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Regioselective Copper-Catalyzed Carboxylation of Allylboronates with Carbon Dioxide

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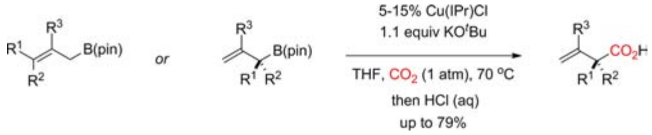
ABSTRACT



In the presence of a Cu(I)/NHC catalyst, the reactions of allylboronic pinacol esters with CO_2 (1 atm) are highly regioselective, giving exclusively the more substituted β,γ-unsaturated carboxylic acids in most cases. A diverse array of substituted carboxylic acids can be prepared via this method, including compounds featuring all-carbon quaternary centers.

Considering the increasing scarcity and cost of fossil resources, the use of CO_2 as a nontoxic, inexpensive, and abundant reagent in synthetic applications is of considerable interest.[1] In this regard, C–C bond forming reactions represent a highly useful process. For example, direct carboxylation of strongly nucleophilic allylmetals such as organolithiums and Grignard reagents with CO_2 provides a straightforward method to prepare β,γ-unsaturated carboxylic acids, highly versatile building blocks incorporating two modifiable functional groups (Scheme 1a).[2–4] A major drawback of these reactions, however, is the high reactivity of the metal–carbon bond, which is incompatible with a number of sensitive functional groups.

In a seminal report, Shi and Nicholas showed that activation of CO_2 by the less polar allylstannanes is possible under palladium catalysis, albeit at high pressures (33 atm) of CO_2 (Scheme 1b).[5] Later, Wendt et al. were able to carboxylate allylstannanes with CO_2 at ambient pressure using a pincer-type palladium complex.[6] More recently, Hazari et al. employed (η^3-allyl)Pd(L)(carboxylate) (L = PR_3 or NHC) and allyl-bridged Pd(I) dimers for the carboxylation of allylstannanes and allylborons with CO_2 (1 atm) with high activities.[7] Despite these novel developments,

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(1) For reviews on CO_2 transformations, see: (a) Dell'Amico, D. B.; Calderazzo, F.; Labella, L.; Marchetti, F.; Pampaloni, G. *Chem. Rev.* **2003**, *103*, 3857. (b) Louie, J. *Curr. Org. Chem.* **2005**, *9*, 605. (c) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (d) Federsel, C.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6254. (e) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010**, *39*, 3347. (f) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kuhn, F. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8510.

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(3) For examples on applications of β,γ-unsaturated carboxylic acids in synthesis, see: (a) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875. (b) Fekner, T.; Muller-Bunz, H.; Guiry, P. J. *Org. Lett.* **2006**, *8*, 5109. (c) Yang, S.-H.; Caprio, V. *Synlett* **2007**, *8*, 1219. (d) O'Connor, P. D.; Kim, U. B.; Brimble, M. A. *Eur. J. Org. Chem.* **2009**, 4405. (e) Hartog, T. D.; Macia, B.; Minnaard, A, J.; Feringa, B. L. *Adv. Synth. Catal.* **2010**, *352*, 999. (f) Gu, Z.; Zakarian, A. *Org. Lett.* **2011**, *13*, 1080.

(4) For other CO_2 transformations leading to β,γ-unsaturated carboxylic acids, see: (a) Tokuda, M.; Kabuki, T.; Katoh, Y.; Suginome, H. *Tetrahedron Lett.* **1995**, *36*, 3345. (b) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2001**, *123*, 2895. (c) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2002**, *124*, 10008. (d) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254. (e) Takaya, J.; Sasano, K.; Iwasawa, N. *Org. Lett.* **2011**, *13*, 1698.

(5) Shi, M.; Nicholas, K. M. *J. Am. Chem. Soc.* **1997**, *119*, 5057.

(6) (a) Johansson, R.; Wendt, O. F. *Dalton Trans.* **2007**, 488. (b) Johnson, M. T.; Johansson, R.; Kondrashov, M. V.; Steyl, G.; Ahlquist, M. S. G.; Roodt, A.; Wendt, O. F. *Organometallics* **2010**, *29*, 3521.

(7) (a) Wu, J.; Green, J. C.; Hazari, N.; Hruszkewycz, D. P.; Incarvito, C. D.; Schmeier, T. J. *Organometallics* **2010**, *29*, 6369. (b) Hruszkewycz, D. P.; Wu, J.; Hazari, N.; Incarvito, C. D. *J. Am. Chem. Soc.* **2011**, *133*, 3280. (c) Wu, J.; Hazari, N. *Chem. Commun.* **2011**, *47*, 1069. (d) Hazari, N.; Hruszkewycz, D. P.; Wu, J. *Synlett* **2011**, *13*, 1793–1797. (e) Hruszkewycz, D. P.; Wu, J.; Green, J. C.; Hazari, N.; Schmeier, T. J. *Organometallics* **2012**, *31*, 470–485.

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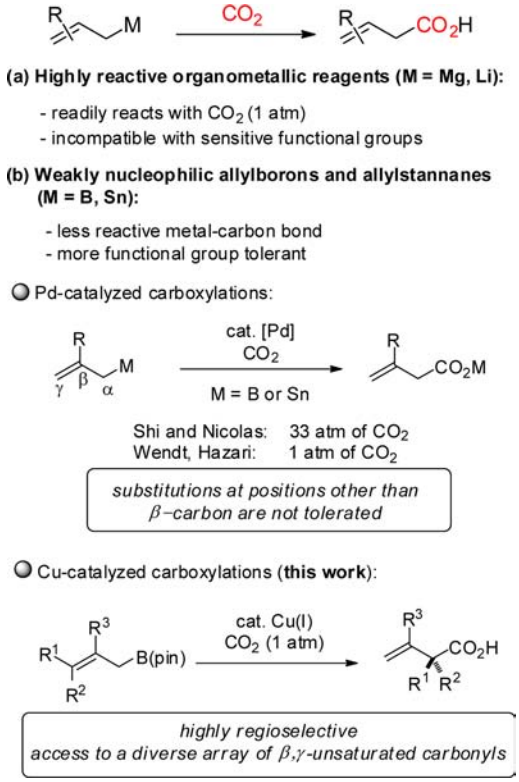
carboxylation of allylborons and allylstannanes possessing substituent(s) at positions other than the β-carbon remains elusive under palladium catalysis.[5,6b,7c]

Scheme 1. Direct Carboxylation of Allylmetals with CO_2



We were attracted to the Cu(I)-catalyzed reactions of carbon nucleophiles with CO_2 that have captured the attention of several groups over the past few years.[8] In particular, the Hou group,[8d,f] the Iwasawa group[8e] and the Sawamura group[8g] independently showed that carboxylations of aryl-, alkenyl-, and alkylborons with CO_2 (1 atm) can be facilitated in the presence of a Cu(I) catalyst. We questioned whether a direct carboxylation strategy with CO_2 (1 atm) could be developed to enable the synthesis of a diverse array of β,γ-unsaturated carboxylic acids. We speculated that an allylcopper(I) species resulting from the transmetalation of an allylboronate with a Cu(I) catalyst could readily react with CO_2.[9] Encouraged by many important advances in the synthesis of allylboronic esters,[10] we explored the reaction of these environmentally friendly organoborons with CO_2 under copper catalysis.

We set out to investigate the reaction of allylboronic pinacol ester **1a** with CO_2 (1 atm) where several products could be formed, including **2a** (branched), **2a′** (linear), and the isomerized compounds (Table 1).[11] Pleasingly, a combination of [Cu(IPr)Cl] (10 mol %) and $\mathrm{KO^{t}Bu}$ (1.1 equiv) gave **2a** in 75% yield as determined by ^{1}H NMR of the crude mixture (Table 1, entry 1), with only a trace of **2a′** being formed. Under these conditions, isomerized products **2a-i** or **2a′-i** were not observed. Further screening revealed that in situ generation of the catalyst from CuCl/IPrCl resulted in a lower yield of **2a** (entry 2). The less bulky ligand IMes or a different base KOMe[12] was also active for this reaction, giving **2a** in 60% and 71% yields, respectively (entries 3 and 4). The reaction could be run with as low as 5 mol % of Cu(IPr)Cl without affecting the yield of **2a** to any significant extent (entries 5 and 6). Phosphine ligands such as BINAP and CyJohnphos could also lead to moderate yields of **2a** (entries 7 and 8). Both the Cu(I) catalyst and base were critical to the formation of **2a**, as no product was formed in the absence of either one (entries 9 and 10).

Under the optimized conditions, a variety of β,γ-unsaturated carboxylic acids were synthesized via carboxylation of allylboronates (Table 2). In most cases (except entries 7 and 8), we could only observe traces of other byproducts by ^{1}H NMR in the crude mixture after workup. Allylboronic esters with a primary alkyl substituent at the γ-carbon reacted with CO_2 under copper catalysis to give the corresponding branched carboxylic acids in 54−79% yield (entries 1−6). The reaction yield and selectivity were greatly hampered when a sterically demanding substituent was introduced at the γ-carbon (entries 7 and 8).

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(8) For reviews, see: (a) Correa, A.; Martin, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201. (b) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3482. (c) Wenzhen, Z.; Xiaobing, L. *Chin. J. Catal.* **2012**, *33*, 745. For Cu-catalyzed carboxylation of organoborons, see: (d) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (e) Takya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697. (f) Ohishi, T.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 8114. (g) Ohmiya, H.; Tanabe, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 1086. For related Cu-catalyzed carboxylation of other carbon nucleophiles, see: (h) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670. (i) Goossen, L.; Rodriguez, N.; Manjolinho, F.; Lange, P. P. *Adv. Synth. Catal.* **2010**, *352*, 2913. (j) Zhang, W.-Z.; Li, W.-J.; Zhang, X.; Zhou, H.; Lu, Z.-B. *Org. Lett.* **2010**, *12*, 4748. (k) Yu, D.; Zhang, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *23*, 20184. (l) Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 523. (m) Inamoto, K.; Asano, N.; Kobayashi, K.; Yonemoto, M.; Kondo, Y. *Org. Biomol. Chem.* **2012**, *10*, 1514. (n) Motokura, K.; Kashiwame, D.; Miyaji, A.; Bab, T. *Org. Lett.* **2012**, *14*, 2642. (o) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314. (p) Inomata, H.; Ogata, K.; Fukuzawa, S.-I.; Hou, Z. *Org. Lett.* **2012**, *14*, 3986.

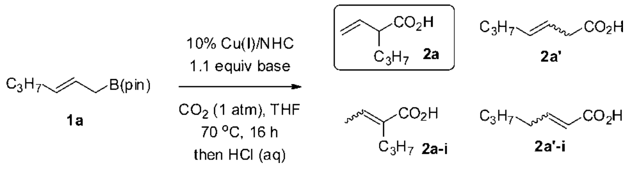
(9) For reports on Cu(I)-catalyzed allylations of carbonyls, see: (a) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *5*, 1055 and references therein. (b) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem . Soc.* **2011**, *133*, 3332.

(10) For prepration of allylboronic esters from allyl halides via a Grignard reagent, see: (a) Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.-G.; Podestá, J. C. *Eur. J. Org. Chem.* **2009**, 3964. (b) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *J. Org. Chem.* **2011**, *76*, 9602. For Pd-catalyzed borylation of allyl alcohols, see: (c) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (d) Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, *14*, 2293. (e) Selander, N.; Paasch, J. R.; Szabó, K. J. *J. Am. Chem. Soc.* **2011**, *133*, 409. For Pd- and Ni-catalyzed borylation of allyl halides, see: (f) Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (g) Zhang, P.; Roundtree, I. A.; Morken, J. A. *Org. Lett.* **2012**, *14*, 1416. For Cu-catalyzed borylation of allylic alcohol derivatives, see: (h) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (i) Ito, H.; Ito, S.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (j) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634. (k) Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972. (l) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410. (m) Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423.

(11) Isomerized products were observed in the Pd(0)-catalyzed reactions (ref 5).

(12) KOMe was previously shown to be superior to $\mathrm{KO^{t}Bu}$ in the Cu-catalyzed carboxylation of alkylboranes (ref 8f).

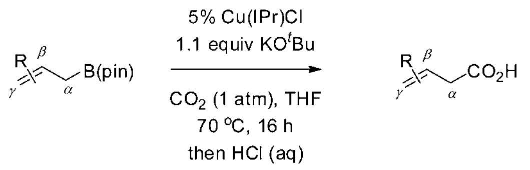
Table 1. Screening Conditions for Cu(I)-Catalyzed Carboxylation of **1a** with CO_2[a]

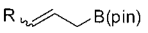
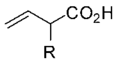
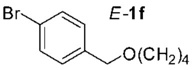
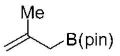
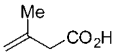
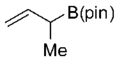
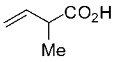
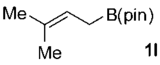
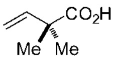
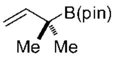
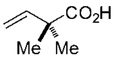
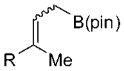
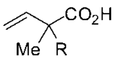
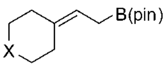
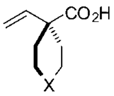
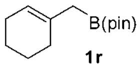
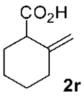


entry	Cu(I)	L	base	**2a** (%)[b]	**2a′** (%)[b]
1	Cu(IPr)Cl	–	KO^{t}Bu	75	trace
2	CuCl	IPrCl	KO^{t}Bu	62	trace
3	CuCl	IMesCl	KO^{t}Bu	60	trace
4	Cu(IPr)Cl	–	KOMe	71	trace
5	Cu(IPr)Cl[c]	–	KO^{t}Bu	77	trace
6	Cu(IPr)Cl[d]	–	KO^{t}Bu	28	trace
7	CuCl[c]	BINAP	KO^{t}Bu	40	8
8	CuCl[c]	CyJohnPhos[e]	KO^{t}Bu	61	trace
9	–	–	KO^{t}Bu	0	0
10	Cu(IPr)Cl	–	–	0	0

[a] 10 mol % Cu(I)/L, 1.1 equiv of base, CO_2 (1 atm), 1 mL of THF, 70 °C, 16 h. [b] Determined by ^1H NMR of the crude mixture after workup using an internal standard. [c] 5 mol % was used. [d] 3 mol % was used. [e] 10 mol % of ligand was used.

Table 2. Cu-Catalyzed Carboxylation of Substituted Allylboronic Pinacol Esters[a]



entry	allylboronates	acids	isolated yields (%)[b]
			
1	R = *n*-C_3H_7, *E*-**1a**	**2a**	76
2	R = Me, *E*-**1b**	**2b**	79
3	R = $PivO(CH_2)_4$, *E*-**1c**	**2c**	67
4	R = $BzO(CH_2)_4$, *E*-**1d**	**2d**	54
5	R = $TBSO(CH_2)_4$, *E*-**1e**	**2e**	54
6	R =  *E*-**1f**	**2f**	64
7	R = Et_2CH, *E*-**1g**	**2g**	trace
8	R = Ph, *E*-**1h**	**2h**	30[c]
9	R = H, **1i**	**2i**	68
10	 **1j**	 **2j**	65
11	 **1k**	 **2b**	62
12[d]	 **1l**	 **2l**	69
13[d]	 **1m**	 **2l**	54
			
14[d]	R = C_2H_5, **1n**[e]	**2n**	57
15[d]	R = C_5H_{11}, **1o**[e]	**2o**	41
			
16[d]	X = CH_2, **1p**	**2p**	64
17[d]	X = NBoc, **1q**	**2q**	58
18[f]	 **1r**	 **2r**	50

[a] 1 equiv of allylboronate, 5 mol % Cu(IPr)Cl, 1.1 equiv of base, THF, 70 °C, 16 h. [b] Isolated yields. [c] The linear isomer **2h′** was also isolated in 13%. [d] 15 mol % Cu(IPr)Cl was employed. [e] A mixture of *E*- and *Z*-isomers were employed. [f] 10 mol % Cu(IPr)Cl was employed.

While **1g** led to only a trace amount of the carboxylic acid product as determined by ^1H NMR (entry 7), the reaction of cinnamylboronate **1h** afforded **2h** in 30% isolated yield together with the regiomeric product **2h′** being formed in a significant amount (entry 8). Nonsubstituted allylboronate **1i** could be carboxylated in 68% isolated yield (entry 9). Reactions of allylboronates with a methyl substituent at either the α- or β-carbon led to the corresponding carboxylic acids in 62% and 65% yields, respectively (entries 10 and 11).

Since the branched carboxylic acid was favored over the linear regioisomer, we became interested in the construction of all-carbon quaternary centers,[13] a highly valuable structural motif present in a wide range of biologically active compounds, employing the current CO_2 transformation. **1l** indeed reacted with CO_2 to give **2l** in 69% yield, albeit at a higher catalyst loading (15 mol %) (entry 12). At lower catalyst loadings (5–10 mol %), a significant amount of unreacted starting material could be observed in the crude mixture. Other γ,γ-disubstituted allylboronates also underwent the reactions with CO_2 to afford α,α-disubstituted β,γ-unsaturated carboxylic acids in 41–64% yields (entries 14–17).

Reactions of cyclic allylboronates proceeded with excellent regioselectivity (entries 16–18). Compounds featuring an exocyclic olefin can be prepared by the reaction of cyclohexenyl **1r** with CO_2 under copper catalysis (entry 18).

A range of functionalized allylboronates could react with CO_2 under the Cu-catalyzed conditions (entries 3–6 and 17),

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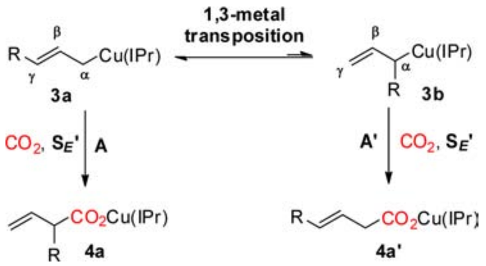
(13) For some recent examples on the synthesis of all-carbon quaternary centers, see: (a) Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10366. (b) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522. (c) Evans, P. A.; Oliver, S.; Chae, J. *J. Am. Chem. Soc.* **2012**, *134*, 19314.

(14) It should be noted that potassium *O*-alkylcarbonate, which can be formed by the reaction of CO_2 with a potassium alkoxide, may play a role in the carboxylation. In fact, a reaction of **1a** with KO_2COMe, prepared from CO_2 and KOMe, in the presence of 5% Cu(IPr)Cl at 70 °C resulted in a 64% yield of **2a**.

(15) For a discussion on 1,3-metal transposition in allylic metals, see: Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642.

Scheme 2. A Possible Explanation for the Observed Regioselectivity



demonstrating the advantage of the current method over reactions employing strongly nucleophilic organolithiums and Grignard reagents. Substrates incorporating an ester (OPiv **1c** and OBz **1d**), silyl ether **1e**, benzyl ether **1f**, and *N*-Boc protecting group **1q** were successfully converted to the corresponding β,γ-unsaturated carbonyls. In addition, the allylboronate **1f** incorporating an aryl bromide moiety could undergo the carboxylation in 64% yield (entry 6).

Interestingly, the reactions of regioisomeric allylboronic esters led to the same product under these conditions (e.g., **1b** vs **1k** and **1l** vs **1m**), suggesting that the carboxylations of these isomers likely proceed via a common intermediate (*vide infra*). In these cases, reactions starting with the primary allylboronates (**1b** or **1l**) were more efficient compared to the secondary and tertiary isomers (**1k** or **1m**).

Hou et al. previously showed that the carboxylation of aryl- or alkylborons with CO_2 in the presence of catalytic Cu(IPr)Cl and an alkoxide (KO^{t}Bu or MeOLi) proceeds via a reaction of an organocopper intermediate with CO_2.[8d,f] The regioconvergence observed in the current reaction (Table 2, entries 2 vs 11, and 12 vs 13) could be explained by a reaction of CO_2 with an allylcopper, which exists in a metallotropic equilibrium between two σ-complexes (Scheme 2).[14] Allylmetals with ionic characteristics (such as allyllithium, magnesium, and zinc reagents) are known to undergo a rapid 1,3-metal transposition.[15] Allylcopper is in this category.[9a] The branched carboxylic acid could be formed via carboxylation of the more sterically accessible **3a** at the γ-carbon (S_E' mechanism, pathway **A**).[2b,16] However, a mechanism involving carboxylation of the branched allylcopper(I) **3b** at the α-carbon (S_E2 mechanism) is also possible.

Delivery of CO_2 to the γ-carbon of **3a** (S_E' mechanism, pathway **A**) becomes challenging when a sterically demanding group is introduced, resulting in low yields of the reactions (Table 2, entries 7 and 8). For **1h**, the linear carboxylic acid **2h**′ (R = Ph) could be formed via S_E'-carboxylation of **3b** (pathway **A**′), which is also problematic due to the steric interactions between R and the metal center. Overall, carboxylation of these substrates is not efficient via either pathway **A** or **A**′. For **1g** (R = Et_2CH), both pathways are largely inhibited.

In conclusion, we have shown that allylboronates react with CO_2 (1 atm) under copper catalysis to afford a diverse range of cyclic and acyclic β,γ-unsaturated carboxylic acids. In most cases studied, excellent regioselectivity was observed, favoring the more substituted carboxylic acids.

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Supporting Information Available. Full experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] For discussions on reactions of allylpalladium with CO_2, see refs 6b and 7a. For a discussion on reactions of allylmetals with electrophiles, see ref 2b.

The authors declare no competing financial interest.