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A New Type of Catalytic Tandem 1,4-Addition−Aldol Reaction Which Proceeds through an (Oxa-π-allyl)rhodium Intermediate

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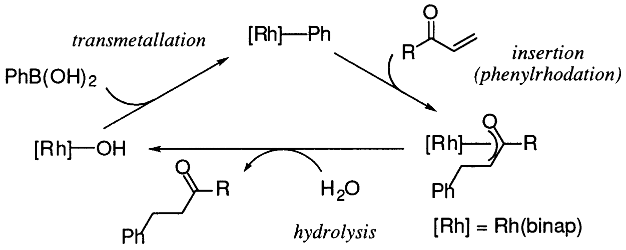
Regioselective generation of metal enolates by 1,4-carbometalation of α,β-unsaturated ketones followed by aldol reaction with aldehydes is an important tool in organic synthesis.[1] One of the useful examples recently developed is the copper-catalyzed 1,4-addition of organozinc reagents and aldol reaction of the resulting zinc enolates with aldehydes.[2] In this type of catalytic tandem 1,4-addition−aldol reaction, it is generally recognized that the catalyst works for the first step (1,4-addition) but has nothing to do with the second step (aldol reaction).[3] Here we wish to report a new type of the tandem 1,4-addition−aldol reaction, where a rhodium complex catalyzes both of the two carbon−carbon bond-forming reactions, the catalytic cycle consisting of the 1,4-addition of an organorhodium species to an α,β-unsaturated ketone and the aldol addition of the resulting (oxa-π-allyl)rhodium intermediate to an aldehyde.

Rhodium-catalyzed 1,4-addition of organoboronic acids to alkenes[4] and alkynes,[5] including its application to catalytic asymmetric synthesis,[6−8] is one of the recent topics in transition metal-catalyzed organic reactions. We have recently revealed the catalytic cycle for the asymmetric addition of phenylboronic acid to α,β-unsaturated ketones (Scheme 1).[9] The catalytic cycle involves an (oxa-π-allyl)rhodium complex as a key intermediate which undergoes hydrolysis giving the hydrophenylation product and a hydroxorhodium species. Under nonaqueous reaction conditions, we attempted the tandem 1,4-addition−aldol reaction and found that it is realized with high selectivity by use of 9-aryl-9-borabicyclo[3.3.1]nonanes (B-Ar-9BBN)[10] as an organoboron reagent and [Rh(OMe)(cod)]$_2$[11] as a catalyst.

Scheme 1



A mixture of *tert*-butyl vinyl ketone (**1a**), 9-(4-fluorophenyl)-9-borabicyclo[3.3.1]nonane (B-(4-FC$_6$H$_4$)-9BBN, **2m**), benzaldehyde (**3x**), and 3 mol % [Rh(OMe)(cod)]$_2$ in toluene was allowed to stand at 20 °C for 2 h (Scheme 2). Aqueous oxidative workup followed by silica gel chromatography gave 96% isolated yield of the 1,4-addition−aldol reaction product **4amx** with high syn selectivity (syn/anti = 9.6/1)[12] (entry 1 in Table 1). The selectivity in giving the three components coupling product **4amx** is so high that either of the two components coupling products resulting from 1,4-addition to the enone or arylation of the aldehyde was not detected at all. The reaction of 9BBNs substituted with phenyl (**2n**) or 4-methoxyphenyl (**2o**) also proceeded with high syn selectivity to give a quantitative yield of the corresponding 1,4-addition−aldol products (entries 2 and 3). An alkenylborane reagent, B-(E)-1-heptenyl-9BBN **2p**, is also successfully used for the syn-selective 1,4-addition−aldol reaction (entry 4). The use of the 9BBN reagents **2** is essential for the tandem 1,4-addition−aldol reaction. The organoboron reagents where boron is bonded to oxygen ligands, such as B-arylcatecholborane, B-arylpinacolborane, or triarylcyclotriboroxane ((ArBO)$_3$), gave no detectable amounts of the 1,4-addition−aldol products. The rhodium complex [Rh(OMe)(cod)]$_2$ is a catalyst of choice for the present reaction. The catalytic activity is lower with Rh(acac)(C$_2$H$_4$)$_2$ or [RhCl(cod)]$_2$.[13] The tandem 1,4-addition−aldol reaction also took place in the combination of some other enones and aldehydes. The chemical yield and the syn selectivity are all high in the reactions with phenyl vinyl ketone (**1b**), methyl vinyl ketone (**1c**), and alkyl aldehydes **3y** and **3z** (entries 5−8).

Scheme 2

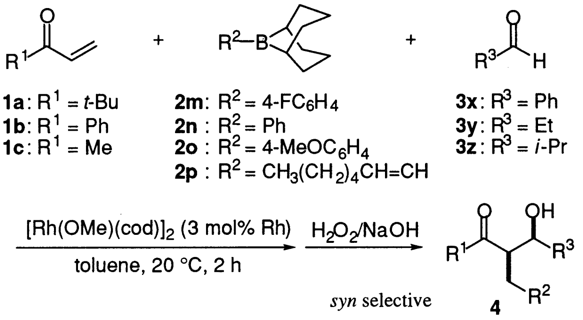


Table 1. Rhodium-Catalyzed Tandem Conjugate Addition−Aldol Reaction of Enone **1**, B-R-9BBN **2**, and Aldehyde **3**[a]

entry	enone 1	B-R-9BBN 2	aldehyde 3	product 4	yield (%)[b]	syn/anti[c]
1	**1a**	**2m**	**3x**	**4amx**	96	9.6/1
2	**1a**	**2n**	**3x**	**4anx**	97	10.7/1
3	**1a**	**2o**	**3x**	**4aox**	99	8.9/1
4[d]	**1a**	**2p**	**3x**	**4apx**	85	21.4/1
5	**1a**	**2m**	**3y**	**4amy**	72	12.4/1
6	**1b**	**2m**	**3x**	**4bmx**	88	9.0/1
7	**1b**	**2m**	**3z**	**4bmz**	93	9.0/1
8	**1c**	**2m**	**3x**	**4cmx**	99	5.7/1

[a] The rhodium-catalyzed tandem conjugate addition−aldol reaction was carried out with enone **1** (0.22 mmol), B-R-9BBN **2** (0.22 mmol), and aldehyde **3** (0.20 mmol) in 0.7 mL of toluene in the presence of 3 mol % [Rh(OMe)(cod)]$_2$ at 20 °C for 2 h. [b] Isolated yield by silica gel chromatography. [c] Diastereomeric ratios were determined by ^{1}H NMR. [d] Reaction for 6 h.

NMR experiments carried out in toluene-d_8 at 20 °C showed that the 1,4-addition forming a boron enolate or any other catalytic

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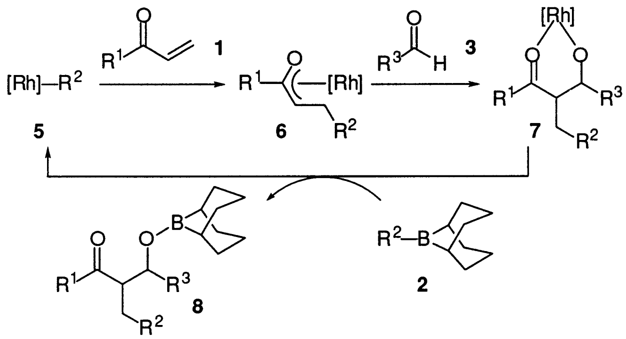
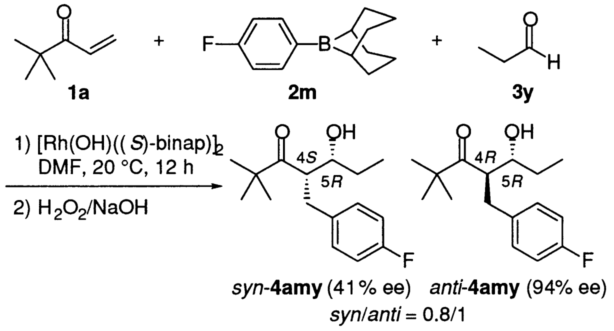
Scheme 3



Scheme 4



reactions does not take place in the solution containing α,β-unsaturated ketone **1a**, 9BBN **2m**, and 3 mol % rhodium catalyst $[Rh(OMe)(cod)]_2$. On addition of benzaldehyde (**3x**) to the solution at the same temperature, all of the three compounds, **1a**, **2m**, and **3x**, began decreasing at the same rates, and new resonances, which were assigned to the boron aldolate of the 1,4-addition−aldol product **4amx**,[14] appeared. These results indicate that the catalytic cycle involves the aldol reaction of (oxa-π-allyl)rhodium **6** with aldehyde forming rhodium aldolate **7**,[15] which undergoes the transmetalation of the aryl or alkenyl group from 9BBN **2** to give the boron aldolate **8** and the organorhodium intermediate **5** (Scheme 3). The high syn selectivity may suggest the six-membered ring transition states of (*Z*) rhodium enolate at the aldol reaction.[15] It is interesting that both of the two carbon−carbon bond-forming reactions, 1,4-addition and aldol reaction, are catalyzed by a rhodium complex in one catalytic cycle. The chemoselectivity at both of the two steps is surprisingly high, the intermediates **5** and **6** reacting with enone **1** and aldehyde **3**, respectively, with perfect selectivity. The rhodium- or iridium-catalyzed reductive aldol reaction reported[16] by Morken using a hydrosilane is supposed to proceed by a similar catalytic cycle involving (oxa-π-allyl)metal intermediates generated by the hydrometalation of enones.

Catalytic asymmetric synthesis was examined with $[Rh(OH)((S)\text{-binap})]_2$ (3 mol %) as a chiral catalyst (Scheme 4). Unfortunately, the rhodium-binap complex was not as catalytically active as $[Rh(OMe)(cod)]_2$, but the reaction of enone **1a**, 9BBN **2m**, and aldehyde **3y** in DMF at 20 °C for 12 h gave 44% yield of the 1,4-addition−aldol product, which consists of syn isomer (41% ee (4*S*,5*R*)) and anti isomer (94% ee (4*R*,5*R*))[17] in a ratio of 0.8 to 1.[18] The formation of the enantiomerically enriched products is important because it can rule out the intermediacy of a boron enolate in the present reaction, which would lead to racemic aldol products.

To summarize, a new type of tandem 1,4-addition−aldol reaction was realized by use of *B*-Ar-9BBN, where both the 1,4-addition and the aldol reactions are catalyzed by a rhodium complex. Future studies will address the optimization of the catalytic asymmetric tandem reaction.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) ^1H NMR (toluene-d_8) for syn isomer: δ 0.45 (s, 9H), 1.10−1.93 (br m, 14H), 3.06 (dd, J = 13.3, 10.1 Hz, 1H), 3.13 (dd, J = 13.3, 3.8 Hz, 1H), 3.70 (ddd, J = 10.1, 8.0, 3.8 Hz, 1H), 5.39 (d, J = 8.0 Hz, 1H), 6.70 (t, J = 8.7 Hz, 2H), 6.84 (dd, J = 8.6, 5.5 Hz, 2H), 6.99 (tt, J = 7.4, 1.4 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 7.30 (dd, J = 7.1, 1.5 Hz, 2H).

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