgCl$		53/18
6	^{i}PrMgBr		63/1
7	^{n}PrMgBr		43/2
8	EtMgBr		51/3
9	^{i}PrMgCl	NaBr	24/17
10	^{i}PrMgCl	NaCl	29/18
11	^{i}PrMgCl	LiCl	65/2
12	**^{i}PrMgCl**	**LiBr**	**85/− (78)**
13[c]	^{i}PrMgCl	LiBr	34/11

[a] Reaction conditions: (i) **1a** (1.0 mmol), Cp_2TiCl_2 (0.05 mmol), Grignard reagent (1.1 mmol, diethyl ether solution), diethyl ether (4 mL), N_2, 30 °C, 24 h; (ii) CO_2 bubble, THF (4 mL), room temperature, 0.5 h; [b] NMR yield, trichloroethylene as the internal standard, isolated yield in parentheses. [c] The reaction was treated directly in THF.

Table 2. Scope of Styrene Derivatives in Hydrocarboxylation[a]



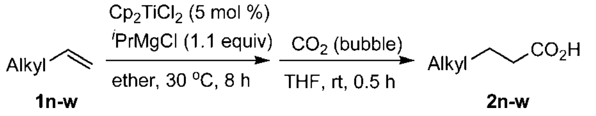
entry	styrene	product	yield of **2/2′** (%)[b]
1	 **1a**	 **2a**	78/-
2	 **1b**	 **2b**	76/-
3	 **1c**	 **2c**	70/-
4	 **1d**	 **2d**	58/-
5	 **1e**	 **2e**	67/-
6	 **1f**	 **2f**	66/-
7	 **1g**	 **2g**	79/-
8	 **1h**	 **2h**	85/-
9	 **1i**	 **2i**	92/-
10	 **1j**	 **2j**	53/-
11	 **1k**	 **2k**	82/-
12	 **1l**	 **2l**	47/-
13	 **1m**	 **2m**	-/23

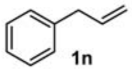
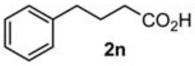
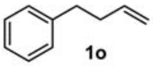
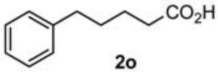
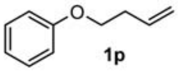
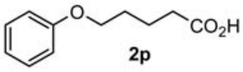
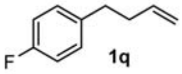
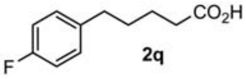
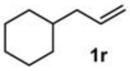
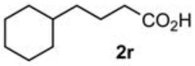
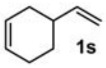
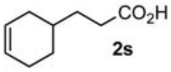
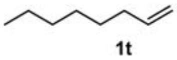
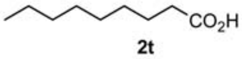
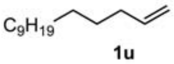
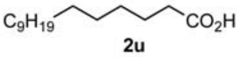
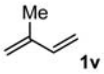
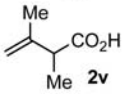
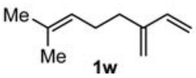
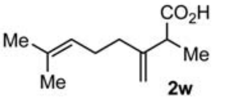
[a] Reaction conditions: (i) **1** (1.0 mmol), Cp_2TiCl_2 (0.05 mmol), ^{i}PrMgCl (1.1 mmol, diethyl ether solution), LiBr (1.1 mmol), diethyl ether (4 mL), N_2, 30 °C, 24 h. (ii) CO_2 bubble, THF (4 mL), room temperature, 0.5 h; [b] Isolated yield.

EtMgBr also gave the α-carboxylated product **2a** in 43% and 47% yields with high regioselectivity, respectively (entries 7 and 8). In order to further improve the yield and regioselectivity, we tried to add the other anhydrous salts such as NaCl, NaBr, LiCl, and LiBr to the reaction mixture, respectively, when ^{i}PrMgCl was used in the reaction (entries 9−12). To our delight, the α-carboxylated product **2a** was obtained with high yield when LiBr was added (entry 12). The addition of LiBr not only improved the regioselectivity of the reaction by giving the α-carboxylated acid **2a** exclusively but also dramatically increased the yield to 85%, which may be attributable to both halogen exchange with ^{i}PrMgCl to form ^{i}PrMgBr and increased solubility of Grignard reagents in the system. Notably, when the reaction was treated directly in THF, the mixture of two products **2a** and **2a′** were obtained in 34% and 11% yield, respectively (entry 13).

Under the optimal conditions, we first examined the scope of this reaction using aryl terminal alkenes as the starting materials. The representative results are summarized in Table 2. A range of styrene derivatives could conduct the hydrocarboxylation for formation of α-carboxylic acids in moderate to good yields with excellent regioselectivity. The styrene derivatives bearing alkyl substituents at any position of the phenyl ring can work smoothly to afford the corresponding benzylic acids (entries 1, 2, and 4−6). The styrene derivatives with strongly electron-donating group on phenyl ring, such as methoxyl group also proceeded efficiently to give the desired product **2h** and **2i** in high yields, respectively (entries 8 and 9).

Table 3. Scope of Alkyl Terminal Alkenes in Hydrocarboxylation[a]



entry	alkenes	product	yield of 2/2′ (%)[b]
1	 **1n**	 **2n**	-/59
2	 **1o**	 **2o**	-/49
3	 **1p**	 **2p**	-/65
4	 **1q**	 **2q**	-/60
5	 **1r**	 **2r**	-/43
6	 **1s**	 **2s**	-/60
7	 **1t**	 **2t**	-/67
8	 **1u**	 **2u**	-/51
9	 **1v**	 **2v**	-/74
10	 **1w**	 **2w**	-/87

[a]Reaction conditions: (i) **1** (1.0 mmol), Cp_2TiCl_2 (0.05 mmol), ^iPrMgCl (1.1 mmol, diethyl ether solution), diethyl ether (4 mL), N_2, 30 °C, 8 h; (ii) CO_2 bubble, THF (4 mL), room temperature, 0.5 h; [b]Isolated yield.

When *p*-methoxylstyrene was employed, benzylic acid **2j** was obtained in lower yield even with longer reaction time (entry 10). When 2,5-dimethylstyrene **1g** and 2,5-dimethoxylstryene **1k** were utilized in this reaction, the target products **2g** and **2k** were also obtained in good yields (entries 7 and 11). However, 3,4-dimethoxystyrene gave a reduced yield, which was probably due to coordination of Grignard reagent with adjacent methoxyl groups. It is noteworthy that when 2,4,6-trimethylstyrene was used the *β*-carboxylated product **2m** was obtained in 23% yield with a reversal regioselectivity, which was possibly due to the bulky steric hindrance effect of two *o*-methyl groups. When *p*-fluorostyrene and *p*-chlorostyrene were used, trace amount of products were detected by GC−MS. Stronger electron-withdrawing groups on the phenyl ring, such as −CN, −COOMe, and $-NO_2$, were tolerated, but the desired products were not obtained.

To establish the full scope of the reaction, we further explored alkyl terminal alkenes. It is noteworthy that the alkyl terminal alkenes were also able to proceed smoothly in good yields with formation of terminal carboxylic acids rather than *α*-carboxylic acids, which maybe more stable due to the smaller elctronic density on the primary carbon anion as in the case of the addition of boron hydrides to alkenes.[15] The representative results are shown in Table 3. Alkenes tolerated various functional groups such as phenyl, phenolic hydroxyl, fluoro, cyclohexyl, and cyclohexenyl groups (entries 1−6). Terminal alkenes with long carbon chains could also be transformed smoothly to give the corresponding aliphatic acids **2t** and **2u** in good yields, respectively (entries 7 and 8). Furthermore, the reaction was also applied to commercially available 1,3-dienes such as isoprene **1v** and myrcene **1w** to afford *β*,*γ*-unsaturated substituted carboxylic acids **2v** and **2w** in high yields with excellent regioselectivity (entries 9 and 10). Notably, when alkyl-substituted alkenes were employed in the reaction, LiBr did not affect the yield and regioselectivity of products.

In summary, Cp_2TiCl_2-catalyzed an efficient hydrocarboxylation of aryl- and alkylalkenes with CO_2 has been developed, giving *α*-aryl carboxylic acids and alkanoic acids in good yields with excellent regioselectivity. The alkylmagnesium compounds are easily and widely available through Cp_2TiCl_2-catalyzed hydromagnesiation, and thus the overall process represents a reductive carboxylation of alkenes with CO_2.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00665.

Full experimental procedures, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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