

CO Dissociation Mechanism in Racemization of Alcohols by a Cyclopentadienyl Ruthenium Dicarbonyl Catalyst

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Supporting Information

ABSTRACT: ¹³CO exchange studies of racemization catalyst $(\eta^5$ -Ph₅C₅)Ru(CO)₂Cl and $(\eta^5$ -Ph₅C₅)Ru(CO)₂(Ot-Bu) by ¹³C NMR spectroscopy are reported. CO exchange for the active catalyst form, $(\eta^5$ -Ph₅C₅)Ru(CO)₂(Ot-Bu) is approximately 20 times faster than that for the precatalyst $(\eta^{5}-Ph_{5}C_{5})Ru(CO)_{2}Cl$. An inhibition on the rate of racemization of (S)-1-phenylethanol was observed on addition of CO. These results support the hypothesis that CO dissociation is a key step in the racemization of sec-alcohols by $(\eta^{5}-Ph_{5}C_{5})Ru(CO)_{2}Cl$, as also predicted by DFT calculations.

echanistic studies of hydrogen transfer reactions using Mruthenium catalysts have recently attracted considerable attention,¹ due to the extensive applications of these catalysts in racemizations and (transfer) hydrogenations.^{1a,2} For example, ruthenium catalyst 1 has successfully been employed as a racemization catalyst in dynamic kinetic resolution (DKR) of sec-alcohols. Ruthenium catalyst 1 is used in combination with a lipase and an acyl donor to afford the corresponding enantiomerically pure acetates in high yields and ee's (Scheme 1).³

Ruthenium catalyst 1 is highly efficient in racemizing secalcohols, and we have previously studied the racemization mechanism of this catalyst in detail.⁴ Ruthenium complex 1 is activated by t-BuOK to produce ruthenium tert-butoxide complex 2. We recently showed that this ligand exchange takes place via assistance of coordinated CO, with the formation of an acyl intermediate A (Scheme 2, step i).⁵ Rapid alkoxide migration from carbon to ruthenium converts intermediate A to complex 2 within a few minutes at room temperature. Subsequent alcoholalkoxide exchange produces a ruthenium sec-alkoxide complex 3 (Scheme 2, step *ii*). Racemization proceeds via an inner-sphere mechanism which makes the participation of a free ruthenium hydride species, $(\eta^5 - Ph_5C_5)Ru(CO)_2H$, improbable.^{3b} Since secalkoxide complex 3 is an 18-electron complex, racemization via β -hydride elimination requires creation of a free coordination site on ruthenium, which can be formed by either $\eta^5 \rightarrow \eta^3$ ring slippage⁴ to give intermediate 4 or by loss of a CO ligand⁶ forming intermediate 5 (Scheme 2, step iii or iv). On the basis of the observation^{1c} that CO exchange does not occur in the related Shvo hydride (η^{5} -Ph₄C₄COH)Ru(CO)₂H, CO exchange in 3 was considered to be unfavored, and therefore, the $\eta^5 \rightarrow \eta^3$ ring slip pathway was previously proposed.^{4,7} However, recent density functional theory (DFT) calculations showed that the potential energy barrier for $\eta^5 \rightarrow \eta^3$ ring slip in 3 was higher than expected, 42 kcal/mol.⁶ This is ascribed to steric factors

Scheme 1. Schematic DKR of 1-Phenylethanol (CALB = Candida antarctica Lipase B)^{3b}







between the phenyl groups, since the potential energy barrier drops 11 kcal/mol when the phenyl groups are exchanged for hydrogen atoms. The calculated potential energy barrier is lower for the mechanism involving CO dissociation. The energy required for creating an active 16-electron species by dissociation of a CO ligand was calculated to be 22.6 kcal/mol.⁶ These results suggest that loss of a CO ligand is more favored compared to the $\eta^5 \rightarrow \eta^3$ ring slippage pathway. Recently we reported the coordination of an olefin to ruthenium during the racemization which strongly suggests the creation of a vacant site on ruthenium during racemization.⁸ Also, Nolan and co-workers have reported the use of well-defined 16-electron N-heterocyclic carbene- (NHC) and phosphine-containing ruthenium(II) complexes as effective

Received: November 1, 2010 Published: February 11, 2011

Journal of the American Chemical Society



Time (h)

Figure 1. 13 CO incorporation (%) versus time (h) for ruthenium chloride 1.

racemization catalysts of aromatic and aliphatic *sec*-alcohols.⁹ We now report results, involving CO exchange and CO inhibition, which strongly support a CO dissociation pathway in the racemization of secondary alcohols by the activated form of ruthenium catalyst **1**.

An interesting question to answer is whether CO dissociation or exchange can be observed from ruthenium catalyst 1 or ruthenium tert-butoxide complex 2. In preliminary CO exchange experiments, ¹³CO-labeled ruthenium catalyst 1 (44% ¹³CO) was treated with *t*-BuOK (1.2 equiv) in toluene- d_8 in an NMR tube. Analysis by ¹³C NMR after addition of ¹²CO (g) (0.3 equiv and 0.9 equiv) to the preformed ¹³CO-labeled tert-butoxide complex 2 showed no free ¹³CO at 184.7 ppm¹⁰ in either reaction after 12 h. This could, however, be attributed to problems with detection of small amounts of dissociated ¹³CO. Instead, attempts of studying the incorporation of ¹³CO in unlabeled ruthenium catalyst 1 and tert-butoxide complex 2 were made. The rate of incorporation was studied by addition of ¹³CO (g) (0.0124 mmol, 0.32 equiv) to ruthenium chloride 1 (0.039 mmol, 1 equiv) in dry toluene- d_8 at room temperature in four separate reactions. The reactions were analyzed by ¹³C NMR after 3, 6, 24, and 40 h, respectively. Under the specified reaction conditions the maximum amount of ¹³CO incorporation that can theoretically be achieved is 14% (see Supporting Information). After 24 h of reaction time the ¹³CO incorporation was 8.6%. The ¹³CO content was determined by comparison of the integrals to a reference spectrum for unlabeled ruthenium catalyst 1 (1.1% ¹³C content). The plotted results show that ¹³CO incorporation slows down considerably after prolonged reaction times, as expected for this type of equilibrium reaction (Figure 1).

A similar study was performed with ruthenium tert-butoxide complex 2. ¹³CO (g) (0.0124 mmol, 0.32 equiv) was added to preformed complex 2 (0.039 mmol, 1 equiv) dissolved in dry toluene- d_8 at room temperature in three separate reactions. Analyses by ¹³C NMR were made after 30, 60, and 90 min, respectively. The rate of ¹³CO incorporation for ruthenium *tert*butoxide complex 2 was found to be approximately 20 times faster than that for ruthenium chloride 1. After only 30 min of reaction time the ¹³CO incorporation was 5.0% (Figure 2). For ruthenium chloride complex 1, it took approximately 10 h to reach 5.0% ¹³CO incorporation. The ¹³CO content was determined by comparison of the integrals to a reference spectrum for unlabeled ruthenium tert-butoxide complex 2 (1.1% ¹³C content).¹¹ This dramatic increase in rate is attributed to the back-donation from the *t*-BuO group, which stabilizes the intermediate **6** and most likely also the transition state for the CO dissociation. Thus, dissociation of CO is expected to be more facile in tert-butoxide complex 2 compared to chloride complex 1.^{6,12}



Figure 2. 13 CO incorporation (%) versus time (min) for ruthenium *tert*-butoxide complex 2.

Scheme 3. Proposed Mechanism for ¹³CO Exchange on Complex 2 (steps *i* and *ii*) and for the Formation of Complex 7 (steps *iii* and *iv*)



During the CO exchange studies of ruthenium *tert*-butoxide complex 2, the peaks for complex 2 disappeared gradually, and formation of a new complex was observed. The new complex was observed only after ~50 min when the concentration of carbon monoxide was low (0.3 equiv of ¹³CO). At higher carbon monoxide concentrations (>1 equiv of ¹³CO) significant amounts of this new complex were observed in less than 20 min. The new complex was therefore first thought to be a decomposition product due to the sensitivity of ruthenium *tert*-butoxide complex 2 toward moisture and air. At closer inspection of the ¹³C NMR the new complex was assigned as carboalkoxydicarbonyl-ruthenium complex 7¹³ (Scheme 3, See Supporting Information for characterization details).

Dissociation of CO from ruthenium *tert*-butoxide complex **2** produces intermediate **6** with a free coordination site at the metal center (Scheme 3; step *i*). Intermediate **6** is the 16-electron complex responsible for the racemization. Coordination of a ¹³CO molecule to ruthenium in **6** is now possible producing ¹³CO-enriched ruthenium *tert*-butoxide complex (Scheme 3; step *ii*). In a competing pathway, alkoxide migration from ruthenium to CO produces an alkoxycarbonyl complex **B** with a free coordination site at ruthenium (Scheme 3; step *iii*). Complex **7** is then formed irreversibly after coordination of CO (Scheme 3; step *iv*). It is interesting to note that the latter pathway does not lead to any CO exchange of **2** since step *iv* is irreversible. Nolan has recently shown that a 16-electron cyclopentadienylruthenium complex with an NHC ligand, analogous to **6**, is an active racemization catalyst for *sec*-alcohols.^{9b}

The irreversible formation of complex 7 (Scheme 3; step iv) is based on the observation that 7 cannot be converted back into complex **2**, even under reduced pressure. Furthermore, it was



Figure 3. Effect of added CO on the racemization of (*S*)-1-phenylethanol (120 μ L, 0.99 mmol) by 1 (6.4 mg, 0.01 mmol, 1 mol %). 250, 300, 350, and 400 μ L of CO corresponds to 0.0104, 0.0125, 0.0146, and 0.0166 mmol.

found that complex 7 is not active as a racemization catalyst for *sec*-alcohols which is in accordance with the irreversibility.¹⁴ The equilibrium between 2 and B (step *iii*) was confirmed by the observed first-order dependence of [CO] in the formation of complex 7 from complex 2 (see Supporting Information).

The effect of the carbon monoxide concentration on the rate of racemization of *sec*-alcohols was also studied. *t*-BuOK (0.03 mmol, 3 mol %) was added to ruthenium chloride 1 (0.01 mmol, 1 mol %) in dry toluene (2.0 mL). ¹²CO (250–400 μ L, 0.011–0.017 mmol) was added via syringe after formation of ruthenium *tert*-butoxide complex 2. (*S*)-1-phenylethanol (0.99 mmol, 1 equiv, >99% ee) was added to the reaction. Aliquots for GC analysis were withdrawn after 1, 3, and 10 min. Each experiment was run twice, and the mean values were plotted in a graph. A control racemization experiment without any added CO was also performed as a reference.

A catalyst loading of 1 mol % produces an efficient system, capable of racemizing the substrate within 3 min at room temperature (Figure 3; purple). The results show that addition of 250 μ L of CO had a negligible effect on the rate of racemization (Figure 3; dark blue). When $300 \,\mu\text{L}$ of CO was added, the rate of racemization decreased to less than half. This shows some inhibition of the racemization process by CO (Figure 3; pink). Addition of 350 μ L of CO led to a substantial decrease in rate. (Figure 3; green). A further decrease in racemization rate was observed when 400 μ L of CO was added. The sample still exhibited 80% ee after 10 min of reaction time (Figure 3; light blue). At higher concentrations of added CO the racemization of (S)-1-phenylethanol was completely inhibited, and no racemization could be detected within 10 min. This suggests that formation of 7 or corresponding 7' is fast at high concentrations of CO.

The inhibition by carbon monoxide on the racemization of *sec*alcohols strengthens the hypothesis that reversible CO dissociation is a key step in the racemization mechanism.

In conclusion we have found that CO exchange, monitored by ¹³C NMR and the use of ¹³CO, occurs with ruthenium chloride **1** and ruthenium *tert*-butoxide complex **2** in the racemization mechanism of *sec*-alcohols. The CO exchange is approximately 20 times faster for ruthenium *tert*-butoxide complex **2** compared to that for ruthenium chloride complex **1**. During the CO exchange experiments on ruthenium *tert*-butoxide complex **2**, formation of carboalkoxydicarbonylruthenium complex 7 was observed. The effect of different concentrations of CO on the rate of racemization of (*S*)-1-phenylethanol was also investigated, and it was found that small amounts of added CO have a negligible effect on the racemization rate. At higher concentrations, inhibition

of the racemization rate was observed, providing additional support for reversible CO dissociation as a key step in the racemization mechanism of *sec*-alcohols.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The Swedish Research Council, the European Research Council (ERC AdG 247014), the Berzelius Center EXSELENT, and the Knut and Alice Wallenberg foundation are gratefully acknowledged for financial support.

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(11) Although the ¹³CO exchange with chloride 1 within experimental error fits with an equilibrium of a theoretical maximum of 14% (Figure 1), the corresponding exchange with *tert*-butoxide complex 2 does not. This is because some ¹³CO is irreversibly tied up in complex 7. Also, there is some decomposition of complex 2 due to traces of air and humidity. In addition, the theoretical maximum of 14% was based on the assumption that the commercial ¹³CO is 99% ¹³CO. The purity seems to be lower.

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(14) It was also found that complex 7 (12 CO) does not undergo exchange with 13 CO when left for 24 h.