Rhodium(I)-Catalyzed 1,4-Addition of Arylboronic Acids to Acrylic Acid in Water: One-Step Preparation of 3-Arylpropionic Acids

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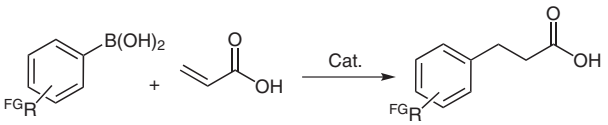
Abstract: A practical method for the one-step preparation of 3-arylpropionic acids through rhodium-catalyzed 1,4-addition of arylboronic acids to acrylic acid is reported. The method is applicable to a broad scope of aryl boronic acids and displays a wide functional group tolerance operating in water as the optimal reaction medium.

Key words: boronic acids, acrylic acid, water, conjugate addition, rhodium

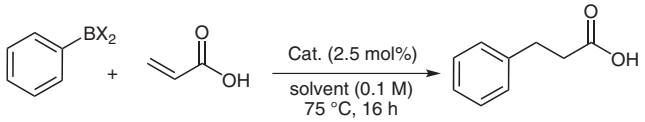
Formation of C–C bonds via rhodium catalysis has become a powerful emergent tool in organic synthesis.[1] Of particular value is the rhodium-catalyzed conjugate addition of arylboronic acids to activated and unactivated alkenic substrates (Miyaura–Hayashi reaction) such as enones,[2] unsaturated esters,[3] aldehydes,[4] amides,[5] phosphonates,[6] sulfones,[7] allyl amines,[8] allyl sulfones,[9] borylalkenes,[10] bicyclic alkenes[11] and vinyl-[12] and alkynylarenes.[13] However, to the best of our knowledge, the use of α,β-unsaturated carboxylic acids as Michael acceptors in such a transformation is unknown.[14] This is surprising since the resulting 3-arylpropionic acids are highly selective agonists of the sphingosine-1-phosphate receptor (S1P1) and therefore of significant interest to medicinal chemistry.[15] Herein, we disclose a one-step protocol for the preparation of 3-arylpropionic acids employing the first rhodium-catalyzed 1,4-addition of arylboronic acids to acrylic acid[16] yielding valuable 3-arylpropionic acids employing water as the optimal reaction medium (Scheme 1).



Scheme 1 1,4-Addition of arylboronic acids to acrylic acid

As a model system, we studied the reaction of phenylboronic acid with acrylic acid employing standard conditions used for the Miyaura–Hayashi reaction (Table 1) and first looked at the influence of the nature of the organoboron reagent.

Table 1 Reaction Conditions for the 1,4-Addition of Phenylboron Reagents to Acrylic Acid[a]



Entry	Catalyst[b]	$PhBX_2$[c]	Solvent	Yield (%)[d]
1	$[Rh(cod)OH]_2$	PhB(pin)	H_2O	31
2	$[Rh(cod)OH]_2$	$PhBF_3K$	H_2O	52
3	$[Rh(cod)OH]_2$	Ph_4BNa	H_2O	0
4	$[Rh(cod)OH]_2$	$(PhBO)_3$	H_2O	93
5	$[Rh(cod)OH]_2$	$PhB(OH)_2$	H_2O	96
6	$[Rh(cod)Cl]_2$	$PhB(OH)_2$	H_2O	93
7	$[Rh(cod)_2BF_4]$	$PhB(OH)_2$	H_2O	12
8	$[RhCl_3 \cdot 3H_2O]$	$PhB(OH)_2$	H_2O	0
9	$[Ir(cod)Cl]_2$	$PhB(OH)_2$	H_2O	<10
10	$[Ru(cod)Cl_2]_n$	$PhB(OH)_2$	H_2O	0
11	$[Rh(cod)OH]_2$	$PhB(OH)_2$	*t*-BuOH	64
12	$[Rh(cod)OH]_2$	$PhB(OH)_2$	acetone	54
13	$[Rh(cod)OH]_2$	$PhB(OH)_2$	dioxane	0

[a] Reaction conditions: $[Rh(cod)OH]_2$ (0.005 mmol), acrylic acid (0.2 mmol) and $PhBX_2$ (0.5 mmol) in degassed solvent (1.8 mL) were heated in a closed Schlenk vessel at 75 °C for 16 h under argon.[17]
[b] cod: 1,5-cyclooctadiene.
[c] pin: pinacol.
[d] Isolated yields.

Phenylboronic pinacol ester and potassium phenyltrifluoroborate showed modest activity in the presence of $[Rh(cod)OH]_2$ in water (31% and 52% respectively, entries 1 and 2). While sodium tetraphenylborate was completely ineffective (entry 3), phenylboroxine, an alternative reagent for phenylboronic acid, gave high yields in this 1,4-addition process (93%, entry 4), comparable to its parent compound (96%, entry 5). $[Rh(cod)Cl]_2$ was also shown to be effective in such a transformation (93%, entry 6).[18] Notably, the reaction between phenylboronic acid and acrylic acid was run on a 2.5-mmol scale and furnished slightly lower yield (82%; see Supplemen-

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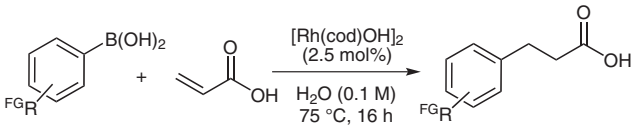
tary Information). An excess of boronic acid proved necessary due to competing protodeborylation.[1a] Using cationic rhodium or Rh(III) precursors (entries 7 and 8) or changing the metal catalyst from iridium (entry 9) to ruthenium (entry 10) were deleterious. A screening of suitable reaction media revealed water to be the optimal medium in terms of catalyst activity (entries 5 and 11–13). It is worth noting that the aqueous medium turns the process heterogeneous, allowing for facile product separation by simple EtOAc extraction. With the optimal, highly active catalyst system in hand (Table 1, entry 5), we explored the substrate scope of the reaction (Table 2).

Table 2 Scope of the Rhodium-Catalyzed 1,4-Addition of Arylboronic Acids to Acrylic Acid[a]



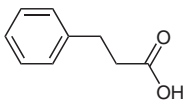
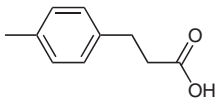
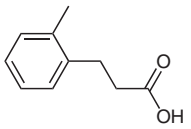
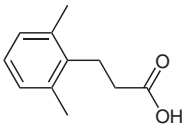
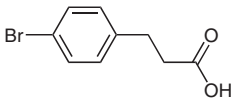
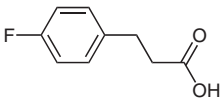
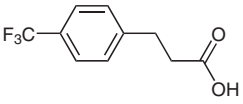
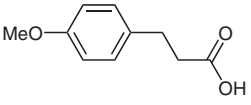
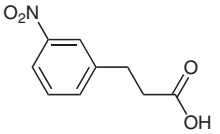
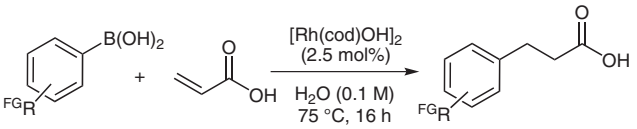
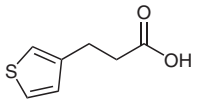
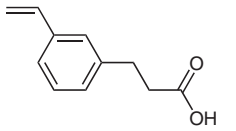
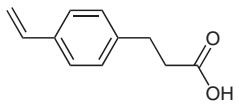
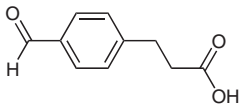
Entry	Product	Yield (%)[b]
1		96
2		80
3		90
4[c]		83
5		91
6		87
7		83
8		94
9		90

Table 2 Scope of the Rhodium-Catalyzed 1,4-Addition of Arylboronic Acids to Acrylic Acid[a] (continued)



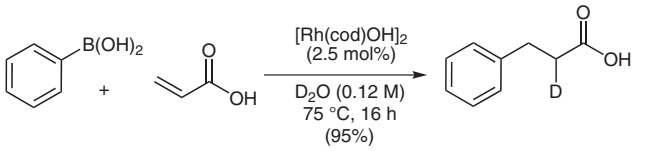
Entry	Product	Yield (%)[b]
10		76
11		72
12		71
13		95

[a] Reaction conditions: $[Rh(cod)OH]_2$ (0.005 mmol), acrylic acid (0.2 mmol) and arylboronic acid (0.5 mmol) in degassed H_2O (1.8 mL) were heated in a closed Schlenk vessel at 75 °C for 16 h under argon.[17]
[b] Isolated yields.
[c] T = 100 °C.

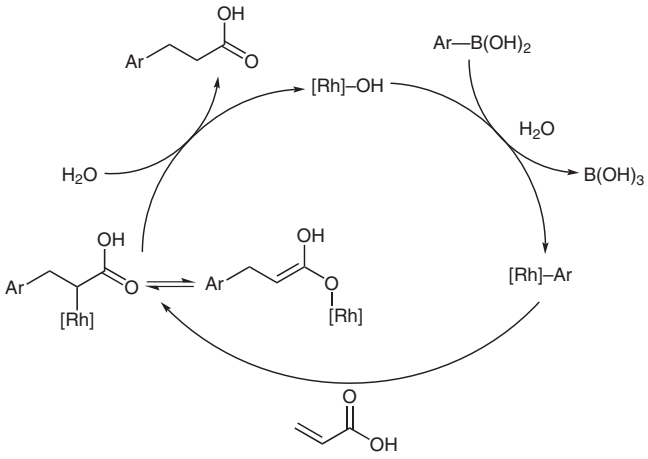
Good yields were obtained for the addition of phenylboronic acid and *p*-tolylboronic acid to acrylic acid (entries 1 and 2, 96% and 80% yield, respectively). Sterical hindrance is tolerated at the boronic acid reaction partner as exemplified by the formation of 3-(2′-methylphenyl)propionic acid (entry 3) and 3-(2′,6′-dimethylphenyl)propionic acid (entry 4) in high yields (90% and 83%, respectively). It is noteworthy that known alternative accesses to these compounds require multistep synthesis.[19] Both electron-donating as well as electron-withdrawing substituents in the arylboronic acid system were well tolerated (entries 5–9). Furthermore, aryl bromides are inert under these reaction conditions, and allow further functionalization via palladium-based cross-coupling methodology. Moreover, heteroaromatic boronic acids as well as styryl boronic acids were efficient reaction partners (entries 10–12), thus highlighting the wide functional group tolerance of this catalyst system. Again, a previously reported multistep-demanding synthesis of 3-(3′-thienyl)propionic acid could be replaced by our simple one-step protocol (entry 10).[20] Even though certain rhodium catalysts are known to promote the addition of arylboronic acids to aldehydes, an unprotected aldehyde function proved compatible with the reaction conditions (entry 13).

Taking into account that α-deuterated 3-phenylpropionic acid (100% deuteration in α-position, Scheme 2) is obtained when benzene boronic acid reacts with acrylic acid in D_2O, the following mechanism could be proposed

(Scheme 3): transmetallation of arylboronic acid to [Rh(I)]OH furnishes an arylrhodium(I) complex,[12] which after coordination of acrylic acid followed by insertion into the Rh–Ar bond would provide the rhodium enolate, which may be either O- or C-bound. Hydrolysis of this rhodium enolate with water would release the desired 3-arylpropionic acid and explains the α-deuterium incorporation upon use of D_2O. The fact that we observed high yield of the 1,4-addition product compared to a competing protodeborylation of the arylboronic acid under the experimental conditions applied, suggests that the insertion of acrylic acid into the Rh–Ar bond is faster than the oxidative addition of the carboxylic acid to the rhodium center followed by the protolytic cleavage of the rhodium–aryl bond.



Scheme 2 1,4-Addition of phenylboronic acid to acrylic acid in D_2O



Scheme 3 Proposed reaction mechanism for the rhodium-catalyzed 1,4-addition of arylboronic acids to acrylic acid

In summary, we have developed the first rhodium-catalyzed 1,4-addition of arylboronic acids to acrylic acid furnishing valuable 3-arylpropionic acids in good to high yields operating in water as the reaction medium. This methodology is applicable to a variety of substrates, displays a wide functional group tolerance and expands the scope of rhodium-catalyzed C–C bond-forming reactions.

Supporting Information including experimental details and spectroscopic data of all new compounds is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) α- and β-Substituted α,β-unsaturated carboxylic acids did not react under the conditions developed herein. Neither did alkylboronic acids (methyl and butylboronic acids) nor alkenylboronic acids (potassium vinyltrifluoroborate and vinylboronic acid pinacol ester).
(17) Slightly lower yields were obtained when non-degassed H_2O was used.
(18) Frost and co-workers reported the failure of the reaction between 1-naphthalene boronic acid and free α,β-unsaturated carboxylic acid with $[Rh(COD)Cl]_2$ (see ref 3b). In our hands, the use of 2-naphthalene boronic acid in the presence of acrylic acid did not work with $[Rh(COD)OH]_2$ either, which tends to prove the poor reactivity of naphthalene boronic acid derivatives when mixed together with free carboxylic acid under such conditions.
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