

Sodium Tetraarylborates as Effective Nucleophiles in Rhodium/Diene-Catalyzed 1,4-Addition to β,β -Disubstituted α,β -Unsaturated Ketones: Catalytic Asymmetric Construction of Quaternary Carbon Stereocenters

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Catalytic asymmetric construction of all-carbon quaternary stereocenters is a subject of great importance in synthetic organic chemistry,¹ and 1,4-addition of organometallic reagents to β,β -disubstituted α,β -unsaturated compounds represents a powerful method for creating such stereocenters. In this context, some effective examples have appeared in the copper-catalyzed asymmetric 1,4-addition of highly reactive nucleophiles such as diorganozincs,² Grignard reagents,³ and triorganoaluminums.⁴ In contrast, the use of air-stable, easily handled organoboron nucleophiles such as organoboronic acids has been limited to the reactions of α,β -unsaturated pyridyl sulfones⁵ and 3-substituted maleimides⁶ under rhodium catalysis. In this communication, we show that air-stable sodium tetraarylborates can function as effective nucleophiles in rhodium/diene-catalyzed 1,4-addition to β,β -disubstituted α,β -unsaturated ketones and that highly efficient asymmetric catalysis can be achieved by employing a readily available chiral diene ligand.

Rhodium-catalyzed 1,4-addition of organoboronic acids to β -mono-substituted α,β -unsaturated compounds has been extensively investigated during the past decade,⁷ and $[\text{Rh}(\text{OH})(\text{cod})]_2$ is one of the most active catalysts known to date.⁸ Unfortunately, however, our initial attempt to apply this catalyst system to the reaction of 3-methyl-2-cyclohexen-1-one (**1a**), a β,β -disubstituted α,β -enone, with phenylboronic acid resulted in no formation of 1,4-adduct **2aa** but instead led to full consumption of the nucleophile by hydrolysis (Table 1, entry 1). Suppression of hydrolysis of the nucleophile by employing a phenylboronic acid ester under aprotic conditions did produce **2aa**, but in only 20% yield (entry 2). These results indicate that the insertion step of the enone into a phenylrhodium intermediate had to be accelerated by properly tuning the reaction system.⁹ In this regard, we were able to find that sodium tetraphenylborate¹⁰ can be used as an effective nucleophile to generate the desired 1,4-adduct **2aa** in significantly higher yield (73–76% yield; entries 3 and 4). It is worth noting that the use of potassium phenyltrifluoroborate¹¹ as the nucleophile or a rhodium/bisphosphine complex such as $[\text{RhCl}(\text{binap})]_2$ as the catalyst (entries 5 and 6) did not give **2aa** under conditions otherwise identical to those of entry 4.

To gain some insight into the high activity of sodium tetraphenylborate under the Rh/cod catalyst system, we conducted a stoichiometric reaction using $\text{Rh}(\text{cod})(\eta^6\text{-C}_6\text{H}_5)\text{BPh}_3$ (**3**), which can be readily prepared from $[\text{RhCl}(\text{cod})]_2$ and sodium tetraphenylborate at room temperature.¹² As shown in eq 1, reaction of complex **3** with **1a** proceeded smoothly at 60 °C to give **2aa** in 63% yield after aqueous workup. This outcome, along with the results in Table 1, entries 1 and 2, indicates that triphenylborane, which is generated by transmetalation of the phenyl group from boron to rhodium in complex **3**, might act as an effective Lewis acid¹³ to assist in the insertion of **1a** into the phenyl–rhodium bond.

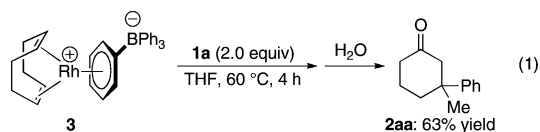


Table 1. Rhodium-Catalyzed 1,4-Addition of Phenylboron Reagents to 3-Methyl-2-cyclohexen-1-one (**1a**)

entry	Rh catalyst	Ph-B	additive	yield (%) ^a
1	$[\text{Rh}(\text{OH})(\text{cod})]_2$	$\text{PhB}(\text{OH})_2$	H_2O	0
2	$[\text{Rh}(\text{OH})(\text{cod})]_2$	$\text{PhB}(\text{OR})_2^b$	none	20
3	$[\text{RhCl}(\text{cod})]_2$	Ph_4BNa	H_2O	73 ^c
4	$[\text{RhCl}(\text{cod})]_2$	Ph_4BNa	MeOH	76 ^c
5	$[\text{RhCl}(\text{cod})]_2$	PhBF_3K	MeOH	0
6	$[\text{RhCl}(\text{binap})]_2$	Ph_4BNa	MeOH	0

^a Determined by ¹H NMR analysis against an internal standard.

^b (OR)₂ = OCH₂CMe₂CH₂O. ^c Isolated yield.

On the basis of the above consideration, a proposed catalytic cycle for the present catalysis is illustrated in Figure 1. Complex **3**, initially formed by the reaction of $[\text{RhCl}(\text{cod})]_2$ with sodium tetraphenylborate, undergoes transmetalation to give a phenylrhodium species and triphenylborane. Subsequent insertion of enone **1a** into the phenyl–rhodium bond with the aid of Lewis acidic triphenylborane, followed by protonolysis, produces 1,4-adduct **2aa** along with the formation of an alkoxorhodium intermediate. Ligand exchange of this intermediate with sodium tetraphenylborate then regenerates complex **3** to complete the cycle.

Because this reaction is effectively catalyzed by a rhodium/diene complex, the use of a chiral diene ligand^{14,15} would lead to the development of its asymmetric variant. As shown in eq 2, we found that employing our conventional chiral dienes such as (*R,R*)-Bn-bod* and (*R,R*)-Ph-bod*¹⁶ in the reaction of **1a** with sodium tetraphenylborate induced excellent enantioselectivity of $\geq 98\%$, but the chemical yield of **2aa** turned out to be only moderate (48–65% yield). The use of chiral diene (*R*)-**4**, which can be rapidly prepared

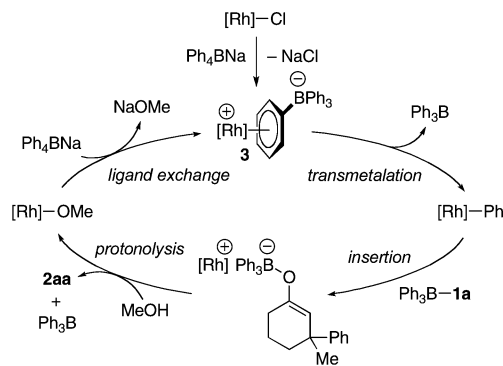
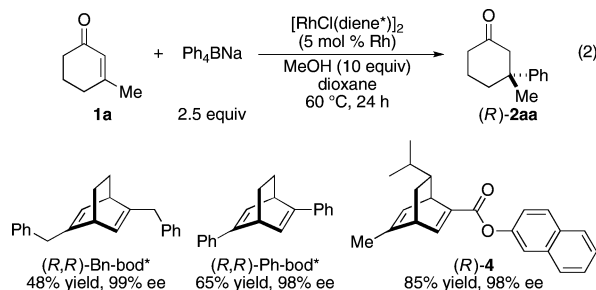


Figure 1. Proposed catalytic cycle for the rhodium-catalyzed 1,4-addition of sodium tetraphenylborate to **1a** [$[\text{Rh}] = \text{Rh}(\text{cod})$].

in an enantiopure form by a stereoselective [4 + 2] cycloaddition between commercially available (*R*)- α -phellandrene and 2-naphthyl propiolate,¹⁷ significantly improved the chemical yield of **2aa** while retaining the high enantioselectivity (85% yield, 98% ee). This high activity of Rh/(*R*)-**4** can presumably be attributed to the acceleration of both the transmetalation¹⁸ and insertion¹⁹ steps due to the electron-withdrawing nature of (*R*)-**4**.



Under the catalysis of Rh/(*R*)-**4**, several cyclic enone substrates effectively undergo β -phenylation to give the corresponding ketones with a quaternary carbon stereocenter in high yield and enantioselectivity (75–83% yield, 89–98% ee; Table 2, entries 1–4). For acyclic enones, (*R,R*)-Bn-bod* induces better enantioselectivity (92–94% yield, 78–91% ee; entries 5 and 6),²⁰ and it is noteworthy that *E* and *Z* substrates gave the opposite enantiomers enriched with each other. With regard to the nucleophilic component, not only phenyl but also some other aryl groups can be added to enone **1a** with high efficiency (62–84% yield, 91–97% ee; entries 7–10).

In summary, we have developed a rhodium-catalyzed 1,4-addition of tetraarylborates to β,β -disubstituted α,β -unsaturated ketones. Highly efficient asymmetric catalysis to create quaternary carbon stereocenters by employing a readily available chiral diene ligand [(*R*)-**4**] has also been described.

Table 2. Rhodium-Catalyzed Asymmetric 1,4-Addition of Sodium Tetraarylborates to **1**

entry	1	Ar	time (h)	product	yield (%) ^a	ee (%) ^b
1	1a	Ph	24	(<i>R</i>)- 2aa	83	98
2	1b	Ph	24	(<i>R</i>)- 2ba	79	98
3	1c	Ph	24	(<i>S</i>)- 2ca	80	98
4	1d	Ph	48	(<i>R</i>)- 2da	75	89
5 ^c	(<i>E</i>)- 1e	Ph	60	(<i>S</i>)- 2ea	92	78
6 ^c	(<i>Z</i>)- 1e	Ph	60	(<i>R</i>)- 2ea	94	91
7 ^d	1a	4-MeC ₆ H ₄	48	(<i>R</i>)- 2ab	73	91
8	1a	4-FC ₆ H ₄	60	(<i>R</i>)- 2ac	62	91
9	1a	3-MeC ₆ H ₄	24	(<i>R</i>)- 2ad	84	95
10 ^e	1a	3-ClC ₆ H ₄	48	(<i>R</i>)- 2ae	65	97

^a Isolated yield. ^b Determined by chiral HPLC with hexane/2-propanol. ^c (*R,R*)-Bn-bod* was used as the ligand. ^d The reaction was conducted in THF. ^e The reaction was conducted at 90 °C with 10 mol % rhodium catalyst.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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