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Racemization of Secondary Alcohols Catalyzed by Cyclopentadienylruthenium Complexes: Evidence for an Alkoxide Pathway by Fast β-Hydride Elimination–Readdition

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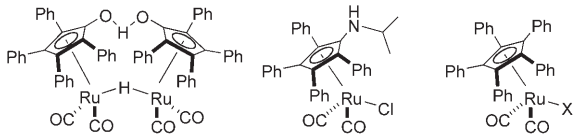
Abstract: The racemization of *sec*-alcohols catalyzed by pentaphenylcyclopentadienyl–ruthenium complex **3a** has been investigated. The mechanism involves ruthenium–alkoxide intermediates: reaction of *tert*-butoxide ruthenium complex **4** with a series of *sec*-alcohols with different electronic properties gave ruthenium complexes bearing a secondary alkoxide as a ligand. The characterization of these alkoxide complexes by NMR spectroscopy together with a study of the reaction using in situ IR spectroscopy is consistent with a mechanism in which the alkoxide substitution step and the β-hydride elimination step occur without CO dissociation. The alkoxide substitution reaction is proposed to begin with hydrogen bonding of the incoming alcohol to the active ruthenium–alkoxide intermediate. Subsequent alkoxide exchange can occur via two pathways: i) an associative pathway involving a η^3-CpRu intermediate; or ii) a dissociative pathway within the solvent cage. Racemization at room temperature of a 1:1 mixture of (*S*)-1-phenylethanol and (*S*)-1-phenyl-[D_4]-ethanol gave only *rac*-1-phenylethanol, and *rac*-1-phenyl-[D_4]-ethanol, providing strong support for a mechanism in which the substrate stays coordinated to the metal center throughout the racemization, and does not leave the coordination sphere. Furthermore, racemization of a *sec*-alcohol bearing a ketone moiety within the same molecule does not result in any reduction of the original ketone, which rules out a mechanism where the intermediate ketone is trapped within the solvent cage. These results are consistent with a mechanism where η^3-Ph_5C_5–ruthenium intermediates are involved. Competitive racemization on nondeuterated and α-deuterated α-phenylethanols was used to determine the kinetic isotope effect k_H/k_D for the ruthenium-catalyzed racemization. The kinetic isotope effect k_H/k_D for *p*-X-$C_6H_4CH(OH)CH_3$ was 1.08, 1.27 and 1.45 for X = OMe, H, and CF_3, respectively.

Keywords: alcohols · hydrides · racemization · reaction mechanisms · ruthenium

Introduction

Catalytic racemization of *sec*-alcohols mediated by transition-metal complexes has attracted much attention in recent years.[1] In particular, racemization accomplished by ruthenium complexes **1**–**3** is of great importance since these complexes have been successfully combined with an in situ enzymatic resolution leading to deracemization of *sec*-alcohols via dynamic kinetic resolution (DKR).[1a–5]



1 **2** **3a**: X = Cl **3b**: X = Br **3c**: X = I

Recently, we have reported on a DKR catalyzed by complexes **3a-b** in combination with an enzyme (Scheme 1).[5]

Mechanistic studies led us to propose the catalytic racemization cycle shown in Scheme 2.[5b] Ruthenium halide precatalyst **3a** is activated by *t*BuOK, with concomitant formation

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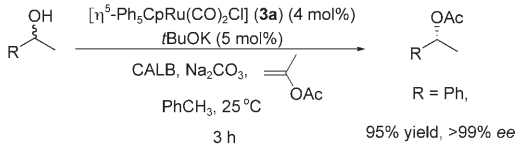
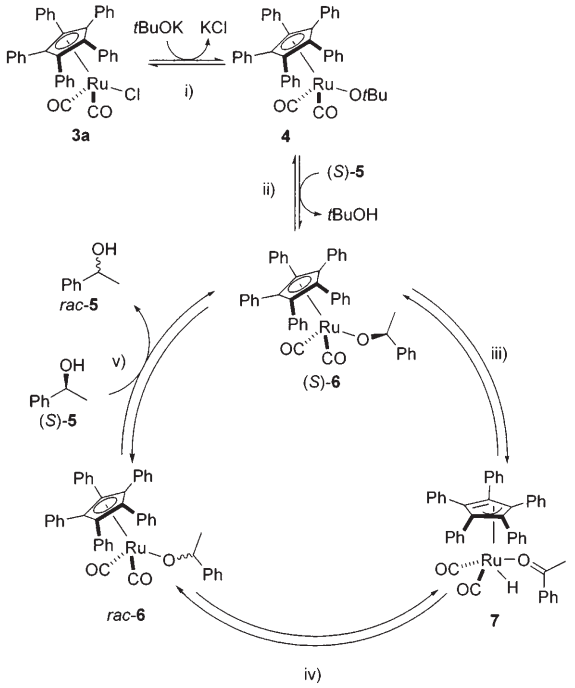


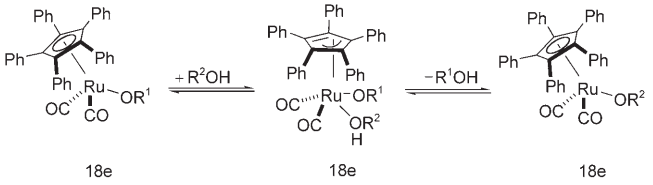
Scheme 1. DKR of *sec*-alcohols (CALB = *Candida antarctica* lipase B).



Scheme 2. Proposed mechanism in racemization of *sec*-alcohols catalyzed by **3a**.

of ruthenium–*tert*-alkoxide complex **4**.[6] This *tert*-alkoxide–ruthenium complex was characterized by ^{13}C NMR spectroscopy. The formation of this intermediate was also supported by a strong color change of the reaction mixture from yellow to red. Furthermore, addition of (*S*)-1-phenylethanol [(*S*)-**5**] to a solution of *tert*-alkoxide **4** resulted in immediate racemization to give *rac*-**5**, as confirmed by chiral GC analysis. The alkoxide ligand substitution (step ii), which would generate *sec*-alkoxide complex **6**, was studied by addition of *tert*-amyl alcohol **4** in [D_8]toluene. *tert*-Amyl alcohol was chosen to avoid β-hydride elimination from the new alkoxide complex. It has also been observed that the presence of a ketone in the racemization of *sec*-alcohols catalyzed by **3a**–**b**[5] and related catalysts[4] does not interfere to give reduced ketone. We have therefore proposed a mechanism in which β-hydride elimination from the *sec*-alkoxide complex **6** produces a hydride ketone complex **7**.[5b] In this proposed mechanism the newly formed ketone stays coordinated to ruthenium during the racemization.

One of the key steps in the catalytic cycle of the racemization is the alkoxide substitution reaction. There are two principal mechanisms for ligand substitution reactions: i) a dissociative pathway, and ii) an associative pathway.[7] A dissociative pathway would imply an ionic dissociation of the alkoxide and a subsequent protonation of the latter species by the incoming alcohol, followed by recombination of the metal center and the newly generated alkoxide. The associative pathway would seem to require a $\eta^5 \rightarrow \eta^3$ ring slippage[8] (Scheme 3) since the alkoxide complex has 18 electrons, and CO dissociation is considered unlikely.[9]

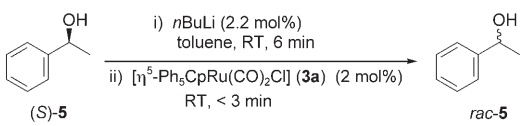


Scheme 3. Alkoxide exchange via an associative substitution.

A detailed study of the alkoxide substitution reaction mechanism involving *sec*-alkoxide–Ru complexes in the catalytic cycle is currently lacking. Also, mechanistic details concerning the C–H bond cleavage step (β-hydride elimination) are missing. Here we present a mechanistic investigation of these key steps involved in the racemization of alcohols catalyzed by cyclopentadienylruthenium complexes **3**. In addition, we describe results from attempted trapping experiments using an intramolecular ketone trap. These attempted trapping experiments provide support for a mechanism where the newly formed ketone from β-hydride elimination stays coordinated and rules out a pathway where the generated ketone stays in the solvent cage due to slow diffusion.

Results

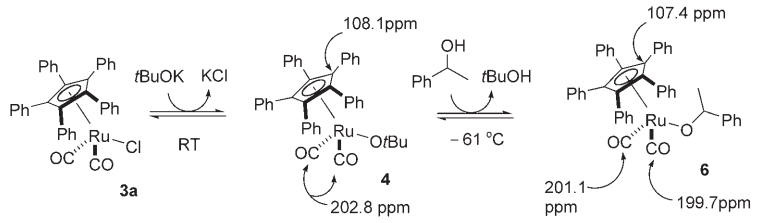
Studies on *sec*-alkoxide formation and ligand substitution reactions: In our previous study on catalytic racemization of (*S*)-1-phenylethanol [(*S*)-**5**], we proposed the formation of secondary alkoxide Ru complex (*S*)-**6** by alkoxide substitution of the *tert*-butoxide ligand of **4** with (*S*)-1-phenylethanol.[5b] We envisioned that similarly to *tert*-butoxide complex **4**, a secondary ruthenium alkoxide (i.e., **6**) could also be formed directly from Ru–chloride **3a** by reaction with lithium α-phenylethoxide. Thus, a catalytic amount of *n*BuLi was added to a solution of (*S*)-**5** in toluene, and after 6 min catalytic amounts of Ru–chloride **3a** were added (Scheme 4). The reaction mixture immediately turned dark red, which is a clear indication for the formation of a Ru–alkoxide complex (ruthenium *tert*-butoxide complex **4** in toluene gives a red solution). After less than 3 min at room



Scheme 4.

temperature, analysis by chiral GC showed that complete racemization had occurred (*ee* = 0).

To obtain further insight into the mechanism of the racemization, *sec*-alkoxide complex **6** was characterized by NMR spectroscopy at low temperatures. Complex **3a** was mixed with a slight excess of *t*BuOK in an NMR tube in [D_8]toluene at room temperature. Once *tert*-butoxide complex **4** had been formed, as confirmed by ^{13}C NMR spectroscopy, the NMR tube was cooled down in a liquid nitrogen bath. Then, 1 equiv of 1-phenylethanol (**5**) was added. After less than 5 min at −61 °C the formation of a new complex, assigned as complex **6**, was observed by ^{1}H NMR spectroscopy. A very poorly resolved quartet and a broad singlet appeared at δ 5.07 and 3.71 ppm, respectively. The former was assigned as the benzylic proton of complex **6**, and the latter as the O*H* group of *t*BuOH, which is produced after the substitution reaction (Figure 1, Scheme 5). A small broad peak at δ 4.9 ppm was also observed; this signal was assigned as the benzylic proton of the remaining 1-phenylethanol.



Scheme 5.

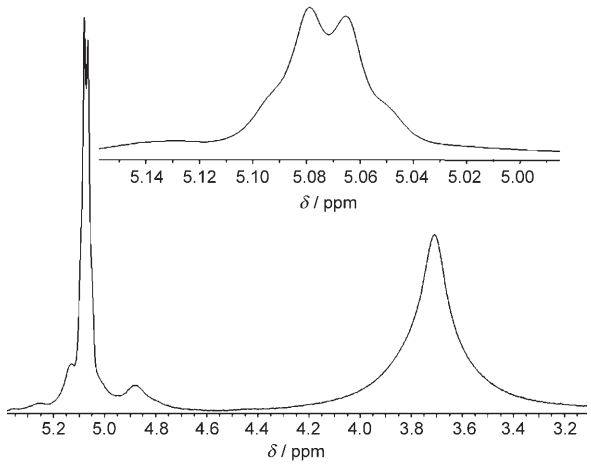


Figure 1. ^{1}H NMR of the reaction of Ru-O*t*Bu complex (**4**) with 1-phenylethanol (**5**, 1 equiv) at −61 °C in [D_8]toluene.

Surprisingly, no hydride resonance was observed at this temperature, which may be due to one of the following reasons: i) β-hydride elimination is inhibited at low temperature, or ii) any hydridic intermediate is not observed on the NMR time scale. The ^{13}C NMR spectrum of this mixture also confirmed the formation of a new complex. Two peaks appeared in the region corresponding to the quaternary carbon of the cyclopentadienyl ring (typically 106–112 ppm). The minor signal (about 20%) arises from the Cp ring of *tert*-butoxide–Ru complex **4** (108.14 ppm), and the major one (about 80%) was assigned to the Cp ring carbons of the newly formed complex **6** (107.38 ppm). Furthermore, the new complex showed two different resonances for the CO groups (201.1 and 199.7 ppm). This is consistent with coordination of the chiral *sec*-alkoxide to the Ru center, which makes the carbonyl groups diastereotopic. The carbonyl resonances were clearly distinguishable from those of the CO resonances of complex **4**, which appear together as one peak at 202.8 ppm (Scheme 5). The resonances corresponding to *t*BuOH were also observed in the ^{13}C NMR spectrum (31.3 and 68.2 ppm), providing further evidence in support of the alkoxide exchange.

Addition of another equivalent of 1-phenylethanol (**5**) to the NMR tube resulted in a shift of the equilibrium towards **6**;[10] the only alkoxide complex detected by ^{13}C NMR spectroscopy was ruthenium complex **6**. The signals from **6** were accompanied by the two peaks from *t*BuOH, and broad resonances from 1-phenylethanol (**5**). The observation of broad resonances in the ^{13}C NMR spectrum of **5** suggests the involvement of a fast exchange process. In the ^{1}H NMR spectrum of the same reaction mixture the intensity of the broad singlet at 4.8 ppm, corresponding to free 1-phenylethanol (**5**), increased (Figure 2a). The poorly resolved quartet (ben-

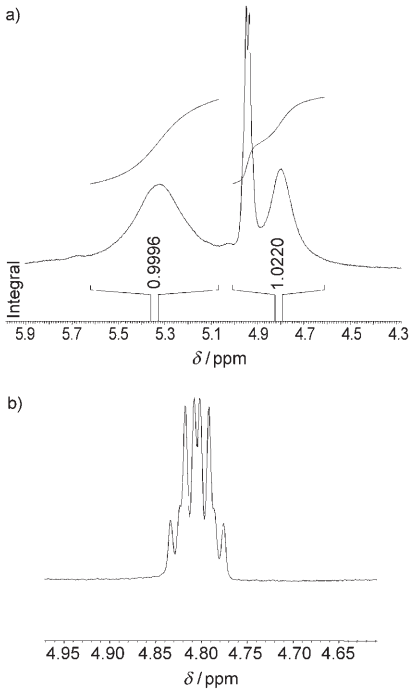
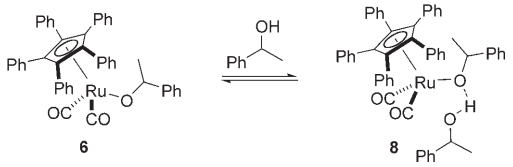


Figure 2. a) ^{1}H NMR spectrum of the reaction of Ru-O*t*Bu complex (**4**) with 1-phenylethanol (**5**, 2 equiv) at −61 °C in [D_8]toluene. b) ^{1}H NMR spectrum of 1-phenylethanol (**5**) in [D_8]toluene at −61 °C.

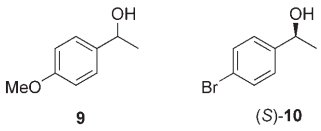
zylic proton of coordinated 1-phenylethoxide) moved slightly upfield (4.95 ppm). Surprisingly, the ^{1}H NMR spectrum of a pure sample of 1-phenylethanol at −61 °C shows a nicely resolved multiplet (dq) at δ 4.8 ppm (benzylic proton) (Figure 2b), and a broad singlet at 2.6 ppm (O*H*). The dramatic downfield shift of the O*H* resonance of **5** in the experiment (5.3 ppm, which appears together with the O*H* resonance of *t*BuOH), compared with that of a pure sample of **5** (2.6 ppm) at the same temperature, and the fact that the benzylic proton of free alcohol **5** in the experiment appears as a broad singlet, clearly indicate that there is a fast exchange process where the excess of 1-phenylethanol (**5**) is interacting with ruthenium complex **6** (Figure 2a). The interaction probably takes place through hydrogen bonding (**8**, Scheme 6).[11,12] It is well known that a temperature decrease leads to a spectacular strengthening of hydrogen bonding, and δ_H of the bridging protons usually reach high values.[13]



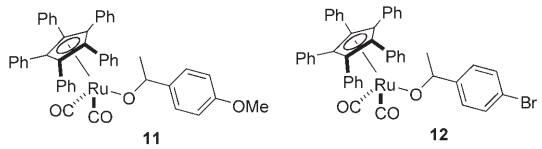
Scheme 6.

When *tert*-butoxide–Ru complex **4** was allowed to react with 6 equiv of 1-phenylethanol at −61 °C, only one peak at δ 4.5 ppm was observed for the benzylic protons of both coordinated *sec*-alkoxide and free 1-phenylethanol, indicating a faster dynamic alkoxide exchange when the amount of 1-phenylethanol (**5**) is increased. The O*H* group was observed at δ 5.9 ppm.

Similar experiments were performed with two other *sec*-alcohols, *rac*-1-(4′-methoxyphenyl)ethanol (**9**), and (*S*)-1-(4′-bromophenyl)ethanol [(*S*)-**10**].



In both experiments, an excess of the alcohol (2 equiv) was added to a solution of *tert*-butoxide–Ru complex (**4**), which had been previously cooled down in a liquid nitrogen bath. The spectra were recorded at −50 °C. In the case of alcohol **9**, the results were comparable to those obtained for 1-phenylethanol, and *sec*-alkoxide **11** was characterized by ^{13}C NMR spectroscopy. However, for the electron-deficient alcohol [(*S*)-**10**], the ^{13}C NMR spectrum showed a mixture of complex **4** and the newly formed *sec*-alkoxide **12**. The reaction shifted towards **12** when the temperature was raised to 0 °C. Importantly, *sec*-alkoxides **11** and **12** in each case showed two different resonances for the CO groups, confirming coordination of the chiral alkoxides to the Ru atom. Five more equivalents of (*S*)-**10** were added to the NMR tube containing complex **12** at room temperature. After 10 min the reaction mixture was worked-up. Analysis by chiral gas chromatography showed that complete alcohol racemization had occurred (*ee* = 0).



The above results clearly indicate that the substrate coordinates to the ruthenium atom, and that in the alkoxide substitution reaction the incoming alcohol interacts with the alkoxide through hydrogen bonding.[11,12,14,15] The fact that two different CO resonances are observed in each of the ^{13}C NMR spectra of complexes **6**, **11**, and **12** is consistent with that CO dissociation does not take place. To further confirm that CO dissociation does not occur, we followed the reaction sequence **3a** → **4** → **6** by in situ IR spectroscopy.[16] The IR spectrum of a solution of **3a** in toluene showed two bands at $\tilde{\nu}$ 1999 and 2048 cm^{-1} for the CO groups. When a slight excess of *t*BuOK (1.3 equiv, 0.5 M in THF) was added to the flask, these two bands immediately disappeared (within seconds) and the reaction mixture changed from yellow to red. Two new bands for the CO groups appeared at $\tilde{\nu}$ 1962 and 2018 cm^{-1} corresponding to complex **4**. After a few minutes, (*S*)-1-phenylethanol [(*S*)-**5**, 1 equiv] was added. Once again, the reaction took place within a few seconds, and complex **6** was formed, showing CO stretching frequencies of $\tilde{\nu}$ 1970 and 2024 cm^{-1}. Complex **6** gradually decomposed, probably due to the presence of water (humidity) in the probe (Figure 3). After work-up, GC analysis showed that racemization had taken place. All the three complexes (**3a**, **4**, and **6**) observed using IR spectroscopy showed two bands due to the symmetric and asymmetric stretch of two CO ligands, indicating the *cis* configuration of the CO groups into the octahedral Ru^{II} complexes. No stretching frequency of free CO (2143 cm^{-1}) was detected. These results are consistent with a mechanism without dissociation of CO.

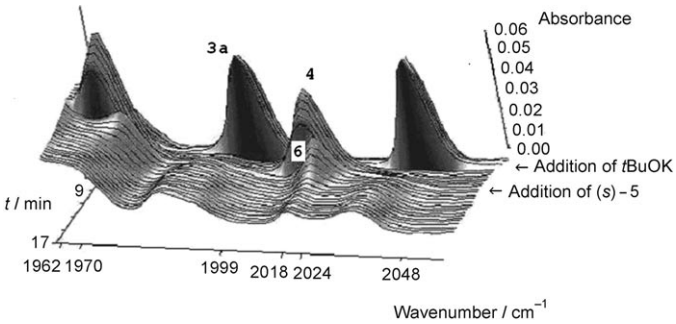
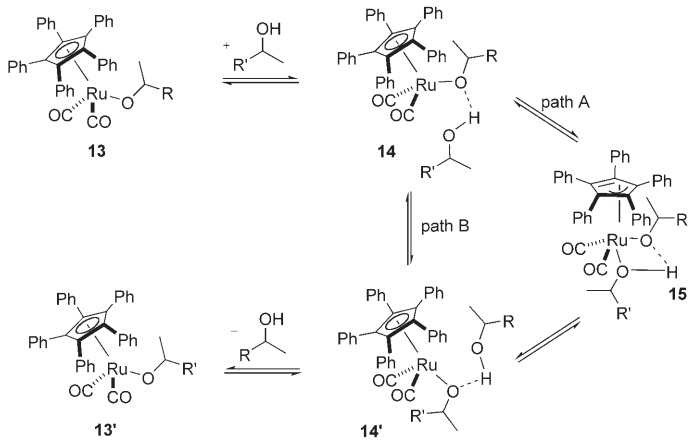


Figure 3. ^{1}H NMR spectrum of the reaction of Ru-Cl complex (**3a**) with *t*BuOK, followed by addition of (*S*)-**5**.

An ionic dissociation of the alkoxide (Scheme 2, steps ii and v) seems unlikely since enantiopure esters are produced under DKR conditions (cf. Scheme 1): If free alkoxide were formed in the racemization process involved in the DKR of Scheme 1, it is expected that non-enantioselective chemical acylation of the alcohol by the acylating agent (isopropenyl acetate) would occur. Indeed, the use of a large excess of *t*BuOK in the DKR process according to Scheme 1 led to ester products of very low enantiomeric excess.[5]

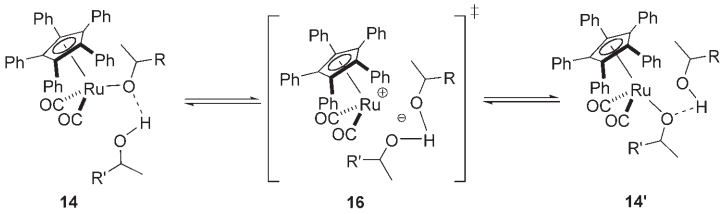
Two mechanisms are considered for the alkoxide exchange reaction (paths A and B, Scheme 7). In both mechanisms, the incoming alcohol interacts with alkoxide **13** through hydrogen bonding (**14**). In the associative mechanism (path A) the incoming hydrogen bonded alcohol coordinates to the Ru center to give **15**. To avoid breaking the 18e rule, the η^5-C_5Ph_5 ring would have to change hapticity to η^3 to accommodate this new ligand.[17] Phenyl groups on the cyclopentadienyl are known to favor η^5 to η^3 ring slip since they stabilize the η^3 intermediate by conjugation with the aromatic rings.[18] Furthermore, Kirchner et al. have characterized η^3-cyclopentadienylruthenium complexes by NMR spectroscopy,[19] which were formed by reaction of η^5-cyclopentadienylruthenium complexes with PMe_3.



Scheme 7.

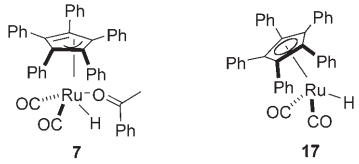
In the displacement mechanism (**14** → **14′**), the hydrogen bonded alcohol attacks ruthenium with displacement of the alkoxide in an S_Ni-type mechanism (path B, Scheme 7).[20,21] This would involve transition state **16** (Scheme 8). In this mechanism a ring slip is avoided and the cyclopentadienyl ring would stay η^5 during the exchange.

Study of the β-hydride elimination step and formation of ketone intermediates: Various mechanisms have been proposed for Ru-catalyzed hydrogen transfer involving alcohols/ketones and amines/imines,[9c,d,22–24] a transformation involved in the Ru-catalyzed racemization of alcohols and amines. In some of those mechanisms the substrate is coordinated to the Ru center prior to hydrogen transfer,[1c,22,23] whereas in other mechanisms it is suggested that the substrate is hydrogenated/dehydrogenated outside the coordination sphere of the Ru.[9c,d,22,25] In some instances, it is difficult to determine whether hydrogen transfer occurs inside or outside the coordination sphere of the metal.[6a,c,24]



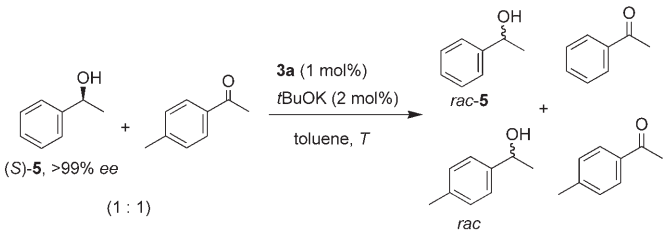
Scheme 8. Path B of Scheme 7.

We have previously proposed that the most likely pathway for the racemization of alcohols catalyzed by **3a** and **3b** involves β-hydride elimination from an alkoxide complex to give a η^3-Ph_5C_5 hydride ketone ruthenium complex (**7**) (step ii, Scheme 2) that undergoes reversible insertion (step iii, Scheme 2).[5,26] Thus, the ketone stays coordinated to the metal center and does not leave the coordination sphere. The very long induction period (2.5 h) in the racemization catalyzed by η^5-Ph_5C_5 ruthenium hydride **17** in the presence of a catalytic amount of acetophenone indicates that the latter complex is not an abundant catalytic species in the racemization.[5b] If hydride **17** were an intermediate, the high rate of the racemization would require it to add fast to the ketone and generate the fast alkoxide racemization catalyst, which is not observed.



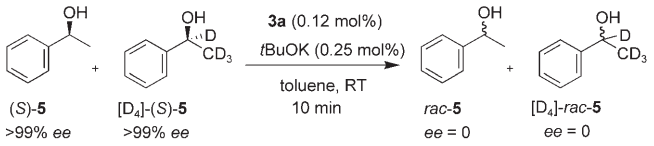
This conclusion was supported by the lack of ketone exchange in the racemization of (*S*)-**5** performed in the presence of *p*-tolyl methyl ketone (1 equiv) at ambient temperature (Scheme 9). After 5 min, complete racemization of (*S*)-**5** to *rac*-**5** had occurred but only 1% of the added ketone had been converted to alcohol [1-(*p*-tolyl)ethanol] (about 3% of acetophenone was also observed).[5b] When the same experiment was performed at 80°C, considerable amounts of the added ketone (*p*-tolyl methyl ketone) had been converted to 1-(*p*-tolyl)ethanol (35%) after only 5 min (similar amount of acetophenone was also produced). This percentage increased very slowly with time (39% after 120 min). Thus, when the temperature is increased there is more ketone dissociation, which can be explained by an entropy effect.

To further confirm that the substrate stays coordinated to Ru (as an alcohol or ketone) throughout the racemization cycle at room temperature, we have performed racemization of a 1:1 mixture of (*S*)-**5** and [D_4]-(*S*)-**5** (Scheme 10). The



Scheme 9. Crossover experiment: racemization of (*S*)-**5** in the presence of 1 equiv of *p*-tolyl methyl ketone.

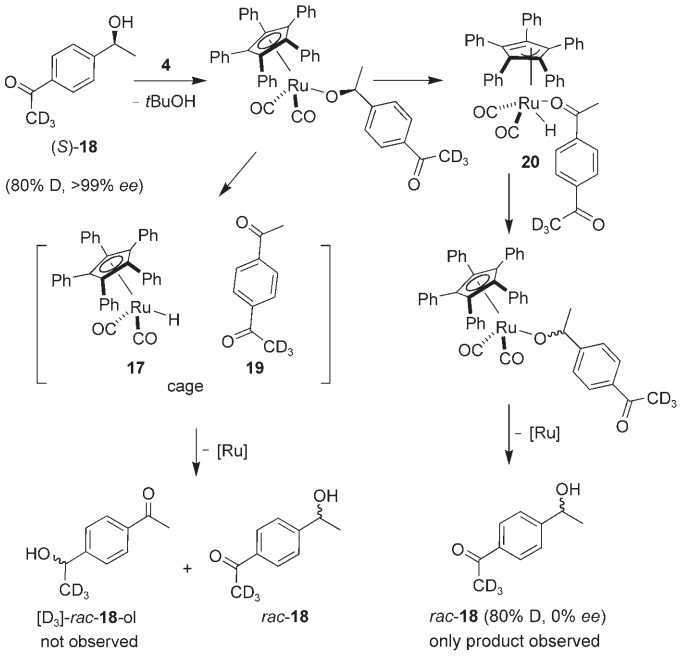
racemization reaction was followed by GC. It was found that complete racemization had occurred within 10 min. Furthermore, neither $PhCH(OH)CD_3$ ([D_4]-*rac*-**5**) nor $PhCD(OH)CH_3$ ([α-D]-*rac*-**5**) could be detected in the ^1H NMR spectrum, which shows that no crossover of deuterium had occurred. These results require that the intermediate ketone stays coordinated to the metal center and do not leave the coordination sphere.



Scheme 10. Racemization of a 1:1 mixture of (*S*)-**5** and [D_4]-(*S*)-**5**.

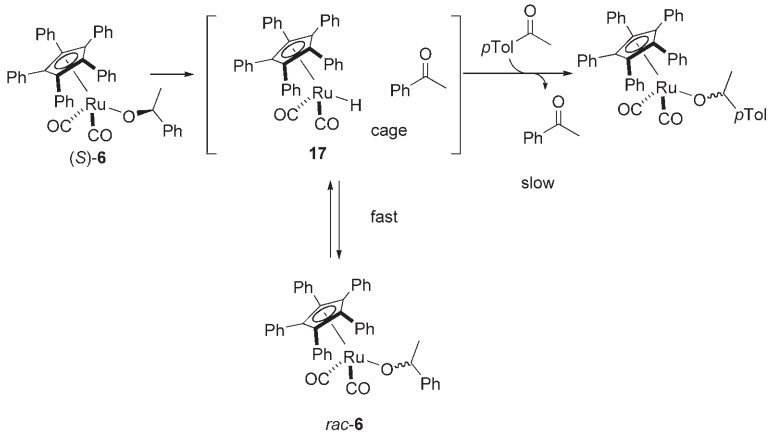
An alternative mechanism that could also explain the lack of ketone exchange or crossover of deuterium at room temperature is shown in Scheme 11:[27] if after β-hydride elimination from the alkoxide complex **6**, the newly generated ketone stays in the solvent cage due to slow diffusion, and immediately inserts into the Ru–H bond, exchange with an external ketone would not take place.

To provide persuasive evidence that such a mechanism is not operating, we studied the racemization of substrate (*S*)-**18** which contains a ketone moiety within the same molecule. If the ketone produced after β-hydride elimination from the alkoxide complex does not stay coordinated to ruthenium before migratory insertion, but it is trapped in the solvent cage, either the α-deuterated or the nondeuterated carbonyl group of diketone **19** could be attacked by the hydride to give the product (Scheme 12).



Scheme 12.

Racemization of (*S*)-**18** (80% D) was carried out using 0.5 mol% of ruthenium complex **3a** and 0.6 mol% of *t*BuOK. GC analysis showed that complete racemization had occurred after 30 min ($ee = 0$). Furthermore, ^1H NMR analysis showed that *rac*-**18** contained the same degree of deuterium at the α-carbon of the carbonyl group as in the starting (*S*)-**18** (80% D) and no deuterium at the β-carbon of the alcohol could be detected (Scheme 12). The fact that the α-deuterated carbonyl group is not reduced indicates that the ketone produced after β-hydride elimination from a Ru–alkoxide stays coordinated to the ruthenium atom in complex **20**, thus providing strong support for a ring slip mechanism via a η^3-Ph_5C_5 hydride ketone ruthenium complex intermediate (cf. **7** in Scheme 2). Recently, experimental[23a] as well as theoretical[28] support was provided for a ring slip mechanism in hydrogen transfer from hydroxycyclopentadienyl ruthenium hydride com-

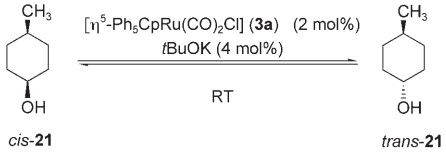


Scheme 11.

plexes to imines and the reversible β-elimination of coordinated amine.

From the mechanistic studies using NMR spectroscopy, it was concluded that the alkoxide exchange reaction (step ii, Scheme 2) is rapid at very low temperature (−61 °C) (see above). However, from these experiments it was not possible to determine if racemization occurs at this low temperature. No resonances from Ru-H intermediates could be detected. Two possible explanations can account for this observation: i) β-hydride elimination does not take place at low temperatures, or ii) β-hydride elimination takes place, but the Ru–H intermediate cannot be observed due to a fast readdition of the hydride to the ketone (very fast migratory insertion, step iv, Scheme 2). We therefore studied the epimerization of *cis*-4-methylcyclohexanol (*cis*-**21**) with the catalytic system **3a**/*t*BuOK by ^{1}H NMR spectroscopy at low temperatures. The two diastereoisomers, *cis*-**21** and *trans*-**21**, can be readily distinguished from one another by ^{1}H NMR spectroscopy.

The epimerization of *cis*-**21** was first studied at room temperature using catalytic amounts of ruthenium complex [η^5-$Cp(Ph)_5Ru(CO)_2Cl$] (**3a**) (2 mol %) and *t*BuOK (4 mol %) (Scheme 13). After five minutes, GC and NMR analyses showed a mixture of alcohols *cis*-**21** and *trans*-**21** in a 26:74 ratio. Prolonged reaction time did not change this ratio, indicating that the equilibrium had been reached. When the epimerization was studied starting from *trans*-**21** under identical reaction conditions, the same *cis*/*trans* ratio (26:74) of alcohol **21** was obtained after five minutes.



Scheme 13.

Then, the reaction shown in Scheme 13 was studied in an NMR tube at −50 °C starting from *cis*-**21**. The first recording after ca 10 min showed *cis*-**21** and *trans*-**21** in a ratio of 30:70 (Figure 4a). When the ^{1}H NMR spectrum was recorded after 2 h, the 30:70 mixture had been transformed into a 19:81 *cis*/*trans* mixture (Figure 4b).[29] This experiment shows that the ruthenium-catalyzed isomerization of *sec*-alcohols (racemization, epimerization) occurs quite fast at −50 °C. No hydride resonances were observed in the expected region, around −10 ppm during epimerization of *cis*-**21** at −50 °C.[30] The failure to observe hydride resonances by ^{1}H NMR suggests that the β-hydride elimination and readdition of the hydride are very fast processes on the NMR time scale.

It is also of interest to determine if the β-hydride elimination is the rate-determining step in the racemization mechanism of secondary alcohols catalyzed by Ru complex **3a**. To determine the kinetic deuterium isotope effect, we racemized a 1:1 mixture of alcohols (*S*)-**5** and [α-D]-(*S*)-**5**

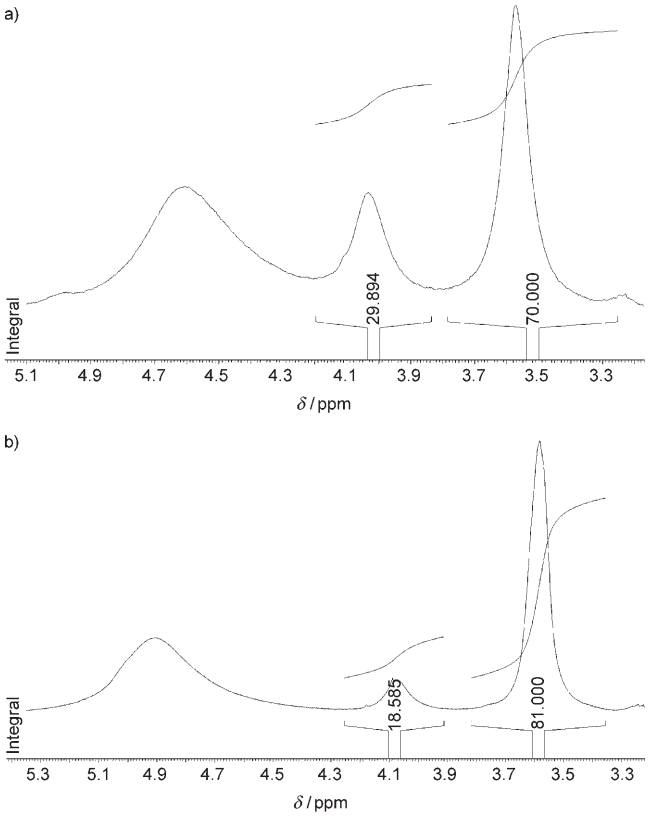
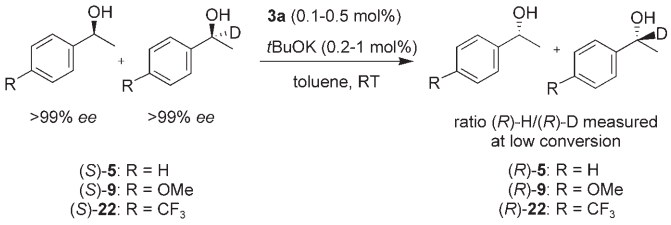


Figure 4. a) ^{1}H NMR spectrum of *cis*-4-methylcyclohexanol (*cis*-**21**) and *trans*-4-methylcyclohexanol (*trans*-**21**) in a 30:70 ratio at −50 °C in [D_8]toluene. δ_{CHOH} = 4.0 (*cis*) and 3.5 ppm (*trans*), δ_{CHOH} ≈ 4.6–4.9 ppm (*cis* + *trans*). b) ^{1}H NMR spectrum of a thermodynamic mixture of *cis*- and *trans*-**21** (19:81) was obtained at −50 °C within about 2 h in the presence of the ruthenium complex. δ_{CHOH} = 4.0 (*cis*) and 3.5 ppm (*trans*), δ_{CHOH} ≈ 4.6–4.9 ppm (*cis* + *trans*).

(Scheme 14), and measured the ratio of (*R*)-**5** and [α-D]-(*R*)-**5** at very low conversion (less than 12 % of racemization). This was done by the use of a GC-MS method where



Scheme 14.

a chiral GC was coupled to the mass spectrometer. The peak of the *R* enantiomer could then be analyzed for its deuterium content. Similar studies were performed with two other *sec*-alcohols with different electronic properties, methoxy-substituted alcohol **9** and trifluromethyl-substituted alcohol **22**.

A moderate isotope effect was observed for the racemization of 1-phenylethanol (**5**) (see Table 1). Interestingly, for

the more electron rich alcohol **9**, a negligible isotope effect was obtained, which suggests that the relative rate of β-hydride elimination has increased compared to the unsubstituted case. For the electron-deficient alcohol **22**, on the other hand, the isotope effect was larger. This shows that for the more electron-deficient alcohol the β-hydride elimination step becomes more rate-determining than for the more electron-rich ones. This is in accordance with the slower rate for oxidation (dehydrogenation) of benzylic alcohols with electron-deficient groups in the *p*-position compared with those with an electron-donating group in the *p*-position.[31,32]

Table 1. Kinetic isotope effects for racemization of secondary alcohols by **3a**.[a]

Entry	Compound	R	k_H/k_D[b]
1	(*S*)-**5**	H	1.27 ± 0.06
2	(*S*)-**9**	OMe	1.08 ± 0.17
3	(*S*)-**22**	CF_3	1.45 ± 0.13

[a] The reaction was run in toluene (1.0 mL) under an argon atmosphere using 0.1–0.5 mol% of **3a** and a 1:1 mixture of deuterated and nondeuterated alcohol (1–2 mmol). The reaction mixtures were analyzed by GC-MS (chiral GC). [b] Average of at least three measurements on each sample.

Conclusion

The mechanistic studies presented provide a detailed picture of secondary alcohols racemization catalyzed by pentaphenylcyclopentadienyl–ruthenium complex **3a**, and demonstrate for the first time the intermediacy of ruthenium secondary alkoxide complex. The racemization cycle begins with the activation of ruthenium chloride complex **3a** by *t*BuOK, to give a tertiary alkoxide (**4**). Reaction of **4** with the secondary alcohol produces a secondary ruthenium alkoxide. In this step there is no CO dissociation. The most likely pathway for racemization involves β-elimination from the *sec*-alkoxide complex to give a hydride ketone intermediate, in which the cyclopentadienyl ligand coordinates in a η^3 mode to the ruthenium center. This intermediate undergoes a fast reversible insertion. Convincing evidence for a racemization mechanism inside the metal coordination sphere was provided by the racemization of a secondary alcohol with a ketone moiety in the same molecule, which did not lead to any reduction of the ketone. Furthermore, isotope labeling of the alcohol substrate in competitive experiments confirms the mechanism in which the substrate (as an alcohol or as a ketone) stays in the coordination sphere of ruthenium throughout the racemization cycle. From the study of the β-hydride elimination step at low temperature, it was concluded that readdition of the hydride to the ketone intermediate takes place quickly. The isotope effect found for the racemization shows that the β-hydride elimination step becomes more rate-determining for electron-deficient secondary alcohols.

Experimental Section

All reactions were carried out under dry argon atmosphere in flame-dried glassware. Solvents were purified by standard procedures. Flash chromatography was carried out on 60 Å (35–70 μm) silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 300 MHz and at 100 or 75 MHz, respectively. Chemical shifts (δ) were reported in ppm, using the residual solvent peak in $CDCl_3$ (δ_H 7.26 and δ_C 77.00) or in [D_8]toluene (δ_H 2.09 and δ_C 20.4) as internal standard, and coupling constants (J) are given in Hz. Enantiomeric excess were determined by analytical gas chromatography employing a CP-Chirasil-Dex CB column, using racemic compounds as references.

Formation of [(η^5-Ph_5Cp)Ru(CO)$_2$(O*t*Bu)] (4) and reaction with 1-phenylethanol: **[(η^5-Ph_5Cp)Ru(CO)$_2$(1-phenylethoxide)] (6)**: A solution of *t*BuOK in THF (82 μL, 0.04 mmol; 0.5 M) was added to an NMR tube. The THF was evaporated under reduced pressure. Then [(η^5-Ph_5Cp)Ru(CO)$_2$Cl] (**3a**) (20 mg, 0.03 mmol) was placed in the NMR tube. The tube was evacuated and filled with argon before adding dry [D_8]toluene (0.5 mL). The tube was shaken vigorously and a fine new precipitate of KCl was formed and allowed to settle. The quantitative formation of complex **4** was observed by ^{13}C NMR spectroscopy:[5] ^{13}C NMR ([D_8]toluene, 75 MHz, −61 °C) (selected peaks): δ = 202.79, 108.16, 73.11, 34.16 ppm. The NMR tube was cooled down in a liquid nitrogen bath. Then a solution of 1-phenylethanol (1.1 equiv, 46 μL, 0.092 mmol; 0.753 M in [D_8]toluene) was added. At −61 °C the formation of complex **6** was observed by ^{13}C NMR spectroscopy in less than 4 min (the NMR spectrum showed a mixture of **4**/**6** in a 1:4 ratio). After addition of another equiv of 1-phenylethanol complex **6** was the only complex observed by ^{13}C NMR spectroscopy: ^{13}C NMR ([D_8]toluene, 75 MHz, −61 °C) (selected peaks): δ = 201.08 (CO), 199.69 (CO), 152.68 (*ipso* C of 1-phenylethoxide), 107.38 (quaternary carbon of Cp ligand), 85.77 (CH_3CH(O)Ph), 30.94 ppm (CH_3). The resonances of the 1-phenylethoxide ligand differ from those of 1-phenylethanol in [D_8]toluene at −61 °C (δ 146.75 (*ipso* C), 69.98 (CH_3CH(OH)Ph), 25.82 ppm (CH_3).

Formation of 4 and reaction with 1-(4-methoxyphenyl)ethanol: **[(η^5-Ph_5Cp)Ru(CO)$_2$[1-(4-methoxy)phenylethoxide)] (11)**: Similarly to the generation of complex **6**, a solution of 1-(4-methoxyphenyl)ethanol (**9**) (2 equiv, 71 μL, 0.06 mmol; 0.876 M in [D_8]toluene) was added to a cooled (liquid nitrogen bath) freshly prepared solution of complex **4**. Complex **11** was formed in less than 5 min at −48 °C: ^{13}C NMR ([D_8]toluene, 75 MHz, −48 °C) (selected peaks): δ = 201.13 (CO), 199.68 (CO), 159.24 (*C*-OMe), 144.53 (*ipso* C of 1-(4-methoxyphenyl)ethoxide), 113.74 [*C*-C-(OMe)], 107.39 (quaternary carbon of Cp ligand), 85.05 (CH_3CH(O)Ar), 54.31 (OMe), 31.10 ppm (CH_3).

Formation of 4 and reaction with 1-(4-bromophenyl)ethanol: **[(η^5-Ph_5Cp)Ru(CO)$_2$[1-(4-bromo)phenylethoxide)] (12)**: A solution of (*S*)-1-(4-bromophenyl)ethanol (**10**) (2 equiv, 71 μL, 0.06 mmol; 0.878 M in [D_8]toluene) was added to a cooled (liquid nitrogen bath) freshly prepared solution of **4**. After 5 min at −48 °C, ^{13}C NMR showed a mixture of **12** and **4**. The equilibrium did not shift to **12** until the temperature was raised to −10 °C: ^{13}C NMR ([D_8]toluene, 75 MHz, 25 °C) (selected peaks): δ = 201.07 (CO), 199.98 (CO), 151.60 (*ipso* C of 1-(4-bromophenyl)ethoxide), 120.46 (*C*-Br), 108.02 (quaternary carbon of Cp ligand), 84.88 (CH_3CH(O)Ar), 30.06 ppm (CH_3).

In situ IR spectroscopy

Formation of 4 and reaction with 1-phenylethanol to yield complex 6: Toluene (3 mL) was added to a two-necked flask containing ruthenium chloride **3a** (40 mg, 0.063 mmol). A yellow solution was formed. The IR showed two bands at $\tilde{\nu}$ 1999 and 2048 cm^{-1} for the CO groups of **3a**. A solution of *t*BuOK (0.5 M in THF; 164 μL, 0.09 mmol) was added under an argon atmosphere. The reaction mixture immediately turned red. Two new bands appeared at $\tilde{\nu}$ 1962 and 2018 cm^{-1} corresponding to **4**. Then, (*S*)-**5** (0.753 M in toluene; 83 μL, 0.063 mmol) was added. Once again, the reaction took place within few seconds, and **6** was formed, showing stretching frequencies of 1970 and 2024 cm^{-1}.

General procedure for racemization of (*S*)-5 catalyzed by ruthenium–halide complexes: To a Schlenk type flask containing Ru complex **3a**

(3.2 mg, 0.005 mmol) in toluene (2 mL), a solution of *t*BuOK (0.5 M in THF; 20 μL, 0.01 mmol) was added under an argon atmosphere. After 6 min, (*S*)-1-phenylethanol (120 μL, 1 mmol) was added. Samples of the reaction mixture were collected under a rigorous argon atmosphere and analyzed by chiral GC. After 30 min, chiral GC analysis showed complete racemization of 1-phenylethanol.

Preparation of 1-[4-[(1*R*)-1-hydroxyethyl]phenyl]-(2-[D_3])-ethanone [(*S*)-18]:[33] 1-[4-(1-Hydroxyethyl)phenyl]-ethanone[34] (1.43 g, 8.7 mmol), NaOH (0.035 g, 0.87 mmol) and D_2O (6 mL, 300 mmol) were stirred at room temperature under an argon atmosphere during 19 h. The reaction mixture was extracted with dry Et_2O (5×6 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was treated with *Candida antarctica* lipase B (CALB) (0.244 g) and isopropenyl acetate (2.7 mL, 24.3 mmol) in toluene (10 mL) under an argon atmosphere. After 2 h, the enzyme was filtered off, and the solvent evaporated. After purification by column chromatography (silica gel, pentane/EtOAc 4:1) (*S*)-**18** (0.676 g, 46%) was obtained as a colorless liquid in >99% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.94 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 4.97 (q, J = 6.7 Hz, 1H), 2.59 (m, 0.60H), 1.93 (br s, 1H), 1.51 ppm (d, J = 6.7 Hz, 3H). The integral at δ = 2.59 indicate a deuteration degree of 80%.

Determination of the deuterium isotope effect in racemization of (*S*)-1-arylethanols: Deuterium isotope effect for racemization of (*S*)-1-phenylethanol. Ruthenium catalyst **3a** (0.13 mol%) was dissolved in toluene (0.5 mL) under an argon atmosphere. A solution of *t*BuOK (0.25 M in THF, 0.26 mol%) was added. After 6 min, a solution of a 1:1 mixture (2 mmol) of deuterated and nondeuterated alcohol ([D]-(*S*)-**5** and (*S*)-**5**) in toluene (0.5 mL) was added. The reaction was quenched with dilute HCl at <12% conversion to the *R* alcohol. The reaction mixture was analyzed by GC-MS using a chiral column connected to the mass spectrometer and from the deuterium content in the *R* alcohol a kinetic isotope effect k_H/k_D of 1.27±0.06 was obtained.

Acknowledgements

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