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Ruthenium Catalyzed Selective Hydroboration of Carbonyl Compounds

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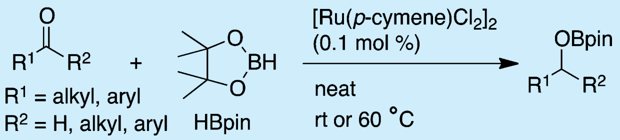
Ⓢ *Supporting Information*

ABSTRACT: Using the [Ru(*p*-cymene)Cl_2]$_2$ (**1**) complex, catalytic hydroboration of aldehydes and ketones with pinacolborane under neat and mild conditions is reported. At rt, chemoselective hydroboration of aldehydes over the ketones is also attained. Mechanistic studies confirmed the immediate formation of monohydride bridged dinuclear complex [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)] (**1b**) from the reaction of **1** with pinacolborane, which catalyzed the highly efficient hydroboration reactions. The catalytic cycle containing mononuclear Ru−H species and intramolecular 1,3-hydride transfer is postulated.



Boronate esters are excellent synthetic surrogates in organic synthesis, and an assortment of chemical transformation is developed to incorporate them into organic substrates.[1,2] The organoboronates are stable, nontoxic compounds and are thus preferred over the other organometallic compounds. Thus, a number of catalytic methods are employed for the synthesis of alkyl and vinyl boronates.[2,3] Particularly, among metal-catalyzed reactions rhodium catalysts are extensively used in hydroboration.[3] Use of ruthenium catalysts in hydroboration of alkenes resulted in either mixture of products[4] or provided dehydrogenative vinyl boronates in addition to the hydroboration.[5] Efficient conversion of carbonyl compounds into the corresponding alcohols is an important transformation in organic synthesis.[6] Transition metal complexes of molybdenum[7] and titanium,[8] and main group zinc complexes,[9] are reported to catalyze the hydroboration of carbonyl compounds.[10] While ruthenium catalyzed synthesis of organoboronates is well explored,[4,5,11] its application in hydroboration of carbonyl compounds is limited to one interesting example, which is based on bifunctional catalysis.[12] Moreover, chemoselective hydroboration of aldehydes over ketones is a synthetically valuable and unknown transformation. Our interest in the hydroboration of carbonyl compounds emanated from the recently reported ruthenium catalyzed hydrosilylation reaction of aldehydes.[13] Herein, we report highly efficient hydroboration of aldehydes and ketones and chemoselective hydroboration of aldehydes under mild conditions using the [Ru(*p*-cymene)Cl_2]$_2$ as a precatalyst.

Initial studies focused on the hydroboration of aldehydes catalyzed by [Ru(*p*-cymene)Cl_2]$_2$ (**1**). Upon stirring a neat solution of benzaldehyde (1 mmol) and pinacolborane (1 mmol, HBpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane) with complex **1** (0.1 mol %) at rt, hydroboration occurs rapidly to provide the $PhCH_2OBpin$. ^1H NMR analysis of the reaction mixture indicated the quantitative conversion of aldehydes in 4 h (TON > 990). Upon hydrolysis, benzyl alcohol was obtained in 92% yield after column chromatography (entry 1, Table 1). Control experiments performed without a catalyst confirmed the absence of any significant hydroboration of aldehydes with pinacolborane at rt.[14]

Further, a range of aromatic and aliphatic aldehydes were subjected to hydroboration with pinacolborane using [Ru(*p*-cymene)Cl_2]$_2$ (0.1 mol %). Aromatic aldehydes containing one or more electron-donating functional groups (entries 2−6, Table 1) or both electron-donating and -withdrawing substituents (entries 10−11) required 4 to 4.5 h to provide the complete conversion of aldehydes. Representatively, *p*-tolyl pinacolboronate ester was isolated (in 98% yield, entry 2) and characterized. Aromatic aldehydes containing only electron-withdrawing functional groups (entries 7−9) and aliphatic aldehydes underwent fast hydroboration, and quantitative conversions of aldehydes (TON > 990) were observed within 3 h at rt. Reactions occur under neat conditions; solvent is used only for the solid aldehydes. Progress of the hydroboration reactions was monitored by TLC and ^1H NMR of the reaction mixture, which confirmed the quantitative conversion of aldehydes. Hydrolysis of the resulting boronate esters provided the corresponding alcohols in very high yields (Table 1).

Hydroboration of ketones using complex **1** required heating the reaction mixture at elevated temperature. When a neat solution of ketone, pinacolborane, and [Ru(*p*-cymene)Cl_2]$_2$ **1** (0.1 mol %) was heated at 60 °C, 60% to >99% conversion of ketones (TON: 600 to >990) to the corresponding boronate esters was observed by ^1H NMR analyses of the reaction mixtures. Boronate ester from the reaction of benzophenone and pinacolborane was isolated in 75% yield (entry 6, Table 2) and characterized by single-crystal analysis.[15] Further hydrolysis of the boronate esters provides the secondary alcohols in good yields (Table 2). As observed in the case of aldehydes, both aliphatic and aryl ketones with different substituents are tolerated. The efficiency of this catalytic system is remarkable when compared to the boron-substituted analogue of the Shvo

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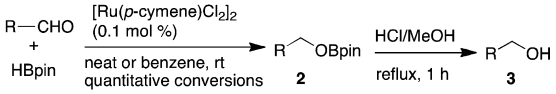
Table 1. Hydroboration of Aldehydes Catalyzed by [Ru(*p*-cymene)Cl_2]$_2$[a]



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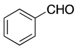
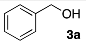
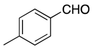
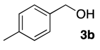
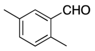
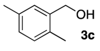
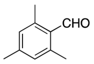
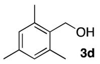
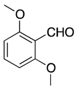
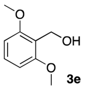
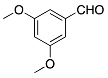
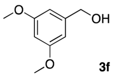
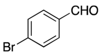
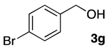
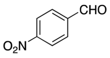
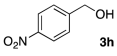
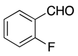
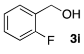
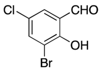
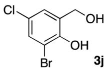
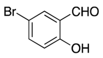
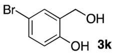
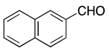
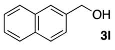
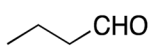
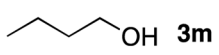
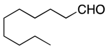
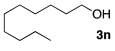
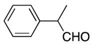
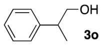
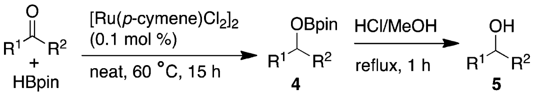
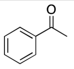
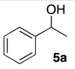
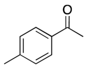
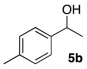
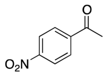
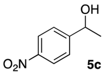
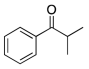
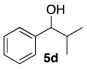
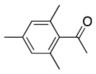
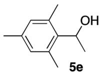
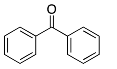
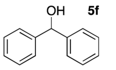
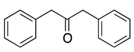
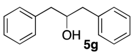
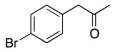
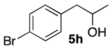
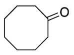
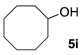
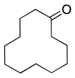
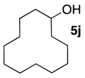
1		4	>99	 3a	92
2		4.5	>99	 3b	96
3		4	>99	 3c	92
4		4	>99	 3d	92
5[b]		4.5	>99	 3e	96
6[b]		4.5	>99	 3f	98
7[b]		3	>99	 3g	95
8[b]		3	>99	 3h	98
9		3	>99	 3i	93
10[b]		4	>99	 3j	93
11[b]		4.5	>99	 3k	92
12[b]		4	>99	 3l	89
13		3	>99	 3m	n.c
14		3	>99	 3n	92
15		4	>99	 3o	91

[a] Reaction conditions: Aldehyde (1 mmol), pinacolborane (1 mmol), and [Ru(*p*-cymene)Cl_2]$_2$ **1** (0.1 mol %) are stirred at room temperature as a neat solution. [b] Benzene (1 mL) added as aldehyde is a solid. [c] Conversions of aldehydes are based on ^{1}H NMR analysis of the reaction mixture. [d] Isolated yields of 1° alcohols by column chromatography. n.c.: not calculated.

Table 2. [Ru(*p*-cymene)Cl_2]$_2$ Catalyzed Hydroboration of Ketones[a]



entry	ketones	conv (%)[c]	alcohols	yield (%)[d]
1		85	 5a	82
2		88	 5b	81
3[b]		90	 5c	83
4		73	 5d	66
5		89	 5e	84
6		n.c	 5f	65
7		60	 5g	55
8		>99	 5h	92
9		85	 5i	80
10[b]		n.c	 5j	52

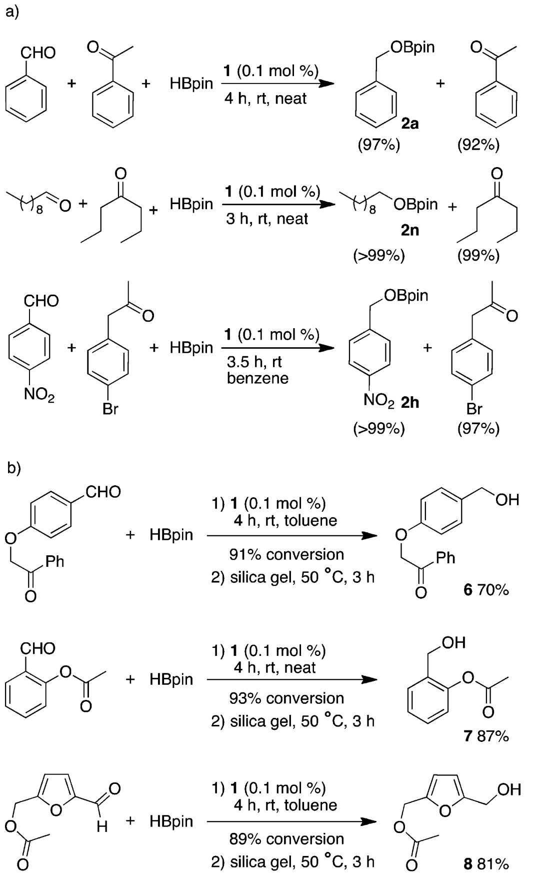
[a] Reaction conditions: Ketone (1 mmol), pinacolborane (1 mmol), and [Ru(*p*-cymene)Cl_2]$_2$ **1** (0.1 mol %) are heated together as a neat solution at 60 °C for 15 h. [b] Benzene (1 mL) added as ketone is a solid. [c] Conversions of ketones are based on ^{1}H NMR analysis of the reaction mixture. [d] Isolated yields of 2° alcohols by column chromatography. n.c.: not calculated.

catalyst, which required 70 °C heating for 3 to 4.5 days at 4 mol % catalyst loading to provide moderate conversions.[12]

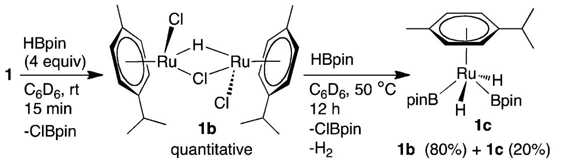
Further, using **1**, the challenging chemoselective hydroboration of aldehydes over the ketones is explored. Reaction of equimolar amounts of benzaldehyde, acetophenone, and pinacolborane were reacted together with **1** (0.1 mol %) under neat conditions, which resulted in 97% conversion of benzaldehyde in 4 h. ^{1}H NMR analysis indicated the presence of 92% of unreacted acetophenone in the reaction mixture. Similar chemoselectivity is also observed in competitive catalytic hydroboration reactions of 1-decanal over the 4-heptanone and *p*-nitro benzaldehyde over 1-(4-bromophenyl)propan-2-one (Scheme 1a). Aldehyde substrates that are embedded with functional groups such as ketones and esters also exhibited chemoselective hydroboration. 4-(2-Oxo-2-phenylethoxy)benzaldehyde, 2-formylphenyl acetate, and (5-formylfuran-2-yl)methyl acetate were independently reacted with an equimolar amount of pinacolborane and **1** (0.1 mol %) in toluene or under neat conditions at room temperature for 4 h. ^{1}H NMR analyses of these reaction mixtures indicated the chemoselective hydroboration of aldehydes over the other functional groups. The corresponding alcohols **6–8** were isolated in good yields after hydrolysis of the boronate esters, and characterization of the products confirmed further that ketone and ester motifs remain intact (Scheme 1b).

In situ monitoring of the reaction progress by ^{1}H NMR spectroscopy revealed the zero-order kinetics for the hydroboration of benzaldehyde (see Figure S1). The hydride region in the ^{1}H NMR of the reaction mixture displayed a singlet resonance at $\delta_{\text{Ru–H}}$ −10.18 ppm immediately, and the observation is comparable to that of the hydrosilylation reaction catalyzed by **1**.[13] Reaction of [Ru(*p*-cymene)Cl_2]$_2$ **1** and pinacolborane (4 equiv) provided monohydrido bridged dinuclear ruthenium complex [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)] **1b** at room temperature (Scheme 2). We previously prepared and characterized the structure of complex **1b** from the reaction of **1** with triethylsilane, as it was identified as a potential catalytic intermediate in the hydrosilylation of aldehydes.[13] Interestingly, complex **1** reacts with pinacolborane (15 min)

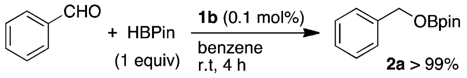
Scheme 1. Chemoselective Hydroboration of Aldehydes Catalyzed by [Ru(*p*-cymene)Cl$_2$]$_2$ 1



Scheme 2. Reaction of [Ru(*p*-cymene)Cl$_2$]$_2$ 1 with Pinacolborane: Preparation of Intermediate 1b



Scheme 3. Catalytic Hydroboration by an Isolated Intermediate 1b [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)]

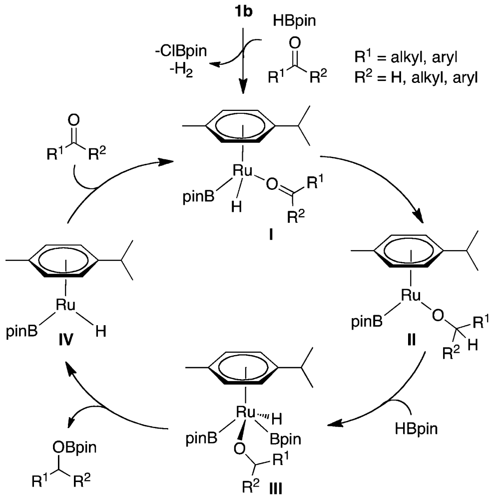


much faster than it reacts with triethylsilane (30 min) to provide complex **1b** quantitatively.[16] Complexes **1** and **1b** also reacted further with triethylsilane and provided a mononuclear Ru(IV) dihydride complex [(η^6-*p*-cymene)Ru(H)$_2$(SiEt$_3$)$_2$] ($\delta_{\mathrm{Ru-H}}$, −13.53 ppm).[13] Attempts to prepare an analogous pinacolborane Ru(IV) dihydride complex from the prolonged reaction (12 h) of either complex **1** or **1b** with an excess of pinacolborane (4 to 8 equiv) at 50 °C provided a mixture of complexes **1b** and **1c** in the ratio 80:20, respectively.[17,18] Efforts made to isolate complex **1c** from this reaction mixture proved to be unsuccessful. Hence, the structure of complex [(η^6-*p*-cymene)Ru(H)$_2$(Bpin)$_2$] ($\delta_{\mathrm{Ru-H}}$, −13.48 ppm; $\delta_{\mathrm{Ru-B}}$ 34.39 ppm)[5] **1c** is tentatively assigned based on the analogous silyl ruthenium dihydride complex [(η^6-*p*-cymene)Ru(H)$_2$(SiEt$_3$)$_2$].[13,19]

When isolated pure complex **1b** (0.1 mol %) was used as a catalyst in the hydroboration of benzaldehyde with pinacolborane, quantitative hydroboration was observed in 4 h, confirming the similar reactivity and efficiency as those of [Ru(*p*-cymene)Cl$_2$]$_2$ **1** and thus indicating the potential intermediacy of **1b** in catalysis (Scheme 3). To ascertain any role of complex **1c** in catalysis,[20] hydroboration of benzaldehyde with pinacolborane was performed using 1 and 2 mol % loadings of **1**.[21] Similarly, hydroboration of acetophenone with 1 mol % of **1** was also carried out and all the reactions were monitored by the ^{1}H NMR, which indicated that no hydride signal corresponding to **1c** ($\delta_{\mathrm{Ru-H}}$, −13.48 ppm) appears in the reaction mixtures, thus confirming its noninvolvement in the catalytic hydroboration of aldehydes and ketones.

On the basis of the above-mentioned observations, we postulate that under the experimental conditions intermediate **1b** reacts with pinacolborane upon splitting into monomeric [(*p*-cymene)RuHCl] and [(*p*-cymene)Ru(Cl)$_2$] complexes[22] to provide Ru(II) intermediate **I**, which may involve the intermediacy of Ru(0) species and the B−H activation.[23] Reductions of carbonyl functional groups occur by an intramolecular 1,3-transfer of a "hydride" ligand to the "carbonyl" motif to provide **II**. Further oxidative addition of pinacolborane to intermediate **II** results in formation of a Ru(IV) intermediate **III**, which reductively eliminates the boronate esters and generates **IV**. Coordination of the carbonyl compound to **IV** regenerates **I** to close a catalytic cycle (Scheme 4).

Scheme 4. Plausible Mechanism for the Hydroboration of Carbonyl Compounds



In conclusion, efficient hydroboration of aldehydes and ketones was achieved using the commercially available and cheap ruthenium complex [Ru(*p*-cymene)Cl$_2$]$_2$. At rt, chemoselective hydroboration of aldehydes is demonstrated. Mechanistic studies revealed that the reaction of pinacolborane with [Ru(*p*-cymene)Cl$_2$]$_2$ **1** provides [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)] **1b**. Perhaps, further oxidative addition of pinacolborane may generate the catalytically active mononuclear Ru species. The catalytic cycle consists of 1,3-hydride transfer from the metal center to the carbonyl group, and reductive elimination of boronate esters from a Ru(IV) intermediate is postulated.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02352.

Experimental procedures, and spectral and single-crystal X-ray data for **4f** (PDF)

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Notes

The authors declare no competing financial interest.

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(15) See Supporting Information (CCDC 1418431).

(16) The reaction of complex **1** with 0.5 equiv of pinacolborane in C_6D_6 was carried out in an NMR tube. Complete formation of complex **1b** and ClBpin (observed by ^{11}B NMR, δ = 27.9 ppm) required 5 h at room temperature.

(17) The attempts made to increase the amount of complex **1c** formations under different conditions failed. In the ^{1}H NMR spectra for the reaction mixtures, multiple signals appeared in the metal-hydride region designating the decomposition of intermediate complexes.

(18) The ^{11}B NMR spectrum of this reaction mixture displayed signals that correspond to HBpin (δ = 28.4 ppm), ClBpin (δ = 27.9 ppm), and a singlet at δ = 34.39 ppm, which confirmed the presence of Ru-Bpin species. This boron chemical shift is comparable to that of other Ru-Bpin complexes reported in the literature; see ref 5.

(19) $[Cp^*Rh(H)_2(Bpin)_2]$ and $[Cp^*Ir(H)_2(Bpin)_2]$ are reported, and the corresponding Rh^V−H and Ir^V−H signals appeared at δ −11.9 ppm and δ −15.8 ppm, respectively. (a) For a rhodium complex, see: Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, Y.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 2538–2552. (b) For an iridium complex, see: Kawamura, K.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8422–8423.

(20) Ru(IV) dihydride complex $[(\eta^6\text{-}p\text{-cymene})Ru(H)_2(SiEt_3)_2]$ catalyzed the hydrosilylation albeit at a slower rate compared to complexes **1** and **1b**.

(21) Interestingly, with 1 and 2 mol % loadings of **1**, hydroboration occurred rapidly to provide 80% and 89% conversion of benzaldehyde (^{1}H NMR), respectively, within 5 min. Under both conditions, the reaction completed within 30 min.

(22) However, ^{1}H NMR studies of the reaction mixture could not confirm the formation of these monomers. Only the presence of Ru−H corresponds to complex **1b** which was observed during and upon completion of the catalytic reaction, indicating that it could also be a resting state for the catalytically active species.

(23) B−H activation by a PNP ruthenium pincer complex was recently reported. See: Anaby, A.; Butschke, B.; Ben-David, Y.; Shimon, L. J. W.; Leitus, G.; Feller, M.; Milstein, D. *Organometallics* **2014**, *33*, 3716–3726.