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Direct carboxylation of allylic halides with carbon dioxide in the presence of indium[†]

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A highly regioselective indium-mediated allylation of carbon dioxide starting from simple allylic halides (X = I, Br, Cl) has been developed. No transition metal catalyst is needed and an inert atmosphere is not necessary. The reaction tolerates a wide range of synthetically attractive functional groups with a very high branched regioselectivity.

The activation of carbon dioxide has been a hot topic, which boasts great potential in the field of energy and environmental protection Moreover, CO₂ excels in carbon–carbon bond formation reactions as a nontoxic, abundant and inexpensive, yet highly inactive C1 starting material, especially in the synthesis of carboxylic acids.¹ Thus, smooth transformations using cheap and easily acquired reagents such as arenes,² alkenes,³ allenes,⁴ alkynes,⁵ aryl halides⁶ and benzyl halides⁷ have drawn widespread attention.

Although the catalyzed carboxylation of aryl halides mediated by a stoichiometric amount of metal has been well established,⁶ similar transformation in allyl halides is surprisingly unsettled.⁷ Traditional reactions of allyl lithium or Grignard reagents with CO₂ seriously suffer from the substrate scope for the functionality group tolerance due to the high reactivity of these allylmetal reagents.⁸ On the other hand, transition metal-catalyzed carboxylation reactions starting from preformed allylmetals including allylstannanes and allylboranes encounter the problem of toxicity and sometimes affording a mixture of 2- and 3-alkenoic acids.⁹⁻¹² To solve this problem, in most cases, highly electron-rich ligands such as pincer-type diphosphine and NHC are necessary.



Scheme 1 Previous work and our concept of the allylation of CO₂.

Thus, the direct carboxylation of allyl halides in the presence of a metal which display wide functional group tolerance is surely the best choice for the synthesis of 3-alkenoic acids. Thus, identifying a metal for the direct transformation of allylic halides to 3-alkenoic acids with a practical regioselectivity referring the position of C==C bonds in the products as well as branched *vs.* linear selectivity is highly desired (Scheme 1). With great advantages including its nontoxic nature, wide functional group tolerance and friendly operation, allylindium species has shown its potential in the allylation in the last few decades.¹³ Although the allylation of aldehydes and ketones were well established, the related allylation of CO_2 mediated by indium has never been reported. Herein, we report the realization of our concept using indium.

After trying some metals with common solvents, we observed that when allyl bromide was treated with 0.67 equiv. of indium powder¹⁴ in DMF at 60 °C with a CO₂ balloon, the expected product **2a** was afforded albeit in only 14% yield. Rescreening in other solvents did not give better results. After some trials, we found that pressure plays a critical role in the reaction: the yield sharply increased upon raising the pressure of CO₂ and reached the peak (68%) with 2 MPa of

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 CO_2 (Table 1, entry 5, for the effect of pressure on the reaction, see Scheme S1, ESI[†]). It should be pointed out that such a pressure is easy to achieve in the laboratory and industrial processes.

The yield dropped to 32% at 45 °C and 6% at rt (19 °C) (Table 1, entries 7 and 8). Increasing the ratio of In:allyl bromide did not improve the yield (Table 1, entries 9 and 10). Interestingly, when 1.0 equiv. of $CsF^{5l,o,15}$ was added, the yield with allyl bromide was further improved to 72% (Table 1, entry 11).

Table 1 Optimization of the reaction conditions^{a,b} CO₂ (x MPa) In + соон x solvent, temp., 14 h 2a Entry Solvent CO_2 (MPa) Temp. (°C) Ratio In:S.M. Yield of 2a^c 1 DMF 0.1 14 60 1:1.52 DMF 3.0 60 1:1.5 59 3 THF 3.0 60 1:1.523 DMI 39 4 3.060 1:1.5DMF 5 2.060 1:1.568 DMF 60 44 6 0.5 1:1.57 32 DMF 2.045 1:1.58 DMF 2.0 r.t. (19) 1:1.5 6 9 DMF 2.060 1:1.369 10 DMF 2.060 1:1.1 65 72^d 11 DMF 2.0 60 1:1.5 61^e 12 DMF 2.0 60 1:1.5

 a The reaction was conducted with 1.5 mmol of allylic halide and In (powder, 425 mesh) under CO₂ in 5 mL of an anhydrous solvent. b For a complete list of optimization of reaction conditions, see ESI. c Determined by ¹H NMR analysis using CH₂Br₂ as the internal standard. d 1.0 equiv. of CsF was added. e 1.0 equiv. of LiCl was added.

It is worth noting that allyl chloride may also react upon addition of 1.0 equiv. of LiI although the yield is a little bit lower as compared with allyl bromide (Table 2, entry 2); allyl iodide afforded the adduct in 54% yield (Table 2, entry 3).

Table 2	Survey of ot				
	In + 0.67 equiv.	X	CO ₂ (2.0 MPa) DMF, 60 °C, 14 h	СООН	
Entry	X		Additive		Yield of 2 a ^b
1 2 3	Cl Cl I		 LiI (1.0 equiv.) 		n.d. 55 54

^{*a*} The reaction was conducted with 1.5 mmol of allylic halide and 1.0 mmol of In (powder, 425 mesh) under a 2 MPa CO_2 atmosphere in 5 mL of anhydrous DMF at 60 °C. ^{*b*} Determined by ¹H NMR analysis using CH_2Br_2 as the internal standard.

The substrate scope of the reaction has been explored under the optimal conditions (Table 1, entry 11). The reaction proceeds with both 2-aryl, -benzyl, and -alkyl-substituted allylic bromides (Table 3, entries 1–5). In addition to **2b**, the reaction of 2-phenylallyl bromide also afforded 2-phenylpropene (9%) and a trace amount of 2,5-diphenyl-1,6-hexadiene.

 Table 3
 The scope of In-mediated allylation of carbon dioxide^a

	ln + 0.67 equiv.	R Br 1 1.0 equiv.	CsF (1.0 equiv.) CO ₂ (2.0 MPa) DMF, 60 °C, 14 h	R СООН 2	
Entry		R			Yield of 2 ^b
1	Ph 4 Northell				69 (2b)
2	1-Naphthyl				63 (46) (2 C)
3	Bn				72 (2d)
4	<i>p</i> -tol				58 (2e)
5		^{'n} C ₆ H		$62^{d}(40^{c})(2\mathbf{f})$	

^{*a*} The reaction was conducted with 1.5 mmol of **1**, 1.0 mmol of In (powder, 425 mesh) and 1.5 mmol of CsF under a 2 MPa CO_2 atmosphere in 5 mL of anhydrous DMF at 60 °C. ^{*b*} Isolated yield. ^{*c*} The reaction was conducted in the absence of CsF. ^{*d*} The reaction was conducted using 1.2 mmol of **1c**.

The carboxylation reaction of several commercially available allylic bromides was also attempted, which was followed by esterification to afford the benzyl ester **3g–j**. In addition to 2-methylallyl bromide [Scheme 2, eqn (1)], 3-bromocyclohexene may also undergo the reaction to afford the corresponding ester **3h** in 61% yield [Scheme 2, eqn (2)]. Importantly, the carboxylation of crotyl bromide afforded the branched product **3i** specifically with no linear regioisomer formed as judged by ¹H NMR analysis of the crude mixture [Scheme 2, eqn (3)]. An all-carbon quaternary center was also formed *via* such a transformation by using 3-methyl-2-butenyl bromide affording **3j** [Scheme 2, eqn (4)].

Br 1.0 equiv.	In (0.67 equiv.) CsF (1.0 equiv.) CO ₂ (2.0 MPa) DMF, 60 °C, 14 h	DCC (0.73 equiv.) DMAP (0.07 equiv.) BnOH (0.77 equiv.) DCM, 0 °C , 3 min then rt., 1.5 h	COOBn 3g	68%	(1)
Br 1.0 equiv.	In (0.67 equiv.) CsF (1.0 equiv.) CO ₂ (2.0 MPa) DMF, 60 °C, 14 h	DCC (1.05 equiv.) DMAP (0.1 equiv.) BnOH (1.1 equiv.) DCM, 0 °C, 3 min then rt., 1.5 h	COOBn 3h	61%	(2)
Br 1.0 equiv.	In (0.67 equiv.) CsF (1.0 equiv.) CO ₂ (2.0 MPa) DMF, 60 °C, 14 h	DCC (1.05 equiv.) DMAP (0.1 equiv.) BnOH (1.1 equiv.) DCM, 0 °C, 3 min then rt., 2.5 h	COOBn 3i	65%	(3)
Br 1.0 equiv.	In (0.67 equiv) CsF (1.0 equiv) CO ₂ (2.0 MPa) DMF, 60 °C, 14 h	DCC (1.05 equiv.) DMAP (0.1 equiv.) BnOH (1.1 equiv.) DCM, 0 °C, 3 min then rt., 2.5 h	COOBn 3j	41%	(4)

Scheme 2 Reaction of commercially available allylic bromides.

Substrates with *p*-F, *p*-Cl and *p*-CF₃-substituents may be applied (Table 4, entries 1–3). Furthermore, functional groups such as ester and cyano group may be well tolerated (Table 4, entries 4 and 5). Although the acetyl group is not compatible, the ketal functionality survived the carboxylation affording **2p** in good yield (Table 4, entry 6). The reaction of propargyl bromide under the same conditions led to a complicated mixture.

The same product was obtained from both 2-butenyl and 3-buten-2-yl chlorides, indicating the common delocalized allylic intermediate for such a transformation (Scheme 3).

 Table 4
 Study on the functional group tolerance^a



^{*a*} The reaction was conducted with 1.5 mmol of 1, 1.0 mmol of In (powder, 425 mesh), 1.5 mmol of CsF under a 2 MPa CO_2 atmosphere in 5 mL of anhydrous DMF at 60 °C. ^{*b*} Isolated yield. ^{*c*} Without CsF.



Scheme 3 Carboxylation reactions of linear and branched allylic chlorides.

In conclusion, we have developed a novel and convenient way to synthesise β , γ -unsaturated carboxylic acid directly from CO₂ and allylic halides. No transition metal catalyst is necessary. The reaction tolerates many synthetically useful functional groups such as halogen, CF₃, ester, cyano, acetal and the same branched products were specifically obtained when starting from either α - or γ -substituted allylic halides. The pressure effect and addition of CsF are responsible for this transformation. Further research on this type of carboxylation reaction is underway in our group.

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