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Inter- and Intramolecular Additions of 1-Alkenylboronic Acids or Esters to Aldehydes and Ketones Catalyzed by Rhodium(I) Complexes in Basic, Aqueous Solutions

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Abstract: Grignard-type addition reaction of 1-alkenylboronic acids or their esters to aldehydes or ketones were carried out in aqueous MeOH or DME in the presence of KOH (1 equivalent) and an RhCl(dppf) or Rh(OH)(dppf) catalyst (3 mol%). The utility of the protocol was demonstrated in the corresponding intramolecular reaction giving cyclic homoallylic alcohols.

Key words: alkenylboron, rhodium catalyst, addition

Metal-catalyzed Grignard-type reaction of main-group organometallic compounds is attractive as a method for alkylation of carbonyl compounds that has a potential application to asymmetric synthesis using an optically active metal catalyst. Although insertion of a carbon-heteroatom π -bond into a late metal-carbon bond is rare compared with that of a carbon-carbon π -bond, a catalytic cycle that occurs by a transmetalation-insertion process was recently found to be a convenient alternative for alkylation of aldehydes or aldimines. It has been shown that the additions of arylstannanes¹ and arylsilanes² to aldehydes, ketones or imines are catalyzed by rhodium complexes, Ni(acac)₂/PPh₃ catalyzes the methylation of aldehydes with trimethylaluminum,³ and allylstannanes⁴ and allylsilanes⁵ add to aldehydes and imines in the presence of PdCl₂(PPh₃)₂ or PtCl₂(PPh₃)₂. Rhodium(I) complexes are efficient catalysts for the addition of aryl- or 1-alkenylboronic acids^{6,7} or potassium trifluoroborates⁸ to aldehydes or imines. Arylrhodium(I) complexes, proposed as an intermediate of the catalytic cycle, have recently been demonstrated to insert aldehydes into an aryl-rhodium bond.⁹

In connection with our interests in rhodium-catalyzed reactions of organoboron compounds,^{6,10} we report here the alkylation of aldehydes and ketones with 1-alkenylboronic acids or boronic esters. Intermolecular reaction of 1-alkenylboronic acids or esters can be limitedly used for aldehydes (Scheme 1), whereas analogous addition to ketones occurred smoothly in the corresponding intramolecular version (Scheme 2).

<<Scheme 1>>

The results of addition of (*E*)-1-hexenylboronic acid or its ester to benzaldehyde are summarized in Table 1. The catalysts for addition of arylboronic acids to aldehydes, RhCl(dppf) and Rh(acac)(dppf),^{6a} resulted in significantly low yields (entry 1). In contrast, the presence of aqueous KOH had a great accelerating effect as was demonstrated by Fürstner⁷ (entries 2-5). The reaction provided a mixture of allylic alcohol and ketone **3** and **4** depending on the rhodium(I) complexes employed. Since rhodium complexes catalyze the positional isomerization of a double bond, the reaction was accompanied by a ketone derivative **4** derived from secondary isomerization of **3**. 1-Phenylheptan-1-one was indeed obtained quantitatively when

1-phenyl-2-hepten-1-ol was treated with Rh(acac)/dppf in aqueous KOH at 80 °C. The related reaction of 1-alkenylsilanes also suffered from such secondary isomerization.^{2b} The added base should contribute to the conversion of an RhCl or Rh(acac) complex to the corresponding Rh(OH) species¹¹ that can undergo transmetalation with organoboronic acids.^{6,10} An Rh(OH)(dppf) complex *in situ* generated from [RhOH(cod)]₂ and dppf was indeed an excellent catalyst to selectively yield **3** at room temperature (entry 7), whereas **4** was again the major product at 80 °C (entry 6). Although Rh(OH)(dppf) was found to be a selective catalyst in a single aqueous medium, a homogeneous system using an organic solvent can be advantageous for various aldehydes. The complex prepared *in situ* from [Rh(OH)(cod)]₂ and dppf or *t*-Bu₃P gave a catalyst that was efficient for the synthesis of **3** in a basic, aqueous MeOH (entries 8 and 9). On the other hand, the corresponding ketone **4** was selectively given at 80 °C in aqueous DME (entry 10). Although the reaction of boronic esters was much slower than that of boronic acid, the trimethylene glycol ester afforded a comparable yield at 80 °C (entry 11). The pinacol ester resulted in a moderate yield, and no addition product was obtained for the catechol ester (entries 12 and 13).

<<Table 1>>

The addition of (*E*)-1-hexenylboronic acid to the representative aldehydes is shown in Table 2. No addition was observed for 4-methoxybenzaldehyde even at 80 °C (entry 1) due to its high electron density on the aromatic ring. In contrast, the boronic acid smoothly added to 4-chloro, 4-methoxycarbonyl-, and 4-trifluoromethyl derivatives (entries 3-7) under the conditions optimized for benzaldehyde (entry 2). Formation of allylic alcohols **3** predominated at 25 °C in a basic, aqueous methanol (method A). On the other hand, the ketones **4** were selectively given at 80-100 °C in a basic, aqueous DME (method B). Additions of 4-cyano- and 4-nitrobenzaldehyde were strongly retarded, presumably due to coordination of these polar functional groups to the metal center (entries 8 and 9). Fortunately, these reactions proceeded smoothly under the conditions of method B, by which allylic alcohols **3** were unexpectedly predominated over the formation of ketones. Additions to aliphatic aldehydes such as cyclohexanecarbaldehyde also gave an alcohol product at 80 °C (entry 10). Since the boronic acid neutralizes the added base in the form of RB(OH)₃K, side-reactions associated with the base, such as saponification of esters (entry 5) and Cannizzaro reaction of aromatic aldehydes, were not significant. However, hexanal resulted in 7% yield because of its high sensitivity to the bases (entry 11).

<<Table 2>>

Intermolecular addition of 1-alkenylboronic acids can be limitedly used for aldehydes; however, the corresponding intramolecular version can be extended to the addition of pinacol esters of boronic acids to ketones (Scheme 3). Rhodium-catalyzed hydroboration of terminal alkynes with catecholborane (HBcat) is a convenient method¹² for preparation of (*Z*)-alkenylboronates **6** and **9** desirable for six- and five-membered cyclization. The reaction requires the protection of aldehydes, but ketone, ester and amide derivatives can be directly hydroborated without protection of the carbonyl group with 97-99% *Z*-selectivities. The catechol esters thus synthesized were converted into pinacol esters **6** and **9** for isolation by chromatography on silica gel. The intramolecular addition to the carbonyl group was easily achieved by a Rh(OH)(cod) catalyst *in situ* generated from [RhCl(cod)]₂ and KOH. Although the six-membered cyclization afforded an allylic alcohol **7** in a yield of 91%, the five-membered cyclization was followed by dehydration, leading to the formation of three inseparable tautomers of cyclopentadienes **10**.

<<Scheme 2>>

Further studies are in progress to elucidate possible synthetic applications.

Typical procedures for **6** and **7**:

A 25-ml two neck flask equipped with a magnetic stirring bar and a rubber septum cap was charged with [Rh(cod)Cl]₂ (0.07 g, 0.15 mmol) and then flushed with argon. Cyclohexane (30 ml), P^tPr₃ (0.114 ml, 0.6 mmol), Et₃N (1.4 ml, 10 mmol), and catecholborane (1.20 g, 10 mmol) were successively added. After being stirred for 30 min, **5** (1.2 mmol) was added in one portion and the mixture was then stirred at room temperature for 2 h. Pinacol (1.77 g, 15 mmol) in cyclohexane (10 ml) was added. The resulting mixture was stirred at room temperature for 12 h to convert the catechol ester into the pinacol ester. The product was isolated by chromatography over silica gel with hexane/ethyl acetate (10/1) to give **6** (2.17 g, 82 %). ¹H NMR (400 MHz, CDCl₃) δ 6.46 (dt, *J* = 13.4, 8.1 Hz, 1H), 5.47 (dt, *J* = 13.4 Hz, 1.2 Hz 1H), 2.43 (dd, *J* = 8.1, 1.2 Hz, 2H), 2.35 (s, 2H), 2.13 (s, 3H), 1.27 (s, 12H), 1.02 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 208.9, 150.5, 82.9, 53.9, 44.4, 34.0, 32.5, 26.9, 24.8. ¹¹B NMR (128 MHz, CDCl₃) δ 29.64. IR (neat) 1710 cm⁻¹. MS (EI) *m/z* 266 (M⁺, 11), 251 (43), 208 (71), 165 (94), 164 (48), 151 (35), 123 (37), 122 (44), 121 (30), 111 (61), 110 (42), 109 (44), 108 (85), 107, (100), 101 (97). HRMS (EI) calcd for C₁₅H₂₇BO₃ 266.2053, found 266.2029.

A flask charged with [Rh(cod)Cl]₂ (0.007 g, 0.015 mmol) was flushed with argon. Ethanol (3 ml), **6** (1 mmol), and aqueous KOH (3 M, 1 ml, 3 mmol) were then added successively. The mixture was stirred at 60 °C for 1 h. GC analysis shown the formation of **7** (91 %). ¹H NMR (400 MHz, CDCl₃) δ 5.61-5.66 (m, 1H), 5.54-5.57 (m, 1H), 1.73-1.81

(m, 2H), 1.48-1.63 (m, 2H), 1.20 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H).
¹³C NMR (100 MHz, CDCl₃) δ 132.4, 127.0, 68.8, 50.4, 38.9, 31.0, 30.9, 29.7, 27.8. IR (neat): 3450 cm⁻¹.

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Table 1. Reaction Conditions^a

entry	2	Rh catalyst	additive (eq)	solvent	temp/°C	yield/%	(3/4) ^b
1	2a	[RhCl(cod)] ₂ /dppf	none	H ₂ O	80	2	(0/100)
2	2a	[RhCl(cod)] ₂ /dppf	KOH (6)	H ₂ O	80	95	(0/100)
3	2a	[RhCl(coe) ₂] ₂ /dppf	KOH (6)	H ₂ O	80	89	(13/77)
4	2a	Rh(acac)(coe) ₂ /dppf	KOH (6)	H ₂ O	80	62	(15/85)
5	2a	[Rh(cod) ₂]BF ₄ /dppf	KOH (6)	H ₂ O	80	75	(0/100)
6	2a	[RhOH(cod)] ₂ /dppf	none	H ₂ O	80	81	(0/100)
7	2a	[RhOH(cod)] ₂ /dppf	none	H ₂ O	25	77	(100/0)
8	2a	[RhOH(cod)] ₂ /dppf	KOH (1)	MeOH/H ₂ O (6/1)	25	78	(94/6)
9	2a	[RhOH(cod)] ₂ /2P ^t Bu ₃	KOH (1)	MeOH/H ₂ O (6/1)	25	67	(99/1)
10	2a	[RhCl(cod)] ₂ /dppf	KOH (1)	DME/H ₂ O (6/1)	80	80	(0/100)
11	2b	[RhCl(cod)] ₂ /dppf	KOH (1)	DME/H ₂ O (6/1)	80	81	(81/19)
12	2c	[RhCl(cod)] ₂ /dppf	KOH (1)	DME/H ₂ O (6/1)	80	51	(100/0)
13	2d	[RhCl(cod)] ₂ /dppf	KOH (1)	DME/H ₂ O (6/1)	80	0	

^aA mixture of benzaldehyde (1 mmol), (*E*)-1-hexenylboronic acid or ester (**2**, 2.0 mmol), KOH (0-6 mmol), and a rhodium catalyst (0.03 mmol, 3 mol%) in solvent (3 ml) was stirred for 16 h at the temperature shown in Table.

^bGC yields.

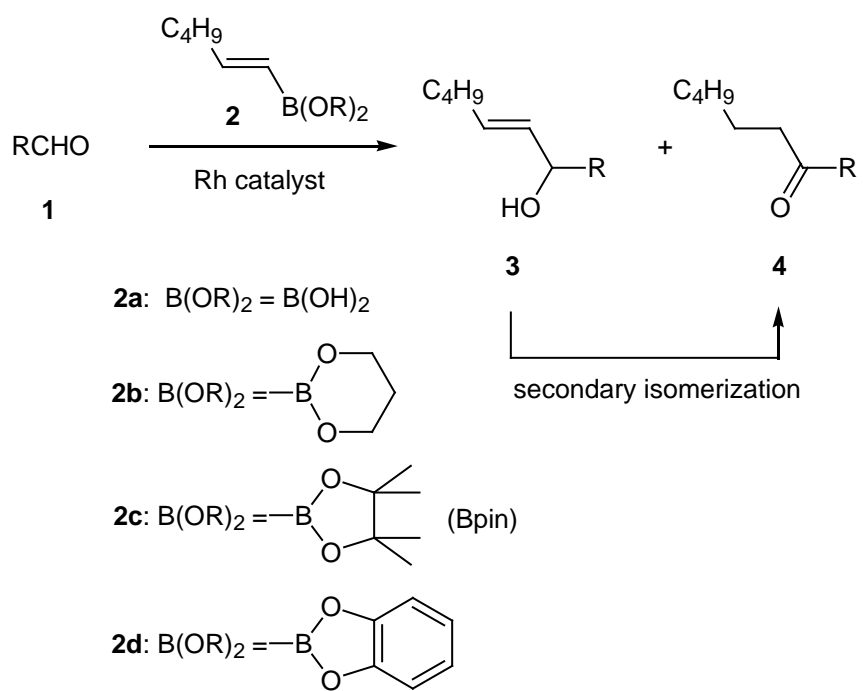
Table 2. Addition of (*E*)-1-Hexenylboronic Acid (**2a**) to Aldehydes^a

entry	aldehydemethod	A ^a	
		yield/% (3/4)	yield/% (3/4)
1	4-MeOC ₆ H ₄ CHO	0	0
2	C ₆ H ₅ CHO	78 (94/6)	96 (0/100)
3	4-ClC ₆ H ₄ CHO	72 (97/3)	77 (25/75)
4 ^c	4-ClC ₆ H ₄ CHO	-	82 (0/100)
5	4-MeO ₂ CC ₆ H ₄ CHO	69 (91/9)	-
6	4-CF ₃ C ₆ H ₄ CHO	80 (90/10)	89 (17/83)
7 ^c	4-CF ₃ C ₆ H ₄ CHO	-	91 (0/100)
8	4-NCC ₆ H ₄ CHO	0	78 (100/0)
9	4-O ₂ NC ₆ H ₄ CHO	0	60 (85/15)
10	<i>cyclo</i> -C ₆ H ₁₁ CHO	0	77 (100/0)
11	C ₅ H ₁₁ CHO	0	7 (100/0)

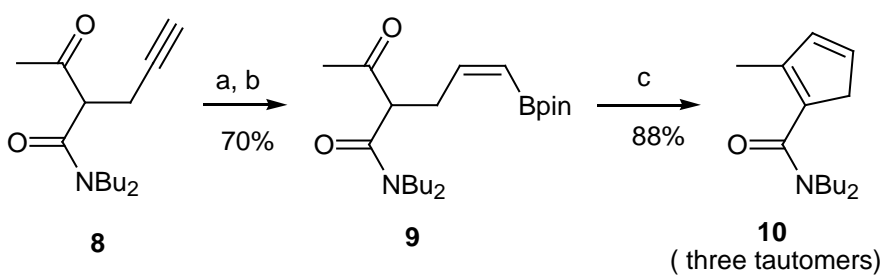
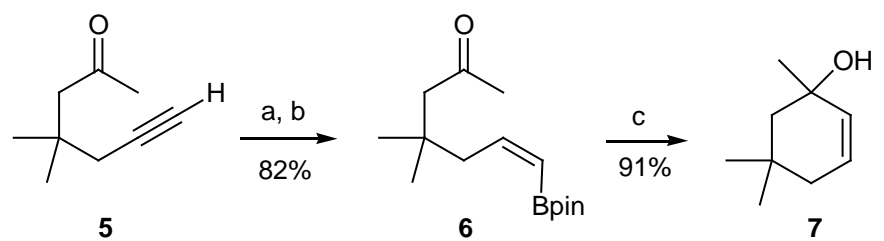
^aMethod A: A mixture of an aldehyde (1.0 mmol), (*E*)-1-hexenylboronic acid (2.0 mmol), KOH (1.0 mmol), [RhOH(cod)]₂ (0.015 mmol, 3 mol%), dppf (0.03 mmol, 3 mol%) in MeOH/H₂O (6/1) (5 ml) was stirred for 16 h at room temperature.

^bMethod B: A mixture of an aldehyde (1.0 mmol), (*E*)-1-hexenylboronic acid (2.0 mmol), KOH (1.0 mmol), [RhCl(cod)]₂ (0.015 mmol, 3 mol%), dppf (0.03 mmol, 3 mol%) in DME/H₂O (6/1) (5 ml) was stirred for 16 h at 80 °C.

^cThe reactions were carried out at 100 °C.



Scheme 1. Rhodium-Catalyzed Addition to Aldehydes



- a) HBcat, $[\text{RhCl}(\text{cod})]_2 \cdot 2\text{Pr}_3\text{P}$, Et_3N , cyclohexane, rt, 2 h.
 b) pinacol, rt, 12 h.
 c) $[\text{RhCl}(\text{cod})]_2$, KOH, EtOH, 60 °C, 1 h.

Scheme 2. Intramolecular Addition to Ketone Carbonyls