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Ligand effect in racemization and dynamic kinetic resolution of alcohols: Mechanism on cymene ruthenium complexes

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ABSTRACT

A family of ruthenium complexes with different ligands was utilized in racemization of (*R*)-1-phenylethanol to investigate the potential influence of the ligands coordinated to the ruthenium center. Kinetic experiments showed that 16-electron cymene ruthenium complex with two chloro-bridge bonds and 18-electron ones with easily dissociative ligands are highly active for catalytic racemization of alcohols. Possible racemization mechanism for cymene ruthenium complexes was then proposed. Computational analysis of dissociation energy barrier, NBO analysis and reaction potential energy surface suggest that ligand-dissociation process is the vital step of the racemization catalyzed by cymene ruthenium complexes. Thereafter, these complexes were applied in the DKR of secondary alcohols to verify their efficiency and applicability.

Introduction

Optically active secondary alcohols are valuable intermediates in the fine chemical industry [1]. The resolution of racemic mixtures is the most convenient way to prepare enantiomerically pure compounds on an industrial scale [2]. The kinetic resolution (KR) of racemic secondary alcohols by enzymes such as lipases and esterases is widely used to obtain a range of enantiomerically enriched alcohols or their esters [3]. However, the theoretical maximum yield (50%) and the laborious separation of product from the remaining substrate are major drawbacks of the KR procedure. Dynamic kinetic resolution (DKR), in which racemization of unwanted enantiomers is coupled with KR, is an attractive method to overcome these drawbacks with theoretical maximum yield up to 100% (Scheme 1).

Shvo and co-workers reported the synthesis of a cyclopentadienyl diruthenium complex, known as Shvo's catalyst, for hydrogen transfer reactions in 1984 [4]. This catalyst was first introduced to efficient DKR of alcohols in combination with *Candida antarctica* lipase B (CALB) by Bäckvall in 1997 [5]. Afterwards, cyclopentadienyl ruthenium derivants bearing CO [3c,6], PPh_3 [7] and carbene [8] ligands have been prepared for successful racemization of secondary alcohols and DKR in some cases. Now there is an increasing demand for systematical study on the ligand effect during racemization [9]. On the other hand, mechanistic studies of the catalytic racemization by cyclopentadienyl ruthenium complexes have attracted extensive attentions in the past few years [8a,10]. Bäckvall and co-workers suggested catalytic racemization generally proceeds via reversible hydrogen transfer reactions [11]. Recently, they revealed the existence of a CO dissociation process to create a vacant site during the dehydrogenation step [12]. Nolan and co-workers demonstrated the importance of the vacant site on the 16-electron ruthenium center [13]. However, racemization mechanism for ruthenium complexes of other structures remains to be studied and confirmed.

We report herein our successful effort to utilize a family of cymene ruthenium complexes to investigate the potential influence of the ligands coordinated to the metal center on the course of racemization and DKR. Possible racemization mechanisms for cymene ruthenium complexes were proposed and verified by experiments along with computational analysis. Two excellent racemization catalysts, including 16- and 18-electron cymene ruthenium complexes, were then investigated in DKR of a variety of secondary alcohols.

Results and discussion

Ligand effect on catalytic racemization

16-Electron cymene ruthenium complexes **1** and 18-electron ones **2**–**6** were chosen for our study. Triphenylphosphine,

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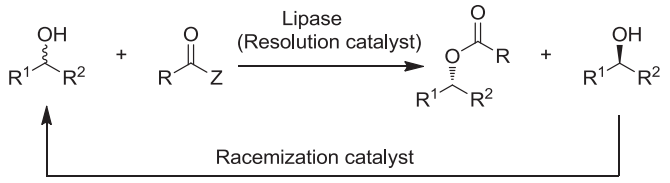


Scheme 1. Schematic DKR of *sec*-alcohols.

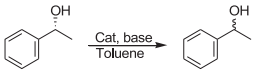
pyridine and N-heterocyclic carbene (NHC) are typical monodentate ligands, while phenanthroline and pentanedione are representative bidentate chelating ligands (Fig. 1). Complexes **2**–**6** were synthesized according to the literature procedures [14].

Since catalytic racemization is vital for efficient DKR, these ruthenium complexes were evaluated using the racemization of (*R*)-1-phenylethanol ((*R*)-**7**) first as template reaction (Table 1). With complex **1** as the model catalyst, ^{t}BuOK is finally chosen as base for racemization after comparison with K_2CO_3, K_3PO_4 and KOH (Entries 1–4). The racemization efficiency is particularly high with ee (ee = enantiomeric excess) getting down below 8% after 24 h (Entry 1). For complexes with monodentate ligands (**2**–**4**), complex **3** with a pyridine ligand performs best with a 13% ee after 24 h (Entry 6). However, catalysts with bidentate chelating ligands (**5**, **6**) racemized less than 20% of (*R*)-**7** after the same time (Entries 8, 9).

Basically, 16-electron complex **1** performs better than 18-electron ones, while complexes with monodentate ligands perform better than that with bidentate chelating ligands. Noticeably, similar complexes with different ligands can perform dissimilarly in racemization.

With the best catalyst **1** and relative good catalysts **2**–**4** in hand, we decided to profile the racemization of (*R*)-**7** with these catalysts to get details of the racemization process, and the results are presented in Fig. 2. As shown in Fig. 2, it took about 350 min for catalyst **1** to racemize 80% of (*R*)-**7**. Among 18-electron catalysts **2**–**4**, catalyst **3** with a pyridine ligand was most efficient and it racemized 80% of (*R*)-**7** within 220 min. After about 500 min, an ee of 20% was achieved by catalyst **2** with a PPh_3 ligand, while catalyst **4** with an NHC ligand is least efficient and only racemized 76% of (*R*)-**7** even after 800 min. Thus the profile also points out that **1** is the best catalyst in our studied ruthenium catalysts.

Table 1
Catalytic racemization of (*R*)-**7** with complexes **1**–**6**.[a]



Entry	Catalyst	Base	ee [%][b]
1	**1**	^{t}BuOK	8
2	**1**	K_2CO_3	30
3	**1**	K_3PO_4	25
4	**1**	KOH	9
5	**2**	^{t}BuOK	17
6	**3**	^{t}BuOK	13
7	**4**	^{t}BuOK	24
8	**5**	^{t}BuOK	97
9	**6**	^{t}BuOK	97

[a] (*R*)-1-Phenylethanol (0.25 mmol), catalyst (Ru: 4 mol%), base (5.0 mol%), 60 °C, toluene (3 mL), 24 h.
[b] On the basis of specific rotation results of two runs.

Mechanism of racemization catalyzed by cymene ruthenium complexes

Based on the mechanism studies on cyclopentadienyl ruthenium complexes [8,10–13] and our experiments, the inner-sphere pathway for the racemization of cymene ruthenium chloride complexes was speculated in which the dissociation of ligand is anticipated to be the key step for 18-electron ruthenium chloride complexes (Scheme 2). Complex **A** was first dehalogenated by potassium *tert*-butoxide (^{t}BuOK), and ruthenium complex **C** formed via a ligand exchange process of complex **B** with alcohol substrate. For 18-electron complexes, a vital ligand-dissociation process took place to form complex **D**. Racemization of **D** was then carried out via β-hydride transfer to the vacant site on ruthenium center, and formed a Ru-hydride intermediate **E**. The ketone was then hydrogenated to form a racemic alcohol.

Quantum-chemical calculations based on the density functional theory (DFT) were used to further prove the mechanism. We focused on the energy barriers required for the loss of ligands first. Calculation results of the energy barriers required for the ligand-dissociation of 18-electron complexes **2**–**4** are shown in Table 2. Ligand-dissociation of **3C** required lower energy, 18.3 kcal/mol, than **2C**, 20.8 kcal/mol, and **4C**, 37.1 kcal/mol in toluene solution. Besides that, the Natural Bond Orbital (NBO) found that the bond

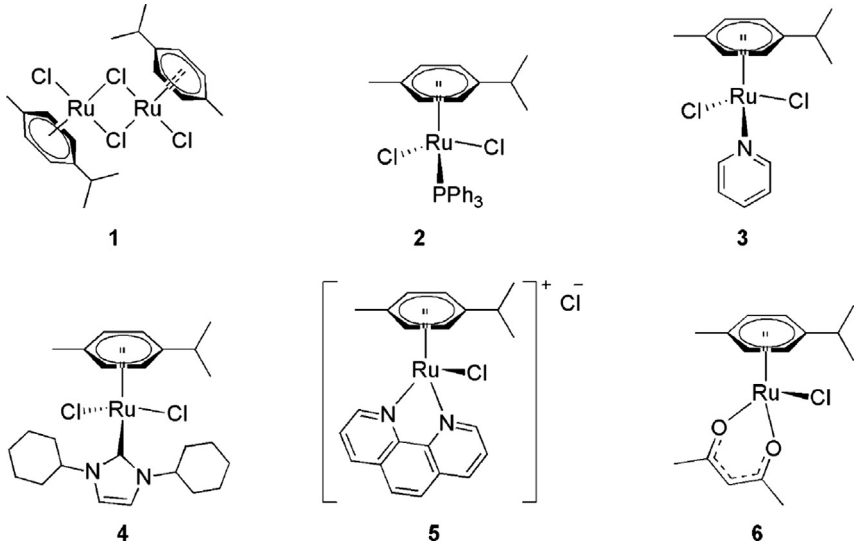


Fig. 1. Ruthenium complexes utilized in racemization and DKR of *sec*-alcohols.

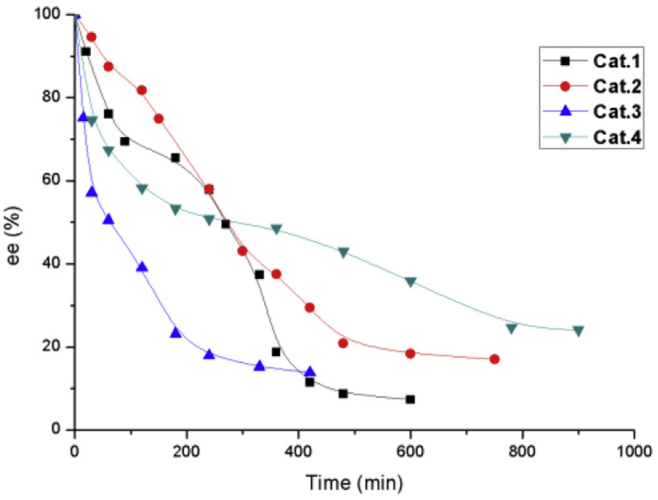
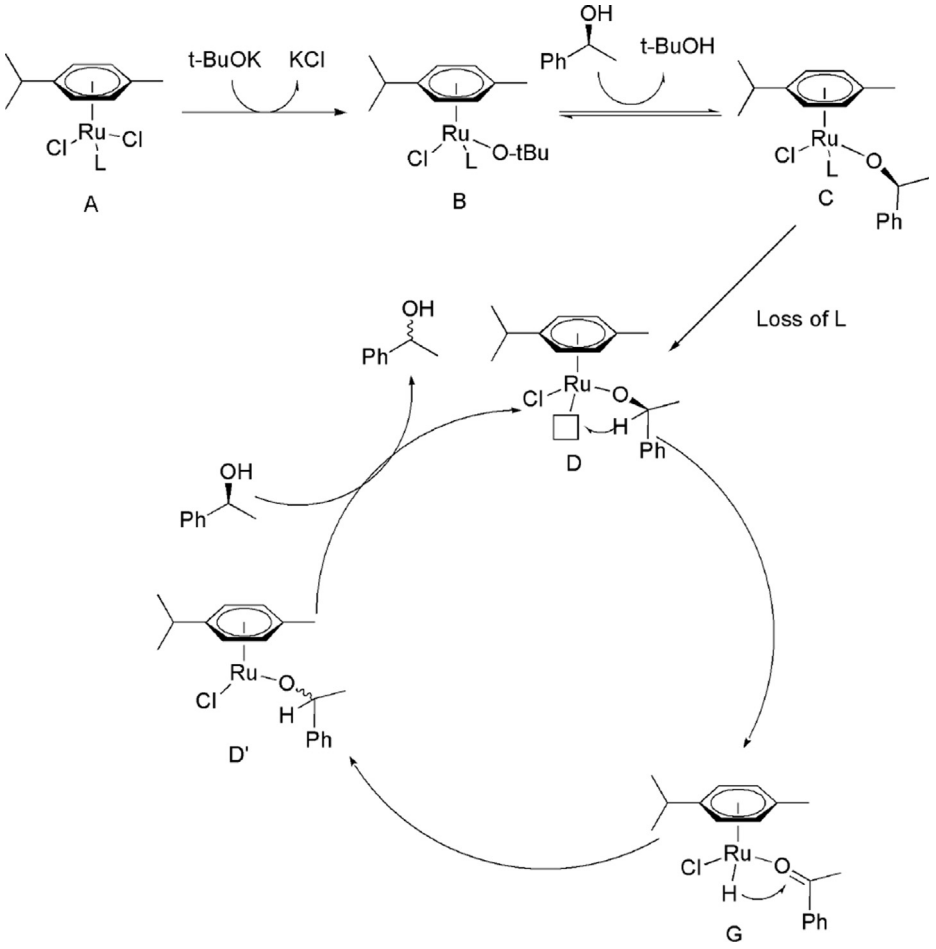


Fig. 2. Kinetic profile for racemization of (*R*)-**7** with catalyst **1**–**4**.

orders of metal-ligand bonds in **2C** (Ru—P bond), **3C** (Ru—N bond) and **4C** (Ru—C bond) are 0.699, 0.499, 0.759, respectively. These results suggest that the Ru—N bond in **3C** is the weakest and most easily broken, while the Ru—C bond in **4C** is the strongest and most difficult to break. Besides, computational analysis of dissociation energy barriers and bond orders is corresponding with their performance in racemization velocity and efficiency, that, **3C** is fastest and most effective. Thus, the computational results verified our anticipation, that ligand-dissociation is the key step of the racemization catalyzed by 18-electron cymene ruthenium complexes. Except that, the Ru—O distance in **1D** is shorter than those in **2C**, **3C**, and **4C**, which is 1.941, 2.090, 2.066, and 2.088 Å respectively (Fig. 3). This may be due to the π-donation by the oxygen lone pair, which would stabilize the 16-electron ruthenium complex **1D** (catalyst **1**) and thus enhance its catalytic efficiency [8]. Summarization of the experimental results in Table 1 and the computational results in Table 2 suggests that 18-electron cymene ruthenium chloride complex will be an excellent racemization catalyst when bearing a weak-bonded ligand on ruthenium center.

A computational analysis of the racemization reaction pathway (**1D**—**1D′**) was undertaken to get insight into the mechanism (Fig. 4). Complex **1D** is the entrypoint into the racemization catalytic cycle and is set as the zero energy point for the following discussion. The C_β—H bond of **1D** engages in a hydrogen bond with chlorine atom in **1E**, and in a β-agostic interaction with the Ru center in **1F**. β-H elimination from **1F** leads to the π-coordinated ketone Ru-hydride complex **1G**. The fact that the energy barriers between β-agostic complex **1F**, π-coordinated complex **1G** and their surrounding transition states are lower than 5 kcal/mol is the evidence that **1G** and **1F** are rather unstable intermediates. Via a barrier of 3.7 kcal/mol, the π-coordinated ketone ruthenium hydride complex **1G** is transformed to the σ-coordinated ketone ruthenium hydride complex **1H**, which is 6.8 kcal/mol more stable than the π-coordinated ketone ruthenium hydride complex **1G**. Complex **1H** is essentially at the midpoint along the racemization



Scheme 2. Proposed mechanism for racemization of chiral alcohols by 18-electron cymene ruthenium chloride complexes.

Table 2
Energy required for ligand-dissociation.

Compound	Barrier (gas phase)/kcal mol^{-1}	Barrier (liquid phase)/kcal mol^{-1}	Ru–P (N or C) bond distance (Å)/bond order	Ru–O/Å
2C	10.7	20.8	2.371/0.699	2.090
3C	10.5	18.3	2.118/0.499	2.066
4C	26.4	37.1	2.066/0.759	2.088

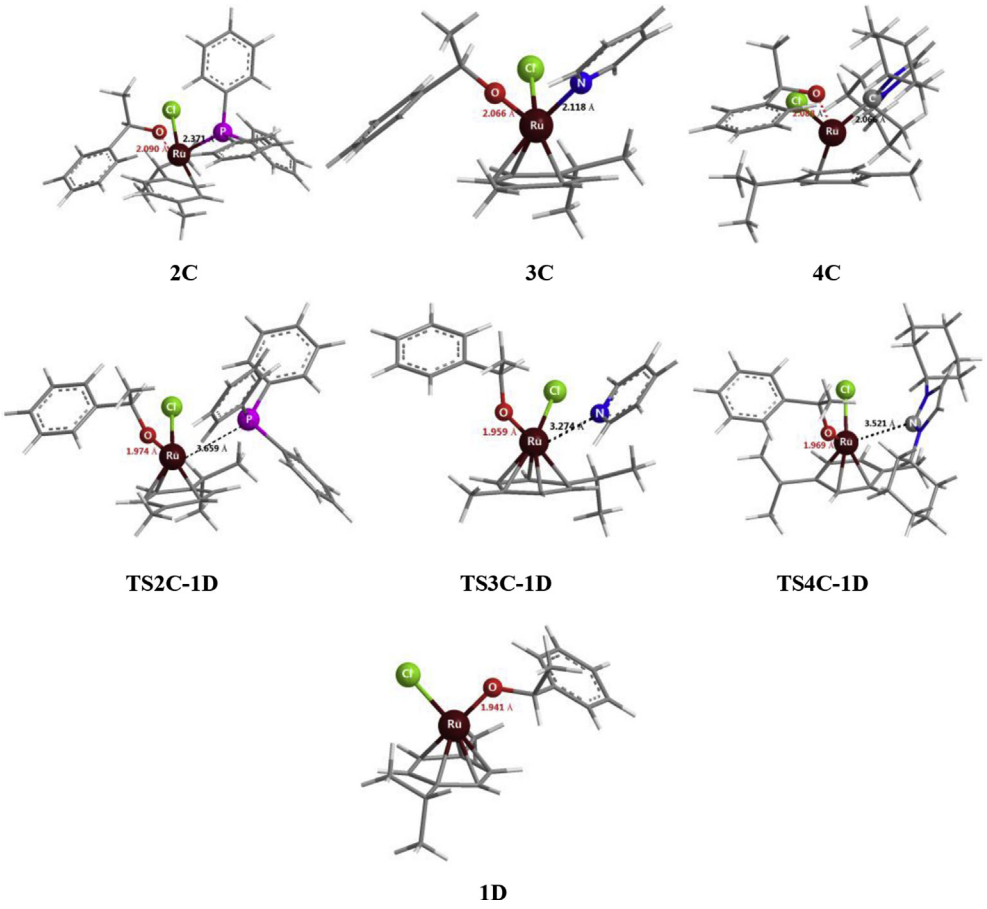


Fig. 3. Optimized geometries of complexes **2C**–**4C**, **1D**, and transition states of ligand dissociation.

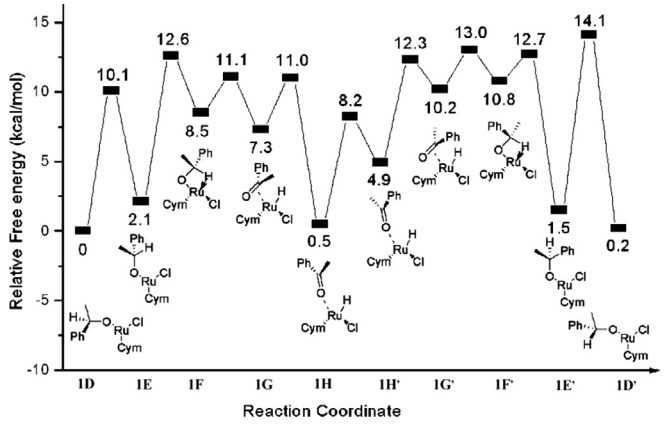


Fig. 4. Schematic reaction pathway for the transformation of (*R*)-**7** into (*S*)-**7** promoted by complex **1**.

reaction pathway. Then rotation around the Ru–O bond of the σ-coordinated ketone, with a barrier 7.7 kcal/mol, leads to another σ-coordinated ketone, **1H′** in Fig. 4, with an opposite orientation of the phenyl and methyl groups relative to the cymene and chlorine ligands. **1H′** is converted to the enantiomer of **1D′** following the reverse passway of **1D** to **1H**. All in all, the pathway from **1D** to **1D′** corresponds to an inversion of configuration at the C_β atom of the alkoxide. The total energy barrier, regardless of forward or backward direction, is only 14.1 kcal/mol, which can be easily surmounted under experimental conditions.

In short, computational analysis indicated that the dissociation of ligands to form vacant sites is crucial to racemization of secondary alcohols catalyzed by 18-electron cymene ruthenium complexes. And the racemization pathway from **1D** to **1D′** supported the mechanism (Scheme 2), which is consistent with the study on 16-electron cyclopentadienyl ruthenium complexes [8].

*Dynamic kinetic resolution of rac-**7** with complexes **1**–**6***

The DKR of *rac*-**7** with complexes **1**–**6** were carried out to gain insight into the suitability of these complexes to Novozyme-435 and

the results were shown in Table 3. Obviously, the excellent yields (above 90%) and ee's (above 92%) were obtained with 16-electron complex **1** (Entry 1) and 18-electron complex **3** with a pyridine ligand (Entry 3), while low yields (below 70%) were obtained with bidentate chelating catalysts **5** and **6** (Entries 5–6). The yields of DKR (Entries 2–4) were consistent with their racemization ability for 18-electron complexes **2**–**4**. Singularly low enantioselectivity (40%) gained with catalyst **4** (Entry 4) was probably caused by the esterification ability [15] of ruthenium complexes with NHC ligands.

Dynamic kinetic resolution of various secondary alcohols

From template reactions, we screened out 16-electron cymene ruthenium complex **1** and 18-electron cymene ruthenium complex **3** with a pyridine ligand by yield and ee in the DKR process. A variety of secondary alcohols **8**–**16**, including electron-deficient and electron-rich ones, were then selected as substrates for the two catalysts and the results are summarized in Table 4. No matter the alcohols were benzylic or aliphatic, these two catalysts almost always gave good to excellent yields and ee values, owing to the natural vacant site for catalyst **1** and the easily-dissociative ligand for catalyst **3**. The exception was for alcohol **15** (entry 15 and 16), the yields were relatively low. In addition, for both catalysts, the halogen-substituted benzylic alcohols seemed to deteriorate the yields to some extent. On the whole, 16-electron catalyst **1** gave slightly better results than 18-electron cymene ruthenium complex **3** probably due to the coordination competition between alcohol and the leaving ligand.

Conclusions

In summary, the DFT calculations indicate that, the dissociation of ligands to form vacant sites is the key step for racemization of secondary alcohols catalyzed by cymene ruthenium complexes, and the complex with weak ligand such as pyridine shows excellent racemization efficiencies, which was proved by kinetic experiments. Computational analysis also demonstrates that the mechanism for interconversion between *R*- and *S*- alcohols catalyzed by the 16-electron cymene ruthenium species involves ruthenium hydride intermediates, which is consistent with former report on cyclopentadienyl ruthenium complexes. Application of 16-electron cymene ruthenium complex **1** and 18-electron **3** with easily-dissociative pyridine ligand in DKR process of various *rac*-alcohols demonstrates that both complexes are efficient and applicable catalysts.

Experimental section

General

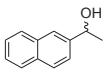
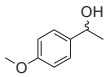
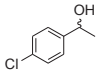
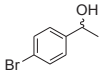
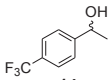
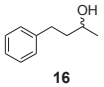
All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques unless otherwise stated.

Table 3
The DKR of *rac*-**7** with complexes **1**–**6**.[a]

Entry	Catalyst	Yield [%][b]	ee [%][c]
1	**1**	91	99
2	**2**	83	98
3	**3**	90	99
4	**4**	70	40
5	**5**	59	96
6	**6**	69	97

[a] *rac*-1-Phenylethanol (0.5 mmol), Novozyme-435 (10 mg), Na_2CO_3 (0.5 mmol), ^{t}BuOK (5 mol%), catalyst (Ru complex: 4 mol%), 60 °C, toluene (5 mL), *p*-chlorophenyl acetate (1.5 mmol), 48 h.
[b] On the basis of ^{1}H NMR analysis [16].
[c] On the basis of specific rotation results of two runs.

Table 4
The DKR of various *sec*-alcohols.[a]

Entry	*rac*-Alcohol	Catalyst	Temp [°C]	Yield [%][b]	ee [%][c]
1		**1**	70	86	98
2		**3**		80	96
	8				
3		**1**	60	92 (85)	>99
4		**3**		95	95
	9				
5		**1**	60	93	95
6		**3**		90	95
	10				
7		**1**	60	88	>99
8		**3**		82	95
	11				
9		**1**	60	82 (73)	>99
10		**3**		76	96
	12				
11		**1**	70	81	94
12		**3**		75	97
	13				
13		**1**	70	95	86
14		**3**		88	90
	14				
15		**1**	70	68	98
16		**3**		63	73
	15				
17		**1**	60	93	94
18		**3**		92	71
	16				

[a] *rac*-Alcohol (0.5 mmol), catalyst (Ru complex: 2 mol%), Novozyme-435 (10 mg), Na_2CO_3 (0.5 mmol), ^{t}BuOK (8 mol%), toluene (5 mL), *p*-chlorophenyl acetate (1.5 mmol), 48 h.
[b] On the basis of ^{1}H NMR analysis [16]. The yields given in parentheses are using isopropenyl acetate as acyl donor.
[c] Determined by HPLC or GC with a chiral column.

Anhydrous solvents were distilled under nitrogen from sodium (hexane, toluene) or calcium hydride (dichloromethane), and methanol was distilled over magnesium and iodine. Complexes **1**, alcohols, acylating agents and other chemical reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker VAVCE-DMX 400 MHz instrument relative to TMS. Enantiomeric excesses were determined by specific rotation, HPLC or GC. Specific rotation was measured by a Rudolph IV-589 Automatic Polarimeter. HPLC was equipped with a capillary column Daicel OD-H. GC was equipped with a capillary column Varian CP 7502.

*Synthesis of complexes **2**–**6***

*[Ru(p-cymene)Cl$_2$(triphenylphosphine)] (**2**)*[14a]

To a suspension of [Ru(*p*-cymene)Cl$_2$]$_2$ (100 mg, 0.163 mmol) in toluene (5 mL), triphenylphosphine (0.36 mmol, 2.2 equiv) was added at room temperature. The resulting mixture was heated to

reflux for 1 h. After the mixture was cooled, the precipitate was filtered, washed with hexane (3 × 5 mL), and dried in vacuum, affording an orange solid (155.6 mg, 84%). ^{1}H NMR (400 MHz, CD_3Cl): δ = 1.10 (d, J = 6.1 Hz, 6H), 1.80 (s, 3H), 2.80 (m, 1H), 4.92 (d, J = 5.8 Hz, 2H), 5.12 (d, J = 5.8 Hz, 2H), 7.20, 7.30, 7.76 (m, 15H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 17.38, 21.52, 29.88, 86.78, 88.70, 95.62, 110.78, 127.54, 129.85, 134.03.

*[Ru(p-cymene)Cl$_2$(pyridine)] (**3**)*[14b]

To a suspension of [Ru(*p*-cymene)Cl$_2$]$_2$ (100 mg, 0.163 mmol) in toluene (5 mL), pyridine (28 μL, 0.36 mmol, 2.2 equiv) was added at room temperature. The resulting mixture was heated to reflux for 3 h. After the mixture was cooled, the precipitate was filtered, washed with hexane (3 × 5 mL), and dried in vacuum, affording a yellow solid (99.2 mg, 79%). ^{1}H NMR (400 MHz, CD_3Cl): δ = 1.31 (d, J = 6.9 Hz, 6H), 2.10 (s, 3H), 3.00 (sept, 1H), 5.22 (d, J = 5.9 Hz, 2H), 5.44 (d, J = 5.7 Hz, 2H), 7.31 (m, 2H), 7.74 (m, 1H), 9.04 (d, J = 4.8 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 18.22, 22.31, 30.67, 82.27, 82.82, 97.03, 103.58, 124.5, 137.5, 154.9.

*[Ru(p-cymene)Cl$_2$(NHC)] (NHC = 1,3-dicyclohexylimidazole-2-ylidene) (**4**)*[14c]

0.55 equiv of silver oxide (0.11 mmol) was added to a suspension of 1,3-dicyclohexylimidazole salt (0.2 mmol) in dichloromethane (5 mL). The mixture was stirred for 6 h at room temperature and in dark environment. [(*p*-cymene)RuCl$_2$]$_2$ (0.11 mmol) was then added to the mixture and reacted overnight. The solution was loaded directly onto a 10 × 3 cm silica column. Elution with dichloromethane removed remaining [(*p*-cymene)RuCl$_2$]$_2$. The orange band was eluted carefully with 1:150 methanol/dichloromethane, and the solvent removed to give an orange solid (76.4 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.26 (m, cyclohexyl), 1.37 (d, J = 4.8 Hz, 2H), 1.47–1.89 (m, cyclohexyl), 2.14 (s, 3H), 2.3–2.4 (m, cyclohexyl), 2.86 (sept, 1H), 4.84 (m, 2H), 5.14 (d, J = 5.8 Hz, 2H), 5.42 (d, J = 5.8 Hz, 2H), 7.06 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 18.87, 23.17, 31.27, 25.48, 26.07, 35.37, 35.88, 59.33, 83.72, 85.32, 97.36, 105.13, 119.38, 171.33.

*[Ru(p-cymene)Cl(phen)]Cl (**5**)*[14d]

2 equiv (0.326 mmol) of phenanthroline were added to a suspension of [(*p*-cymene)RuCl$_2$]$_2$ (100 mg, 0.163 mmol) in dichloromethane (10 mL). The mixture was stirred for 3 h at room temperature, during this time the colour changed from orange to yellow. After evaporation to dryness, the residue was dissolved in water; the solution was filtered and evaporated to dryness giving the product in quantitative yield. ^{1}H NMR (400 MHz, D_2O): δ = 0.83 (d, J = 6.7 Hz, 6H), 2.11 (s, 3H), 2.50 (hept, 1H), 5.90 (d, J = 6.6 Hz, 2H), 6.13 (d, J = 6.6 Hz, 2H), 7.87 (s, 2H), 7.97 (dd, J = 6.8 Hz, J = 7.9 Hz, 2H), 8.58 (d, J = 8.3 Hz, 2H), 9.659 (d, J = 5.6 Hz, 2H). ^{13}C NMR (400 MHz, D_2O): δ = 18.00, 20.93, 30.58, 83.98, 86.17, 103.16, 104.27, 126.42, 127.36, 130.63, 139.02, 145.45, 155.13.

*[Ru(p-cymene)Cl(acac)]Cl (**6**)*[14e]

A suspension of [(*p*-cymene)RuCl$_2$]$_2$ (100 mg, 0.163 mmol) and Na(acac)·H$_2$O (59 mg, 0.425 mmol) in acetone (AR) (10 mL) was stirred for 40 min. The solvent was vacuum-evaporated until dryness and the residue was extracted with dichloromethane (4 × 5 mL). The solvent was then removed in vacuum and the residue dissolved in acetone. The resulting solution was partially concentrated under reduced pressure and an orange solid precipitated in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.8 Hz, 6H), 1.985 (s, 6H), 2.27 (s, 3H), 2.89 (m, 1H), 5.15 (s, 1H), 5.21 (d, J = 5.9 Hz, 2H), 5.45 (d, J = 6.1 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 18.11, 22.30, 27.30, 30.76, 78.88, 82.43, 98.80, 99.62, 186.47.

General procedure for the racemization of (R)-1-phenylethanol

To a 25 mL Schlenk tube containing 5 mL toluene, Ru or Ir complex (0.01 mmol, 4.0 mol%) and base (5.0 mol%) were added and stirred for 10 min before (*R*)-1-phenylethanol (>97% ee, 0.25 mmol) was added. The reaction mixture was stirred at 60 °C for 24 h. Toluene was then removed by evaporation under reduced pressure, and the residue was extracted with petroleum ether, and evaporated under reduced to give an oily mixture. The yield was directly determined by ^{1}H NMR. Enantiomeric excesses were calculated using the equation $e.e = \alpha/\alpha_0$ where α and α_0 was the optical rotation of the product and (*R*)-1-phenylethanol respectively.

General procedure for dynamic kinetic resolution of rac-alcohols

To a 25 mL Schlenk tube containing 5 mL toluene, Ru or Ir complex (0.01 mmol, 2.0 mol%) and potassium *tert*-butoxide (0.04 mmol, 5.0 mol%) were added and stirred for 10 min. Sodium carbonate (0.5 mmol), alcohol (0.5 mmol), acylating agents (1.5 mmol) and Novozym-435 (10 mg) were then added. The solvent was then stirred for 24 h at 60 °C or 70 °C. After evaporation to dryness, the mixture was loaded to a 10 × 3 cm silica column. Elution with petroleum ether removed any alcohol. The product was eluted with 3:50 ethyl acetate/petroleum ether, and the solvent removed to give an oily mixture. The yield was directly determined by ^{1}H NMR. Enantiomeric excesses were determined by specific rotation, HPLC or GC.

Computational methods

All theoretical calculations were performed with Gaussian 09 quantum chemistry software at BP86/SVP level for C, H, O, P, N, Cl. For Ru, we use the standard SDD basis set in Gaussian 09 [17–20]. The geometries of reactants, intermediates, products and transition states were fully optimized and characterized by the number of imaginary frequencies. Furthermore, all the extrema were confirmed by calculation of the intrinsic reaction paths [21]. The natural bond orbital (NBO) program in Gaussian 09, Version 3.1 [22], was used to obtain more information about some special bonds. The effect of solvation on reaction energetics was determined by means of single-point self-consistent reaction field (SCRF) calculations using the polarized continuum model (PCM) [23]. Gas-phase optimized structures were used in the single point calculations in toluene as solvent with a relative permittivity of 2.4. Free energies in solution with all non-electrostatic effects are discussed in the text. Computational details are provided in the Supporting Information.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2014.10.011.

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