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Rapid racemization of chiral non-racemic *sec*-alcohols catalyzed by (η^5-$C_5(CH_3)_5$)Ru complexes bearing tertiary phosphine–primary amine chelate ligands☆

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Abstract—A ternary catalyst system of Cp*RuCl(cod)–2-diphenylphosphinoethylamine–KO*t*-Bu (Cp* = η^5-$C_5(CH_3)_5$, cod = 1,5-cyclooctadiene) causes rapid racemization of chiral non-racemic *sec*-alcohols, which results from the reversible hydrogen transfer between *sec*-alcohols and ketones. Both tertiary phosphine and primary amine functionalities in the ligand are responsible for the high rate.

Recently we have developed ternary catalyst systems based on Cp*RuCl(cod)/amine/base for highly effective reductive transformation.[1] The outcome of the reactions are strongly influenced by the amine ligands and the solvents used. *N*,*N*-Dimethylaminoethylamine (**1a**) serves as an excellent ligand for hydrogenation of ketones,[1a] while 2-diphenylphosphinoethylamine (**1b**) ligand is effective not only for hydrogenation of ketones but also for hydrogenolysis of epoxides[1b] (Fig. 1).

Noticeably, 2-propanol is the best solvent in both reactions, but its roles in each reaction differ significantly. We found that in the Cp*RuCl(cod)/**1a**/base catalyst-promoted hydrogenation, 2-propanol only facilitates the heterolytic cleavage of H_2 and does not participate in any redox process.[1] On the other hand, 2-propanol does participate in the redox process in which Cp*RuCl(cod)/**1b**/base catalyst system may effect a hydrogen transfer between alcohols and ketones. We now describe the rapid racemization of chiral non-racemic *sec*-alcohols[2,3] based on the redox properties of this newly developed catalyst system.

1a **1b**

Figure 1. Amine ligands for Cp*Ru(II)-catalyzed reactions.

Our initial experiments focused on the change in ee values of optically active 2-phenylethanol ((*R*)-**2a**, >99% ee) in the presence of Cp*Ru(II)-based catalyst system with several ligands ((*R*)-**2a**:Cp*RuCl(cod):ligand:KO*t*-Bu = 100:1:1:1, [(*R*)-**2a**] = 0.1 M in toluene, 30°C) (Scheme 1) and results are summarized in Table 1.[4] The rate of the reaction was found to be affected by the structure of amine ligands. When **1b** was employed, the starting alcohol was completely racemized within 1 h (entry 2). The turnover frequency (TOF, h^{-1}) of the catalyst, which is defined here by the following equation: $0.99^{\mathrm{TOF}\times T} = 10^{-2} f(T)$ ($f(T)$: the ee value of the alcohol after a reaction time of T h), is estimated to be 479 h^{-1} for **1b**. Changing the primary amino group in **1b** to secondary amino group (**1c**) slightly lowered the catalytic activity and it required 2.4 h for the complete racemization (entry 3). In contrast, the ee value of **2a** remains unchanged with **1d**, 1,2-bis(diphenylphophino)ethane (dppe), or $P(C_6H_5)_3$ over 24 h (entries 4, 8, and 9). These results indicated that NH group in the ligand is crucial for the present racemization.[5,6] In fact, other tertiary phosphine–primary amine hybrid ligands such as **1f** and **1g** also cause the decrease in the ee values, albeit with much slower rate; 13 h and 12 h, respectively for the complete racemization (entries 6 and 7). It is also noted that little decrease of the ee

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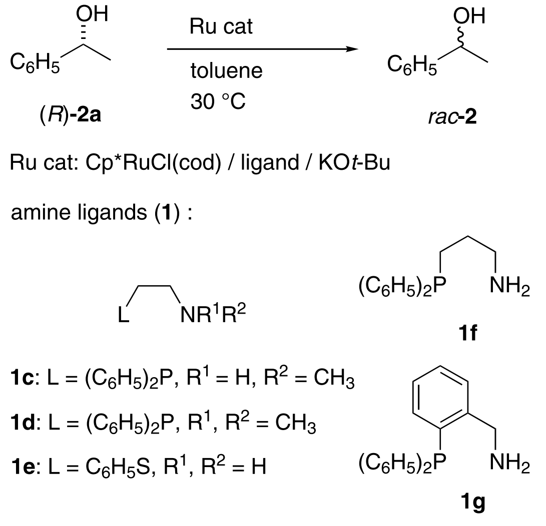


Scheme 1.

Table 1. Reaction of (*R*)-**2a** in the presence of Cp*RuCl(cod)/ligand/KO*t*-Bu catalyst system[a]

Entry	Ligand	TOF,[b] h^{-1}	T^{rac},[c] (h)
1	**1a**	21	22[d]
2	**1b**	479	<1
3	**1c**	191	2.4
4	**1d**	<1	–
5	**1e**	6	77[d]
6	**1f**	36	13
7	**1g**	40	12
8	dppe	<1	–
9	$P(C_6H_5)_3$	<1	–

[a] *Reaction conditions*: **2a**:Ru:**1b**:KO*t*-Bu = 100:1:1:1, [**2a**] = 0.1–0.5 M in toluene.

[b] See text.

[c] Reaction time required for complete racemization, i.e. $f(T)<1$.

[d] Calculated values.

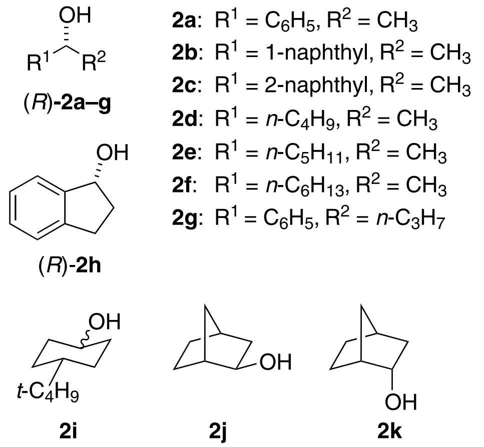
Table 2. Reaction of *sec*-alcohols in the presence of Cp*RuCl(cod)/**1b**/KO*t*-Bu catalyst system[a]

Entry	Alcohol	Time (h)	Products
1	(*R*)-**2a** (>99% ee)	1	**2a** (<1% ee)
2	(*R*)-**2b** (>99% ee)	2	**2b** (<1% ee)
3	(*R*)-**2c** (>99% ee)	8	**2c** (<1% ee)
4	(*R*)-**2d** (>99% ee)	1	**2d** (<1% ee)
5	(*R*)-**2e** (>99% ee)	3	**2e** (2% ee)
6	(*R*)-**2f** (98% ee)	1	**2f** (<1% ee)
7	(*R*)-**2g** (97% ee)	2	**2g** (<1% ee)
8	(*R*)-**2h** (>99% ee)	1	**2h** (<1% ee)
9	*trans*-**2i**	24	**2i** (*trans*:*cis* = 4:1)
10	**2j**	42	**2j**:**2k** = 85:15

[a] *Reaction conditions*: alcohol:Ru:**1b**:KO*t*-Bu = 100:1:1:1, [alcohol] = 0.1–0.5 M in toluene, 30°C.

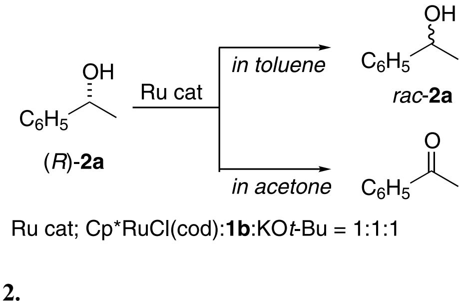
was observed with structurally analogous NN ligand **1a** or SN ligand **1e** (entries 1 and 5). These results clearly indicated that the aminophosphine ligands bearing NH group are responsible for the rapid racemization of **2a**.

A variety of chiral *sec*-alcohols are rapidly epimerized at 30°C in the presence of the Ru catalyst with **1b**.[7] As shown in Table 2, both benzylic alcohols (**2a**–**c**, **2g**–**h**) and aliphatic alcohols (**2d**–**f**) are equally susceptible to this rapid racemization. *trans*-4-*t*-Butylcyclohexanol (*trans*-**2i**), which is the thermodynamically more stable isomer than *cis*-**2i**, is epimerized into the equilibrium mixture (*trans*:*cis* = 4:1) within 24 h. Furthermore, (±)-*exo*-norborneol (**2j**) also give a mixture containing (±)-*endo*-norborneol (**2k**) (**2j**:**2k** = 85:15) after 42 h of reaction.

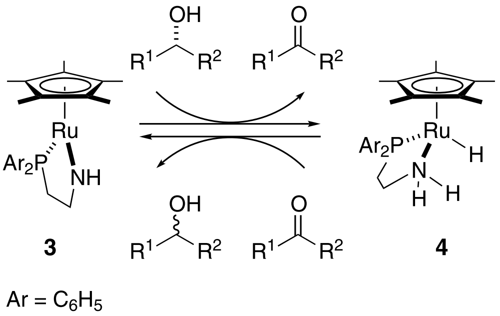


The racemization of optically pure (*R*)-**2a** with **1b** proceeded rapidly in diethyl ether, CH_2Cl_2, or toluene, while the use of methanol, ethanol, or 2-propanol considerably reduced the rate,[8] presumably because these primary or secondary alcoholic solvents serve as hydrogen sources for the hydrogen transfer and therefore they compete with the substrate in the catalysis. This was further confirmed by the isotope-labeling experiment using 2-propan-2-*d*-ol (99.6% atom D). Dissolving 2-propan-2-*d*-ol, Cp*RuCl(cod), **1b**, and KO*t*-Bu in benzene-d_6 (alcohol:Ru:**1b**:KO*t*-Bu = 100:1:1.5:1.5) caused a rapid H–D scrambling between the 2-position and the hydroxyl proton in the alcohol, to afford an 1:1 mixture of $(CH_3)_2CHOH(D)$ and $(CH_3)_2CDOH(D)$ within 1 h at 30°C.

The racemization as well as the H–D scrambling strongly suggest a possible formation of the intermediary ketones. In fact, the reaction of (*R*)-**2a** with the Cp*RuCl(cod)/**1b**/KO*t*-Bu catalyst system *in acetone* resulted in the formation of acetophenone and 2-propanol, instead of racemization (Scheme 2).



Scheme 2.



Scheme 3.

In the absence of any hydrogen acceptor except for the ketone derived from the starting alcohol, the *intramolecular* hydrogen transfer is manifested in the reactions with non-racemic *sec*-alcohols or deuterated 2-propanol employed as the substrates. We believe that mixing Cp*RuCl(cod), **1b**, and KO*t*-Bu may generate Cp*Ru(amido) complex (**3**) in situ and the interconversion between **3** and Cp*RuH(amine) complex (**4**)[1b] should be responsible for this rapid racemization via the hydrogen transfer illustrated in Scheme 3.[5,6] In fact, the catalyst system could promote transfer hydrogenation with a reasonably high activity. Most probably, the labile stereochemistry at the seemingly stereogenic Ru center of **4** may lead to the high reaction rate in this racemization.

In conclusion, we have found that Cp*RuCl(cod)/**1b**/KO*t*-Bu catalyst system effects extremely rapid racemization of chiral non-racemic *sec*-alcohols. In view of recent advances in dynamic kinetic resolution (DKR) of *rac*-secondary alcohols in which the transition metal-catalyzed racemization is coupled with enzymatic transformation of alcohols,[3b,d,9] our racemization catalyst may also contribute to the DKR since it exhibits high catalyst performance under conditions favorable for the enzymatic reactions. Further studies on the DKR using our catalyst system are in progress.

Supplementary material

Experimental procedure for the racemization, HPLC or GLC behavior, and details for isotope-labeling experiments.

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4. *A typical experimental procedure*:[7] A degassed solution of (*R*)-**2a** (452 mg, 3.7 mmol) in anhydrous toluene (37 mL) was transferred to a mixture of Cp*RuCl(cod) (14.1 mg, 0.037 mmol), **1b** (8.5 mg, 0.037 mmol) and KO*t*-Bu (4.2 mg, 0.037 mmol) and the reaction mixture was vigorously stirred at 30°C. The progress of the racemization was monitored with an aliquot by HPLC or GLC analyses (see supplementary material).
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7. The ternary system of Cp*RuCl(cod)/**1b**/KO*t*-Bu was used here as a catalyst for experimental convenience, although the preformed complex Cp*RuCl(**1b**),[1b] which is obtainable from Cp*RuCl(isoprene) and **1a**, epimerized *sec*-alcohols in toluene containing KO*t*-Bu at a comparable rate in comparison to the ternary system.
8. For instance, the ee of optically pure (*R*)-**2a** only dropped to 53% after 1 h and 25% ee after 2 h, respectively, in 2-propanol (0.1 M) under otherwise identical conditions.
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