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Rhodium-Catalyzed Reaction of Aryl- and Alkenylboronic Acids with 2,4-Dienoate Esters: Conjugate Addition and Heck Reaction Products†

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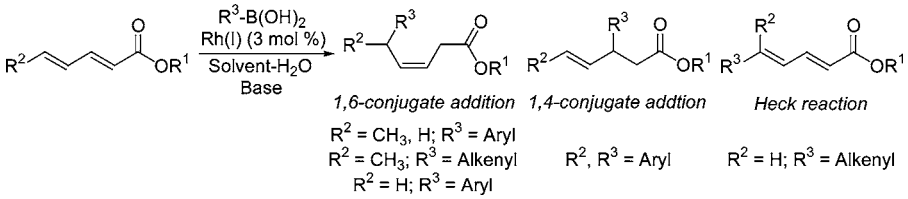
ABSTRACT



We report herein the first examples of the addition of aryl- and alkenylboronic acids catalyzed by Rh^{I} complexes to 2,4-dienoate esters. Three different types of products have been obtained depending on the substitution pattern of the starting ester and the organoboronic acid: 1,6-conjugate addition products, 1,4-conjugate addition products, and Heck reaction products.

The conjugate addition of organometallic reagents to electron-deficient carbonyl compounds is one of the main synthetic methods for C−C bond formation. In this regard, the 1,4-addition to α,β-unsaturated systems has been widely explored, and an ample variety of organometallic compounds and catalysts have been used to achieve this transformation in a highly steroselective fashion.[1] Among the different procedures reported for carrying out conjugate additions to unsaturated carbonyl compounds, the reaction of aryl and alkenylboronic acids under Rh^{I} catalysis (the Hayashi−Miyaura reaction) is especially attractive.[2,3] This synthetic method benefits from the easy preparation of organoboronic acid derivatives, which is particularly important in the case of the alkenyl derivatives, as they can be stereoselectively prepared by hydroboration of alkynes[4] without the need of transmetalation from main group organometallics and is therefore highly functional group tolerant. In addition, these reactions can be carried out in water-containing media, which together with the catalytic use of the transition metal and the low toxicity of boron compounds makes this procedure

† Dedicated to Prof. Joaquín Plumet in honor of his 60th birthday.

(1) See, for example: (a) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 169 (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (d) Urabe, H.; Sato, F. In *Handbook of Grignard Reactions*; Silverman, G. S., Rakinta, P. E., Eds.; Marcel Dekker: New York, 1996; p 577. (e) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin 1999; Vol. 3, Chapter 31. (f) Kanai, M.; Shibasaki, M. In *Catalystic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; p 569. (g) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (h) Krause, N.; Hoffmann. Roder, A. *Synthesis* **2001**, 171. (i) Lipshutz, B. H. In *Organometallics in Organic Synthesis. A Manual*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 2002; p 665 and references therein.

(2) First report: Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

(3) Reviews: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (e) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (f) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 3, p 55.

(4) (a) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695. (b) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482. (c) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399. (d) Josyula, K. V. B.; Gao, P.; Hewitt, C. *Tetrahedron Lett.* **2003**, *44*, 7789.

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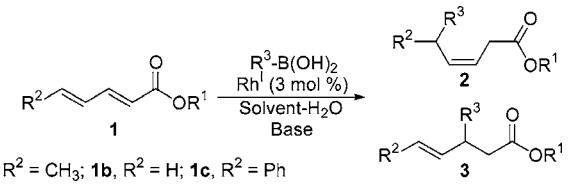
very attractive from an environmental standpoint. However, in comparison with ketones, linear α,β-unsaturated esters are known to be less reactive toward the Rh^I-catalyzed conjugate addition reactions of organoboronic acids.

We report herein the first examples of the addition of aryl and alkenylboronic acids catalyzed by Rh^I complexes to 2,4-dienoate esters. Compared with 1,4-conjugate additions, 1,6-conjugate additions to α,β,γ,δ-diunsaturated carbonyl compounds have been much less studied.[5,6] The 1,6-addition of arylboronic acids to dienones has not been reported,[7] and the 1,6-addition of aryl groups to dienoate esters has only been described recently by means of organomagnesium reagents.

On the other hand, 1,4-dienes constitute versatile synthons for the preparation of a variety of compounds, and the development of new methods for the synthesis of these targets is of continuous interest.[8] The addition of alkenyl groups to dienoate esters may give rise to a new useful method for their synthesis.

The results of the Rh^I-catalyzed reactions of dienoate esters with arylboronic acids are gathered in Table 1. No reaction

Table 1. Rh^I-Catalyzed Reactions of Dienoate Esters with Arylboronic Acids[a]



no.	1	cat.[b]	additive	R^3	2, 3[c] (%)	2/3[d]
1[e,f]	**1a**	A		Ph		
2[f]	**1a**	A		Ph		
3	**1a**	A	Et_3N	Ph	**2a**, **3a** (85)	82:18
4[e]	**1a**	A	Et_3N	Ph		
5[f]	**1a**	A	Et_3N	Ph	**2a**, **3a** (90)	80:20
6[g]	**1a**	A	Et_3N	Ph	**2a**, **3a** (90)	70:30
7	**1a**	A	$Ba(OH)_2$	Ph	**2a**, **3a** (90)	80:20
8	**1a**	A	guanidine	Ph	**2a**, **3a** (90)	79:21
9	**1a**	A	CsF	Ph	**2a**, **3a** (90)	75:25
10	**1a**	B	$Ba(OH)_2$	Ph	**2a**, **3a** (90)	82:18
11	**1a**	C	$Ba(OH)_2$	Ph	**2a**, **3a** (90)	80:20
12	**1a**	A	Et_3N	*p*-MeO-C_6H_4	**2b**, **3b** (85)	85:15
13	**1a**	A	Et_3N	*p*-CF_3-C_6H_4	**2c**, **3c** (90)	90:10
14	**1b**	B	$Ba(OH)_2$	Ph	**2d**, **3d** (65)	100:0
15	**1c**	B	$Ba(OH)_2$	Ph	**2e**, **3e** (85)	20:80
16	**1c**	B	$Ba(OH)_2$	*p*-MeO-C_6H_4	**2f**, **3f** (85)	15:85
17	**1c**	B	$Ba(OH)_2$	*p*-CF_3-C_6H_4	**2g**, **3g** (85)	25:75

[a] Reactions carried out at room temperature with 0.17 mmol of **1**, 2.0 equiv of $R_3B(OH)_2$ and 1.0 equiv of additive with 3 mol % of Rh^I catalyst with respect to **1** in 0.5 mL of dioxane−H_2O (10:1) unless otherwise stated. [b] A = $[RhCl(COD)]_2$, B = $[Rh(COD)_2]BF_4$, C = $[Rh(acetonitrile)_2(COD)]BF_4$. [c] Isolated combined yield after flash chromatography on silica gel. [d] Determined from the ^1H NMR spectra of the crude samples. [e] Reaction in toluene−H_2O (10:1). [f] Reaction at 100 °C. [g] Reaction at 50 °C.

was observed when ethyl sorbate[9] (**1a**, R^1 = Et, R^2 = CH_3) was treated with $PhB(OH)_2$ (2.5 equiv) and $[RhCl(COD)]_2$ (3 mol %) in toluene−H_2O (10:1) or dioxane-H_2O (10:1) as solvent (Table 1, entries 1−2) at 100 °C. However, in the presence of Et_3N (1.0 equiv), the reaction in dioxane−H_2O (10:1) took place at room temperature (Table 1, entry 3) to give compounds **2a** and **3a** in an 82:18 ratio. No reaction was observed in toluene−H_2O (10:1), even in the presence of the base (Table 1, entry 4). No significant variations in yield or regiochemistry were observed with the temperature (Table 1, entries 5 and 6). Other bases or CsF performed similarly to Et_3N (Table 1, entry 3 and entries 7−9), as well as other Rh^I sources (Table 1, entries 10 and 11).

Similar results were obtained in the reactions of **1a** with arylboronic acids bearing electron-donating or electron-accepting substituents on the aryl moiety (Table 1, entries 12 and 13).

When the reaction was carried out using **1b**[10] (R^1 = Bn, R^2 = H) as starting material, we observed better selectivity in favor of the 1,6-conjugate addition product (Table 1, entry 14) as compared with the same reaction conditions starting with **1a** (Table 1, entry 14).

It is worth mentioning that the stereochemistry[11] of the newly generated C=C bond in the 1,6-conjugate addition products **2** was exclusively controlled to be *Z*.[12]

On the other hand, in the case of compound **1c** (R^1 = CH_3, R^2 = Ph),[13] the selectivity changed and the 1,4-addition products **3** became predominant (Table 1, entries 15−17). The stereochemistry of the C=C bond in compounds **3** was determined to remain *E*.[14]

Therefore, the Rh^I-catalyzed conjugate addition of arylboronic acids to compounds **1** (1,6-addition for **1a**,**b** and 1,4-addition for **1c**) can be carried out at room temperature using

(5) Organocopper reagents: (a) Marshall, J. A.; Roebke, H. *J. Org. Chem.* **1966**, *31*, 3109. (b) Marshall, J. A.; Ruden, R. A.; Hirsch, L. K.; Phillippe, M. *Tetrahedron Lett.* **1971**, *12*, 3795. (c) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509. (d) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1. (e) Uerdingen, M.; Krause, N. *Tetrahedron* **2000**, *56*, 2799.

(6) Iron-catalyzed addition of aryl Grignard reagents: Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603.

(7) Rh^I-catalyzed addition of aryl zinc reagents to dienones: Hayahi, T.; Yamamoto, S.; Tokugana, N. *Angew. Chem., Int. Ed.* **2005**,*44*, 4224.

(8) For some leading references, see: (a) Nicolaou, K. C.; Ramphal, J. Y.; Petasis, N. A.; Serhan, C. N. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1100. (b) Agrios, K. A.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 5468. (c) Kobayashi, Y.; Ikeda, E.; *Chem. Commun.* **1994**, 1789. (d) Matsuhashi, H.; Hatanaka, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* **1995** , *36*, 1539. (e) Hara, R.; Nishihara, Y.; Landre, P. D.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 447. (f) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (g) Klaps, E.; Schmid, W. *J. Org. Chem.* **1999**, *64*, 7537. (h) Durand, S.; Parrain, J.-L.; Santelli, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 253. (i) Basavaiah, D.; Kumarugurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85. (j) Travis, B.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 7741. (k) Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* **2003**, 2404 (l) Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* **2004**, 4989, and references therein.

(9) Comercially available.

(10) Compound **1b** was prepared by esterification with BnOH (DCC, DMAP, CH_2Cl_2, 24 h, rt) of 2,4-pentadienoic acid, in turn obtained by a Knoevegagel condesation between acrolein and malonic acid in pyridine. See: Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 95.

(11) Established by NOE experiments.

(12) Similar finds have been reported in Fe(II)-catalyzed additions of ArMgX reagents, in contrast to the additions of organocopper reagents which lead to *E*-alkenes, see ref 6.

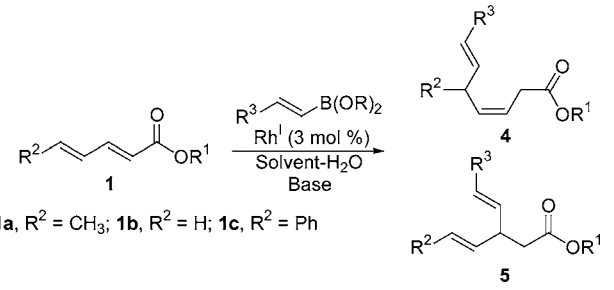
(13) Compound **1c** was prepared by a Wittig reaction of cinnamaldehyde and $Ph_3P{=}CHCO_2Me$ (dioxane, Δ, 6 h, 90%)

(14) Established by inspection of the values of the coupling constants in their ^1H NMR spectra.

dioxane−H_2O as solvent and in the presence of a base (Et_3N or $Ba(OH)_2$ as best choices), either with neutral or cationic Rh^I compounds as the catalysts.

The results of the Rh^I-catalyzed reactions of **1a** (R^1 = Et, R^2 = CH_3) with alkenylboronic acids are gathered in Table 2.

Table 2. Rh^I-Catalyzed Reactions of **1a** with Alkenylboronic Acids[a]



no.	1	additive	R^3	4, 5[b] (%)	4/5[c]
1	**1a**	$Ba(OH)_2$	Ph	**4a**, **5a** (90)	100:0
2	**1a**	$Ba(OH)_2$	*p*-Cl-C_6H_4	**4b**, **5b** (80)	100:0
3	**1a**	$Ba(OH)_2$	*p*-CF_3-C_6H_4	**4c**, **5c** (98)	98:02
4[d]	**1a**	Et_3N	^{n}C_4H_9	**4d**, **5d** (90)	100:0
5	**1c**	$Ba(OH)_2$	Ph		
6	**1c**	$Ba(OH)_2$	*p*-Cl-C_6H_4		
7	**1c**	$Ba(OH)_2$	*p*-CF_3-C_6H_4		

[a] Reactions carried out at room temperature with 0.17 mmol of **1**, 2.0 equiv of $R^3B(OH)_2$, and 1.0 equiv of additive with 3 mol % of $[Rh(COD)_2]BF_4$ with respect to **1** in 0.5 mL of dioxane−H_2O (10:1) unless otherwise stated. [b] Isolated combined yield after flash chromatography on silica gel. [c] Determined from the ^1H NMR spectra of the crude samples. [d] Reaction carried out with 6 equiv of Et_3N using 2-hexenyl-1,3,2-benzodioxaborole instead of the corresponding boronic acid.

We observed that the reaction of arylvinylboronic acids with compound **1a** (Table 2, entries 1−3) took place under the same reaction conditions previously optimized for the additions of arylboronic acids ([Rh(COD]BF_4 (3 mol %), $Ba(OH)_2$ (0.5 equiv), dioxane−H_2O (10:1), room temperature), affording exclusively the corresponding 1,4-dienes **4**. Finally, 2-hexenyl-1,3,2-benzodioxaborole, readily accessible by hydroboration of 1-hexyne,[15] reacted with **1a** under the same reaction conditions but using Et_3N as the base (6 equiv), affording the 1,4-diene **4d** (Table 2, entry 4) without the need to isolate the corresponding boronic acid.

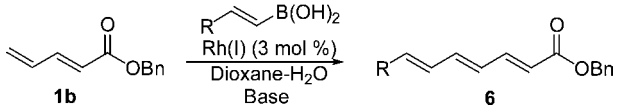
In contrast, no reaction was observed between alkenylboronic acids and dienoate **1c** (R^1 = Et, R^2 = Ph) (Table 2, entries 5 and 6).

In keeping with previous observations (vide supra), the stereochemistryof the newly generated C=C bond in the 1,4-dienes **4** was exclusively controlled to be *Z*, whereas the *E*-geometry of the starting alkenylboronic acid was conserved.

On the other hand, the Rh^I-catalyzed reaction between alkenylboronic acids and dienoate **1b** (Table 3) gave rise to

(15) Tanaka, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479.

Table 3. Rh^I-Catalyzed Reactions of **1b** with Alkenylboronic Acids[a]



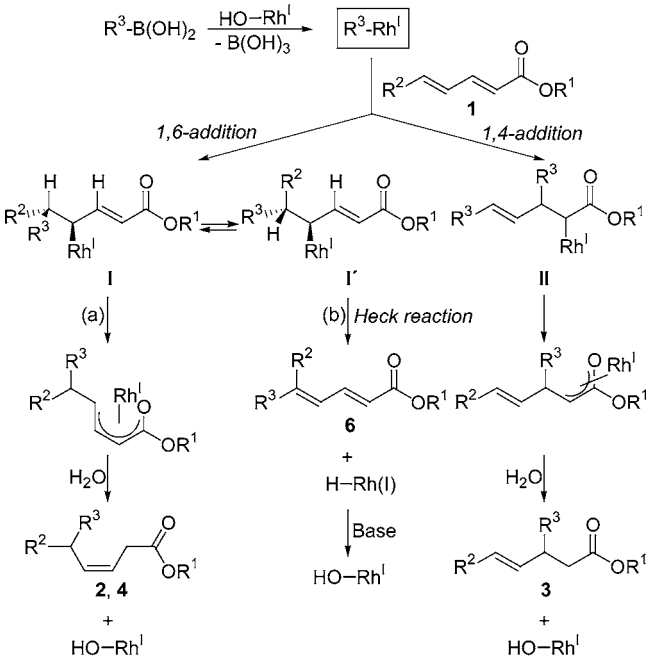
no.	cat.[b]	additive	R	6[c] (%)
1	B	$Ba(OH)_2$	Ph	**6a** (70)
2	B	Et_3N	Ph	**6a** (60)
3	B	CsF	Ph	**6a** (65)
4	A	CsF	Ph	**6a** (65)
5	B	$Ba(OH)_2$	*p*-Cl-C_6H_4	**6b** (70)
6	B	$Ba(OH)_2$	*p*-CF_3-C_6H_4	**6c** (70)
7	B	Et_3N	^{n}C_4H_9	**6d** (70)

[a] Reactions carried out at room temperature with 0.17 mmol of **1b**, 2.0 equiv of $R^3B(OH)_2$, and 1.0 equiv of additive with 3 mol % of Rh^I catalyst with respect to **1** in 0.5 mL of dioxane−H_2O (10:1). [b] A = $[RhCl(COD)]_2$, B = $[Rh(COD)_2]BF_4$. [c] Isolated yield after flash chromatography on silica gel. [d] Reaction carried out with 6 equiv of Et_3N using 2-hexenyl-1,3,2-benzodioxaborole instead of the corresponding boronic acid.

the 2,4,6-trienoates[16] **6** under a variety of conditions as consequence of a Rh^I-catalyzed Heck reaction instead of the expected conjugate addition process.[17]

These reactions can be understood on the basis of the general reaction course proposed for conjugate addition of R−Rh^I species to unsaturated carbonyl compounds (Scheme 1). Transmetalation from boron to rhodium followed by

Scheme 1. Catalytic Cycle for the Rh^I-Catalyzed Reactions of Aryl and Alkenylboronic Acids with Dienoates



insertion of the R^3−Rh^I bond (R^3 = Ar or alkenyl) into the γ,δ-double bond of the dienoate will form an alkyl-Rh^I

intermediate **I**. This can evolve by two different reaction paths: (a) isomerization to a oxo-π-pentadienyl−Rh^I complex, which will give rise to the final 1,6-conjugate addition products **2** and **4** by α-protonation; or (b) *syn*-β-hydride elimination (from conformation **I′**), to give the Heck products **6**. The latter pathway appears to be favored for R^2 = H, R^3 = alkenyl.

Additionally, the R^3−Rh^I complex can also insert into the α,β-double bond of the dienoate to produce another alkyl-Rh^I intermediate **II**, which evolves into an oxo-π-allyl−Rh^I complex that would render the final 1,4-conjugate addition products **3** by α-protonation.

In conclusion, we have realized the Rh^I-catalyzed addition of aryl and alkenylboronic acids in water-tolerant media to α,β,γ,δ-diunsaturated esters, affording the 1,6- or the 1,4-conjugate addition products and the Heck reaction products with high selectivity depending on the substitution pattern of the starting dienoate and the organoboronic acid used. Further developments and synthetic applications of these findings are underway.

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Supporting Information Available: Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) 7-Aryl-2,4,6-trienoates have ben reported as important retinoid X receptor (RXR) selective modulators. See: (a) Michellys, P.-Y.; Ardecky, R. J.; Chen, J.-H.;. Crombie, D. L.; Etgen, G. J.; Faul, M. M.; Faulkner, A. L.; Grese, T. A.; Heyman, R. A.; Karanewsky, D. S.; Klausing, K.; Leibowitz, M. D.; Liu, S.; Mais, D. A.; Mapes, C. M.; Marschke, K. B.; Reifel-Miller, A.; Ogilvie, K. M.; Rungta, D.; Thompson, A. W.; Tyhonas, J. S.; Boehm§, M. F. *J. Med. Chem.* **2003,** *46*, 2683. (b) Michellys, P.-Y.; Ardecky, R. J.; Chen, J.-H.; D'Arrigo, J.; Grese, T. A.; Karanewsky, D. S.; Leibowitz, M. D.; Liu, S.; Mais, D. A.; Mapes, C. M.; Montrose-Rafizadeh, C.; Ogilvie, K. M.; Reifel-Miller, A.; Rungta, D.; Thompson, A. W.; Tyhonas, J. S.; Boehm,, M. F. *J. Med. Chem.* **2003**, *46*, 4087 and references therein.

(17) A Heck product (ethyl cinnamate) has also been isolated in low yield in the attempted 1,4-addition of phenylboronic acid to ethyl acrylate catalyzed by cationic Pd(II) complexes. See: Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768.