(η^5-Triphenylindenyl)Ru(CO)$_2$Cl: A New Ruthenium Catalyst for the Highly Efficient Racemization of Chiral 1-Phenylethanol at Room Temperature

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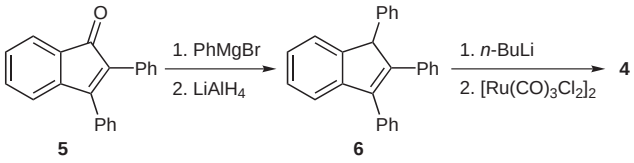
Abstract: A new ruthenium complex, (η^5-triphenylindenyl)Ru(CO)$_2$Cl, was synthesized and successfully applied in the racemization of (*S*)-1-phenylethanol at room temperature. Instead of potassium *tert*-butoxide, stronger bases such as sodium hydride and *n*-butyllithium were used to activate the precatalyst. In situ NMR experiments revealed the presence of ruthenium hydride as a key intermediate in the catalytic cycle.

Key words: organometallic reagents, ruthenium, complexes, catalysis, racemization

Chemoenzymatic dynamic kinetic resolution (DKR) combines an enzymatic kinetic resolution with continuous in situ racemization of substrates by transition-metal catalysts.[1] Pioneered by Williams' work,[2] a number of highly efficient DKR systems have been established (Figure 1). For example, Bäckvall et al. reported the use of Shvo's catalyst **1**[3] in combination with immobilized lipase for the DKR of various functionalized secondary alcohols.[4] Since high temperature is required to activate this dimeric complex, the choice of available biocatalysts has been limited to those thermal stable species. To overcome this drawback, Park and co-workers developed a highly active ruthenium catalyst **2**, which can completely racemize alcohols within 30 minutes at room temperature.[5] However, extended reaction time is necessary when it works in the presence of lipase. In searching of a mild and more efficient catalyst, Bäckvall et al. recently developed ruthenium complex **3**, demonstrating broad substrate scope as well as excellent biocompatibility.[6] Although the detailed racemization mechanism remains to be elucidated, an associative ligand substitution pathway was proposed involving a $\eta^5 \rightarrow \eta^3$ ring slippage.[6b] Because an indenyl ligand can achieve large rate enhancement over a cyclopentadiene ligand in various associative substitution reactions ('indenyl effect'),[7] we envisioned that a new ruthenium complex **4** bearing a triphenylindenyl moiety will racemize alcohols more effectively.

The designed complex **4** can be easily synthesized from 2,3-diphenylindenone (**5**)[8] in two steps[9] (Scheme 1). X-ray diffraction analysis of a single crystal of **4** confirms the expected structure (Figure 2). All five Ru–Cp carbon bond lengths are similar, supporting the η^5-coordination of the indenyl ligand to the ruthenium atom.



Scheme 1

With the new complex in hand, we started to test its catalytic performance in the racemization of (*S*)-1-phenylethanol [(*S*)-**7**] at room temperature (Scheme 2). For comparison, **3** was synthesized according to literature.[6b] In the **3**-mediated racemization of (*S*)-**7**, a Ru *tert*-butoxide species generated from the preliminary mixing of **3** and potassium *tert*-butoxide (*t*-BuOK) was identified as a key intermediate.[6] Following this method, the Ru-*tert*-butoxide corresponding to **4** was prepared by stirring **4** (0.5 mol%, 2.5 mM) and *t*-BuOK (1.0 mol%, 5.0 mM) in toluene (5 mL) for 10 minutes. The reaction mixture changed its color from yellow to dark red during this period, indicative of the formation of Ru-alkoxide. Then (*S*)-**7** was added and the racemization process[10] was monitored with chiral GC. Although the exact kinetics remain to be estab-

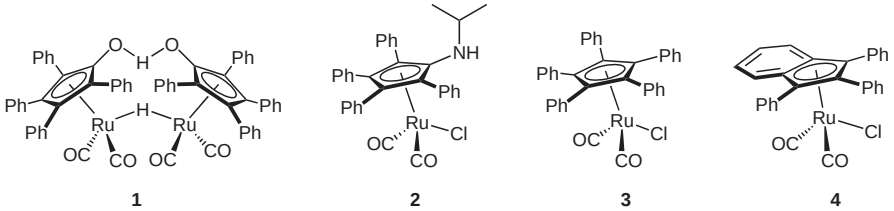


Figure 1

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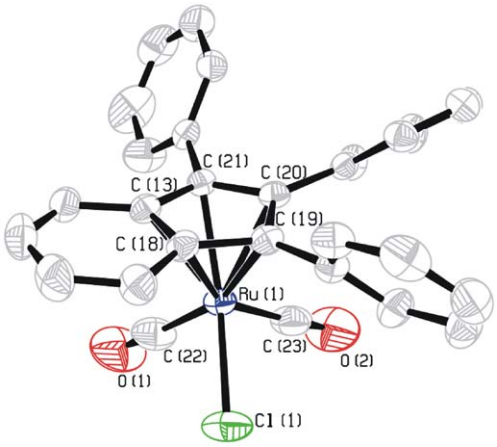


Figure 2 X-ray single crystal structure of **4** at 50% probability for the ORTEP drawing of thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Ru(1)–C(22): 1.913, Ru(1)–C(23): 1.848, Ru(1)–Cl(1): 2.408, Ru(1)–C(18): 2.344, Ru(1)–C(13): 2.341, Ru(1)–C(19): 2.246, Ru(1)–C(20): 2.242, Ru(1)–C(21): 2.200. Space group: P2(1)2(1)2(1). *Z*: 4.

lished, the half time of racemization ($t_{1/2}$) offers an approximate estimation of racemization rate.[6] As shown in Figure 3, pretreatment of **4** with *t*-BuOK led to effective racemization of (*S*)-**7** at room temperature with an estimated half time ($t_{1/2}$) of 31.3 minutes. Unfortunately, this is much slower than that achieved by using **3** under the same reaction conditions ($t_{1/2}$ = 2.1 min). This result demonstrates that in addition to ring slippage, there are some other factors such as steric bulkiness of the precatalyst, which could alter stabilities of some intermediates, contributing to the overall racemization rate.

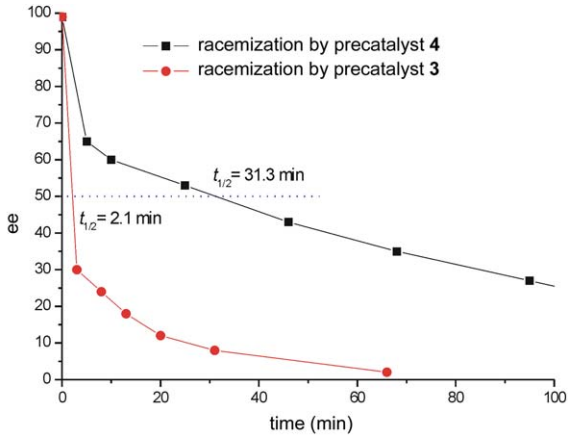
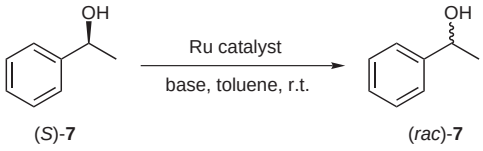
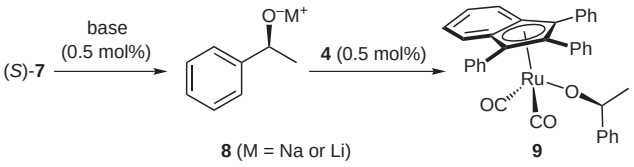


Figure 3



Scheme 2

To our surprise, faster racemization was achieved when **4** was activated with other bases such as sodium hydride (NaH) and *n*-butyllithium (*n*-BuLi). We found that in the absence of *t*-BuOK, **4** can still be activated by treatment of (*S*)-**7** with catalytic amount of NaH (0.5 mol%), producing sodium alkoxide **8** quantitatively. Once mixed with **4** (0.5 mol%), **8** readily converts into Ru-alkoxide **9** showing characteristic dark red color in toluene (Scheme 3). Kinetic studies show a significant rate enhancement compared with the literature method[6] using *t*-BuOK (Figure 4, $t_{1/2}$ = 13.3 min vs. $t_{1/2}$ = 31.3 min). Similarly, *n*-BuLi (0.5 mol%) was used with a $t_{1/2}$ of 15.5 minutes. Increasing the amount of *n*-BuLi (2.5 mol%) further accelerates racemization ($t_{1/2}$ = 6.0 min) so that (*S*)-**7** is completely racemized within 30 minutes (Figure 4). A possible explanation of the observed counterion effect is the different solubilities of the produced KCl, LiCl, and NaCl.



Scheme 3

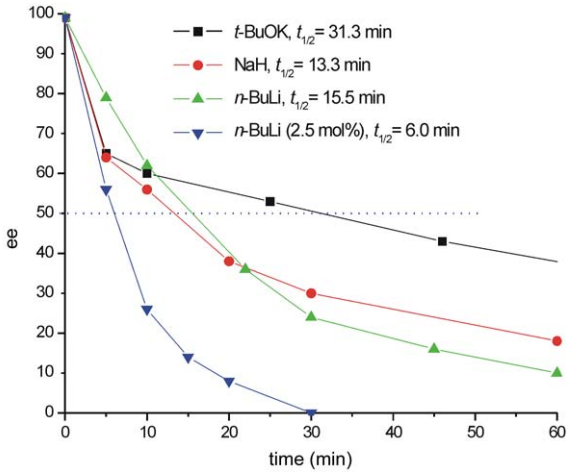
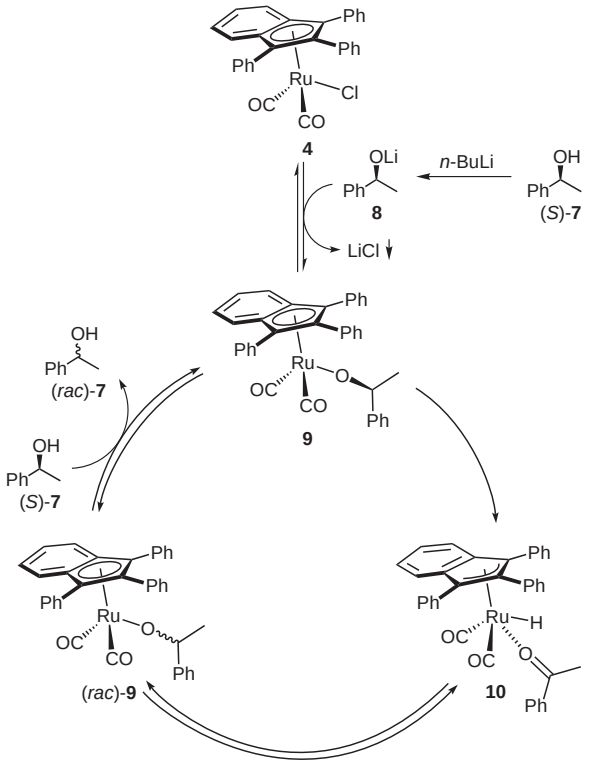


Figure 4

To gain insight into the racemization mechanism, the activation reaction was studied with in situ NMR spectroscopy. Thus freshly prepared lithium alkoxide **8** in d_6-benzene was added into **4** (1 equiv) in an NMR tube and shaken vigorously. A dark red color immediately appeared with simultaneous precipitation of LiCl. A new proton resonance at δ = –11.2 ppm was detected. It is noted that so far no direct experimental evidence has been provided regarding the existence of ruthenium hydride during racemization.[11] Our result identifies the ruthenium hydride **10** as a key intermediate. Therefore, a general mechanism is proposed in Scheme 4. The first step is the activation of precatalyst **4** by **8** with the formation of ruthenium alkoxide **9**. Ring slippage from η^5 to η^3 facilitates

β-hydride elimination, generating ruthenium hydride **10**[12] as revealed by proton NMR. The following migratory insertion of the coordinating ketone into Ru–H bond leads to racemized (*rac*)-**9**. Finally, ligand exchange reaction regenerates **9** with the release of a racemized substrate (*rac*)-**7**.



Scheme 4

In summary, a new ruthenium complex has been synthesized for the racemization of (*S*)-1-phenylethanol at room temperature. An effective method to activate this precatalyst was developed using strong bases such as NaH and *n*-BuLi instead of *t*-BuOK. NMR experiment identifies ruthenium hydride as a key intermediate during racemization. Further mechanistic studies, as well as its combination with biocatalysts for DKR of alcohols, will be reported in due course.

Acknowledgment

Financial support from NIH-GM is appreciated. The X-ray diffraction experiment (NSF grant CHE-0131112) was carried out by Dr. Yennawar.

References and Notes

(1) For a recent review on DKR, see: Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247; and references cited therein.
(2) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623.
(3) Menasche, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885.
(4) (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211. (b) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.
(5) (a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2373. (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972.
(6) (a) Martin-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J.-E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6535. (b) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817.
(7) (a) Hart-Davis, A. J.; White, C.; Mawby, R. J. *Inorg. Chim. Acta* **1970**, *4*, 441. (b) Rerek, M. E.; Ji, L.-N.; Basolo, F. *J. Chem. Soc., Chem. Commun.* **1983**, 1208. (c) Rerek, M. E.; Basolo, F. *J. Am. Chem. Soc.* **1984**, *106*, 5908.
(8) **1,2,3-Triphenyl-1*H*-indene (5)**
To a freshly prepared PhMgBr solution (5.68 mmol in 20 mL THF) was added dropwise a solution of 2,3-diphenylindenone (3.54 mmol, 1.0 g) in 10 mL THF at 0 °C. Then the reaction mixture was stirred at 50 °C for 12 h. When it was cooled to r.t., $LiAlH_4$ (26.3 mmol, 1.0 g) was added in portions and then stirred for 6 h. The reaction mixture was quenched with sat. aq NH_4Cl solution, filtered, and extracted with CH_2Cl_2. The organic phase was separated, washed with brine and then dried with Na_2SO_4. After evaporation of the solvent, flash chromatography (EtOAc–hexane = 1:15) on silica gel afforded the product as white powder (0.81 g, 66%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 5.18 (s, 1 H), 7.09–7.28 (m, 14 H), 7.44–7.45 (m, 5 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 58.19, 120.82, 124.14, 126.04, 127.05, 127.11, 127.28, 127.88, 128.21, 128.46, 129.93, 129.07, 129.73, 129.86, 135.89, 135.93, 140.30, 141.23, 145.35, 146.08, 148.70. HRMS: *m/z* calcd: 344.1565; found: 344.1570.
(9) **(η^5-1,2,3-Triphenylindenyl)Ru(CO)$_2$Cl (4)**
Toward the THF (10 mL) solution of **6** (440 mg, 1.28 mmol) was added *n*-BuLi (0.46 mL, 1.32 mmol) at –78 °C. Then it was allowed to warm to r.t. in 10 min. Then, $[Ru(CO)_3Cl_2]_2$ (327 mg, 0.64 mmol) was added into the solution, and stirred for 10 min. Afterwards, silica gel was added and the solvent was removed by evaporation. Flash chromatography (EtOAc–hexane, 1:10) on silica gel afforded the product as an air-stable yellow powder (150 mg, 44%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.00–7.11 (m, 4 H), 7.17–7.20 (m, 1 H), 7.38–7.42 (m, 6 H), 7.49–7.57 (m, 6 H), 7.61–7.65 (m, 2 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 92.01, 111.73, 116.78, 124.57, 128.16, 128.96, 129.03, 129.28, 130.94, 131.00, 131.71, 132.35, 197.19. HRMS [M – Cl$^-$ + MeOH]: *m/z* calcd: 533.0691; found: 533.0690. FT-IR (KBr): 2042, 1986 cm^{-1}.
(10) **Racemization Experiments**
The racemization of (*S*)-**7** was carried out in a 5-mL Schlenk tube at r.t. The two methods to activate **4** are described in this paper. When the racemization started, the reaction mixture was sampled regularly to determine the ee (chiral GC, β-dex 325 capillary column, 120 °C isothermal, t_R = 8.31 min, t_S = 8.50 min).
(11) Previously, only ^{13}C NMR was used to study the formation of Ru *tert*-butoxide. Moreover, the long induction time observed in the attempt to racemize (*S*)-**7** with ruthenium hydride and corresponding ketone gives no convincing evidence in support of the existence of ruthenium hydride during racemization (see ref. 6).
(12) Previous crossover experiments with **3** indicate that the ketone generated from β-hydride elimination stays within the coordination sphere of the Ru atom during racemization (see ref. 6b).