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Carboxylation of Organoboronic Esters with Potassium Methyl Carbonate under Copper Catalysis

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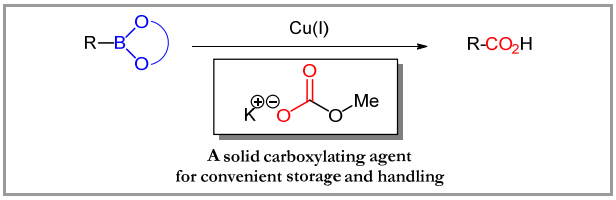
Abstract: In the presence of a copper catalyst, potassium methyl carbonate serves as a versatile carboxylating agent of allyl- and arylboronic esters for the preparation of carboxylic acids.

Key words: copper, organoboron, carbon dioxide, carbonate, carboxylic acid.

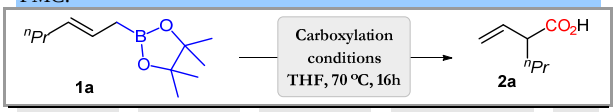
Metal alkyl carbonates such as the commercially available methylmagnesium carbonate (MMC) are efficient carboxylating agents of active methylene groups (i.e. nitroalkanes and ketones), and phenols.[1] We report herein that the conversion of organoboronic esters to carboxylic acids can be conveniently achieved by reactions with potassium methyl carbonate (KO_2COMe, PMC) in the presence of a copper catalyst (Scheme 1).



Scheme 1 Carboxylation of organoboronic esters with PMC.

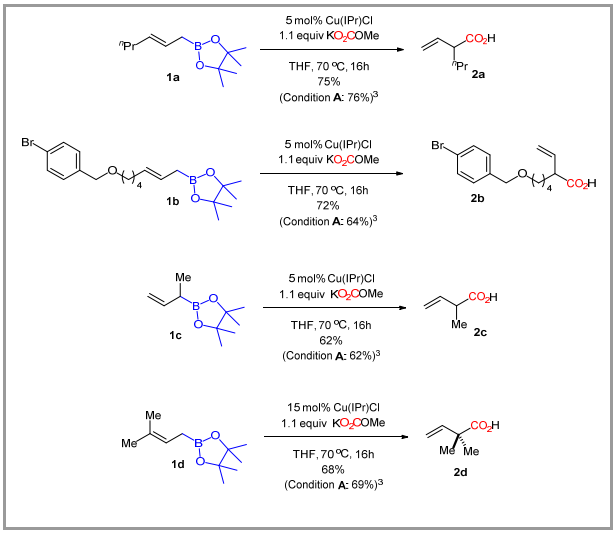
Hou et al. previously showed that arylboronic esters could be carboxylated by CO_2 (1 atm) in the presence of a copper/*N*-heterocyclic carbene (NHC) catalyst and KO^{t}Bu.[2] We later established that allylboronic esters could react with CO_2 (1 atm) under similar conditions to afford β,γ-unsaturated carboxylic acids with very good regioselectivity.[3] For example, **1a** could be converted to the requisite acid **2a** in 77% yield as determined by ^{1}H NMR analysis (Table 1, condition **A**). A similar yield was obtained when KOMe was used as the base additive (Table 1, condition **B**). In addition, we realized that PMC, an adduct of KOMe and CO_2, can also carboxylate **1a** with comparable efficiency (Table 1, condition **C**). PMC is prepared by bubbling CO_2 (1 atm) through a solution of KOMe in methanol as described by Behrendt et al.[4] The solid carboxylating agent can then be conveniently stored for subsequent usage.

Table 1 Carboxylations of allylboronic ester **1a** using CO_2 and PMC.



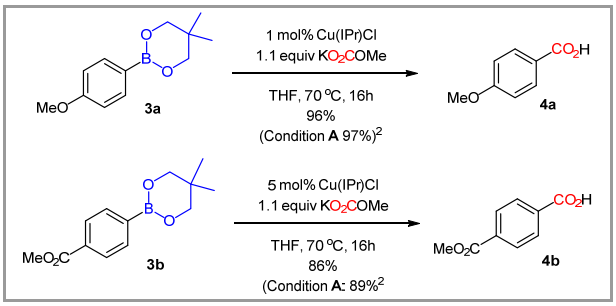
Conditions	Cu(IPr)Cl	Base	Carboxylating agent	**2a** (%)[a]
A (ref .3)	5 mol%	KO^{t}Bu[b]	CO_2[c]	77
B (ref .3)	5 mol%	KOMe[b]	CO_2[c]	75
C	5 mol%	None	KO_2COMe[b]	75

[a] Yields were determined by ^{1}H NMR analysis of the crude mixture after work-up using an internal standard. [b] 1.1 equiv was used. [c] 1 atm of CO_2 was used.



Scheme 2 Copper-catalyzed carboxylation of allylboronic esters with PMC.

Further investigations revealed that the copper-catalyzed carboxylation with PMC is applicable to the synthesis of other β,γ-unsaturated carboxylic acids (Scheme 2). Both the linear (**1b**) and branched (**1c**) substrates were selectively converted to the corresponding branched carboxylic acids in 72% and 62% yields, respectively. **2d** possessing a all-carbon quaternary center could be obtained in 68% yield at a higher catalyst loading. Notably, the efficiency of the reactions with PMC was comparable to those run under a CO_2 atmosphere (condition **A**).[3]

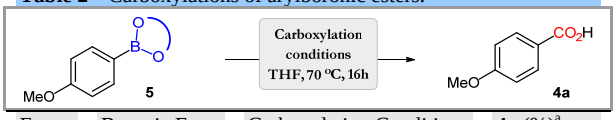


Scheme 3 Copper-catalyzed carboxylation of arylboronic neopentylglycol esters with PMC.

Arylboronic neopentylglycol esters could undergo carboxylation with PMC under copper catalysis to give benzoic acid derivatives in very good yields (Scheme 3). For electron-rich substrate **3a**, only 1 mol% of catalyst was needed to achieve an excellent isolated yield of the desired product **4a**. Again, the yields obtained were similar to those run under CO_2 (condition **A**) as reported by Hou et al.[2]

Notably, Iwasawa et al. reported that rhodium-catalyzed carboxylation of arylboronic neopentylglycol ester with CO_2 was efficient, whereas almost no product could be obtained with arylboronic esters of ethylene glycol, 1,3-propandiol and pinacol.[5] Under copper catalysis, reaction of the 4-methoxylphenylboronic pinacol ester **5a** with CO_2 (Table 2, entry 1) or with PMC (entry 2) both gave very good yields of **4a** as determined by ^{1}H NMR analysis (Table 2, condition **A**). Reactions of boronic esters **5a'** and **5a"** with PMC were also highly efficient (entries 3-4).

Table 2 Carboxylations of arylboronic esters.



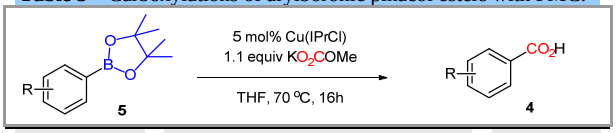
Entry	Boronic Ester	Carboxylating Conditions	**4a** (%)[a]
1	 **5a**	**A**[b]	85
2	 **5a**	**C**[c]	96
3	 **5a'**	**C**[c]	82
4	 **5a''**	**C**[c]	95

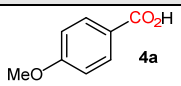
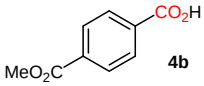
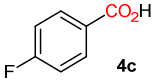
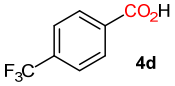
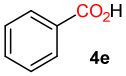
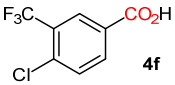
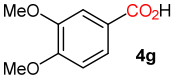
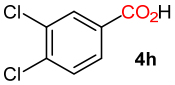
[a] Yields determined by ^{1}H NMR of the crude mixture after work-up using an internal standard. [b] 5 mol% Cu(IPr)Cl, 1.1 equiv KO^{t}Bu, CO_2 (1 atm). [c] 5 mol% Cu(IPr)Cl, 1.1 equiv KO_2COMe.

We further evaluated the scope of arylboronic pinacol esters, a class of organoboron that is widely used in, for example, the Suzuki-Miyaura cross-coupling reactions and can be easily prepared by a number of methods such as Miyaura borylation or iridium-catalyzed C-H borylation.[6] **4a** was isolated in 90% yield in the reaction of **5a** with PMC (Table 3, entry 1). Reaction of the electron-deficient **5b-d** (entries 2-4) led to the isolation of the corresponding carboxylic acids in good yields. Benzoic acid could be prepared from phenylboronic pinacol ester **5e** in 71% (entry 5). Multiply substituted benzoic acids with varied electronic properties could also be prepared from the requisite arylboronic pinacol esters in moderate yields (entries 6-8). A good yield of 77% could be obtained for 3-furoic acid **4i** under the current carboxylation conditions.

In conclusion, potassium methyl carbonate, which can be easily prepared, stored and handled, can serve as a highly efficient carboxylating agent of organoboronic esters under copper catalysis. The yields obtained in these reactions are generally comparable to those run under copper-catalyzed carboxylation with CO_2.

Table 3 Carboxylations of arylboronic pinacol esters with PMC.



Entry	Product	Yield (%)
1	 **4a**	90
2	 **4b**	78
3	 **4c**	89
4	 **4d**	80
5	 **4e**	71
6	 **4f**	62
7	 **4g**	63
8	 **4h**	58
9	 **4i**	77

Experimental Section

Cu(IPr)Cl (Aldrich), KO^{t}Bu (sublimed, Aldrich) and KOMe (Fluka) were used as received. PMC, allyl- and aryl boronic esters were prepared according to literature procedures.[2,3,4] All reactions were carried out under an atmosphere of argon unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel

plate. Flash column chromatography (FC) was undertaken on Merck silica gel 60. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-400 and referenced to residual protiated solvent (resonances downfield to the standard are reported as positive). All ^{13}C NMR spectra were proton decoupled. The abbreviations s, d, t and m stand for the resonance multiplicity singlet, doublet, triplet, and multiplet, respectively. THF was dried over alumina under N_2 using a Grubbs-type solvent purification system.

General procedure for the carboxylation of allylboronic pinacol esters with PMC (Scheme 1): In a glovebox, Cu(IPr)Cl (9 mg, 0.02 mmol, 5 mol%) and PMC (45mg, 0.39 mmol, 1.1 equiv) were charged to a glass reaction tube. A solution of **1** (0.36 mmol) in THF (1 mL) was added. The tube was sealed, taken out of the glovebox, and heated at 70 ^{o}C for 16h. After cooling to rt, water (2 mL) was added and the reaction mixture was acidified with aqueous HCl (1M), and saturated with sodium chloride. After extractions with diethyl ether (3 × 3 mL), the organic phase was dried over anhydrous sodium sulphate and concentrated under vacuo. The product was purified by silica gel column chromatography.

(E)-2-methylhept-3-enoic acid (2a):[3]

Reaction was performed on a 0.36 mmol scale. Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **2a** as colorless oil (34 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 10.51 (bs, 1H), 5.86 – 5.77 (m, 1H), 5.19 – 5.15 (m, 2H), 3.03 (dd, *J* = 15.5, 7.6 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.60 – 1.51 (m, 1H), 1.43 – 1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 180.8, 135.7, 117.7, 50.0, 34.2, 20.3, 13.9.

6-((4-bromobenzyl)oxy)-2-vinylhexanoic acid (2b):[3]

Reaction was performed on a 0.36 mmol scale. Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **2b** as colorless oil (68 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.46 (d, J = 8.4 Hz, 2H), 7.20 (d, J= 8.4 Hz, 2H), 5.86 – 5.77 (m, 1H), 5.20 – 5.16 (m, 2H), 4.43 (s, 2H), 3.45 (t, J = 6.5 Hz, 2H), 3.06 – 3.01 (m, 1H), 1.82 – 1.78 (m, 1H), 1.66 – 1.38 (m, 5H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 180.3, 137.8, 135.6, 131.7, 129.5, 121.6, 118.0, 72.33, 70.4, 50.2, 31.9, 29.6, 23.9.

2-methylbut-3-enoic acid (2c):[3]

Reaction was performed on a 0.36 mmol scale. Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **2c** as colorless oil (22 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 5.98 – 5.89 (m, 1H), 5.17 (t, J = 14.5 Hz, 1H), 3.22 – 3.15 (m, 1H), 1.31 (d, *J* = 7.1 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 180.8, 136.6, 116.6, 43.6, 16.6.

2,2-dimethylbut-3-enoic acid (2d):[3]

Reaction was performed on a 0.36 mmol scale. Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **2d** as colorless oil (28 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.05 (dd, J = 17.4, 10.6 Hz, 1H), 5.17 – 5.09 (m, 2H), 1.33 (s, 6H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 183.2, 142.1, 113.6, 44.9, 24.5.

Representative procedure for the carboxylation of arylboronic esters with PMC:

In a glovebox, Cu(IPr)Cl catalyst and PMC (62.8 mg, 0.55 mmol, 1.1 equiv) were charged to a glass reaction tube. A solution of **3** (0.50 mmol) in THF (1.5 mL) was added. The tube was sealed, taken out of the glovebox, and heated at 70 ^{o}C for 16h. After cooling to rt, water (2 mL) was added and the reaction mixture was acidified with aqueous HCl (1M), and saturated with sodium chloride. After extractions with ethyl acetate (3 × 5 mL), the organic phase was dried over anhydrous sodium sulphate and concentrated under vacuo. The product was purified by silica gel column chromatography.

4-methoxybenzoic acid (4a), Scheme 2:[7]

Reaction was performed on a 0.50 mmol scale of **3a** with Cu(IPr)Cl (2 mg, 0.005 mmol, 1 mol%). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4a** as white amorphous solid (73 mg, 96%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.00 (m, 2H), 7.02 (m, 2H), 3.88 (s, 3H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 167.4, 164.5, 132.5, 123.8, 114.6, 55.9.

4-methoxybenzoic acid (4a), Table 3, entry 1:[7]

Reaction was performed on a 0.36 mmol scale of **5a** with Cu(IPr)Cl (9 mg, 0.018 mmol, 5 mol%). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4a** as white amorphous solid (49 mg, 90%).

4-(methoxycarbonyl)benzoic acid (4b),[6] Scheme 2, equation 2 or Table 3, entry 2:

Reaction was performed on a 0.50 mmol scale of **3b** (Scheme 2, equation 2) or **5c** (Table 3, entry 3) with Cu(IPr)Cl (12 mg, 0.025 mmol, 5 mol%). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4c** as white amorphous solid [(78 mg, 86% for Scheme 2) or 70 mg, 78% for Table 3, entry 3].

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.16 (m, 2H), 8.11 (m, 2H), 3.93 (s, 3H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 166.9, 166.6, 135.4, 134.9, 130.6, 130.3, 52.7.

4-fluorobenzoic acid (4c),[7] Table 3, entry 3:

Reaction was performed on a 0.50 mmol scale of **5d** with Cu(IPr)Cl (12 mg, 0.025 mmol, 5 mol%). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4d** as white amorphous solid (63 mg, 89%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.13 – 8.08 (m, 2H), 7.28 – 7.23 (m, 2H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 167.8, 166.0 (d, J = 141 Hz), 133.3 (d, J = 9 Hz), 128.0, 116.2 (d, J = 22 Hz).

4-(trifluoromethyl)benzoic acid (4d),[7] Table 3, entry 4:

Reaction was performed on a 0.36 mmol scale of **5e** with Cu(IPr)Cl (9 mg, 0.02 mmol, 5 mol%) and PMC (45mg, 0.39 mmol, 1.1 equiv). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4e** as white amorphous solid (55 mg, 80%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.24 (m, 2H), 7.87 (d, J = 8.12 Hz, 2H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 166.5, 135.2, 134.6 (q, J = 32.0 Hz), 131.2, 126.4 (q, J = 4.0 Hz), 124.9 (q, J = 271.0 Hz).

Benzoic acid (4e),[7] Table 3, entry 5:

Reaction was performed on a 0.50 mmol scale of **5b** with Cu(IPr)Cl (12 mg, 0.025 mmol, 5 mol%). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4b** as white amorphous solid (43 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 11.42 (brs, 1H), 8.05 (m, 2H), 7.53 (m, 1H), 7.39 (m, 2H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 172.6, 133.9, 130.4, 129.5, 128.6.

4-chloro-3-(trifluoromethyl)benzoic acid (4f),[7] Table 3, entry 6:

Reaction was performed on a 0.36 mmol scale of **5f** with Cu(IPr)Cl (9 mg, 0.02 mmol, 5 mol%) and PMC (45mg, 0.39 mmol, 1.1 equiv). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4f** as white amorphous solid (50 mg, 62%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.36 (d, J = 2.0 Hz, 1H), 8.26 (m, 1H), 7.82 (d, J = 8.3 Hz, 1H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 165.6, 137.1 (q, J = 2.0 Hz), 135.5, 133.1, 131.1, 129.5 (q, J = 6.5 Hz), 128.9 (q, J = 31.0 Hz), 123.6 (q, J = 271.0 Hz).

3,4-dimethoxybenzoic acid (4g),[7] Table 3, entry 7:

Reaction was performed on a 0.36 mmol scale of **5g** with Cu(IPr)Cl (9 mg, 0.02 mmol, 5 mol%) and PMC (45mg, 0.39 mmol, 1.1 equiv). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4g** as slightly yellow solid (42 mg, 63%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 167.6, 154.5, 150.0, 124.5, 123.7, 113.4, 111.8, 56.21, 56.17.

3,4-dichlorobenzoic acid (4h),[7] Table 3, entry 8:

Reaction was performed on a 0.36 mmol scale of **5h** with Cu(IPr)Cl (9 mg, 0.02 mmol, 5 mol%) and PMC (45mg, 0.39 mmol, 1.1 equiv). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4h** as white amorphous solid (40 mg, 58%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.12 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 8.4, 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 165.7, 137.6, 133.1, 132.3, 132.0, 131.8, 130.2.

3-furoic acid (4i),[7] Table 3, entry 9:

Reaction was performed on a 0.36 mmol scale of **5i** with Cu(IPr)Cl (9 mg, 0.02 mmol, 5 mol%) and PMC (45mg, 0.39 mmol, 1.1 equiv). Purification by silica gel column chromatography (1-5% Et_2O/DCM/0.1 % HCO_2H) afforded **4i** as white amorphous solid (31 mg, 77%).

^{1}H NMR (400 MHz, Acetone-d_6, ppm): δ 8.07 (m, 1H), 7.54 (m, 1H), 6.65 (m, 1H).

^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6, ppm): δ 164.1, 149.0, 145.2, 120.5, 110.7.

Acknowledgment

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(7) These compounds are commercially available.