Generation of Rhodium Enolates via Retro-aldol Reaction and Its Application to Regioselective Aldol Reaction

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Abstract: Retro-aldol reactions of β-hydroxy ketones take place under rhodium catalysis, leading to regioselective formation of the corresponding rhodium enolates. The enolates react with aldehydes *in situ* to afford the corresponding aldol adducts in high yields.

Keywords: aldol reaction, rhodium, carbon-carbon bond cleavage, retro-aldol reaction.

The reaction of aldehydes or ketones with metal enolates is one of the most important reactions in organic synthesis.[1] Methods for the preparation of metal enolates have therefore been extensively studied, which include deprotonation of carbonyl compounds, reduction of α-halo carbonyl compounds,[2] and 1,4-addition of α,β-unsaturated carbonyl compounds.[3] Metal-catalyzed retro-aldol reaction of β-hydroxy carbonyl compounds is a potentially useful and mechanistically interesting method for generating metal enolates. However, there are few reports on this method. The countercation of the enolates is limited to Lewis-acidic aluminum[4] and zirconium.[5,6] In addition, the starting β-hydroxy carbonyl compound is 2-hydroxy-2-methyl-4-butanone (diacetone alcohol) in most cases.[7] In the course of our study on rhodium-catalyzed carbon-carbon bond cleavage,[8] here we report rhodium-catalyzed retro-aldol reactions of various β-hydroxy ketones to allow for exclusively regioselective generation of the corresponding rhodium enolates.

A mixture of β-hydroxy ketone **1a**[9] and benzaldehyde (**2a**) was treated with catalytic amounts of $[RhCl(cod)]_2$, *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA), and cesium carbonate in dioxane at 20 ˚C for 3 h (Scheme 1).[10] The usual workup followed by silica gel column purification afforded hydroxy ketone **3a** quantitatively. None of regioisomer **4** was observed. The yield of **3a** was lower in the absence of TMEDA (77% yield, along with 19%

recovery of **1a**). Phosphine ligands such as PPh_3, PMe_3, $P(^nBu)_3$, $Ph_2PCH_2CH_2PPh_2$ (DPPE), and $P(OEt)_3$ completely suppressed the reaction, whereas the reactions with $P(^tBu)_3$ and $P(^cC_6H_{11})_3$ afforded **3a** in 71% and 51% yields, respectively. An *N*-heterocyclic carbene ligand, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), prohibited the reaction. Addition of alkenes such as *p*-fluorostyrene, norbornadiene, and 1,4-diphenyl-1,3-butadiene resulted in the efficient formation of **3a** in more than 90% yields. Bidentate 2,2'-bipyridyl and tridentate ^{i}Pr-Pybox[11] were similarly effective. Unfortunately, in all the cases, the diastereoselectivity was poor, 6:4 to 4:6. As a precatalyst, $Rh(acac)_3$, $RhCl(PPh_3)_3$, $[RhCl(CO)_2]_2$, and $Rh(OAc)_2$ were completely inactive. Precatalysts $[RhOH(cod)]_2$ and $[RhCl(nbd)]_2$ showed reactivity similar to $[RhCl(cod)]_2$. It is worth noting that the use of $[IrCl(cod)]_2$ led to the formation of two regioisomers, **3a** and **4**, in a ratio of 1:1.

[Insert Scheme 1]

A variety of aldehydes reacted with the rhodium enolate, which was prepared from **1a** via retro-aldol reaction (Table 1). The steric (entries 1–3 and 13) as well as electronic (entries 4–12) nature of the aromatic aldehydes had little influence on the reaction. Unfortunately, the reactions of 4-pyridinecarbaldehyde (entry 15) and unprotected hydroxy aldehyde (entry 16) afforded only traces of the corresponding products. Cinnamaldehyde (**2r**) reacted to

yield the corresponding 1,2-adduct **3r** in high yield (entry 17). Aliphatic aldehydes such as dodecanal (**2s**) and cyclohexanecarbaldehyde (**2t**) underwent the reaction (entries 18 and 19), whereas pivalaldehyde (**2u**) resisted the aldol reaction (entry 20). Cyclohexanone (**2v**) served as a substrate, albeit with modest efficiency (entry 21).

[Insert Table 1]

We next examined the scope of β-hydroxy ketones[9] as the precursors of rhodium enolates (Figure 1). Treatment of benzaldehyde (**2a**) with **1b** or **1c** afforded **5b** or **5c**, respectively. No scrambling of regioisomers **5b** and **5c** was observed. These transformations correspond to regioselective aldol reactions of 3-hexanone with benzaldehyde. Cyclohexyl ketone **1d** underwent retro-aldol reaction to afford **5d** in high yield. Benzyloxy and benzoyloxy groups did not retard the reaction to provide **5f** and **5g**, respectively, in good yields. No isomerization of the olefinic moiety of **1j** was observed in the reaction providing **5j**.

[Insert Figure 1]

The reaction of hydroxy diketone **1h** afforded **5h** through the selective formation of rhodium enolate **6** (Scheme 2). Selective formation of **6** from diketone **7** would be difficult since deprotonation at the α positions of the other carbonyl group is not trivial. β-Hydroxy benzyl ketone **5i** was derived from the exclusive formation of rhodium enolate **8**. Enolate **8**

is not readily available from benzyl ethyl ketone (**9**) because of the acidic nature of the benzylic protons. These two reactions starting from **1h** and **1i** underscore the synthetic utility of the present methodology.

[Insert Scheme 2]

In summary, we have devised a new method for the preparation of rhodium enolates via retro-aldol reaction and applied it to regioselective aldol reactions. The present method is superior to the conventional deprotonation of carbonyl compounds from the viewpoints of regioselectivity and functional group compatibility. Recently, reductive generation of metal enolates has been attracting increasing attention because of its mild conditions and high regioselectivity.[3] However, the reductive method would not allow for using α,β-unsaturated carbonyl compounds as aldol acceptors, which is in contrast to the result of entry 17 in Table 1. With improved stereoselectivity, the present strategy would lead to significant progress in the aldol reaction.

Acknowledgement

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Supplementary data

Supplementary data including the procedure for the preparation of **1** and characterization data for new compounds can be found online alongside the electronic version of the manuscript.

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(9) β-Hydroxy ketones **1** were readily available according to the procedures described as the Supplementary Data.

(10) **Experimental procedure:** $[RhCl(cod)]_2$ (2.5 mg, 0.005 mmol) and cesium carbonate (13 mg, 0.04 mmol) were placed in a 20-mL reaction flask under argon.

1-Hydroxy-2-methyl-1,1-diphenyl-3-butanone (**1a**, 51 mg, 0.20 mmol) in 1,4-dioxane (2.0 mL) was added to the flask. Then *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (6 μL, 0.04 mmol) and benzaldehyde (**2a**, 30 μL, 0.30 mmol) were added to the flask. The mixture was stirred at 20 ˚C for 3 h. A saturated ammonium chloride solution (2 mL) was added, and the organic compounds were extracted with ethyl acetate (10 mL × 3). The combined organic part was dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatographic purification on silica gel by using hexane / ethyl acetate = 5 : 1 as an eluent afforded **3a** (36 mg, 0.20 mmol) in quantitative yield (*syn*/*anti* = 53/47).

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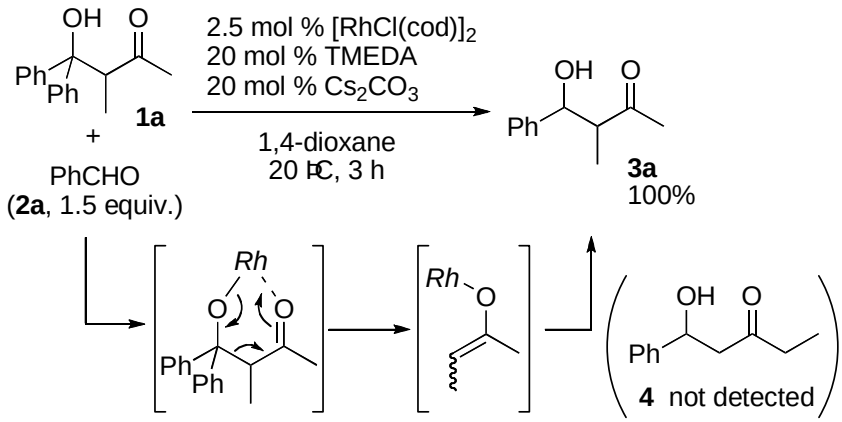
Scheme 1. Rhodium-catalyzed reaction of benzaldehyde (**2a**) with β-hydroxy ketone **1a** via retro-aldol reaction



Scheme 2. Regioselective formation of rhodium enolates

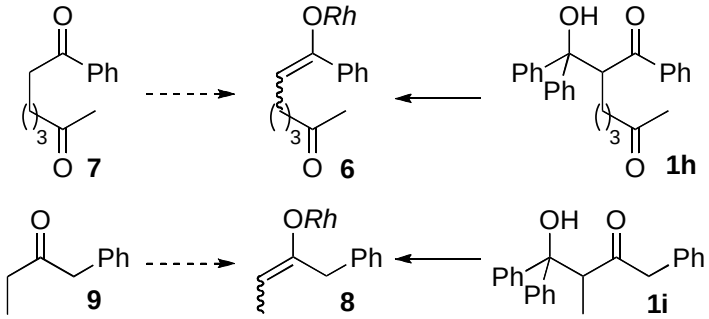
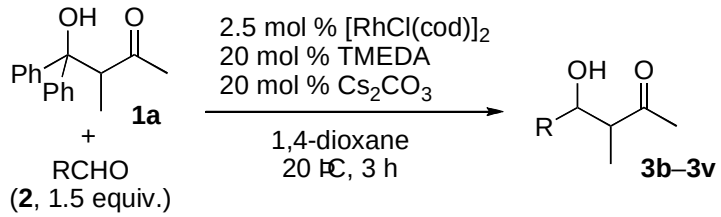


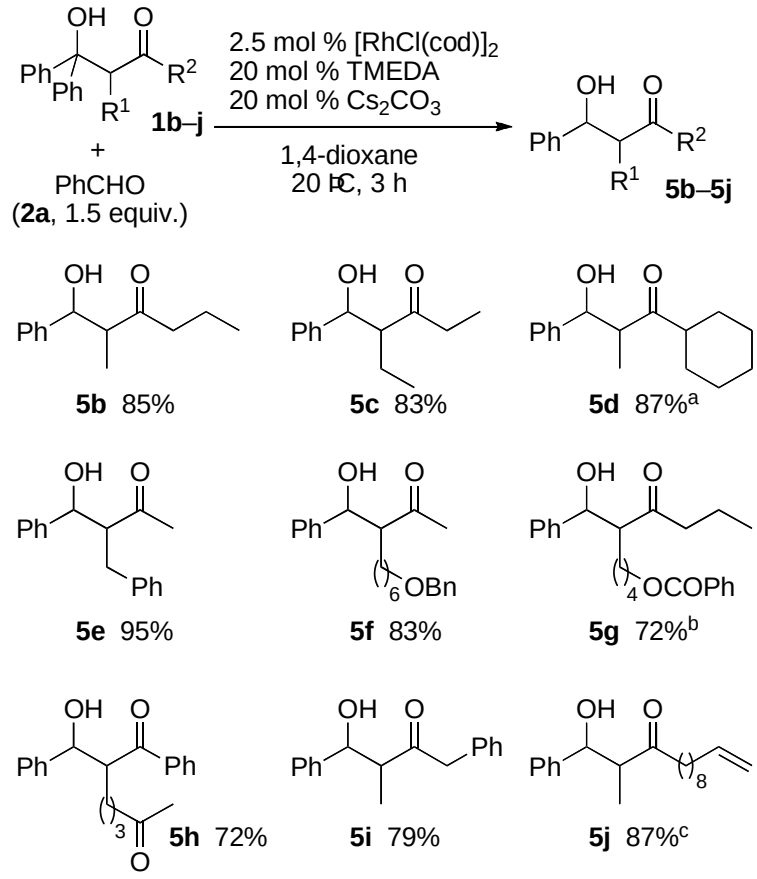
Table 1. Rhodium-catalyzed reaction of various aldehyde **2** with β-hydroxy ketone **1a** via retro-aldol reaction



entry	R	**2**	**3**	yield (%)[a]
1	4-MeC_6H_4	**2b**	**3b**	87
2	3-MeC_6H_4	**2c**	**3c**	80
3	2-MeC_6H_4	**2d**	**3d**	84
4	4-ClC_6H_4	**2e**	**3e**	82
5	3-ClC_6H_4	**2f**	**3f**	90
6	4-BrC_6H_4	**2g**	**3g**	85
7	4-$MeOC_6H_4$	**2h**	**3h**	94
8	4-$CF_3C_6H_4$	**2i**	**3i**	88
9	4-$MeOCOC_6H_4$	**2j**	**3j**	81
10	4-NCC_6H_4	**2k**	**3k**	90
11	4-$Me_2NC_6H_4$	**2l**	**3l**	68[b]
12	4-PhC_6H_4	**2m**	**3m**	89
13	2-naphthyl	**2n**	**3n**	92
14	2-furyl	**2o**	**3o**	86
15	4-pyridyl	**2p**	**3p**	ND[c]
16	4-HOC_6H_4	**2q**	**3q**	ND[c]
17	PhCH=CH	**2r**	**3r**	95
18	*n*-undecyl	**2s**	**3s**	61[b]
19	cyclohexyl	**2t**	**3t**	80[b]
20	*tert*-butyl	**2u**	**3u**	ND[c]
21	(cyclohexanone)	**2v**	**3v**	46

[a] The *syn/anti* ratios range from 6:4 to 4:6 unless otherwise noted. [b] The *syn/anti* ratios are 7:3. [c] Not detected by the ^{1}H NMR analysis of the crude product.

Figure 1. Rhodium-catalyzed reaction of benzaldehyde (**2**) with various β-hydroxy ketones **1** via retro-aldol reaction



(a) 40 ˚C, 1.5 h. (b) 40 ˚C, 2 h. (c) 20 ˚C, 4 h.

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