Pergamon

Tetrahedron Letters 39 (1998) 5545–5548

TETRAHEDRON LETTERS

Efficient Catalytic Racemization of Secondary Alcohols.

Jeong Hwan Koh, Hyun Min Jeong, and Jaiwook Park*

Department of Chemistry and Center for Biofunctional Molecules

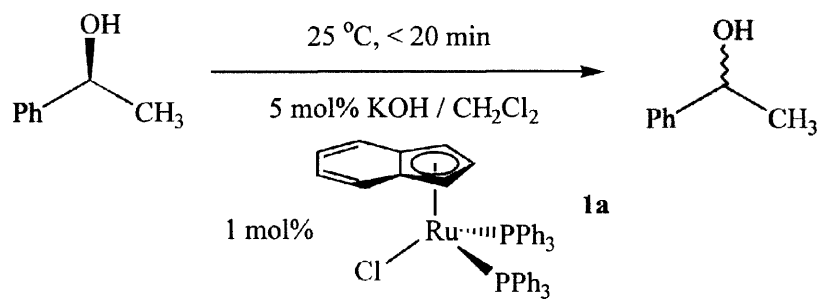
Pohang University of Science and Technology (POSTECH), San 31 Hyoja Dong, Pohang 790-784, Korea

Received 17 March 1998; revised 23 May 1998; accepted 29 May 1998

Abstract: (η^5-Indenyl)RuCl(PPh_3)$_2$ was found to efficiently catalyze the racemization of chiral alcohols such as (*S*)-1-phenylethan-1-ol, (*S*)-1-phenylpropan-2-ol and (*S*)-4-phenylbutan-2-ol at room temperature in the presence of base. The catalytic activity of five other Ru(II) complexes was also investigated. The effects of varying reaction conditions such as reaction temperature, solvent, and base were investigated as well.

Keywords: Racemization; Alcohol; Ruthenium; Catalyst

The resolution of racemic alcohols is one of the practical methods to prepare chiral alcohols which are important intermediates in asymmetric synthesis [1]. One major limitation with the resolution method is that the maximum yield can not be over 50% based on the racemate. As a method to overcome this limitation dynamic kinetic resolution processes (or second-order asymmetric transformations) have been introduced for secondary alcohols [2-4], in which the alcohols are continuously racemized with metal catalysts during an enzymatic resolution process. However, systematic investigations of catalytic racemization are rare in spite of the potential utility of efficient racemization catalysts themselves [5-6]. Here we wish to report our initial results from the investigation of an efficient catalytic system for racemization of chiral secondary alcohols. (η^5-Indenyl)RuCl(PPh_3)$_2$ (**1a**) was found to form a very reactive catalyst which can racemize (*S*)-1-phenylethan-1-ol completely within 20 min at room temperature in the presence of base.

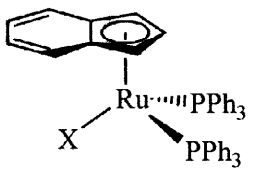


Six Ru(II) complexes **1-3** were prepared and employed in the catalytic racemization reaction to obtain clues for the mechanism as well as the electronic effect of ligands on the reactivity [7-9]†. The results are summarized in Table 1 (entries 2-7). The table also contains results from varying temperature (entries 8-10), base (entries 11-16), and solvent (entries 20-24). The racemization rate is slowed down by exchanging **1a** with the bromide derivative **1b** or with the iodide derivative **1c**. The rate is also slowed down significantly by substitution of one triphenylphosphine in **1a** with a more π-acidic ligand (**2a**: L=$P(OEt)_3$) or with a more

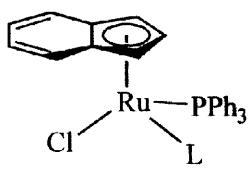
0040-4039/98/$19.00
PII: S0040-4039(98)01116-2

electron-donating one (**2b**: L=PMe_3). The complex **3**, which has an η^5-cyclopentadienyl ligand, is less reactive than **1a**. The rate increases with raising temperature, while lowering to 5 °C almost stops the reaction. Among the bases tested potassium hydroxide proved to be the best one, and even with 1 mol% the racemization is completed within 1 h. Potassium *tert*-butoxide and sodium hydride show rates comparable to that observed with potassium hydroxide. Potassium carbonate and the organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene and triethylamine are much less effective than potassium hydroxide. Solvent polarity does not seem to be a crucial factor for the rate, and the rate in *N,N*-dimethylformamide is comparable to that in benzene. Even without solvent the racemization can be completed within 1 h at 25 °C (entry 17). A notable observation is that acetophenone, which has been known as an essential component to regenerate alkoxide complexes from metal hydride intermediates for racemization of secondary alcohols [2,3], lowers the racemization rate (entry 19). Addition of free triphenylphosphine also decreases the rate (entry 18).

1a: X=Cl
1b: X=Br
1c: X=I



2a: L=$P(OEt)_3$
2b: L=PMe_3



3

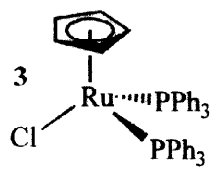


Table 1. Racemization of (*S*)-1-Phenylethan-1-ol[a]

entry	Ru(II)[b]	T (°C)	Base[c]	Solvent[d]	Time	% *ee*[e]
1	no Ru(II)	25	KOH	CH_2Cl_2 + PPh_3[f]	20 min	99
2	**1a**	25	KOH	CH_2Cl_2	20 min	0
3	**1b**	25	KOH	CH_2Cl_2	20 min	8
4	**1c**	25	KOH	CH_2Cl_2	20 min	28
5	**2a**	25	KOH	CH_2Cl_2	23 h	79
6	**2b**	25	KOH	CH_2Cl_2	24 h	97
7	**3**	25	KOH	CH_2Cl_2	20 min	16
8	**1a**	5	KOH	CH_2Cl_2	24 h	99
9	**1a**	15	KOH	CH_2Cl_2	24 h	30
10	**1a**	35	KOH	CH_2Cl_2	10 min	0
11	**1a**	25	KOH[g]	CH_2Cl_2	1 h	0
12	**1a**	25	*t*-BuOK	CH_2Cl_2	1 h	0
13	**1a**	25	NaH	CH_2Cl_2	1 h	0
14	**1a**	25	K_2CO_3	CH_2Cl_2	24 h	41
15	**1a**	25	DBU	CH_2Cl_2	33 h	55
16	**1a**	25	Et_3N	CH_2Cl_2	24 h	99
17	**1a**	25	KOH	without solvent	1 h	0
18	**1a**	25	KOH	PPh_3[h]	1 h	45
19	**1a**	25	KOH	acetophenone[i]	20 min	67
20	**1a**	25	KOH	$ClCH_2CH_2Cl$	20 min	47
21	**1a**	25	KOH	DMF	20 min	53
22	**1a**	25	KOH	THF	20 min	60
23	**1a**	25	KOH	Et_2O	20 min	68
24	**1a**	25	KOH	C_6H_6	20 min	76

[a] > 99 % *ee*. [b] 1.0 mol%. [c] 5.0 mol%. [d] 0.2 M concentration. [e] Measured by HPLC equipped with a chiral column (Chiralcel OB® or Chiralcel OD®). [f] 2 mol%. [g] 1.0 mol%. [h] 3 mol% in CH_2Cl_2. [i] 0.2 M in CH_2Cl_2.

The catalyst **1a** was applied to chiral alcohols with hydroxyl groups at other than the benzylic position (entries 2-4 in Table 2) [10]. The racemization rates of (*S*)-1-phenylpropan-2-ol and (*S*)-4-phenylbutan-2-ol are slowed down to about one tenth of the rate of (*S*)-1-phenylethan-1-ol. It is noteworthy that *meso*-cyclohexan-1,2-diol is converted to a 1:2 mixture of *meso*- and *d,l*-isomers, not the expected statistical ratio of 1:1. This is an example of stereoselective isomerization of diastereotopic hydroxyl groups, which can be applied to diastereoselective isomerization of secondary alcohols.

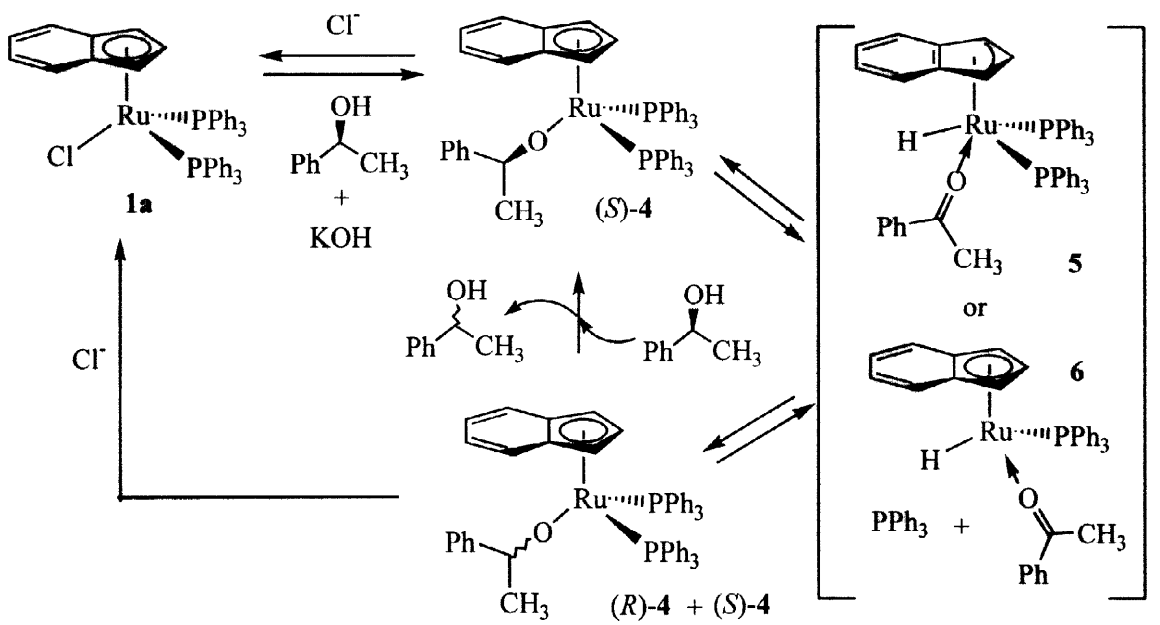
Table 2. Racemization of Secondary Alcohols with **1a** at 25 °C in CH_2Cl_2

entry	Alcohol[a]	Base	Time	% ee[b]
1	(*S*)-1-phenylethan-1-ol	KOH	20 min	0
2	(*S*)-1-phenylpropan-2-ol	KOH	3.5 h	0
3	(*S*)-4-phenylbutan-2-ol	KOH	5 h	0
4	*meso*-cyclohexan-1,2-diol	KOH	5 h	*meso*:*d,l*=1:2[c]

[a] 0.2 M solutions of alcohol (> 95 % *ee*) with 1.0 mol% of **1a** and 5.0 mol% of KOH.
[b] Measured by HPLC equipped with a chiral column (Chiralcel OB® or Chiralcel OD®).
[c] Determined by ^{1}H NMR

At this stage more extensive investigation is required to construct a detailed mechanism for the racemization. However, in Scheme 1 a possible pathway is suggested for the racemization of (*S*)-1-phenylethan-1-ol with **1a** to explain the following observations: 1) During the racemization **1a** is observed by ^{1}H-NMR as the major ruthenium species, and free triphenylphosphine is not detected; 2) the analogues **1b** and **1c** are less reactive than **1a** and are formed in quantitative yields in the reactions of **1a** with potassium bromide and potassium iodide, respectively; 3) **1a** is more reactive than **3** which has cyclopentadienyl ligand; 4) addition of acetophenone or triphenylphosphine lowers the racemization rate.

Scheme 1. A Possible Pathway for Racemization of (*S*)-1-Phenylethan-1-ol with **1a**



The Ru-alkoxide intermediate **4** would be in equilibrium with **1a**. The decreased racemization rate with **1b** or **1c** can be explained by the increased stability of Ru-halide complexes. In order to allow β-hydride elimination process a coordinatively unsaturated intermediate would be generated from **4** by the hapticity

change of the indenyl ligand from η^5 to η^3 to give hydride complex **5** [11], or by the dissociation of a triphenylphosphine ligand to give the intermediate **6**. The former suggestion is more plausible to rationalize the lowered reactivity of **3** in which the hapticity change to η^3 is less facile than in **1a** [12-13]. The coordinatively unsaturated intermediate would be responsible for the decreased racemization rates by the addition of acetophenone or free triphenylphosphine. The intermediate **5** (or **6**) would be in equilibrium with the alkoxide intermediates (*R*)-**4** and (*S*)-**4** through reversible hydride migration with scrambling of the stereochemistry of the α-carbon. Then, substitution of the alkoxide would liberate racemized alcohols.

Preliminary attempts to combine lipase-catalyzed acylation with our catalytic racemization systems were not fruitful due to predominant chemical acylation of alkoxides. We are adjusting reaction condition to overcome this problem and are extending the application scope of the catalytic racemization reactions.

Acknowledgment. We gratefully acknowledge the financial support by Basic Research Institute in POSTECH (Grant No: 1RB9712601) and Center for Biofunctional Molecules.

References

[1] Wang CH, Whitesides GM. Enzymes in Synthetic Organic Chemistry. Elsevier: Amsterdam, 1994.
[2] Larsson ALE, Persson BA, Bäckvall J-E. Angew. Chem. Int. Ed. Engl. 1997; 36: 1211-1212.
[3] Dinh PM, Howarth JA, Hudnott AR, Williams JMJ, Harris W. Tetrahedron Lett. 1996; 37: 7623-7626.
[4] Allen JV, Williams JMJ. Tetrahedron Lett. 1996; 37: 1859-1862.
[5] Hashiguchi S, Fujii A, Tekehara J, Ikariya T, Noyori R. J. Am. Chem. Soc. 1995; 117: 7562-7563.
[6] Genêt J-P, Ratovelomanana-Vidal V, Pinel C. Synlett 1993: 478-480.
[7] Oro LA, Ciriano MA, Campo M, Foces-Foces C, Cano FH. J. Organomet. Chem. 1985; 289: 117-131.
[8] Gamasa MP, Gimeno J, Gonzalez-Bernardo C, Martín-Vaca BM, Monti D, Bassetti M. Organometallics 1996; 15: 302-308.
[9] Wilczewski T, Bochenska M, Biernat JF. J. Organomet. Chem. 1981; 215: 87-96.
[10] The chiral alcohols were prepared according to enzymatic resolution: See Klibanov AM. Acc. Chem. Res. 1990; 23: 114-120.
[11] O'Conner JM, Casey CP. Chem. Rev. 1987; 87: 307- 318.
[12] Rerek ME, Basolo F. J. Am. Chem. Soc. 1984; 106: 5908-5912.
[13] Hart-Davis AJ, White C, Mawby RJ. Inorg. Chim. Acta 1970; 4: 441- 446.

---

† The complexes **1b** and **2a** were confirmed by following characterization data which are not given in references [7-9]. **1b**: Mp 137-138 °C; ^{1}H NMR ($CDCl_3$) δ 7.29-6.90 (m, 34 H), 4.68 (t, J = 2.3 Hz, 1 H), 4.05 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 138.3 (d, J = 20.2 Hz), 138.0 (d, J = 21.3 Hz), 134.7 (t, J = 4.9 Hz), 132.6 (d, J = 9.7 Hz), 131.7, 129.1, 128.7 (d, J = 12.0 Hz), 128.5, 127.7 (t, J = 4.6 Hz), 125.5, 111.5, 90.2, 68.0; ^{31}P NMR ($CDCl_3$) δ 48.52 (s); MS (FAB) *m/z* = 822 $(M+1)^+$. **2a**: High-resolution MS (FAB) *m/z* calcd, 680.0950, found, 680.0956; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 1 H), 7.34 (t, J = 8.1 Hz, 1 H), 7.31-7.19 (m, 15 H), 6.82 (t, J = 8.4 Hz, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 5.25 (d, J = 2.8 Hz, 2 H), 3.84 (qd, J_1 = 7.0 Hz, J_2 = 1.8 Hz, 6 H), 3.31 (br s, 1 H), 1.08 (t, J = 7.0 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 137.2 (d, J = 42.3 Hz), 134.4 (d, J = 10.6 Hz), 129.0 (d, J = 2.0 Hz), 128.0, 127.5 (d, J = 14.8 Hz), 127.4, 126.8, 125.3, 124.6, 122.9, 113.4 (d, J = 6.8 Hz), 90.2, 68.5 (d, J = 11.5 Hz), 61.5 (d, J = 6.9 Hz), 16.7 (d, J = 9.8 Hz); ^{31}P NMR ($CDCl_3$) δ 149.51 (d, J = 47.5 Hz, -$\underline{P}(OEt)_3$), 50.01 (d, J = 47.5 Hz, -$\underline{P}Ph_3$); MS (FAB) *m/z* = 680 (M^+).