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Rhodium-catalyzed Heck-type reaction of arylboronic acids with α,β-unsaturated esters: tuning β-hydrogen elimination *vs.* hydrolysis of alkylrhodium species

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The elusive rhodium-catalyzed Heck-type coupling of arylboronic acids with α,β-unsaturated esters is effected using rhodium chloride as catalyst, indicating the hydrolysis of Rh–C bond could be finely tuned by the steric environment around rhodium.

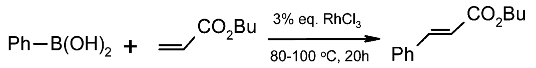
Rhodium(I)-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds has attracted much attention since it was reported in 1997.[1–4] The reaction has been proposed to proceed through a mechanism that begins with transmetalation from organoboron to rhodium(I), followed by insertion of the electron-deficient C=C bond to Rh–Csp^2 and subsequent protonolysis of the resulting Rh–Csp^3 or Rh–O of rhodium enolate after migration.[5] The mechanistically related Heck-type olefination products were not detected since they were found to be more reactive than the parent substrates.[6] Aqueous conditions were also reported to favor the conjugate addition due to the ready hydrolysis of alkylrhodium intermediates.[7] However, Lautens *et al.* reported that, with a substrate incapable of enolization, such as styrene, Heck-type reaction occurred even in water that was expected to facilitate hydrolysis of the resulting Rh–C intermediates, the key-step for conjugate addition, while *ortho*- or *para*-vinylpyridines provided conjugate adducts under otherwise identical conditions through tautomerization of the Rh–C bond to Rh–N.[4,8] All these reports implied that Rh-catalyzed Heck-type reaction of arylboronic acids with α,β-unsaturated esters could not be effected, especially under aqueous conditions. Thus recent efforts have been devoted to non-rhodium catalysts for Heck-type coupling of arylboronic acids with α,β-unsaturated esters.[9–11] Herein, we report the elusive rhodium-catalyzed Heck-type coupling of arylboronic acids with α,β-unsaturated esters.

The key for conjugate addition *vs.* Heck-type reaction of arylboronic acids with α,β-unsaturated esters lies in the competition of hydrolysis or tautomerization with β-H elimination of the alkylrhodium intermediates. From the organometallic chemistry point of view, hydrolysis of Rh–Csp^3 preferably occurs through oxidative addition (OA) of water to RRh^I, generating species R(H)(OH)Rh^{III}, followed by reductive elimination (RE) to give formal protonolysis products R–H although direct hydrolysis of Rh–C is also possible.[12] Both tautomerization and hydrolysis through the OA/RE sequence require a strict steric and electronic environment around the metal, thus leaving a chance for development of rhodium-catalyzed Heck-type reaction by tuning rhodium catalysts. In fact, when equivalent amounts of PhB(OH)$_2$ (**1a**) and butyl acrylate (**2a**) were subjected to 3% eq. of RhCl$_3$(H$_2$O)$_3$ in a toluene/water mixture (3 : 1, v/v) the desired Heck-type product butyl *trans*-cinnamate (**3aa**) formed albeit in low yield (20%) while the conjugate adduct was only formed in trace amounts (< 3%) (Table 1, entry 1). Biphenyl was detected implying that Rh^{III} was reduced to Rh^I species *in situ* through reductive elimination of Rh^{III}(Ph)$_2$. Other metal chlorides, such as PdCl$_2$ or RuCl$_3$, failed to catalyze the reaction of **1a** with **2a** under otherwise identical conditions. These initial results, although not satisfactory, clearly indicated that the reaction course could be tuned by properly choosing the rhodium source.

Addition of phosphine ligands, such as PPh$_3$ and dppf, increased the yields of **3aa** (from 20% to 50%) while P(O^{i}Pr)$_3$ gave a mixture of **3aa** and butyl 3-phenylpropanoate (**3′aa**) (Table 1, entries 2–4). K$_2$CO$_3$ was found to accelerate the reaction, but was not essential. Use of water as co-solvent was necessary, but aqueous/polar solvents such as dioxane, gave a similar result to toluene/H$_2$O (Table 1, entry 8). Wilkinson's catalyst, Rh(PPh$_3$)$_3$Cl, worked similarly to the direct combination of RhCl$_3$ and PPh$_3$ (Table 1, entry 7). Using excess PhB(OH)$_2$ (2.0 eq.) increased the yield (Table 1, entry 5). However, in contrast to the conjugate addition of arylboronic acids to α,β-unsaturated esters, which always requires a large excess of arylboronic acids to achieve good yields due to protodeborylation, use of 2 eq. butyl acrylate gave **3aa** in a higher yield (Table 1, entry 6). This is consistent with the production of the conjugate reduction product, butyl propanoate (up to 40%, GC and GC-Mass). In all cases, except for the ligand P(O^{i}Pr)$_3$, only minor conjugate addition products were detected by GC and ^{1}H NMR

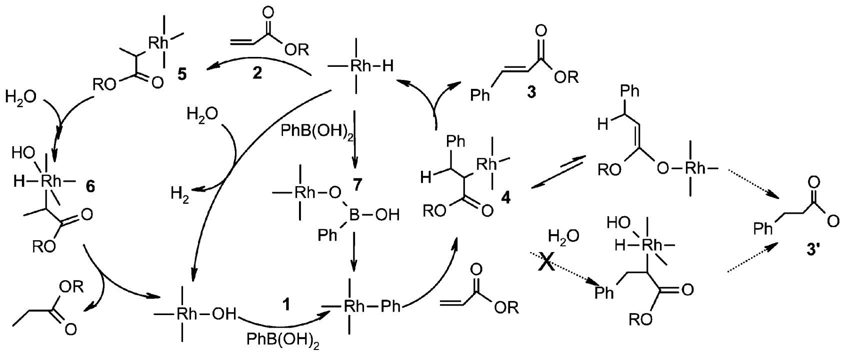
Typical α,β-unsaturated compounds were tested under the optimized condition of 3% eq. RhCl$_3$, 12% eq. PPh$_3$ in toluene/water with a 2 : 1 ratio of olefins to boronic acids (Table 2).† The olefin structure had a marked effect on the reaction. Parent acrylates reacted smoothly, but substituted acrylates, such as methyl methylacrylate, gave **3ad** in low yield (7% by GC-MS) while butyl *trans*-cinnamate remained untouched, indicating steric factors played a critical role in the reaction (Table 2, entries 1, 2 and 4). Electron donor or withdrawing groups (CH$_3$O or CH$_3$OOC) on the arylboronic acid component had little effect on the reaction (Table 2, entries 5 and 6). Acrylonitrile reacted smoothly to offer the desired product **3ac**, while acrylamide looked likely to destroy the catalyst. 2-Cyclohexenone (**2e**), the α,β-unsaturated ketone that is often used as a model substrate in studies of Rh-catalyzed conjugate addition, reacted with **1a** to give both Heck-type coupling product **3ae** and conjugate adduct **3′ae** in low yields.

Table 1 Rhodium-catalyzed Heck-type reaction of PhB(OH)$_2$ with butyl acrylate[a]



Entry	**1a/2a**	Ligand	Solvents (v/v)	Yield[b] (%)
1	1/1	—	Tol/H$_2$O (3/1)	21
2	1/1	PPh$_3$	Tol/H$_2$O (3/1)	50
3	1/1	dppf	Tol/H$_2$O (3/1)	49
4	1/1	P(O^{i}Pr)$_3$	Tol/H$_2$O (3/1)	21[c]
5	2/1	PPh$_3$	Tol/H$_2$O (3/1)	75
6	1/2	PPh$_3$	Tol/H$_2$O (3/1)	85
7	1/2	PPh$_3$[d]	Tol/H$_2$O (3/1)	78
8	1/1	PPh$_3$	Dioxane/H$_2$O (3/1)	45
9	1/1	PPh$_3$	DMF/H$_2$O (3/1)	trace
10	1/1	TPPTS	Tol/H$_2$O (3/1)	trace

[a] When the reaction was conducted in the presence of K$_2$CO$_3$ it completed within 8 h, but yield decreased slightly due to increase of protodeborylation of PhB(OH)$_3$. [b] Determined by GC and butyl propanoate was detected in various amounts. [c] 10% conjugate adduct **3′aa** was also detected. [d] 3% eq. RhCl(PPh$_3$)$_3$ was used.



Scheme 1 A plausible mechanism for the rhodium-catalyzed Heck-type coupling of phenylboronic acid with α,β-unsaturated esters.

Table 2 Rhodium-catalyzed Heck-type reaction of aryl-$B(OH)_2$ with α,β-unsaturated esters[a]

Entry	Aryl (**1**)	EWG (**2**)	**3**	Yield (%)
1	C_6H_5 (**1a**)	CO_2Bu (**2a**)	**3aa**	83
2	C_6H_5 (**1a**)	CO_2Me (**2b**)	**3ab**	78
3	C_6H_5 (**1a**)	CN (**2c**)	**3ac**	69[b]
4	C_6H_5 (**1a**)	(Me) CO_2Me (**2d**)	**3ad**	7[c]
5	4-$MeOC_6H_4$ (**1b**)	CO_2Bu (**2a**)	**3ba**	85
6	4-$MeO_2CC_6H_4$ (**1c**)	CO_2Bu (**2a**)	**3ca**	73
7	C_6H_5 (**1a**)	(**2e**)	**3ae**	5[d]

[a] 2 eq. Olefin used and isolated yields. [b] 10% *cis*-isomer was detected by ^1H NMR. [c] GC-MS yield. [d] GC-MS yield and conjugate adduct 3-phenylcyclohexanone **3′ae** (15%) was also formed

According to Lautens' report, their procedure worked only in water with a water-soluble phosphine ligand (TPPTS) for substrates incapable of enolization and use of organic co-solvents, such as toluene, or common phosphine ligands, such as PPh_3, led to failure of the Heck-type coupling reaction.[4,8] Our results clearly indicated Heck-type reaction of arylboronic acids could occur in organic media and with substrates capable of enolization. Either, aqueous conditions did not show any disadvantage for the Heck-type coupling, although Mori reported Rh-catalyzed Heck-type reaction of organosilicon reagents with α,β-unsaturated carbonyl compounds required anhydrous conditions to avoid hydrolysis of alkylrhodium Rh–C species.[7]

A rationale for the Heck-type coupling *vs*. conjugate addition of arylboronic acids with α,β-unsaturated esters lies in the sterically dependent hydrolysis of Rh–Csp^3 considering that the reaction is very sensitive to steric hindrance of olefins. As shown in Scheme 1, insertion of C=C of α,β-unsaturated ester to Rh–Ph forms the organorhodium Rh–Csp^3 intermediate **4**, which undergoes β-H elimination to provide Heck-type product **3** and Rh–H species. Due to steric hindrance, further insertion of C=C or hydrolysis of **4** did not occur while hydrolysis of its electronic analogue **5** (less sterically crowded) proceeded smoothly to produce the conjugate reduction product. This is also consistent with the fact that substituted acrylates showed very low reactivity in our system. In the case of 2-cyclohexenone, the intermediate of Rh–Csp^3 resulting from slow insertion of C=C isomerized faster to rhodium enolate Rh–O than β-H elimination and subsequently afforded conjugate adduct **3′ae** through hydrolysis of the Rh–O bond. There are three possible paths connecting Rh–H with Rh–Ph to complete the catalysis cycle in the mechanism. The simplest one is the hydrolysis of Rh–H and subsequent transmetalation with $PhB(OH)_2$ generating Rh–Ph. Another possibility involves protonolysis of Rh–H by $PhB(OH)_2$, followed by an intramolecular transmetalation of **7**. The longest one begins with the insertion of C=C of **2a** to Rh–H, forming intermediate Rh–Csp^3 **5**, in which the steric hindrance around Rh is significantly less than in **4**. Thus, oxidative addition of H_2O to **5** and reductive elimination from the resulting hydride **6** regenerate Rh–OH, which is subsequently converted to Rh–Ph through transmetalation with $PhB(OH)_2$. Detection of the conjugate reduction product (GC-MS), butyl propanoate, supported this path. However, the other two paths should also exist since the detected butyl propanoate (GC) is less than the coupling product.

In summary, we have successfully effected the elusive rhodium-catalyzed Heck-type reaction of arylboronic acids with α,β-unsaturated esters or nitrile. Our results clearly demonstrate the hydrolysis *vs*. β-H elimination of alkylrhodium could be finely tuned and should promise new rhodium-based catalysis.

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Notes and references

† General procedure: To a suspension of phenylboronic acid (0.125 g, 1.0 mmol), $RhCl_3(H_2O)_3$ (9 mg, 0.03 mmol) and PPh_3 (30 mg, 0.12 mmol) in toluene/water (15 mL/5 mL) was added butyl acrylate (300 μl, 2.0 mmol) followed by 30 μl mesitylene as internal standard for GC analyses. The mixture was stirred at 100 °C (bath temperature) under nitrogen for 20 h. After cooling to room temperature, samples were taken for GC or GC-MS analyses. The remainder was concentrated and purified by preparative TLC or column chromatography (silica gel) to afford butyl cinnamate (169 mg, 83%).

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