1,6-Conjugate Addition of Boronic Acids to 2-Allylidenemalonates

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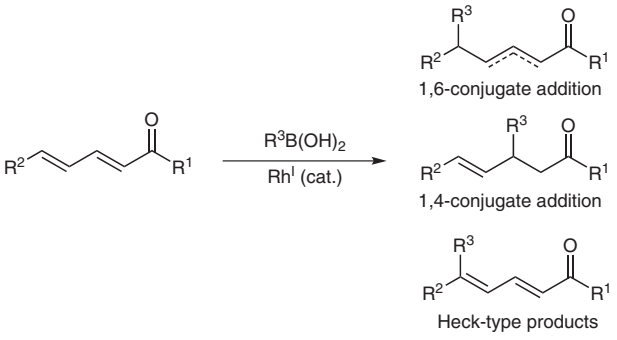
Abstract: The addition of boronic acids to 2-allylidenemalonates under Rh^I or Pd^{2+} catalysis shows an enhanced selectivity for the 1,6-addition reaction in comparison with diunsaturated monoesters. In the case of the Rh^I-catalyzed addition, the position of the new C=C double bond in the final product can be tuned with the choice of the base to give vinylmalonates of alkylidenemalonates.

Key words: addition reactions, catalysis, boron, rhodium, palladium

Conjugate addition reactions of organometallic reagents to α,β-unsaturated carbonyl compounds are one of the main synthetic methods for C–C bond formation.[1] Among the different procedures reported, the reaction of boronic acids under Rh^I catalysis has become increasingly popular.[2,3] Compared with other more traditional methods, such as organocuprate chemistry, the Rh^I-catalyzed conjugate addition of organoboronic acids is highly functional-group tolerant and enjoys more environmentally benign conditions, as the reactions can be carried out in water-containing organic solvents, the heavy metal is used in catalytic amounts, and the boron reagents and subproducts are of low toxicity. This becomes specially relevant in large-scale operations. Additionally, many aryl- and alkenylboronic acids are commercially available or can be easily prepared by a wide variety of methods.



Scheme 1

Among the various kinds of carbonyl compounds used as starting materials in conjugate addition reactions, dienic substrates have not been amply investigated, as a result of the difficulties in controlling the 1,4- or 1,6-regioselectivity.[4,5] In particular, the Rh^I-catalyzed addition boronic acids to α,β,γ,δ-diunsaturated carbonyl compounds may give rise to the formation of the 1,4- or the 1,6-conjugate addition products and Heck-type products (Scheme 1) depending on the substitution pattern of the starting material and the boronic acid (aryl- or alkenylboronic acid).[6–8]

We report herein our results on the addition of boronic acids to 2-allylidenemalonates **1**, which show an enhanced selectivity for the 1,6-addition reaction in comparison with α,β,γ,δ-diunsaturated esters **2** (Scheme 2).

The results of the Rh^I-catalyzed addition of aryl- and alkenylboronic acids to compound **1a**,[9] unsubstituted in δ-position (R^2 = H), are given in Table 1 (entries 1–14). We observed that the 1,6-conjugate addition reaction was favored in all cases when the reaction was carried out with $[(cod)RhCl]_2$ as catalyst in dioxane–H_2O as solvent in the presence of $NaHCO_3$ or Et_3N as bases. Opposite to α,β,γ,δ-diunsaturated ester **2a** (entry 15) the reactions of malonate **1a** with alkenylboronic acids did not give rise to the Heck-type products **6**.[7]

In addition, it was possible to control the position of the new C=C bond formed in the final products. Thus, vinylmalonates **3** (*E*-isomers) were obtained when the reaction was carried out with $NaHCO_3$ (entries 1–7).[10] It is worth mentioning that the 1,6-conjugate addition to linear α,β,γ,δ-dienoates has been reported to give rise to *Z*-alkenes.[4a,7] On the other hand, the alkylidenemalonates **4** were obtained when the reaction was carried out with Et_3N (entries 8–14).[11,12]

In a similar fashion, the reaction of compound **1b**,[9] substituted in δ-position (R^2 = Ph), afforded the corresponding 1,6-addition products **3** (*E*-isomers) instead of the 20:80 mixture of 1,6- and 1,4-addition products observed for **2b** (Table 1, entries 16–18). In this case, no reaction was observed when using $[(cod)RhCl]_2$ as catalyst, either in the presence of $NaHCO_3$ or Et_3N as bases. Optimization of reaction conditions led to the use of $[(cod)_2Rh]BF_4$ as catalyst in dioxane–H_2O as solvent in the presence of $Ba(OH)_2$ as base.[13] Similarly, the reaction of $PhB(OH)_2$ with **1c**,[14] alkyl-substituted in δ-position ($R^2 = {}^nC_6H_{13}$), afforded (*E*)-**3k** (entry 19).

It has been shown recently that the conjugate addition of boronic acids to electron-deficient alkenes can be catalyzed by cationic Pd^{2+} species.[15] In general α,β-unsaturated esters do not perform well in these type of reactions, and the formation of Heck-type products is normally observed.[16] However, the Pd^{2+}-catalyzed conjugate addition reaction of boronic acids to α,β,γ,δ-dienoates has not been reported.

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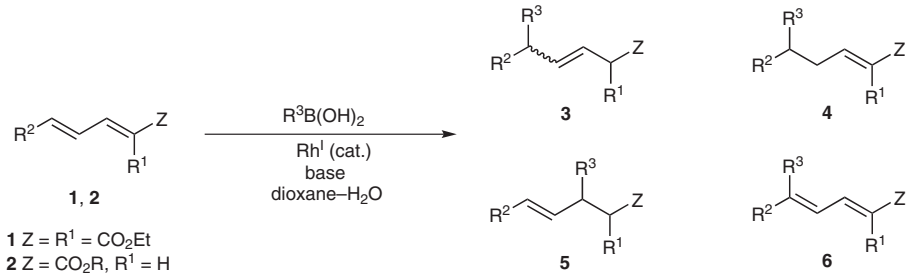


Scheme 2

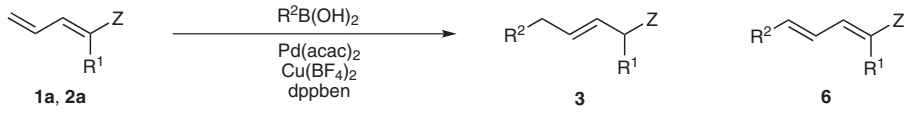
Table 1 Rh^I-Catalyzed Addition of $R^2B(OH)_2$ to **1** and **2**

Entry	**1**, **2**	Z	R^1	R^2	R^3	Rh^I catalyst[a]	Base (equiv)	Solvent[b]	Temp (°C)	Product, yield (%)[c]
1	**1a**	CO_2Et	CO_2Et	H	Ph	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3a** 80
2	**1a**	CO_2Et	CO_2Et	H	4-BrC_6H_4	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3b** 70
3	**1a**	CO_2Et	CO_2Et	H	4-$MeOC_6H_4$	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3c** 70[d]
4	**1a**	CO_2Et	CO_2Et	H	C_6H_5CH=CH	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3d** 80
5	**1a**	CO_2Et	CO_2Et	H	4-MeC_6H_4CH=CH	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3e** 70
6	**1a**	CO_2Et	CO_2Et	H	4-$MeOC_6H_4CH$=CH	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3f** 70
7	**1a**	CO_2Et	CO_2Et	H	4-FC_6H_4CH=CH	A	$NaHCO_3$ (0.1)	6:1	50	(*E*)-**3g** 65[d]
8	**1a**	CO_2Et	CO_2Et	H	Ph	A	Et_3N (1.0)	10:1	25	**4a** 80
9	**1a**	CO_2Et	CO_2Et	H	4-BrC_6H_4	A	Et_3N (1.0)	10:1	25	**4b** 60
10	**1a**	CO_2Et	CO_2Et	H	4-$MeOC_6H_4$	A	Et_3N (1.0)	10:1	25	**4c** 60[d]
11	**1a**	CO_2Et	CO_2Et	H	C_6H_5CH=CH	A	Et_3N (1.0)	10:1	25	**4d** 75
12	**1a**	CO_2Et	CO_2Et	H	4-MeC_6H_4CH=CH	A	Et_3N (1.0)	10:1	25	**4e** 75[e]
13	**1a**	CO_2Et	CO_2Et	H	4-$MeOC_6H_4CH$=CH	A	Et_3N (1.0)	10:1	25	**4f** 65
14	**1a**	CO_2Et	CO_2Et	H	*p*-F-C_6H_4CH=CH	A	Et_3N (1.0)	10:1	25	**4g** 60[e]
15	**2a**	CO_2Bn	H	H	C_6H_5CH=CH	A	Et_3N (1.0)	10:1	25	**6a** 60[f]
16	**1b**	CO_2Et	CO_2Et	Ph	Ph	B	$Ba(OH)_2$ (1.0)	10:1	25	(*E*)-**3h** 85
17	**1b**	CO_2Et	CO_2Et	Ph	4-MeC_6H_4	B	$Ba(OH)_2$ (1.0)	10:1	25	(*E*)-**3i** 60[e]
18	**2b**	CO_2Me	H	Ph	Ph	B	$Ba(OH)_2$ (1.0)	10:1	25	(*Z*)-**3j**, **5a** 85[f,g]
19	**1c**	CO_2Et	CO_2Et	*n*-C_6H_{13}	Ph	B	$Ba(OH)_2$ (1.0)	10:1	25	(*E*)-**3k** 75

[a] Conditions: Rh^I (5 mol%). A = $[(cod)RhCl]_2$. B = $[(cod)_2Rh]BF_4$.
[b] Ratio of dioxane to H_2O.
[c] Isolated yield after silica gel chromatography.
[d] Unreacted starting material (15%) was observed in the ^1H NMR (200 MHz, $CDCl_3$) spectra of the reaction crudes.
[e] Unreacted starting material (20%) was observed in the ^1H NMR (200 MHz, $CDCl_3$) spectra of the reaction crudes.
[f] See ref. 7.
[g] Mixture (*Z*)-**3j**/**5a** = 20:80 (85% overall yield).

We observed that, in the case of **2a** (Table 2, entries 1, 2), the addition of boronic acids under Pd^{2+} catalysis gave rise to the Heck reaction products **5** (Scheme 3).[17] On the other hand, when the reaction was carried out on the malonate derivative **1a** (Table 2, entries 3–5), the corresponding 1,6-addition products **3** (*E*-isomers) were obtained, albeit yields were lower in comparison with the same reaction under Rh^I catalysis.

In conclusion, we have shown that the reaction of boronic acids with allylidenemalonates favors the 1,6-addition products with respect to α,β,γ,δ-diunsaturated esters either under Rh^I or Pd^{2+} catalysis. In the case of the Rh^I-



Scheme 3

catalyzed addition, the position of the new C=C double bond in the final product can be tuned with the choice of the base, allowing the synthesis of either vinylmalonates or alkylidenemalonates.[18]

Table 2 Pd^{2+}-Catalyzed Addition of $R^2B(OH)_2$ to **1** and **2**

Entry	**1**, **2**	Z	R^1	R^2	Yield of **3** and **5** (%)[a]
1	**2a**	CO_2Bn	H	$C_6H_5CH=CH$	**5a** 45
2	**2a**	CO_2Bn	H	Ph	**5b** 40
3	**1a**	CO_2Et	CO_2Et	Ph	(*E*)-**3a** 70
4	**1a**	CO_2Et	CO_2Et	4-$MeOC_6H_4$	(*E*)-**3c** 55
5	**1a**	CO_2Et	CO_2Et	$C_6H_5CH=CH$	(*E*)-**3d** 60

[a] Isolated yield after silica gel chromatography.

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(10) **General Procedure for the Rh^I-Catalyzed Addition of Boronic Acids to 1a with $NaHCO_3$ as Base (Table 1, Entries 1–7)**
To a mixture of boronic acid (2.0 equiv, 0.32 mmol) and $[Rh(cod)Cl]_2$ (5% Rh, 2.0 mg, 0.004 mmol) under Ar was added a solution of **1a** (1.0 equiv, 34 mg, 0.16 mmol) in dioxane–H_2O (6:1, 0.5 mL) followed by $NaHCO_3$ (0.1 equiv, 2.7 mg, 0.032 mmol). The mixture was stirred at 50 °C for 18 h. Evaporation under vacuum afforded the crude reaction products, which were purified by column chromatography (hexane–EtOAc, 85:15).

(11) **General Procedure for the Rh^I-Catalyzed Addition of Boronic Acids to 1a and 2a with Et_3N as Base (Table 1, Entries 8–15)**
To a mixture of boronic acid (2.0 equiv, 0.32 mmol) and $[Rh(cod)Cl]_2$ (5% Rh, 2.0 mg, 0.004 mmol) under Ar was added a solution of **1a** or **2a** (1.0 equiv, 0.16 mmol) in dioxane–H_2O (10:1, 0.5 mL) followed by Et_3N (1.0 equiv, 16.2 mg, 22 μL, 0.16 mmol). The mixture was stirred at 25 °C for 18 h. Evaporation under vacuum afforded the crude reaction products, which were purified by column chromatography (hexane–EtOAc, 85:15).

(12) We have confirmed that isomerization of compounds **3** to **4** is a base-promoted process: treatment of compound (*E*)-**3d** in dioxane–H_2O (10:1) with Et_3N (1.0 equiv) at r.t. (18 h) afforded **4d** (90% isolated yield).

(13) **General Procedure for the Rh^I-Catalyzed Addition of Boronic Acids to 1b,c and 2b with $Ba(OH)_2$ as Base (Table 1, Entries 16–19)**
To a mixture of boronic acid (2.0 equiv, 0.34 mmol) and

[$Rh(cod)_2BF_4$] (5% Rh, 3.5 mg, 0.008 mmol) under Ar was added a solution of **1b** or **2b** (1.0 equiv, 0.17 mmol) in dioxane–H_2O (10:1, 0.5 mL) followed by $Ba(OH)_2·H_2O$ (1.0 equiv, 32.2 mg, 0.17 mmol). The mixture was stirred at 25 °C for 18 h. Evaporation under vacuum afforded the crude reaction products, which were purified by column chromatography (hexane–EtOAc, 85:15).

(14) Compound **1c** was prepared by cross-metathesis reaction between **1a** and 1-octene (5% Grubbs II catalyst, CH_2Cl_2, r.t., 18 h, 60% yield).

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(17) **General Procedure for the Pd^{2+}-Catalyzed Addition of Boronic Acids to 1a and 2a (Table 2)**
To a mixture of $Pd(acac)_2$ (5% Pd, 2,6 mg, 0.008 mmol), 1,2-diphenylphosphinobenzene (dppben, 3.8 mg, 0.008 mmol), $Cu(BF_4)_2·6H_2O$ (12 mg, 0.034 mmol), and boronic acid (0.34 mmol) under Ar was added a solution of the starting material (0.17 mmol) in dioxane–H_2O (10:1, 0.5 mL). The mixture was stirred at 25 °C for 18 h. Evaporation under vacuum afforded the crude reaction products, which were purified by column chromatography (hexane–EtOAc, 95:05).

(18) **Representative Data**
(*E*)-2-(3-Phenylpropenyl)malonic Acid Diethyl Ester (3a)
^{1}H NMR (200 MHz, C_6D_6): δ = 7.08 (m, 5 H), 5.98 (dd, *J* = 7.7, 15.3 Hz, 1 H), 5.62 (dt, *J* = 7.1, 15.2 Hz, 1 H) 4.03 (d, *J* = 7.9 Hz, 1 H), 3.92 (q, *J* = 7.2 Hz, 4 H), 3.12 (d, *J* = 7.1 Hz, 2 H), 0.89 (t, *J* = 7.2 Hz, 6 H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 168.5, 139.7, 135.3, 128.8, 128.7, 126.4, 123.2, 61.8, 55.8, 39.0, 14.2 ppm.
(*E*)-2-(5-Phenylpenta-1,4-dienyl)malonic Acid Diethyl Ester (3d)
^{1}H NMR (300 MHz, C_6D_6): δ = 7.21 (m, 5 H), 6.35 (d, *J* = 15.9 Hz, 1 H), 6.18 (dd, *J* = 8.9, 15.5 Hz, 1 H), 6.09 (dt, *J* = 6.6, 15.9 Hz, 1 H), 5.68 (dt, *J* = 6.8, 15.5 Hz, 1 H), 4.22 (d, *J* = 8.9 Hz, 1 H), 4.05 (q, *J* = 7.0 Hz, 4 H), 2.79 (m, 2 H), 1.00 (t, *J* = 7.1 Hz, 6 H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 168.3, 137.4, 134.3, 131.2, 128.5, 127.5, 127.1, 126.1, 122.8, 61.6, 55.6, 35.7, 14.0 ppm.
(*E*)-2-(3,3-Diphenylpropenyl)malonic Acid Diethyl Ester (3h)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20 (m, 5 H), 7.12 (m, 5 H), 6.08 (dd, *J* = 7.8, 15.7 Hz, 1 H), 5.64 (dd, *J* = 8.9, 15.7 Hz, 1 H), 4.70 (d, *J* = 7.7 Hz, 1 H), 4.12 (q, *J* = 7.3 Hz, 4), 4.02 (d, *J* = 8.9 Hz, 1 H), 1.18 (t, *J* = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.7, 143.4, 139.1, 129.0, 128.9, 126.9, 124.0, 52.1, 55.9, 54.1, 14.5 ppm.
2-(3-Phenylpropylidene)malonic Acid Diethyl Ester (4a)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.21 (m, 5 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 2.82 (m, 2 H), 2.62 (m, 2 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 165.4, 164.0, 148.1, 140.5, 132.5, 128.6, 128.3, 126.3, 61.2, 34.4, 31.4, 14.1, 14.07 ppm.
2-(5-Phenylpent-4-enylidene)malonic Acid Diethyl Ester (4d)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28 (m, 5 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.44 (d, *J* = 15.8 Hz, 1 H), 6.18 (dt, *J* = 6.6, 15.8 Hz, 1 H), 4.3 (q, *J* = 7.3 Hz, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 2.46 (m, 4 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 165.6, 163.8, 148.2, 137.5, 131.3, 1292, 128.5, 128.4, 127.2, 126.1, 61.3, 31.6, 29.5, 14.1 ppm.