Mechanistic Aspects on Cyclopentadienylruthenium Complexes in Catalytic Racemization of Alcohols

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CONSPECTUS

Cyclopentadienylruthenium complexes commonly serve as efficient transition metal catalysts in the racemization of alcohols. The combination of the racemization reaction with enzymatic resolution leads to dynamic kinetic resolution (DKR). In DKR, a theoretical yield of 100% is possible, making it a powerful tool for enantioselective synthesis.

In this Account, we summarize the most important mechanistic aspects of racemization of alcohols reported over the past decade based on both experimental and computational results. Precatalyst activation is often necessary, either by heating the reaction or by adding an alkoxide-type base. The subsequent alcohol-alkoxide exchange is rapid and introduces the substrate into the catalytic cycle. This exchange requires a free coordination site, which may be created via several different mechanisms.

Following alkoxide formation, racemization occurs via β-hydride elimination and subsequent readdition. In cyclopentadienyldicarbonylruthenium alkoxide complexes, which are 18-electron complexes, researchers originally considered two mechanisms for the creation of the free coordination site required for β-hydride elimination: a change in hapticity of the cyclopentadienyl ligand from $\eta5$ to $\eta3$ and dissociation of a CO ligand. Based on computational and experimental results, we have found strong support for the pathway involving CO dissociation.

Researchers had also wondered if the substrate remains coordinated to the metal center (the inner-sphere mechanism) during the hydrogen transfer step(s). Using competition and crossover experiments, we found strong evidence for an inner-sphere mechanism. In summary, we have obtained a detailed picture of the racemization of alcohols by cyclopentadienylruthenium catalysts, leading to the development of more efficient catalytic systems for racemization.
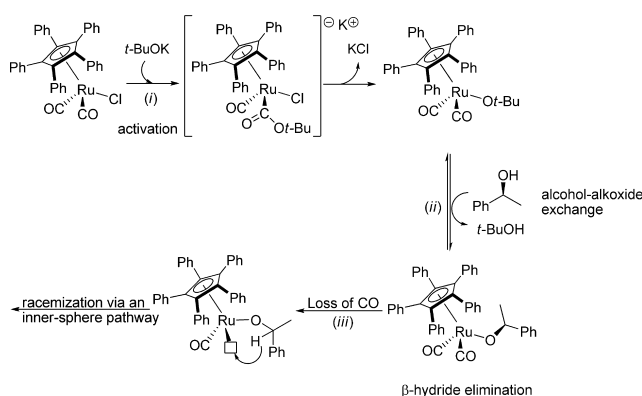
1. Introduction

Kinetic resolution (KR) of a racemate is a common method to prepare enantiomerically enriched compounds, and is based on the difference in reaction rate of two enantiomers with a chiral catalyst. When the resolving agent is an enzyme, the process is termed as an enzymatic kinetic resolution. Although KR is widely used in academic research as well as in industrial applications, it suffers from two main drawbacks: (i) there is a maximum theoretical yield of 50% and (ii) the method requires separation of starting material and product.[1]

In a chemoenzymatic dynamic kinetic resolution (DKR), an enzyme-catalyzed kinetic resolution is integrated with an in situ racemization of the remaining substrate (Scheme 1).[2] By constantly keeping the two enantiomers in equilibrium, the fast-reacting enantiomer is never depleted from the reaction mixture. This technique allows for a yield of up to 100% of the desired enantiomer, thereby overcoming the limitations of a traditional KR. The compatibility of the two catalysts is crucial to ensure an efficient DKR process.[3] The DKR can be made both (*R*)- and (*S*)-selective by altering the choice of the resolving enzyme. In a typical
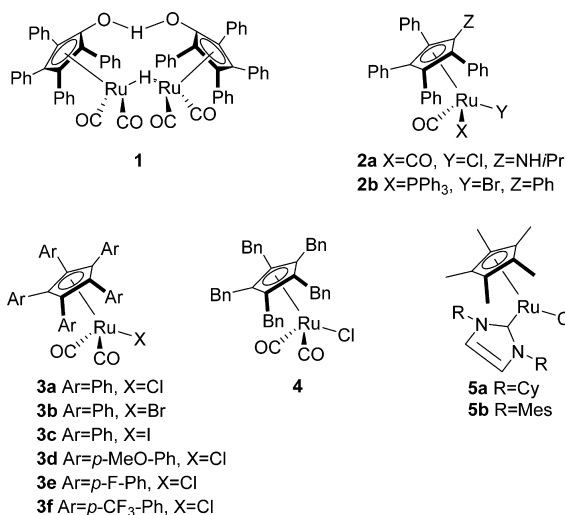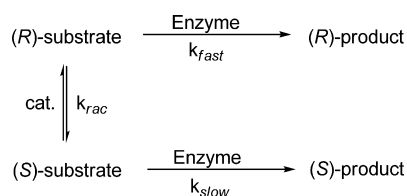
FIGURE 1. Cyclopentadienylruthenium complexes **1**−**5** utilized as racemization catalysts for *sec*-alcohols.

**SCHEME 1.** Principle for an (*R*)-Selective DKR (cat. = catalyst)

chemoenzymatic DKR, an enzymatic resolution is coupled to a transition metal-catalyzed racemization.[4] DKR protocols of this type have attracted considerable interest in recent years, and many examples are reported on alcohols[5,6] and amines.[7]

Racemization is defined as the irreversible formation of a racemate from an enantiomerically enriched compound and always results in loss of optical activity.[8] Different techniques can be utilized for racemization, including transition metal catalysis. The majority of racemization catalysts suitable for DKR of alcohols are ruthenium-based complexes,[9] but examples of rhodium,[10] iridium,[10] aluminum,[11] and vanadium[12] complexes have also been reported in the literature. Cyclopentadienylruthenium complexes **1**−**5** (Figure 1) have all been employed as racemization catalysts for *sec*-alcohols. In this Account, they are discussed with focus on the mechanistic aspects for the racemization. Examples of ruthenium indenyl complexes for catalytic racemization of *sec*-alcohols are also present in the literature.[13,14]

2. Racemization of Alcohols with Cyclopentadienylruthenium Catalysts

Racemization of *sec*-alcohols by transition metal complexes generally proceeds via reversible hydrogen transfer reactions.

**SCHEME 2.** Principle of Transition Metal-Catalyzed Racemization of Alcohols
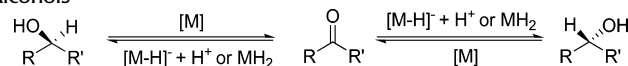
SCHEME 3. Thermal Activation of Shvo's Catalyst **1** into **1a** and **1b** (top) and Their Role in Racemization (bottom)

X = O or NH
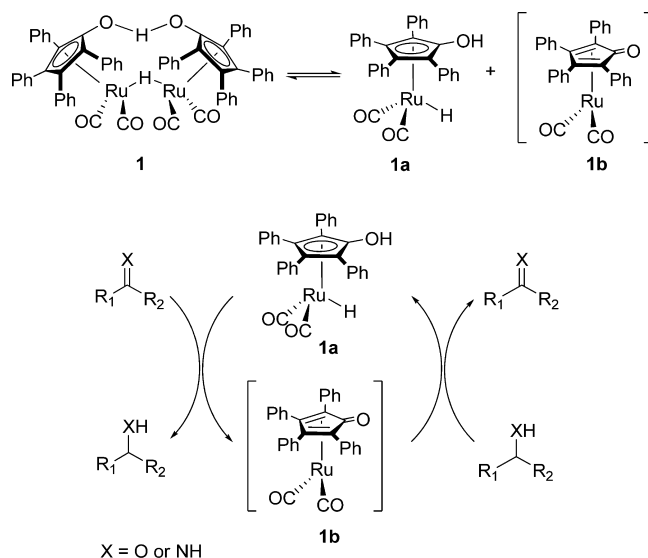
Dehydrogenation of the alcohol by the metal complex produces a ketone and a metal hydride species. Subsequent readdition of metal hydride to the prochiral ketone produces the racemic alcohol (Scheme 2).

Shvo and co-workers reported the synthesis of diruthenium complex **1** for hydrogen transfer reactions in 1984.[15,16] This catalyst has found many synthetic applications in hydrogen transfer reactions.[17,18] It has also been observed that this catalyst can racemize *sec*-alcohols, and in 1997 complex **1** was employed as a racemization catalyst in combination with an enzymatic resolution leading to an efficient DKR.[19] Upon heating, the diruthenium complex **1** dissociates into two catalytically active monoruthenium complexes; an isolable Ru(II) 18-electron complex **1a** and a proposed Ru(0) 16-electron intermediate **1b** (Scheme 3).

2.1. Racemization with the Shvo Catalyst 1. Racemization interconverts the two catalytically active complexes, where complex **1a** acts as the hydrogenation catalyst and complex **1b** as the dehydrogenation catalyst (Scheme 3). Hydrogen mediators are often required as additives to ensure efficient racemization.[19−21] Moreover, the need for thermal conditions to activate the Shvo catalyst **1** limits the choice of enzymes for applications in DKR. Therefore, work has been focused on

SCHEME 4. ^{1}H NMR Study on Catalyst **2a**

SCHEME 5. Proposed Catalytic Cycle for the Racemization of (*S*)-**6** by Catalyst **3a**
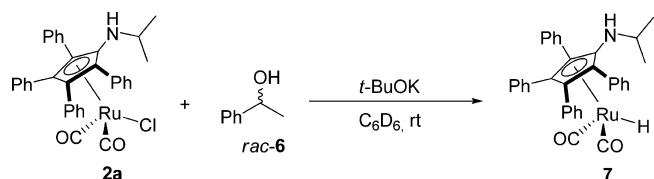

the development of analogues that work at ambient temperature.

2.2. Racemization with Catalysts 2. The group of Kim and Park reported on ruthenium catalyst **2a** for the racemization of *sec*-alcohols at ambient temperature in 2002.[22] Catalyst **2a** is therefore compatible with a wider range of enzymes in DKR of *sec*-alcohols compared to **1**. Furthermore, catalyst **2a** operates without the aid of hydrogen mediators. When a solution of catalyst **2a**, *t*-BuOK, and *rac*-1-phenylethanol (*rac*-**6**) in deuterated benzene was analyzed by ^{1}H NMR, a ruthenium hydride (**7**) was observed as the major species (Scheme 4).[23]

Complex **7** was also found to be effective as a racemization catalyst for *sec*-alcohols, but required addition of a ketone. A drawback with catalyst **2a** is the requirement for the reactions to be run under inert atmosphere. In 2007, Kim and Park reported on a new class of cyclopentadienylruthenium complexes that had one of the carbonyl ligands substituted by a triphenylphosphine ligand (**2b**).[24] Catalyst **2b** (cf. Figure 1) showed comparable efficiency to that of catalyst **2a** under ambient atmosphere in the presence of silver oxide.[24]

2.3. Racemization with Catalysts 3. Bäckvall and co-workers reported on ruthenium catalysts **3a**–**c** for racemization of *sec*-alcohols in 2004.[25,26] Catalyst **3a** (0.5 mol %) was found to be very fast and affected full racemization of (*S*)-**6** within 10 min at room temperature.
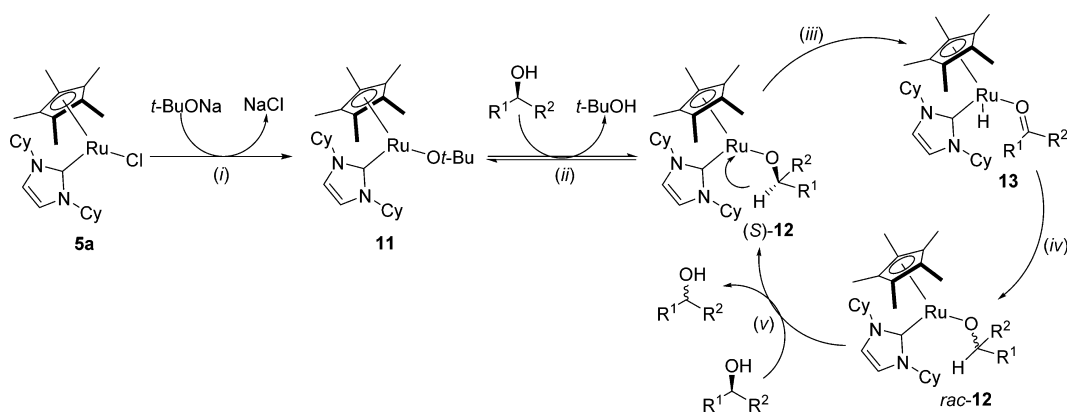
The mechanism for racemization of *sec*-alcohols with catalysts **3** has been extensively studied in our group, both experimentally and theoretically. The proposed mechanism begins with activation of the precatalyst **3a** by *t*-BuOK, which produces ruthenium *tert*-butoxide complex **8** (Scheme 5, step (i)). The next step in the catalytic cycle is the replacement of the alkoxide by (*S*)-**6**, forming ruthenium *sec*-alkoxide complex **9** (Scheme 5, step (ii)).[5,25] Since complex **9** is a coordinatively saturated 18-electron complex, β-hydride elimination, which proceeds via formation of a η^2-π-coordinated ketone that rearranges to η^1-coordinated ketone, requires a free coordination site on ruthenium. This could be formed either via $\eta^5 \rightarrow \eta^3$ ring slippage or via dissociation
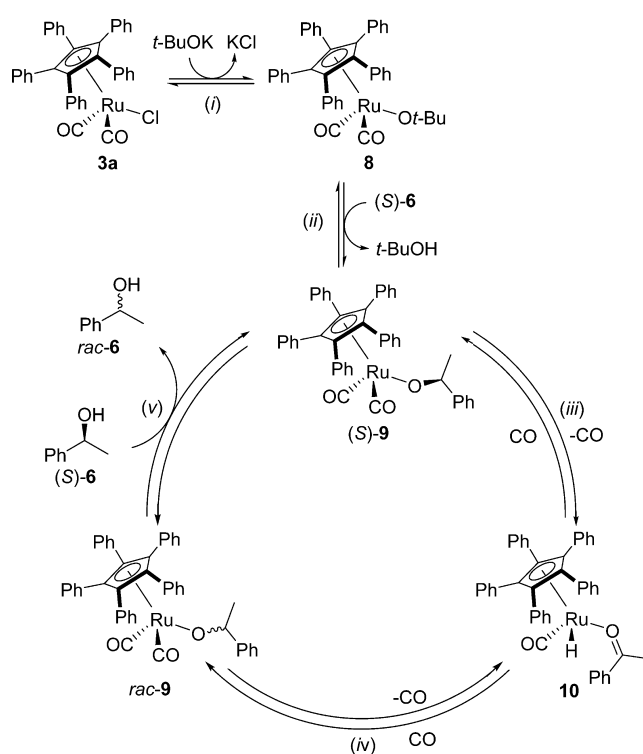
of a CO ligand. Initially, an η^3-ketone-hydride complex was proposed.[5,25] However, more recent results strongly support CO dissociation and formation of complex **10** as the more likely intermediate[27,28] (Scheme 5, step (iii)). Subsequent readdition of the hydride to either face of the prochiral ketone causes racemization of the alcohol and most likely proceeds via the η^2-π-coordinated ketone (Scheme 5, step (iv)). The racemic alcohol is released by another alcohol–alkoxide exchange, thus closing the catalytic cycle (Scheme 5, step (v)).[5,25,29]

2.4. Racemization with Catalyst 4. A modified version of catalyst **3a** with the phenyl groups replaced by benzyl groups was reported by the teams of Kanerva and Leino with co-workers in 2009.[30] Catalyst **4** (cf. Figure 1) showed comparable racemization efficiency to that of catalyst **3a**. A higher racemization rate was observed with catalyst **4** for electron-rich alcohols under ambient atmosphere; however, the racemization rate for electron-deficient alcohols was low.[30] Mechanistic investigations on catalyst **4** have not been published to date, but the mechanism for racemization is expected to be analogous to that of catalyst **3a**.

2.5. Racemization with Catalysts 5. Nolan and co-workers reported on a new class of well-defined 16-electron ruthenium catalysts with *N*-heterocyclic carbene (NHC) ligands

SCHEME 6. Proposed Catalytic Cycle for the Racemization of *sec*-Alcohols by Catalyst **5a**

efficient for racemization of *sec*-alcohols.[31,32] Different NHC ligands were screened in the racemization of (*S*)-**6**, and the best results were obtained with *N,N′*-dicyclohexyli-midazole-2-ylidene (ICy) ligated complex **5a** (cf. Figure 1). With 2 mol % of catalyst **5a**, (*S*)-**6** was completely racemized within 30 min at room temperature. Analogous to catalyst **3a**, precatalyst **5a** requires activation by base. Ruthenium *tert*-butoxide complex **11** was formed after treatment of precatalyst **5a** with *t*-BuONa (Scheme 6, step (i)). ^{1}H NMR data were consistent with catalytically active intermediate **11**.[31] The proposed mechanism for racemization proceeds via alcohol–alkoxide exchange (Scheme 6, step (ii)), forming ruthenium *sec*-alkoxide intermediate **12**. β-Hydride elimina-tion to the vacant site on ruthenium in complex **12** produces 18-electron ketone-hydride intermediate **13** (Scheme 6, step (iii)). Readdition of the hydride to the ketone in **13** occurs via the η^2-π-coordinated ketone (as discussed above) and yields the racemic alcohol (Scheme 6, step (iv)). Another alcohol–alkoxide exchange releases the racemic substrate and closes the catalytic cycle (Scheme 6, step (v)).[31]

3. The Combination of Cyclopentadienyl-ruthenium Catalysts with Enzymes in DKR

During the past decade, DKR has emerged to become a powerful tool for the preparation of enantiomerically pure compounds. Catalyst **2a** was found to be compatible with isopropenyl acetate as acyl donor in the DKR of a wide range of *sec*-alcohols, affording the corresponding acylated pro-ducts in high yields and excellent enantiomeric excess (*ee*).[22,23] Addition of Na$_2$CO$_3$ served to eliminate traces of acetic acid formed and was found to be crucial for an efficient DKR.

Catalyst **3a** has been used in combination with *Candida antarctica* lipase B (CALB) and isopropenyl acetate for DKR of

a wide range of *sec*-alcohols.[5,25] Excellent yields and *ee* of the corresponding enantiopure acetates were obtained for most of the substrates. Furthermore, this DKR system[5] was 1 order of magnitude faster than that previously reported[23] by Park et al. In 2011, a similar substrate scope for catalyst **4** was demonstrated utilizing CALB as the resolving enzyme.[33] Catalyst **5a** has not yet been applied in DKR, but it shows promising activity as a racemization catalyst for *sec*-alcohols.[31,32]

4. Inner-Sphere versus Outer-Sphere Pathway in Racemization

The hydrogen transfer can proceed via two principally different pathways, an *inner-sphere* or an *outer-sphere* me-chanism. In the inner-sphere mechanism, the substrate stays coordinated to the metal center throughout the dehydro-genation/hydrogenation. As opposed to this, in the outer-sphere mechanism, the substrate stays outside the coordi-nation sphere of the metal during dehydrogenation/hydrogenation.[34]

4.1. Mechanism of Racemization of Alcohols with Shvo's Catalyst 1. The mechanism for hydrogen transfer by catalyst **1** has been studied in detail, both experimentally and theoretically, with contributions from several research groups over the past decade. The mechanistic aspects of catalyst **1** in hydrogen transfer reactions have been reviewed recently[17] and will not be further discussed in this Account.

Apart from the mechanistic studies of catalyst **1**, most of the mechanistic work on catalysts **2**–**5** has been carried out with catalysts **3**. Therefore, the rest of this Account will mainly deal with the results from the mechanistic investiga-tions on catalysts **3**.

4.2. Mechanism of Racemization of Alcohols with Cat-alysts 3. Bäckvall and co-workers have carried out work to

determine whether the racemization of *sec*-alcohols with catalyst **3a** proceeds via an inner-sphere or outer-sphere mechanism. To rule out a free hydride as an active catalytic intermediate, the racemization of (*S*)-**6** was tested with 5 mol % of hydride **14** and 5 mol % of added acetophenone (**15**) (Scheme 7). The reaction shows a long induction period of 2.5 h, after which racemization takes off and is complete after an additional 30 min. The results indicate that the reaction of **15** and complex **14** is slow, which further suggests that free ruthenium hydride **14** is not an abundant catalytic species.[5]

The results in Scheme 7 indicate that the ketone stays coordinated to ruthenium in the ruthenium hydride intermediate (cf. Scheme 5). To provide further support for ketone coordination after the β-hydride elimination, racemization of (*S*)-**6** was performed in the presence of ketone **16** (1 equiv) (Scheme 8). When the reaction was performed at room temperature with 1 mol % of catalyst **3a**, only 1% of the added ketone had been converted to alcohol **17**. The same experiment performed at 80 °C showed formation of considerable amounts of alcohol **17** (35% after 5 min). However, the observed ketone exchange at higher temperature can be explained by an entropy effect.[5] This hypothesis is supported by recent work showing that ketone formation as byproducts increases in DKR protocols at higher temperatures.[35,36]
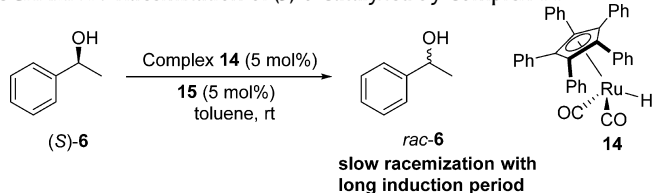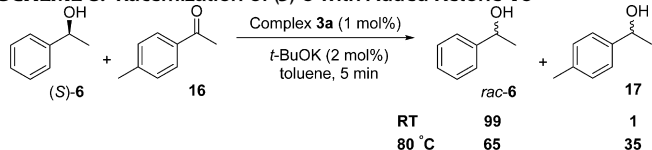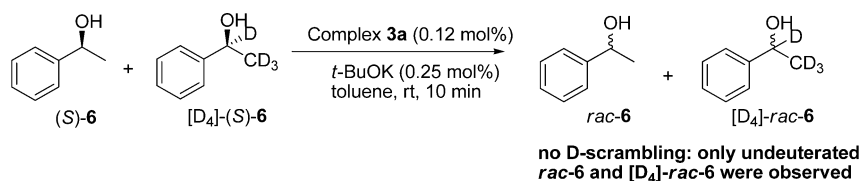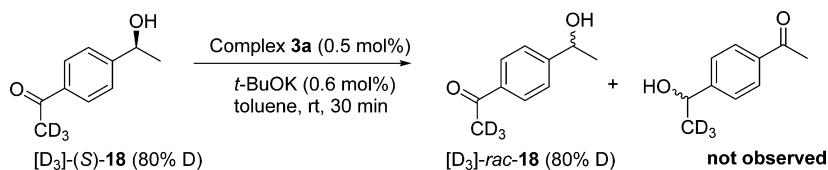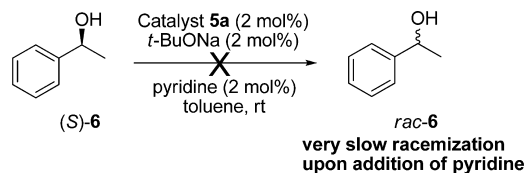
A racemization experiment with a 1:1 mixture of (*S*)-**6** and [D$_4$]-(*S*)-**6** was also performed (Scheme 9). After complete racemization, neither PhCH(OH)CD$_3$ nor PhCD(OH)CH$_3$ could be detected in the ^{1}H NMR spectrum of the reaction mixture, which shows that no crossover of deuterium has occurred. This further supports that an inner sphere mechanism is operating.[37]

The lack of ketone exchange and lack of crossover of deuterium described in the above experiments could also be explained by an alternative mechanism in which the newly formed ketone stays inside the solvent cage after β-hydride elimination. To rule out this mechanism, the racemization was performed with a substrate having a ketone moiety within the alcohol substrate. Racemization of [D$_3$]-(*S*)-**18** with 0.5 mol % of complex **3a** showed [D$_3$]-*rac*-**18** as the sole product (Scheme 10).[37] The fact that no crossover of deuterium or reduction of the α-trideuterated ketone moiety occurs, indicates that the ketone produced by β-hydride elimination from the alkoxide intermediate (cf. complex **9** in Scheme 5) stays coordinated to the metal. These results provide strong support for an inner sphere mechanism.[37]

4.3. Mechanism of Racemization of Alcohols with Catalyst 5.

Also for catalyst **5**, an inner-sphere mechanism was established by racemization of (*S*)-**6** with catalyst **5a** in the presence of ketone **16** (cf. Scheme 8).[31] Complete racemization of (*S*)-**6** was observed without formation of the alcohol from reduction of ketone **16**.

The reaction between (*S*)-**6** and catalyst **5a** was also studied by ^{1}H and ^{13}C NMR spectroscopy at room temperature.[32] These studies showed the presence of ruthenium hydride intermediates; however, free acetophenone could not be detected. This provides further support for an inner-sphere mechanism.[32]

Furthermore, the importance of the vacant site on the ruthenium center was investigated by the addition of pyridine to the racemization of (*S*)-**6** (Scheme 11). A decrease over time in the racemization rate was found with simultaneous addition of pyridine and (*S*)-**6**. Addition of pyridine to the ongoing racemization reaction of (*S*)-**6** also led to a dramatic decrease in the rate of racemization. These

SCHEME 7. Racemization of (*S*)-**6** Catalyzed by Complex **14**

SCHEME 8. Racemization of (*S*)-**6** with Added Ketone **16**

	RT	99	1
	80 °C	65	35

SCHEME 9. Racemization of a 1:1 Mixture of (*S*)-**6** and [D$_4$]-(*S*)-**6** with Catalyst **3a**

no D-scrambling: only undeuterated *rac*-**6** and [D$_4$]-*rac*-**6** were observed

SCHEME 10. Racemization of [D$_3$]-(S)-**18** with Catalyst **3a**

[D$_3$]-(S)-**18** (80% D)

Complex **3a** (0.5 mol%)
t-BuOK (0.6 mol%)
toluene, rt, 30 min

[D$_3$]-*rac*-**18** (80% D) + **not observed**

SCHEME 11. Inhibition of Racemization of (S)-**6** with Catalyst **5a** on Addition of Pyridine

(S)-**6**

Catalyst **5a** (2 mol%)
t-BuONa (2 mol%)
✗
pyridine (2 mol%)
toluene, rt

rac-**6**
very slow racemization upon addition of pyridine

SCHEME 12. Activation of Catalyst **3a** to form **8** via the Formation of Carboalkoxy Intermediate **A**

3a

t-BuOK

A
characterized by ^{13}C NMR and *in situ* FT-IR

KCl

8

experiments suggest that the vacant site is essential for the racemization to proceed, thereby ruling out a $\eta^5 \rightarrow \eta^3$ ring slippage pathway.[31]

5. Activation of Catalysts 3

As stated above, precatalyst activation of **3** by *t*-BuOK is necessary for racemization to proceed. The quantitative formation of ruthenium *tert*-butoxide complex **8** was observed by mixing catalyst **3a** with a slight excess of *t*-BuOK in toluene-*d$_8$*. The ^{1}H and ^{13}C NMR peaks of complex **8** differ from those of complex **3a** as well as from *t*-BuOK and *t*-BuOH in toluene-*d$_8$*. Immediate racemization of (S)-**6** upon addition to a solution of ruthenium *tert*-butoxide complex **8** proves the latter to be a key intermediate in the catalytic cycle. Precatalyst activation is also supported by a strong color change of the reaction mixture from yellow to orange/red.[5,25]

From computational studies a low-energy pathway was identified for activation of the precatalyst via participation of one of the CO ligands, leading to a carboalkoxy intermediate (**A**). The computed potential energy barrier for this transformation was 16.7 kcal/mol.[27] Carboalkoxy intermediate **A** was detected experimentally by NMR spectroscopy and in situ FT-IR measurements (Scheme 12).[38,39] Monitoring by in situ FT-IR showed the disappearance of the two CO bands of **3a** at 2049 and 2001 cm^{-1} (symmetric and asymmetric stretch, respectively), with the simultaneous appearance of a peak at 1933 cm^{-1} (CO) and one at 1596 cm^{-1} (carboalkoxy). The latter two peaks were assigned to carboalkoxy intermediate **A**. After approximately 1 min, the two peaks for ruthenium *tert*-butoxide complex **8** at 2018 and 1962 cm^{-1} started to appear with concomitant disappearance of the peaks for carboalkoxy intermediate **A**. The lifetime of intermediate **A**
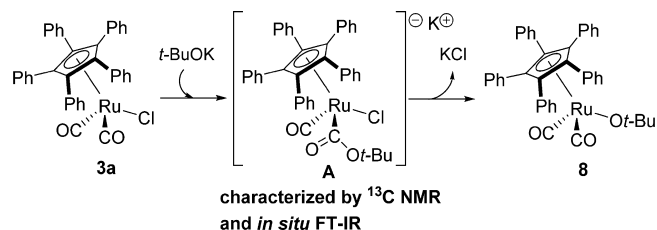
was less than 3 min at room temperature. Carboalkoxy intermediate **A** was also characterized by ^{13}C NMR spectroscopy at −32 °C by the use of ^{13}CO-labeled ruthenium catalyst **3a**. The CO peaks appeared at δ 209.5 ppm (CO) and 208.7 ppm (carboalkoxy), which was in good agreement with the theoretically estimated shifts using density functional theory (DFT) calculations.[38]

6. Studies on the Active Alkoxide Catalyst

6.1. Alcohol−Alkoxide Exchange. After precatalyst activation, the next step in the catalytic cycle is introduction of the substrate (S)-**6**, forming ruthenium *sec*-alkoxide complex **9** (cf. Scheme 5, step (ii)). The ^{13}C NMR spectrum showed two different shifts for the CO groups of complex **9** at δ 201.1 and 199.7 ppm.[37] This is consistent with coordination of the chiral *sec*-alkoxide to the metal center, which makes the two carbonyl ligands diastereotopic. These were clearly distinguishable from the CO ligands of ruthenium *tert*-butoxide complex **8**, which appear together as one peak at δ 202.8 ppm.[37] The reaction between ruthenium *tert*-butoxide complex **8** and (S)-**6** was also studied by in situ FT-IR spectroscopy. Upon addition of (S)-**6** to the reaction vessel, the two bands for complex **8** disappeared within seconds. Two new bands formed at 1970 and 2024 cm^{-1} were assigned as complex **9** (cf. Scheme 5).[37]

6.1.1. Mechanism of Alcohol−Alkoxide Exchange. Further investigation of the alcohol−alkoxide exchange reaction was performed with a tertiary alcohol, which cannot undergo α-CH bond cleavage. *tert*-Amyl alcohol (3 equiv) was added to the preformed ruthenium *tert*-butoxide complex **8** in toluene-*d$_8$* at −40 °C (Scheme 13). Formation of a

SCHEME 13. Alkoxide Exchange Reaction

SCHEME 14. Formation of Two Diastereomers **21a,b** of an Alkoxycarbonyl Complex
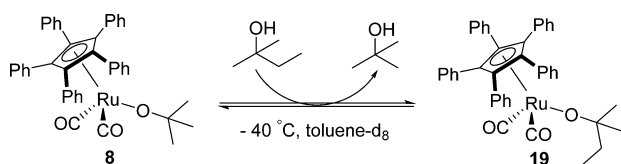
new complex (about 20%) was observed by ^{13}C NMR in less than 10 min which was assigned as complex **19**.[37]

The mechanism for alkoxide exchange can proceed via two principally different pathways, either an associative or a dissociative pathway. A dissociative pathway leads to the formation of free alkoxides, which seems less likely since this may cause chemical acylation in the presence of isopropenyl acetate in the DKR.[37] It has been shown that the use of a large excess of *t*-BuOK in the DKR gives lower enantiopurity of the ester products.[5,25,40] Hence, the formation of enantiomerically pure esters in the DKR would indicate that free alkoxides are not formed. An associative pathway requires formation of a free coordination site on ruthenium, which could either be formed via $\eta^5 \rightarrow \eta^3$ ring slippage or by CO dissociation.[37] The hapticity change $\eta^5 \rightarrow \eta^3$ is known to be favored by phenyl groups on the cyclopentadienyl ring which stabilize the η^3 intermediate.[41] Also, the observation that all three complexes (**3a**, **8**, and **9**) showed two bands for the CO ligands during the in situ FT-IR measurements was used as an argument against CO dissociation. Furthermore, no stretching frequency for free CO (2143 cm^{-1}) was observed during the in situ FT-IR measurements. On the basis of these observations the $\eta^5 \rightarrow \eta^3$ ring slippage was considered as a possible pathway.[37] However, more recent results favor CO dissociation over the $\eta^5 \rightarrow \eta^3$ ring slippage mechanism (vide infra).[27,28] In the formed 16-electron complex, the incoming alcohol most likely interacts with the alkoxide through hydrogen bonding.[37] An alternative low-energy pathway for the alcohol-alkoxide exchange via CO assistance through a carboalkoxy intermediate (cf. Scheme 13) was computationally detected.[27] A carboalkoxy intermediate in the alcohol-alkoxide exchange comparable to that of **A** has, however, not yet been detected experimentally.

6.1.2. Formation of an Alkoxycarbonyl Complex. Another alcohol-alkoxide exchange reaction was studied by reacting ruthenium *tert*-butoxide complex **8** with *sec*-alcohol **20**.[42] 5-Hexen-2-ol (**20**) was investigated due to the slow racemization rate found for this substrate. The hypothesis was that the terminal double bond coordinates to the ruthenium center and blocks the free coordination site
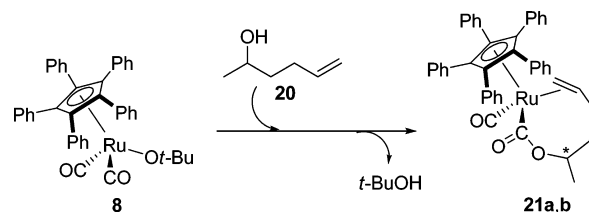
needed for β-hydride elimination. Two diastereomers of an alkoxycarbonyl complex (**21a,b**) having the double bond coordinated to ruthenium were characterized by ^{1}H NMR, ^{13}C NMR, and in situ FT-IR spectroscopy (Scheme 14).[43] IR peaks for complexes **21a,b** were observed at 1982 and 1644 cm^{-1}. This study provides some mechanistic insight by confirming the importance of a vacant site on ruthenium in order for racemization to proceed, as also observed by the group of Nolan in a subsequent study on a related ruthenium complex.[31]

6.2. CO Dissociation Mechanism. 6.2.1. Computational Study. The two possible mechanisms for creation of a free coordination site on ruthenium were investigated theoretically by calculating the potential energy barriers. For the $\eta^5 \rightarrow \eta^3$ ring slippage mechanism, the barrier turned out to be surprisingly high and was calculated to 42 kcal/mol for **9** (Scheme 15, path A). The potential energy barrier for the CO dissociation mechanism was calculated to be 22.6 kcal/mol (Scheme 15, path B), which indicates that this pathway is more favored.[27] Since significant irreversible loss of CO has been ruled out by in situ FT-IR spectroscopy[37] (vide supra), the remaining hypothesis is that reversible CO dissociation accounts for the formation of the free coordination site.[27,28]

6.2.2. CO Exchange. To support the mechanistic hypothesis that reversible CO dissociation is a key step in the racemization mechanism, a [13]CO exchange study was performed.[28] The incorporation of [13]CO was studied by adding gaseous [13]CO (0.013 mmol, 0.3 equiv) to complexes **3a** and **8**. Sample analysis was performed by ^{13}C NMR and under the chosen reaction conditions a theoretical maximum of 14% [13]CO incorporation could be obtained. For the precatalyst **3a**, 5.0% [13]CO incorporation was reached after approximately 10 h. For complex **8**, the incorporation was found to be much faster and 5.0% was reached after only 30 min. The dramatic increase in rate was attributed to the π-donation from the *t*-BuO group to ruthenium, which stabilizes the transition state for CO dissociation.[28] The calculated difference between the transition state energies

SCHEME 15. Two Possible Pathways for Creation of a Free Coordination Site
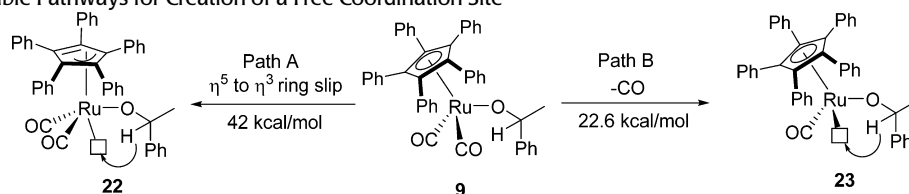
for complexes **3a** and **8** (2−3 kcal/mol) is in good agreement with the experimental rates of [13]CO incorporation found.[43]

During the [13]CO exchange study on complex **8**, formation of a tricarbonylruthenium species was detected. Carboalkoxydicarbonylruthenium complex **24** was observed after approximately 50 min at low concentrations of carbon monoxide (0.3 equiv of [13]CO). At higher concentrations of carbon monoxide (>1 equiv of [13]CO), a quantitative yield of complex **24** was formed in less than 1 h. The proposed mechanism for [13]CO exchange on complex **8** begins with dissociation of CO (Scheme 16, step (i)). The formed intermediate **25** is the 16-electron complex proposed to be responsible for the racemization. Coordination of a [13]CO molecule is now possible, producing [13]CO-enriched complex **8** (Scheme 16, step (ii)). In a competing pathway, reversible alkoxide migration from ruthenium to one of the carbonyl ligands forms 16-electron intermediate **26** (Scheme 16, step (iii)). Irreversible formation of complex **24** is observed after coordination of a [13]CO molecule (Scheme 16, step (iv)). It was demonstrated that complex **24** cannot be converted back into complex **8**, even under heating at reduced pressure. Furthermore, complex **24** was found to be inactive as a racemization catalyst for (S)-**6** which is in accordance with the irreversibility.[28] Recent DFT calculations show that the formation of complex **24** from **8** is highly exothermic with a potential energy barrier of 34.5 kcal/mol. This is in good agreement with the experimental observation that the reaction is irreversible.[44] The observed first-order dependence on [CO] in the formation of complex **24** from **8** confirms the equilibrium between **8** and **26** (Scheme 16, step (iii)).[28,44]

6.2.3. CO Inhibition Study. The effect on the rate of racemization of (S)-**6** under different concentrations of added CO (250−400 μL, 1−1.7 equiv with respect to complex **3a**) was also investigated (Figure 2). Inhibition of the rate of racemization was observed at [CO] ≥ 300 μL. With 300 μL of added CO, the rate decreased to approximately half, compared to a control experiment with no added CO. At [CO] > 400 μL, complete inhibition was observed and no racemization was detected within 10 min. This is in

SCHEME 16. Proposed Mechanism for [13]CO Exchange of Complex **8** (steps (i) and (ii)) and for the Formation of Complex **24** (steps (iii) and (iv))
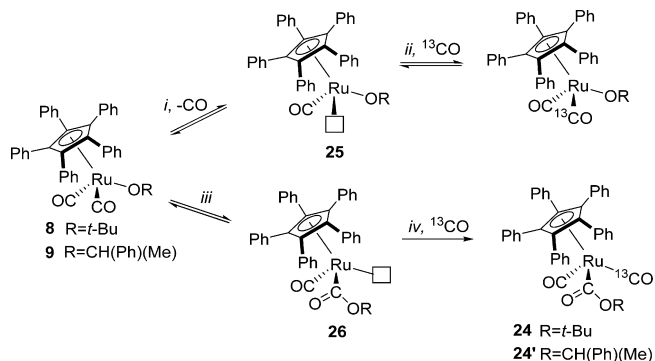
accordance with the observation that formation of **24** or **24′** is fast at high concentrations of CO (cf. Scheme 16). The observed [13]CO exchange along with the inhibition by carbon monoxide on the racemization provides strong experimental evidence for reversible CO dissociation as a key step in the racemization mechanism for *sec*-alcohols.[28]

6.3. Intermediate Hydride Structure. In attempts to detect the intermediate hydride structure, the reaction between ruthenium *tert*-butoxide complex **8** and (S)-**6** was studied by ^{1}H NMR spectroscopy at −61 °C.[37] No hydride resonances were observed, which could be either because racemization is inhibited at low temperatures or that the hydride resonances are not observed on the NMR time scale. The ^{1}H NMR study at −40 °C showed that alkoxide exchange is very rapid even at low temperatures (cf. Scheme 13).[37] However, since no resonances from ruthenium hydride intermediates were observed, it is not certain that the β-hydride elimination also occurs at low temperatures. Therefore, the epimerization of *cis*-4-methylcyclohexanol (*cis*-**27**) was studied by ^{1}H NMR spectroscopy at −50 °C (Scheme 17). The CH−O proton appears at different resonances for the *cis* and *trans* isomers of 4-methylcyclohexanol, which allows for epimerization to be monitored. After 10 min, the recorded spectrum showed a *cis/trans* ratio of 30:70. Prolonged reaction time changed the ratio and after 2 h at −50 °C a *cis/trans* ratio of 19:81 was recorded. This experiment
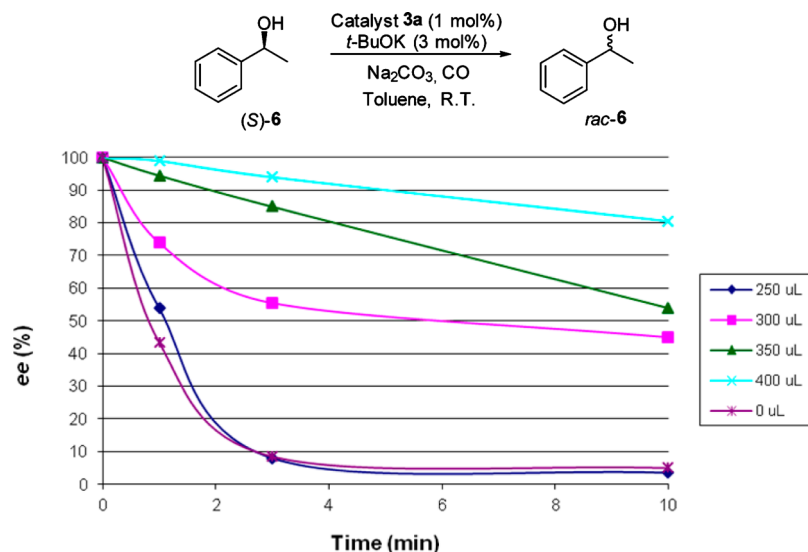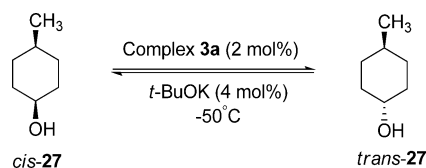
FIGURE 2. CO inhibition of racemization of (S)-**6**.

SCHEME 17. Epimerization of *cis*-4-Methylcyclohexanol (*cis*-**27**) Catalyzed by **3a** at −50°C

shows that epimerization occurs quite rapidly even at low temperatures. Therefore, the failure to detect any hydride intermediates was ascribed to that the concentration of hydrides is too low or that β-hydride elimination and subsequent readdition is too fast to be detected on the NMR time scale.[37]

6.4. Kinetic Isotope Effects. To find out whether the β-hydride elimination is the rate-determining step in the racemization mechanism, a 1:1 mixture of (S)-**6** and [α-D]-(S)-**6** was investigated in the racemization with catalyst **3a**. Similar experiments were also performed with two other *sec*-alcohols, methoxy-substituted alcohol **28** and trifluoromethyl-substituted alcohol **29** (Scheme 18).[37]

A moderate kinetic isotope effect was observed for (S)-**6** ($k_H/k_D = 1.27 \pm 0.06$). For the more electron-rich alcohol (S)-**28**, a negligible isotope effect was found ($k_H/k_D = 1.08 \pm 0.17$), which suggests that the β-hydride elimination becomes less rate-determining than that for (S)-**6**. A larger isotope effect was found for the more electron-deficient alcohol (S)-**29** ($k_H/k_D = 1.45 \pm 0.13$), which suggests that the β-hydride elimination becomes more rate-determining for this alcohol than for (S)-**6**.[37]
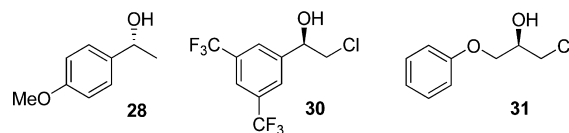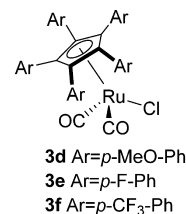

FIGURE 3. Substrates **28** and **30**−**31** evaluated for racemization with catalysts **3d**−**f**.

7. Modified Catalyst Development

The observed kinetic isotope effects indicate that the electronic properties of the substrate have a large impact on the rate-determining step of the racemization reaction. For an electron-deficient alcohol, the rate-determining step is the β-hydride elimination, whereas for an electron-rich alcohol the readdition of the hydride to the ketone intermediate becomes more rate-determining. With these results in hand, the Bäckvall research group envisioned that the racemization for some substrates could become more efficient by better matching the electronic properties of the catalyst to the substrate. The modified catalysts **3d-f** were prepared and evaluated for the racemization of electron-rich substrate **28** and of electron-deficient substrates **30** and **31** (Figure 3).[45]

Electron-rich catalyst **3d** gave the fastest racemization for electron-rich substrate **28**. In accordance with the hypothesis,

SCHEME 18. Determination of Kinetic Deuterium Isotope Effects for Substrates **6**, **28**, and **29**

(*S*)-**6** R=H
(*S*)-**28** R=OMe
(*S*)-**29** R=CF$_3$

(*R*)-**6** R=H
(*R*)-**28** R=OMe
(*R*)-**29** R=CF$_3$
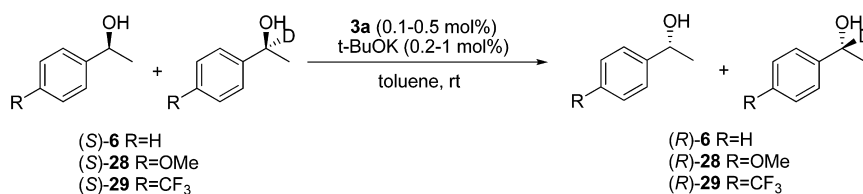
the electron-deficient catalysts **3e** and **3f** gave the fastest racemization for electron-deficient substrates **30** and **31**. These observations demonstrate that fine-tuning of the electronic properties of the catalyst with respect to the substrate results in more efficient racemization. The scope of racemization and DKR with cyclopentadienylruthenium catalysts can therefore be extended to include substrates that have proven to be difficult with catalyst **3a**.[45]

8. Conclusions

Cyclopentadienylruthenium complexes **1**−**5** have found extensive use as transition metal catalysts for racemization. In several cases, this racemization has also been integrated with an enzymatic kinetic resolution leading to efficient DKR protocols for *sec*-alcohols affording the corresponding enantiomerically enriched esters. The racemization generally proceeds via reversible hydrogen transfer reactions. The mechanistic aspects of racemization with cyclopentadienylruthenium complexes have been studied over the past decade, and the most important points have been summarized in this Account. It has been shown that increased understanding of the racemization mechanism has led to the development of more efficient catalytic systems for racemization.

BIOGRAPHICAL INFORMATION

Madeleine C. Warner was born in Stockholm, Sweden in 1984. She received her M.Sc. in synthetic organic chemistry from Stockholm University in 2008. Immediately thereafter, she joined the group of Prof. Jan-E. Bäckvall for doctoral studies at the Department of Organic Chemistry, Stockholm University. Current research focus lies on delineating the mechanism of ruthenium catalyzed hydrogen transfer reactions and asymmetric synthesis of small chiral molecules via dynamic kinetic resolution.

Jan-Erling Bäckvall was born in Malung, Sweden, in 1947. He received his Ph.D. from the Royal Institute of Technology, Stockholm, in 1975 with Prof. B. Åkermark. After postdoctoral work (1975−1976) with Prof. K. B. Sharpless at Massachusetts Institute of Technology, he joined the faculty at the Royal Institute of Technology. He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997, he moved to Stockholm University where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences, Finnish Academy of Science and Letters, and Academia Europaea. He is a member of the Nobel Committee for Chemistry. He is a member of a number of Editorial Boards of journals, and he is the Chairman of the Editorial Board of *Chemistry—A European Journal*. His current research interests include transition metal-catalyzed organic transformations, biomimetic oxidations, and enzyme catalysis.
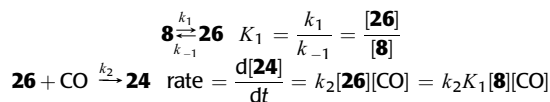
FOOTNOTES

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The authors declare no competing financial interest.

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44 If **8** is in equilibrium with **26** with irreversible formation of **24** from **26**, we have:

$$\mathbf{8} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathbf{26} \quad K_1 = \frac{k_1}{k_{-1}} = \frac{[\mathbf{26}]}{[\mathbf{8}]}$$

$$\mathbf{26} + CO \xrightarrow{k_2} \mathbf{24} \quad \text{rate} = \frac{d[\mathbf{24}]}{dt} = k_2[\mathbf{26}][CO] = k_2 K_1[\mathbf{8}][CO]$$

This gives a first-order dependence on [CO]. Without an equilibrium between **8** and **26**, $k_2[CO] > k_{-1}$. It is reasonable to assume that $K_1 < 1$ (i.e., $k_{-1} > k_1$), since **26** cannot be observed by NMR in a solution of **8**. As a consequence, $k_2 \gg k_1$ and the steady state approximation can be applied which gives the rate $\approx k_1[\mathbf{8}]$.

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