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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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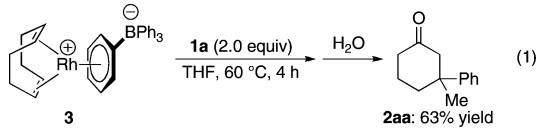
Catalytic asymmetric construction of all-carbon quaternary stereocenters is a subject of great importance in synthetic organic chemistry,[1] and 1,4-addition of organometallic reagents to β,β-disubstituted α,β-unsaturated compounds represents a powerful method for creating such stereocenters. In this 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 sulfones[5] and 3-substituted maleimides[6] 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.

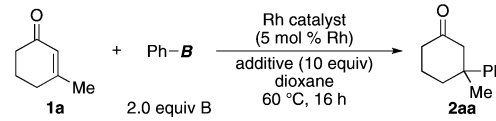
Rhodium-catalyzed 1,4-addition of organoboronic acids to β-monosubstituted α,β-unsaturated compounds has been extensively investigated during the past decade,[7] and $[Rh(OH)(cod)]_2$ is one of the most active catalysts known to date.[8] Unfortunately, however, our initial attempt to apply this catalyst 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 tetraphenylborate[10] 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 phenyltrifluoroborate[11] as the nucleophile or a rhodium/bisphosphine complex such as $[RhCl(binap)]_2$ 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 $Rh(cod)(\eta^6\text{-}C_6H_5)BPh_3$ (**3**), which can be readily prepared from $[RhCl(cod)]_2$ 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 acid[13] to assist in the insertion of **1a** into the phenyl−rhodium bond.



(1)

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	$[Rh(OH)(cod)]_2$	$PhB(OH)_2$	H_2O	0
2	$[Rh(OH)(cod)]_2$	$PhB(OR)_2$[b]	none	20
3	$[RhCl(cod)]_2$	Ph_4BNa	H_2O	73[c]
4	$[RhCl(cod)]_2$	Ph_4BNa	MeOH	76[c]
5	$[RhCl(cod)]_2$	$PhBF_3K$	MeOH	0
6	$[RhCl(binap)]_2$	Ph_4BNa	MeOH	0

[a] Determined by ^1H NMR analysis against an internal standard. [b] $(OR)_2 = OCH_2CMe_2CH_2O$. [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 $[RhCl(cod)]_2$ 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 ≥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

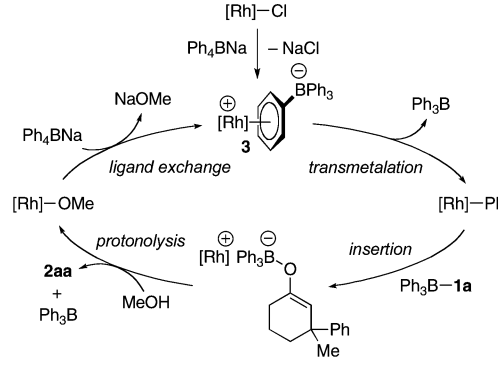


Figure 1. Proposed catalytic cycle for the rhodium-catalyzed 1,4-addition of sodium tetraphenylborate to **1a** {[Rh] = Rh(cod)}.

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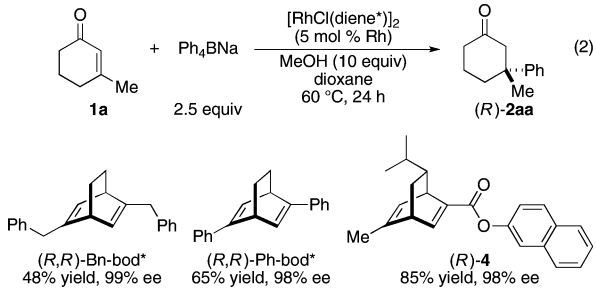
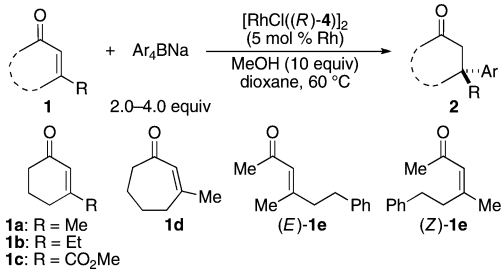
in an enantiopure form by a stereoselective [4 + 2] cycloaddition between commercially available (*R*)-α-phellandrene and 2-naphthyl propiolate,[17] significantly improved the chemical yield of **2aa** while retaining the high enantioselectivity (85% yield, 98% ee). This high activity of Rh/(*R*)-**4** can presumably be attributed to the acceleration of both the transmetalation[18] and insertion[19] 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	(*R*)-**2aa**	83	98
2	**1b**	Ph	24	(*R*)-**2ba**	79	98
3	**1c**	Ph	24	(*S*)-**2ca**	80	98
4	**1d**	Ph	48	(*R*)-**2da**	75	89
5[c]	(*E*)-**1e**	Ph	60	(*S*)-**2ea**	92	78
6[c]	(*Z*)-**1e**	Ph	60	(*R*)-**2ea**	94	91
7[d]	**1a**	4-MeC_6H_4	48	(*R*)-**2ab**	73	91
8	**1a**	4-FC_6H_4	60	(*R*)-**2ac**	62	91
9	**1a**	3-MeC_6H_4	24	(*R*)-**2ad**	84	95
10[e]	**1a**	3-ClC_6H_4	48	(*R*)-**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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(20) In the presence of (*R*)-**4**, (*E*)-**1e** gave (*S*)-**2ea** with 66% ee and (*Z*)-**1e** gave (*R*)-**2ea** with 72% ee.

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