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Highly Efficient 1,4-Additions of Electron-Deficient Aryl Boronic Acids with a Novel Rhodium(I) Quinonoid Catalyst[§]

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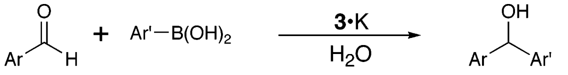
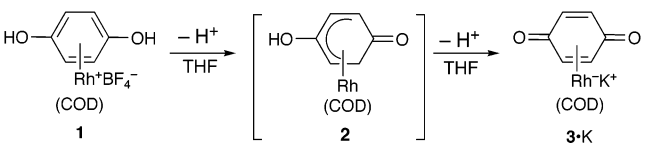
Summary: Rhodium(I) quinonoid catalysts are a remarkably efficient new class of reagents for the conjugate addition of aryl boronic acids. Herein, we describe the use of these reagents in catalyzing the highly efficient addition of a broad range of boronic acids, including heteroaromatic and the first example of trihalogenated aryl boronic acids.

The rhodium(I)-catalyzed conjugate addition of aryl boronic acids to electron-deficient olefins is a mild approach to carbon−carbon bond formation.[1] This approach has been shown to be more chemoselective and widely applicable for molecules with reactive functionality than traditional cuprate or Grignard chemistry.[2] In addition, the enantioselective rhodium-catalyzed conjugate addition reaction with chiral ligands, as shown by Hayashi and others, demonstrates the application of this methodology toward asymmetric synthesis.[3] While this methodology is mild and highly effective for most substrates, aryl boronic acids with electron-withdrawing substituents undergo competitive proto-deborylation.[4] Attempts to favor 1,4-addition have included increasing aryl boronic acid equivalents, increasing catalyst loading, altering the aqueous/organic solvent ratio, decreasing temperature, and in situ generation of aryl boronate reactants.[5] The highest reported yields are afforded with 2−10 equiv of aryl boronic acid, ≥3 mol % catalyst loading, and prolonged reaction at 90−100 °C.[6] Herein, we report that the use of a new rhodium quinone catalyst provides a mild, highly effective, and operationally facile procedure for conjugate addition of aryl boronic acids to 2-cyclohexen-1-one.

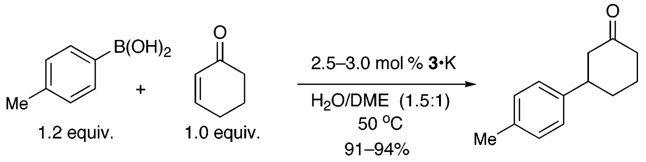


(1)

Scheme 1. Double Deprotonation of Rhodium Hydroquinone 1 to Active Quinonoid Complex 3·K



Scheme 2. An Example of Conjugate Addition with an Aryl Boronic Acid Using Preformed Quinonoid Catalyst 3·K



We recently reported the development of the anionic rhodium η^4-quinonoid complex **3**·K and found that it efficiently catalyzes the 1,2-addition of aryl boronates to aldehydes according to eq 1.[7] The oxygen-sensitive **3**·K was synthesized and isolated by double deprotonation of the hydroquinone precursor complex **1** in THF, via the neutral semiquinone **2** (Scheme 1). We now report that preformed catalyst **3**·K is also effective in conjugate 1,4-addition reactions, as described in Scheme 2. The air-sensitivity of anionic catalyst **3**·K is a drawback in this procedure, necessitating greater catalyst loadings than may otherwise be required. In addressing this problem, it was found that the operational ease of the catalyzed conjugate additions of aryl boronic acids can be greatly facilitated by the in situ generation of catalyst **3**·M (M = Li, Na, K, Cs) from the air-stable rhodium hydroquinone salt **1**. The conjugate addition reactions in DME/H_2O with catalyst **3**·Li, which is generated in situ from **1** and LiOH, are highly efficient and afford excellent yields with negligible side products in short reaction times at 50 °C (Table 1). A significant aspect of the new procedure is the low catalyst loading (0.5 mol % reduced from 2.5 mol % in Scheme 2) and low boronic acid equivalency (1.2 equiv) relative to the conjugate acceptor as compared to the conditions reported in the literature. An evaluation of counterions indicates that **3**·Li is more efficacious than the corresponding potassium salt **3**·K (Table 1, entries 4−6). This counterion effect was also evident in catalyzed 1,2-additions[7] and may be ascribed to general acid activation of the organic electrophile (vide infra).

Preliminary results showed that the reaction exhibited a marked dependence on base equivalency, which was studied through systematic variation (Table 1). The role of base in the conjugate addition of aryl boronic acids to electron-deficient

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[§] This communication is dedicated to the memory of Prof. Nabi Magomedov; dear friend, conscientious scientist, and devoted scholar.

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(1) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229−4231. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196, and references therein. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (d) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465−475.

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(6) (a) Chapman, C. J.; Frost, C. G. *Adv. Synth. Catal.* **2002**, *345*, 353−355. (b) Moss, R. J.; Wadsworth, K. J.; Chapman, C. J.; Frost, C. G. *Chem. Commun.* **2004**, 1984−1985. (c) Paquin, J.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850−10851.

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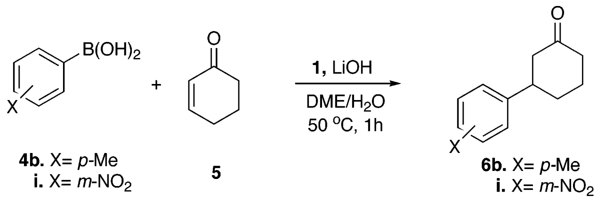
Table 1. Base Study for an Electron-Rich and Electron-Poor Boronic Acid Conjugate Addition to 2-Cyclohexen-1-one



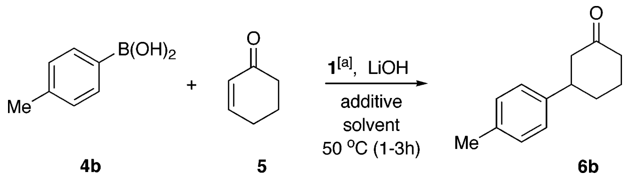
entry	**1** (mol %)	LiOH (mol %)	**6b** yield[a] (%)	**6e** yield[a] (%)
1	0.5	0	4	0
2	0.5	0.25	17	23
3	0.5	0.5	30	38
4	0.5	0.75	63 (31)[b]	46 (33)[b]
5	0.5	1.0	90 (31)[b]	57 (59)[b]
6	0.5	2.0	96 (81)[b]	87 (56)[b]
7	0.5	120	99	19

[a] Isolated yield after silica gel chromatography. [b] Yield in parentheses arises from substitution of KOH in place of LiOH.

olefins is not well understood.[8] For the conjugate addition of *p*-tolyl boronic acid to 2-cyclohexen-1-one, stoichiometric LiOH (1.2 equiv) affords excellent yield of desired ketone **6b** (99%, entry 7, Table 1), although the reaction is equally productive with 2.0 mol % of base (96%, entry 6). The most dramatic change in yield was seen upon increasing base from 0.75 mol % (63%) to 1.0 mol % (90%) (entries 4, 5). This behavior is consistent with complete activation of hydroquinone **1** into the active quinonoid catalyst **3**·Li where 1 mol % of LiOH is required for complete double deprotonation of the precatalyst. In contrast, the *m*-nitrophenyl boronic acid analogue affords the highest yield of desired ketone **6i** (87%) with 2.0 mol % of LiOH. Increasing the base quantity to 120 mol % results in reduced yield (19%, entry 7) and a prevalent side product, nitrobenzene, resulting from proto-deborylation. This study demonstrates that base is required for the reaction and 2.0 mol % provides optimal yield of the desired conjugate addition product.

During further studies to optimize the reaction conditions, a series of additives and bases were examined. Catalytic amounts of carbonate bases, Na_2CO_3 (2.0 mol %) or Cs_2CO_3 (2.0 mol %), are effective at producing high-yielding conjugate additions with boronic acid **4a** (Table 2, entries 6, 8), while stoichiometric amounts (120 mol %) of carbonate bases (entries 7, 9) attenuated reactivity. Pyridine, either catalytic or quantitative, arrests all reactivity, and consistent with this observation is the lack of product with pyridine boronic acids. Additional hydroquinone shows no detectable effect upon reaction outcome, while lithium salts, such as LiCl or $LiBF_4$, either diminish the amount of product or completely arrest the reaction. The addition reaction can be run in the absence of organic solvent; however, stoichiometric base (120 mol %) is required for efficient reaction (entry 10 versus 11).[9] This result is presumably due to the solubilization of the boronic acid into the aqueous phase by formation of the corresponding -ate complex.

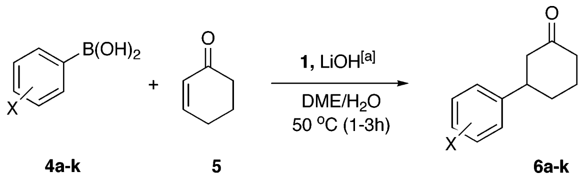
Table 2. Role of Additives and Alternate Bases upon Conjugate Addition Reaction



entry	LiOH (mol %)	additive (mol %)	solvent	**6a** yield[b] (%)
1	0.5	hydroquinone (2.0)	DME/H_2O	31[c]
2	0.5	$LiBF_4$ (120)	DME/H_2O	
3	0.5	LiCl (120)	DME/H_2O	20
4		pyridine (2.0)	DME/H_2O	
5		pyridine (120)	DME/H_2O	
6		Cs_2CO_3 (2.0)	DME/H_2O	97
7		Cs_2CO_3 (120)	DME/H_2O	68
8		Na_2CO_3 (2.0)	DME/H_2O	93
9		Na_2CO_3 (120)	DME/H_2O	74
10	2.0		H_2O	
11	120		H_2O	99

[a] 0.5 mol %. [b] Isolated yield after silica gel chromatography. [c] Compare to Table 1, entry 3.

Table 3. Conjugate Addition of a Variety of Boronic Acids to 2-Cyclohexen-1-one



entry	boronic acid[b] (**4**)	**1** (mol %)	product	yield[c] (%)
1	a. X = H	0.5	**6a**	98
2	b. X = *p*-Me	0.5	**6b**	97
3	c. X = *o*-Me	0.5	**6c**	99
4	d. X = 4-NH-Boc	0.5	**6d**	99
5	e. X = *p*-OMe	0.5	**6e**	97
6	f. X = *p*-Cl	0.5	**6f**	99
7	g. X = *p*-F	0.5	**6g**	94
8	g. X = *p*-F[d]	0.5	**6g**	99
9	h. X = 3-Cl, 4-F	0.5	**6h**	96
10	i. X = *m*-NO_2	0.5	**6i**	85
12	i. X = *m*-NO_2	2.0	**6i**	93
13	i. X = *m*-NO_2[e]	0.5	**6i**	92
14	j. X = 3,4,5-tri-F[d]	2.0	**6j**	70
15	k. X = 2,3,4-tri-F	2.0	**6k**	30

[a] 2.0 mol %. [b] 1.2 equiv relative to 1-cyclohexen-2-one. [c] Isolated yield after silica gel chromatography. [d] From boroxime. [e] 1.5 equiv of boronic acid.

The preferred reaction conditions, outlined as a general procedure in the Experimental Section, are highly effective and facile for a range of boronic acid substrates. Using 2-cyclohexen-1-one as our conjugate acceptor, a number of different aryl boronic acids were studied with our optimized reaction conditions (Table 3). Ketone products **6a**−**g** (entries 1−7) are afforded in high yields, with low catalyst loading (0.5 mol %) and low boronic acid equivalency (1.2 equiv). Electron-deficient boronic acids (entries 5−9) are afforded in excellent yields (94−99%) without any procedural modification from the earlier analogues. Improved yields (92−93%) of *meta*-nitro analogue **6i** were achieved either by increasing the catalyst loading (2.0 mol %, entry 12) or by increasing equivalencies of boronic acid (1.5 equiv, entry 13). Trifluoro analogues **6j** and **6k** (entries 14, 15) were afforded in good to moderate yields (70% and 30%, respectively). This is the first report of conjugate addition of a trihalogenated aryl boronic acid. Efforts are underway to further optimize the additions of trifluorophenyl boronic acids **4j** and **4k**. Both *2,4*-bis(trifluoromethyl)phenyl boronic acid and *ortho*-nitro phenyl boronic acid failed to produce the desired addition products under our standard conditions. The 4-, 5-, or 6-indoloboronic acids (Table 4) undergo conjugate addition,

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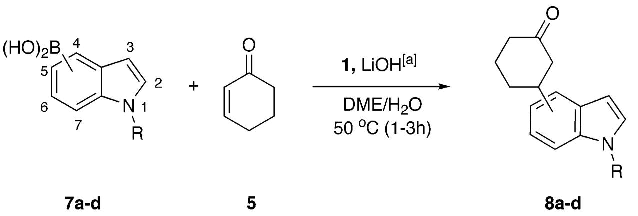
(8) (a) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000−6004. For base studies with the Suzuki coupling: (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980.

(9) It was found that diethyl ether and THF can be used in place of DME; however no reaction is observed in toluene.

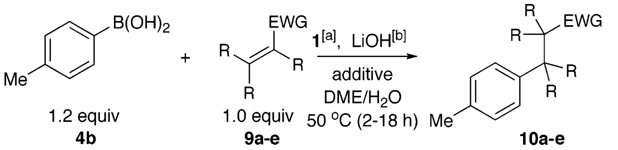
Table 4. Indole Boronic Acid Conjugate Addition to 2-Cyclohexen-1-one

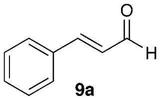
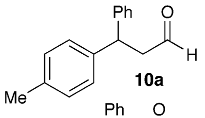
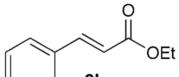
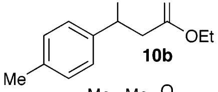
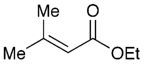
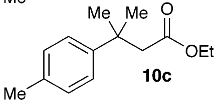
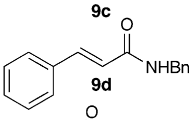
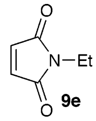
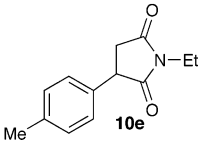


entry	boronic acid(**7**)	**1** (mol %)	product	yield[b] (%)
1	a. 2-B(OH)$_2$ R = Boc	0.5	**8a**	
2	b. 4-B(OH($_2$ R = H	0.5	**8b**	80
3	c, 5-B(OH)$_2$ R = H	0.5	**8c**	63
4	d, 6-B(OH)$_2$ R = H	0.5	**8d**	86

[a] 2.0 mol %. [b] Isolated yield after silica gel chromatography.

Table 5. Conjugate Addition to a Variety of Conjugate Acceptors



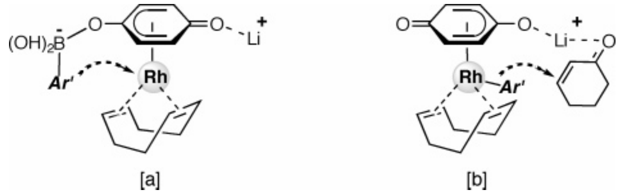
entry	substrate	product	yield[c] (%)
1	 **9a**	 **10a**	96[d]
2	 **9b**	 **10b**	95[d]
3	 **9c**	 **10c**	14[e]
4	 **9d**	--	--
5	 **9e**	 **10e**	97

[a] 0.5 mol %. [b] 2.0 mol %. [c] Isolated yield after silica gel chromatography based on **9**. [d] 1 mol % **1** and 4.0 mol % LiOH. [e] 1.5 equiv of **4b** and 150 mol % LiOH.

while N-Boc-2-indoloboronic acid (entry 1) does not afford any product. The additions of 4-indoloboronic acid (entry 2, Table 4) and *o*-tolyl boronic acid (entry 3, Table 3) show that *ortho* substitution can be tolerated, despite the attenuated reactivity observed for *o*-substituted boronic acids and documented difficulties of reactions with N-Boc-protected pyrrole-2-boronic acids.[10]

The catalytic system presented is similarly efficient with a range of substrates (Table 5). The conjugate addition of *p*-tolyl boronic acid (**4b**) was studied with a selection of conjugate acceptors. The addition to cinnamaldehyde (**9a**) and ethyl cinnamate (**9b**) were highly efficient, providing the products in 96% and 95% isolated yields, respectively (Table 5, entries 1, 2). The β,β-disubstituted olefins are a problem for many catalytic systems, providing no observed conjugate additions,[10] but our preliminary studies have found that **4b** can be added to ethyl 3,3-dimethylacrylate (**9c**) in modest yield (Table 5, entry 3). Reactions with α,β-unsaturated secondary amide **9d** failed to provide any of the desired conjugate addition (Table 4, entry 4); however, cyclic imide **9e** produced the corresponding product **10e** in 97% isolated yield (Table 5, entry 5). Further studies are underway to determine the scope of substrates and to improve addition to highly hindered systems.

Scheme 3. (a) General Base Activation of the Boronic Acid to the -ate Complex and (b) General Acid Activation of the Electron-Deficient Olefin



We hypothesize that the reactivity observed for quinone complex **3**•Li is due to bifunctional activation in catalyzing the reaction of boronic acids and electron-deficient olefins. In the activation of the boronic acid, the alkoxide of the hydroquinone ligand can act as a nucleophile to activate the boronic acid directly for transmetalation to the rhodium center (Scheme 3).[11,12] After formation of the rhodium aryl species, the lithium counterion can act as a general acid to preorganize and activate the conjugate acceptor for carbometalation. This preorganization acts to accelerate the rate of conjugate addition in relation to the rate of proto-deborylation, thereby allowing the use of extremely electron-deficient aryl boronic acids. Mechanistic studies are underway to elucidate the details of this new class of Rh^{I} catalysts and shall be described in future publications.

In conclusion, we have developed an efficient procedure for the conjugate addition of electron-deficient aryl boronic acids to 2-cyclohexen-1-one. This catalyst system is noteworthy due to the operational ease of use and high isolated yields with low levels of catalyst and boronic acid loading in an aqueous solution. The yields of addition products, using extremely electron-deficient aryl boronic acids including the first report of trihalogenated aryl boronic acids, are excellent with minimal proto-deborylation and a complete absence of Heck type products.[13] The scope of substrates and asymmetric additions using this new and highly effective rhodium hydroquinone catalyst will be reported in due course.

Experimental Section

The rhodium(I) hydroquinone catalyst was synthesized by the previously reported procedure.[7]

General Procedure. A 1 dram vial fitted with a Teflon cap was charged with aryl boronic acid (1.2 mmol), enone (1.0 mmol), and dimethoxyethane (DME, 1.0 mL). A solution of **1** (0.02 M DME, 0.250 mL, 0.005 mmol, 0.5 mol %) followed by an aqueous LiOH solution (1.0 M, 0.020 mL, 0.020 mmol, 2.0 mol %) were added. The headspace of the vial was flushed with N_2, and deoxygenated H_2O (1.5 mL) was added. The vial was capped, and the resulting mixture was stirred at 50 °C for 1 h. The reaction mixture was

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[10] Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, *12*, 2006−2014.

[11] We cannot eliminate the possibility that the lithium counterion acts as a Lewis acid to bring a boron-ate complex into proximity of the Rh center to facilitate transmetalation.

[12] For mechanistic analysis with a related system: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem Soc.* **2002**, *124*, 5052−5058.

[13] (a) Zou, G.; Wang, Z.; Zhu, J.; Tang, J. *Chem Commun.* **2003**, 2438−2439. (b) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774−10775.

diluted with a saturated solution of NH_4Cl (5 mL), extracted with 25% EtOAc/hexanes (2 × 5 mL), dried (Na_2SO_4), filtered through a silica plug, and concentrated to afford pure product as characterized by ^1H and ^{13}C NMR and high-resolution mass spectrometry.

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