

Generation of rhodium enolates via retro-aldol reaction and its application to regioselective aldol reaction

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Received 24 January 2008; revised 7 February 2008; accepted 12 February 2008

Available online 14 February 2008

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.

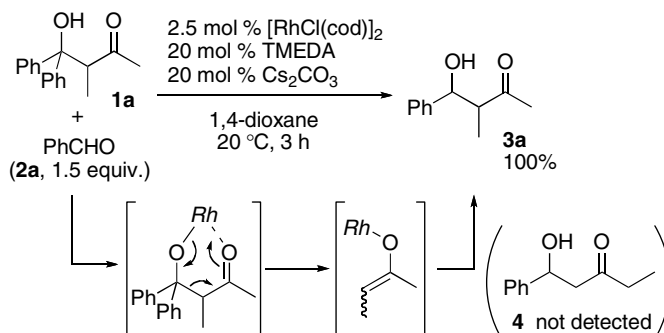
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Keywords: Aldol reaction; Rhodium; Carbon–carbon bond cleavage; Retro-aldol reaction

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 counteraction of the enolates is limited to Lewis-acidic aluminum⁴ 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 $[\text{RhCl}(\text{cod})]_2$,

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 , $\text{P}(n\text{Bu})_3$, $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$ (DPPE), and $\text{P}(\text{OEt})_3$ completely suppressed the reaction, whereas the reactions with $\text{P}(\text{tBu})_3$ and $\text{P}(\text{C}_6\text{H}_{11})_3$ afforded **3a** in 71% and 51% yields, respectively. An *N*-heterocyclic carbene ligand, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes),



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

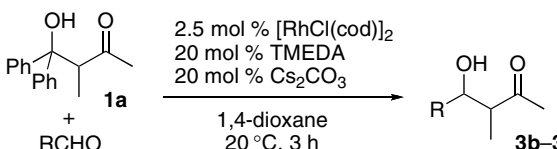
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prohibited the reaction. Addition of alkenes such as *p*-fluorostyrene, norbornadiene, and 1,4-diphenyl-1,3-butadiene resulted in the efficient formation of **3a** in more than 90% yields. Bidentate 2,2'-bipyridyl and tridentate ^tPr-Pybox¹¹ were similarly effective. Unfortunately, in all the cases, the diastereoselectivity was poor, 6:4 to 4:6. As a precatalyst, Rh(acac)₃, RhCl(PPh₃)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.

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 reac-

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 ₆ H ₄	2b	3b	87
2	3-MeC ₆ H ₄	2c	3c	80
3	2-MeC ₆ H ₄	2d	3d	84
4	4-ClC ₆ H ₄	2e	3e	82
5	3-ClC ₆ H ₄	2f	3f	90
6	4-BrC ₆ H ₄	2g	3g	85
7	4-MeOC ₆ H ₄	2h	3h	94
8	4-CF ₃ C ₆ H ₄	2i	3i	88
9	4-MeOCOC ₆ H ₄	2j	3j	81
10	4-NCC ₆ H ₄	2k	3k	90
11	4-Me ₂ NC ₆ H ₄	2l	3l	68 ^b
12	4-PhC ₆ H 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 ₆ H ₄	2q	3q	ND ^c
17	PhCH=CH	2r	3r	95
18	<i>n</i> -Undecyl	2s	3s	61 ^b
19	Cyclohexyl	2t	3t	80 ^b
20	<i>tert</i> -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 ¹H NMR analysis of the crude product.

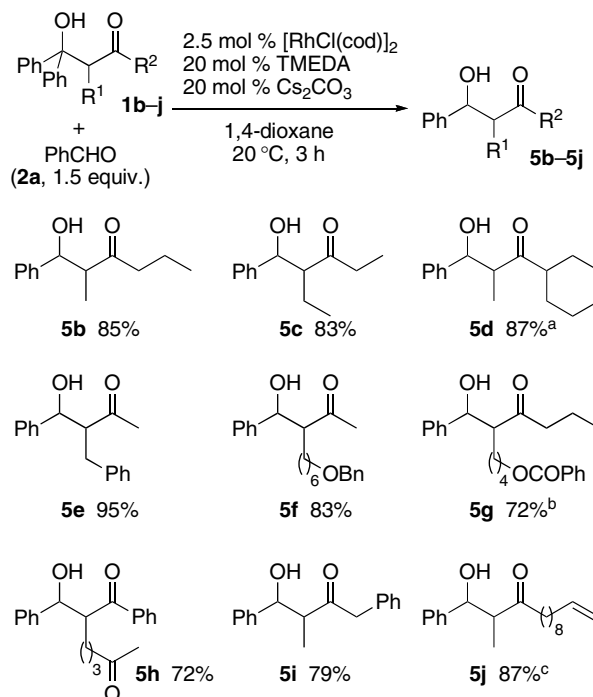
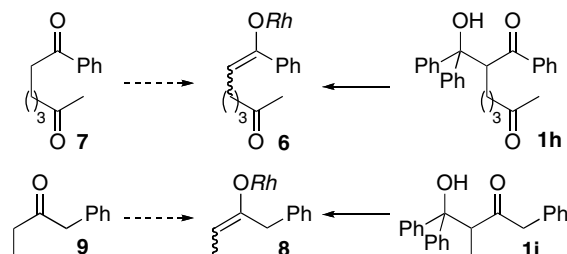


Fig. 1. Rhodium-catalyzed reaction of benzaldehyde (**2**) with various β-hydroxy ketones **1** via retro-aldol reaction: (a) 40 °C, 1.5 h. (b) 40 °C, 2 h. (c) 20 °C, 4 h.

tion (entry 20). Cyclohexanone (**2v**) served as a substrate, albeit with modest efficiency (entry 21).

We next examined the scope of β-hydroxy ketones⁹ as the precursors of rhodium enolates (Fig. 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. Benzoyloxy 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**.

The reaction of hydroxy diketone **1h** afforded **5h** through the selective formation of rhodium enolate **6** (Scheme 2). The 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



Scheme 2. Regioselective formation of rhodium enolates.

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.

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 shown in Table 1. With improved stereoselectivity, the present strategy would lead to significant progress in the aldol reaction.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Government of Japan. H.O. acknowledges JSPS for financial support.

Supplementary data

Supplementary data (procedure for the preparation of **1** and characterization data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.062.

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- β -Hydroxy ketones **1** were readily available according to the procedures described as Supplementary data.
- Experimental procedure*: $[\text{RhCl}(\text{cod})_2]$ (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 \times 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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