Isomerization of Imines Catalyzed by Ruthenium-Hydride Complexes

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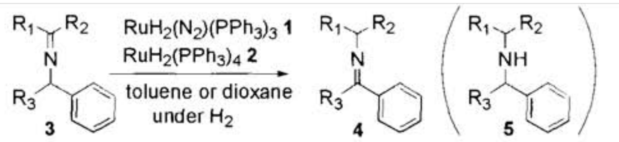
Imine isomerization *via* [1,3]-hydrogen shift catalyzed by dihydrido(dinitrogen)tris(triphenylphosphine)ruthenium(II) or dihydridotetrakis(triphenylphosphine)ruthenium(II) complexes is described. In toluene under hydrogen atmosphere, ruthenium-dihydride complexes could cause the isomerization of ketimines to aldimines effectively.

On the biochemical transamination, α-keto acids are converted to the corresponding amino acids *via* imine isomerization. Several attempts have been made to mimic natural transaminase.[1] Base catalyzed imine isomerization (methylene azomethine rearrangement) was extensively studied and it was shown that the reaction involves the 2-aza-allyl anion intermediate.[2,3] Imine isomerization is a useful method for the synthesis of various amino compounds as synthetic applications.[4]

Though transition metal catalyzed isomerization of olefins has been extensively studied,[5] to our knowledge, there is only one example of the imine isomerization by transition metal complex without base[6,7]: rhodium hydride complex, $RhH(PPh_3)_4$ isomerized *N*-(α-methylbenzylidene)benzylamine to *N*-benzylidene-α-methylbenzylamine with a very low activity.[6] We found that ruthenium dihydride species, $RuH_2(PPh_3)_4$, causes effectively the transfer hydrogenation of imines in propan-2-ol even in the absence of base.[8] It suggests that the addition of ruthenium-dihydride to the C=N bond occurs to form ruthenium hydridoamide species and protonation by propan-2-ol will give amines. We examined the reaction of imines with various ruthenium(II)-hydride complexes in aprotic solvents and found that $RuH_2(N_2)(PPh_3)_3$ **1** and $RuH_2(PPh_3)_4$ **2** could cause the imine isomerization in the absence of base (Scheme 1).



3a R_1 = Ph, R_2 = Me, R_3 = H
3b R_1 = 2'-Napthyl, R_2 = Me, R_3 = H
3c R_1 = Cy, R_2 = Me, R_3 = H
3d R_1 = Ph, R_2 = H, R_3 = Me
3e R_1 = Cy, R_2 = H, R_3 = Me
3f R_1 = Cy, R_2 = H, R_3 = H

Scheme 1. Reagents and conditions.

The isomerization of *N*-(α-methylbenzylidene)benzylamine **3a** using the catalyst **1** was performed in dry dioxane and toluene under several kinds of atmosphere (Table 1). Dihydride complexes **1** and **2** caused the isomerization of **3a** to afford **4a** under nitrogen or argon atmosphere, though the yields were low. Using the hydride complexes bearing CO or Cl ligand, no isomerization of imine proceeded.

Dihydridoruthenium-triphenylphosphine complex is known to change to orthometallated ruthenium(II) species[9] *via* zero valent ruthenium under argon. In order to suppress the formation of orthometallated species, the isomerization of **3a** using the catalyst **1** was performed under hydrogen atmosphere and the yield of **4a** was much increased and the turn over reached up to ca. 130 (Entry 12). The stereochemistry of imines is almost in the *E*-configuration. The *E*/*Z* ratio of starting **3a** was 95/5 and the ratio of recovered **3a** was 94/6-97/3 and **4a** has only *E*-configuration. In the present isomerization

Table 1. Isomerization of **3a** under various atmosphere[a]

Entry	Catalyst	Solvent	/Atmosphere	Time /h	S/C	Conv /%[b]	Yield/%[b] 4a	5a
1	$RhH(PPh_3)_4$	toluene	H_2	6	100	7	5	2
2	$RuHCl(PPh_3)_3$	dioxane	N_2	3	10	0	0	0
3	$RuHCl(CO)(PPh_3)_3$	dioxane	N_2	3	10	0	0	0
4	$RuH_2(PPh_3)_4$	dioxane	N_2	3	10	5	5	0
5		dioxane	H_2	3	10	28	14	14
6		toluene	H_2	6	100	44	40	4
7	$RuH_2(N_2)(PPh_3)_3$	toluene	N_2	6	10	9	9	0
8		toluene	Ar	6	10	9	9	0
9		toluene	H_2	6	10	75	38	37
10		toluene	H_2	6	100	62	54	8
11		toluene	H_2	14	200	66	56	10
12	$RuH_2(N_2)\{P(p\text{-Tol})_3\}_3$	toluene	H_2	6	100	63	50	13
13	$RuH_2(N_2)\{P(p\text{-}FC_6H_4)_3\}_3$	toluene	H_2	6	100	52	45	7
14	$RuH_2(dppb)_2$	toluene	H_2	6	100	0	0	0

[a] The reaction catalyzed by ruthenium or rhodium-hydride complexes was performed in dry dioxane (100 °C) and toluene (110 °C). [b] Determined by 270 MHz ^1H NMR analysis.

Table 2. Isomerisation of **3a-3f** under H_2[a]

Entry	Ru Cat.	Substrate	Conv. /%[b]	Yield/%[b] 4	Yield/%[b] 5
1	**1**	**3a**	62	54	8
2	**2**	**3a**	44	40	4
3	**1**	**3b**	38	30	8
4	**2**	**3b**	9	7	2
5	**1**	**3c**	49	49	0
6[c]	**1**	**3c**	68	68	0
7	**2**	**3c**	12	12	0
8	**1**	**3d**	13	13	0
9	**1**	**3e**	0	0	0
10	**1**	**3f**	0	0	0

[a] The reaction was carried out at 110 °C using 1 mol% of **1** or **2** in dry toluene for 6 h under hydrogen atmosphere. [b] Determined by 270 MHz ^{1}H NMR analysis. [c] Result of the reaction for 18 h.

reaction under hydrogen atmosphere, hydrogenation product **5a** was formed concomitantly. The reaction time course of **3a** by the catalyst **1** under hydrogen indicated the parallel formation of **4a** and **5a**. In the case of low S/C ratio, isomerization and hydrogenation occurred in nearly same amounts. However, the degree of hydrogenation decreased in higher S/C ratios (Entry 7, 11 and 12). In the case of the substrate **3c**, no hydrogenation product was observed (Table 2).

Various imines (**3a-3f**) were examined for the isomerization using catalyst **1** and **2** under hydrogen atmosphere (Table 2). In all cases, the mass balance of the reaction was very good. The ruthenium dihydride **1** is much more effective than **2**. We consider that coordinatively unsaturated ruthenium dihydride species, which is generated from **1** or **2** by the dissociation of nitrogen molecule or triphenylphosphine, is the reactive species. A coordinatively saturated ruthenium dihydride complex having two dppb ligands did not show isomerization activity. In the transfer hydrogenation of imines catalyzed by ruthenium complexes in propan-2-ol, aldimines are more easily reduced than ketimines.[8] In the isomerization in toluene, however, aldimines (**3d-3f**) could be hardly isomerized by the catalyst **1**.

In summary, the ruthenium dihydride complexes **1** and **2** could catalyze the isomerization of ketimines to aldimines under hydrogen atmosphere. The asymmetric imine isomerization with chiral ruthenium catalysts to obtain chiral amines is under way.

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