Tetrahedron 66 (2010) 3707–3716

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of a novel ruthenium(II) complex and its unique behaviors in enzymatic dynamic kinetic resolution of secondary alcohols

Qihui Chen [a,b], Chengye Yuan [a,*]

[a] State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Feng-lin Rd., Shanghai 200032, China
[b] State Key Laboratory of Structure Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou 350002, China

ARTICLE INFO

Article history:
Received 12 January 2010
Received in revised form 17 March 2010
Accepted 19 March 2010
Available online 24 March 2010

Keywords:
Dynamic kinetic resolution
Cyclopentadienyl benzoyl ruthenium
Racemization
Candida Antarctica lipase **B**
Secondary alcohols

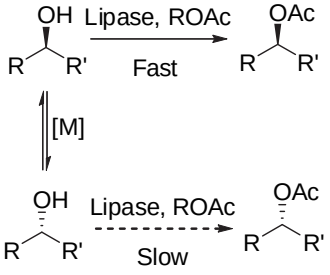
ABSTRACT

A cyclopentadienyl benzoyl ruthenium(II) complex **3** was first prepared as an efficient catalyst in *Candida Antarctica* lipase **B** (CALB) mediated dynamic kinetic resolution (DKR) of secondary alcohols. With the aid of this ruthenium complex **3**, (*S*)-1-phenylethanol was completely racemized within 25 min, and in combination with CALB, series of secondary alcohols bearing various functional groups were resolved in an efficient DKR manner. A detailed mechanism involving the C–H bond activation was presented for the formation of complex **3** by capturing the crucial intermediate in this pathway. Related mechanistic studies were carried out to illustrate this type of DKR catalyst is based on the racemization of secondary alcohols. The novelty of its structure, its unique catalytic behavior as well as its wide scope of application of various substrates and its higher efficiency make complex **3** as an important alternative to those complexes, which are commonly used in DKR process.

1. Introduction

Enzymatic kinetic resolution (KR) as a useful protocol for the preparation of chiral compounds has been widely used in pharmaceutical and agrochemical industries.[1] However, it has an intrinsic disadvantage that only 50% of the stereoisomers that needed could be obtained. In order to overcome this limitation, dynamic kinetic resolution (DKR), in which an in situ racemization process is coupled with kinetic resolution (KR) improved by lipase, has been developed. In recent years, the metal-catalyzed dynamic kinetic resolution of racemic alcohols has drawn increasing attentions (Scheme 1).[2]

The first example of dynamic kinetic resolution of alcohols was reported by Williams, in which a simple transition–metal complex $[Rh_2(OAc)_4]$ was used as racemization catalyst for secondary alcohols. However, this system seemed less effective.[3] In 1997, the Bäckwall group firstly introduced a practical system for dynamic kinetic resolution of secondary alcohols by using Shvo's complex **1** in combination with an immobilized lipase,[4] and with the aid of this system; various types of alcohols have been studied by the Bäckvall group and later by the Park group.[5] However, high reaction temperature and special additive were usually needed for this



Scheme 1. Metal-catalyzed DKR for alcohols.

system. Until 2002, the Park group reported another type of racemization catalyst **2a**, which could racemize chiral alcohols quickly and make dynamic kinetic resolution of alcohols more effective than any other catalyst, but strong base *t*-BuOK and prolonged reaction time are necessary.[6] Later, the Bäckwall group found that a more active catalyst **2b** made DKR of secondary alcohols completed in 3 h, but also this system requires strong base.[7] More recently, the Kim and Park group found some DKR systems milder and reusable by using catalyst **2c–e**.[8] However, for catalysts **2a–e**, a good leaving group is usually needed. Furthermore, for some substrates, which easily coordinate to ruthenium atom such as β-hydroxyl phosphonate, only less efficient DKR systems were reported.[5j] Thus, new classes of metal catalysts are needed for the

* Corresponding author. Fax: +86 21 5492 5379; e-mail address: yuancy@mail.sioc.ac.cn (C. Yuan).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.069

racemization of alcohol leading to a DKR process. Very recently, an unexpected ruthenium complex, namely cyclopentadienyl benzoyl ruthenium(II) complex **3** (as shown in Fig. 1) was reported in our laboratory, which makes DKR of secondary alcohols efficient by combining *Candida Antarctica* lipase B.[9] However, the mechanism of synthesis of catalyst **3** and the mechanism comprised in racemization process haven't been fully elucidated. Herein, we intend to give insight into synthesis of complex **3** and its racemization mechanism. Beside this, the scope of substrates structure was significantly enlarged including those substrates that easily coordinate with ruthenium atom.

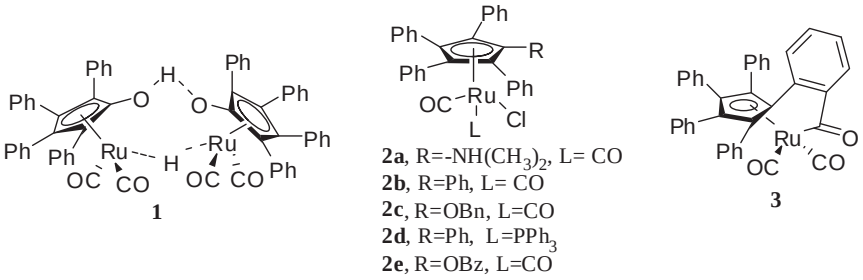


Figure 1. Racemization catalysts.

2. Results and discussion

2.1. Insight into the reaction pathway in the synthesis of catalyst 3

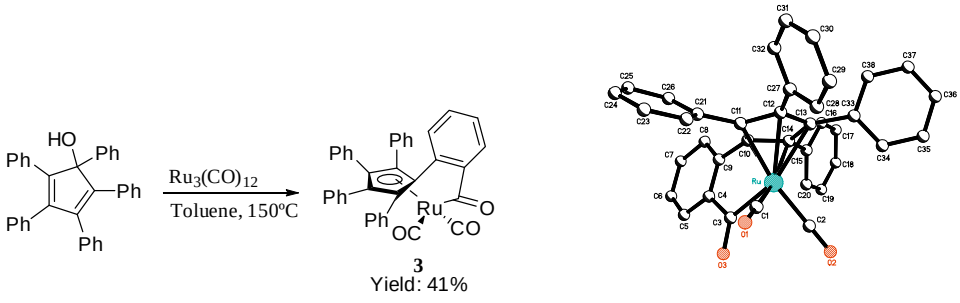
As indicated by Scheme 2, pentaphenylcyclopenta-2, 4-dienol was reacted with $Ru_3(CO)_{12}$ in toluene in schlenk tube at 150 °C for 72 h to give cyclopentadienyl benzoyl ruthenium(II) complex **3** in a yield of 41%. Surprisingly, ruthenium(II) complex **3** bears an unusually metallic spiro structure, which has been confirmed by single crystal X-ray diffraction analyses.

molecular of H_2O is formed. The phenyl anion coordinates to the ruthenium(II) atom at the same time, resulting in the formation of complex **c**. Also due to the strong steric strain of four member metallic spiro, the unstable complex **c** easily coordinates to the CO existed in the reaction system to produce a more stable ruthenium(II) complex **3**.

Our initial attempts to capture complex **a** or complex **b** directly by slow down the reaction temperature or shortening the reaction time were unsuccessful. This may be ascribed to that ruthenium complex **a** is hard to be formed at low temperature, while at the higher temperature complex **a** is very active and easily converted to compound **b** and then to compound **c**. This postulation may be supported by the reported synthesis of tetraphenylcyclopenta-2, 4-dienonyl tricarbonyl ruthenium(0) complex (the reaction temperature usually required 150 °C).[5l]

Gratifyingly, the existence of the key species, complex **c**, can be confirmed by adding 4-methoxyphenylisocyanide. The expected insertion product **4** was isolated when excessive 4-methoxyphenylisocyanide was added.

From the proposed mechanism, it is clear that one molecule of water should be created during the formation of complex **3**. Our experimental data demonstrated that addition of 4 Å molecular

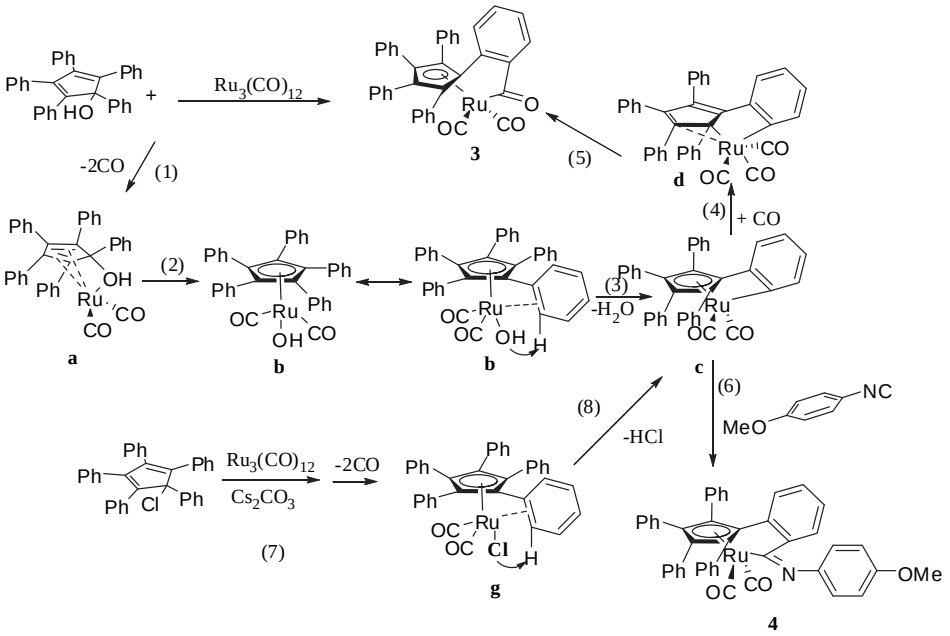


Scheme 2. Synthesis of cyclopentadienyl benzoyl ruthenium(II) complex **3**.

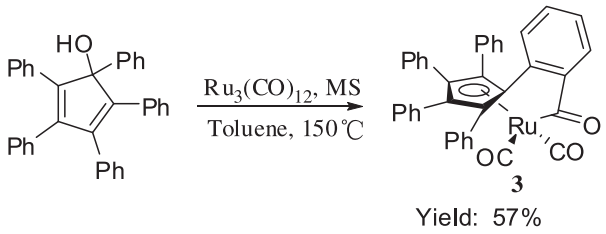
We propose a mechanism for the preparation of complex **3** (Scheme 3) by capturing some crucial intermediates in our experiments. First, $Ru_3(CO)_{12}$ may coordinate to pentaphenylcyclopenta-2, 4-dienol in toluene at high temperature and release two molecules of CO to form ruthenium(0) complex **a**. Complex **a** is very active at high temperature, thus an intramolecular oxidation addition may take place, leading to the ruthenium(II) complex **b**, in which ruthenium(II) atom coordinates to the conjugated pentaphenylcyclodienyl. Due to the strong steric hindrance of phenyl groups, the ruthenium atom can approach the C–H bond of phenyl ring and activate it. (The similar phenomenon was also observed in ruthenium complex **2b** in Bäckwall's work.[7b]) Then the OH^- may snatch the hydrogen activated by ruthenium(II) atom, and one molecular of H_2O and compound **c** are formed (as shown as Scheme 3 (3)). A similar reaction system was designed as shown in the part ((7)–(8)) of Scheme 3. It is known that pentaphenylcyclopentadienyl chloride can easily react to $Ru_3(CO)_{12}$, affording pentaphenylcyclopentadienyl ruthenium(II)

sieves will result substantial increase the chemical yield of ruthenium(II) complex **3** was increased from 41% to 57% (Scheme 4). This is an indirect experimental evidence showing the formation of water. However, the catalytic effect of the molecular sieve could not be excluded in such case.

So far, we can ensure that both intermediate **c** and water are formed during the preparation of complex **3**. We deduced that the OH^- snatches the hydrogen, which is activated by ruthenium(II) atom, and one molecular of H_2O and compound **c** are formed (as shown as Scheme 3 (3)). A similar reaction system was designed as shown in the part ((7)–(8)) of Scheme 3. It is known that pentaphenylcyclopentadienyl chloride can easily react to $Ru_3(CO)_{12}$, affording pentaphenylcyclopentadienyl ruthenium(II)



Scheme 3. Insight into the mechanism of preparation of complex **3**.

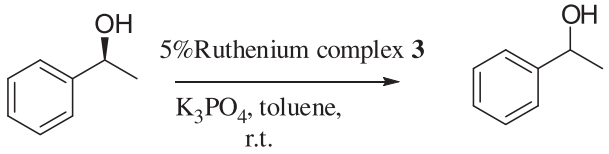


Scheme 4. Comparisons with different reaction systems.

chloride.[7a–b] The inorganic base Cs_2CO_3 was used here to eliminate the HCl resulted from the reaction. As we expected, a small mount of complex **3** with 10% chemical yield was isolated. Because the OH^- is a stronger base, more amounts of complex **3** can be obtained in our reaction system. So far, we can demonstrate that a route that contains ruthenium(II) mediated C–H bond activation exists in our synthesis of cyclopentadienyl benzoyl ruthenium(II) complex **3**.

2.2. A mechanistic study on catalyst 3 mediated racemization of secondary alcohols

We found that complex **3** catalyzed the racemization of chiral secondary alcohols quite efficiently even at room temperature. A more recent study showed that, complex **3** (5 mol%) could racemize (*S*)-1-phenylethanol within 25 min (Scheme 5, Fig. 2), 90% of **3** being recycled without observed loss of activity. We also observed that this reaction system turned pale red after 15 min.



Scheme 5. Racemization of (*S*)-1-phenylethanol catalyzed by 5% ruthenium **3** and K_3PO_4.

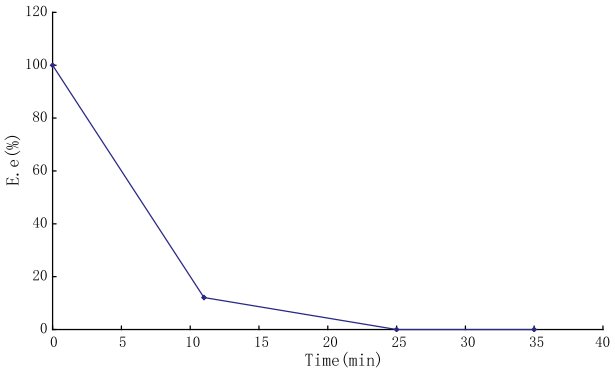


Figure 2. Racemization of (*S*)-1-phenylethanol catalyzed by 5% ruthenium **3** and K_3PO_4.

Compare with catalyst **2a–e**, our ruthenium complex **3** does not bear a good leaving group coordinated to ruthenium atom, so there should be an alternative hydrogen transfer route in ruthenium complex **3** catalyzed racemization. The color change during the racemization indicates that a new complex must be formed. So NMR experiments were firstly carried out to explain the racemization. It was pity that there were no resonances that show the formation of new species such as a ruthenium hydride in the racemization system. The only clue was that the ^1H NMR of pure phenylethanol was different from it in the racemization system.[10]

To further understand the raceimzation process, we wish to study the racemization kinetics. As 5% ruthenium **3** racemizes (*S*)-1-phenylethanol completely within 25 min, it is hard to track it; so we turn to study the racemization kinetics catalyzed by 0.5% ruthenium **3**. From the Figure 3, we can find that, in the first 9 min, the chiral alcohol cannot be racemized; which implies that the ruthenium **3** cannot catalyze the racemization directly. Thus the real active intermediate must be a new complex formed after 9 min in the racemization system. Very recently, the Bäckvall group found that the ligand CO could be exchanged, which also might improve

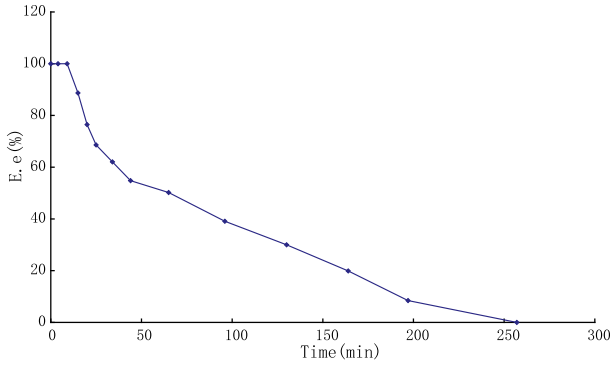
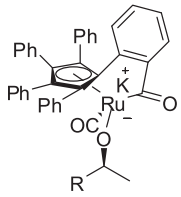


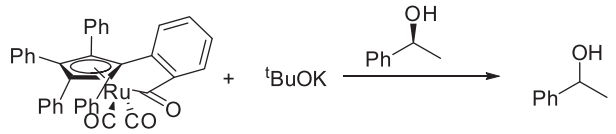
Figure 3. Racemization of (*S*)-1-phenylethanol catalyzed by 0.5% ruthenium **3**.

the racemization of secondary alcohol.[11] So we postulated that the real active intermediate was composed of ruthenium **3** and alcoholic minus-ion (Scheme 6).



Scheme 6. A possible active intermediate.

It is difficult to capture or isolate the possible active intermediate as shown in Scheme 6. In order to prove this possible active intermediate, we prepared a similar system in situ by mixing the ruthenium complex **3** with equal *t*-BuOK (Scheme 7, Fig. 4). With aid of this new system, the (*S*)-1-phenylethanol could be racemized immediately; the pale red color was also observed in this case. This phenomenon may demonstrate that the active intermediate is indeed composed of ruthenium **3** and alcoholic-minus.



Scheme 7. Racemization of (*S*)-1-phenylethanol catalyzed by 0.5% ruthenium **3** and *t*-BuOK.

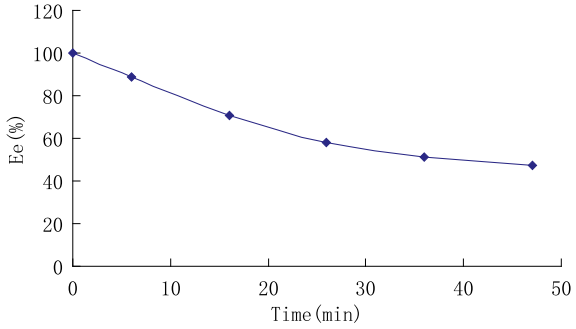


Figure 4. Racemization of (*S*)-1-phenylethanol catalyzed by 0.5% ruthenium **3** and *t*-BuOK.

As far as we know, racemization of alcohols catalyzed by transition-metal is usually a hydrogen transfer process, which in most cases runs as a first-order reaction. However, in our racemization system, the concentration of real catalyst is changing during the whole reaction. So the equation was described as Scheme 8.

$$v = dc/dt = k[\text{active ruthenium complex}][\text{chiral alcohols}]$$

Scheme 8. Kinetic equation for the racemization catalyzed by ruthenium **3**.

This equation is supporting the fact that the racemization process was catalyzed kinetically by ruthenium **3** (Fig. 3). In the first 9 min, the active ruthenium complex has not formed, so the alcohol could not be racemized. In the second part (for the time from 9 min to 20 min), the rate of racemization(v) increases remarkably due to the rate of increase of the active ruthenium complex is faster than that of the decrease of chiral alcohol. Next, the rate of racemization(v) was slower down is related to the diminish amount of chiral alcohol. While the alcohol is completely racemized, the rate of racemization(v) is zero, although the hydrogen transfer process still undergoes quite nicely. Compared to Figure 4, the rate of racemization catalyzed by ruthenium complex **3** and *t*-BuOK turns out slower, this experimental observation could be rationalized by the decrease of chiral alcohol in the reaction system.

Actually, the value of *k* of ruthenium **3** can be calculated. When racemization was carried out as shown in Scheme 7, the concentration of active ruthenium complex is a constant, so the value of *k* can be probably calculated as shown in Figure 5 (k_A=0.021 min^{-1}, k_B=0.019 min^{-1}). This proves that, for the substrates, the racemization is a first-order reaction. So the value of *k* in this racemization system may be 0.020 min^{-1}, but the rate of racemization (v) is also affected by the concentration of active ruthenium complex.

Based on these experiments, a possible mechanism of racemization of chiral alcohol catalyzed by ruthenium **3** in the presence of K_3PO_4 could be tentatively postulated as shown in Scheme 9. As proposed by us, in the racemization system, when the ruthenium **3** and the chiral secondary alcohol approach the heterogeneous K_3PO_4 in the form of (**a**) (as supported by lit.[10]), the alcoholic hydroxyl is activated by ruthenium **3**. So the base K_3PO_4 can easily snatch the hydrogen of the chiral alcohol to produce an active intermediate (**b**), which was also supported by our investigation on racemization kinetics as well as the color change during the experiment. Meanwhile, in the DKR process, the acetone resulted from KR does not interfere with the racemization process. These evidences indicated that in our present case, the racemization is an intramolecular hydrogen transfer process. As shown by Backvall[7b], that racemization of chiral secondary alcohol by catalyst **2b** is a process via an intramolecular hydrogen transfer mechanism. Similarly, we supposed that a reversible intramolecular hydrogen transfer process as shown by (**b**), (**c**), and (**d**) may exist in our DKR system. In the structure of (**c**), the ketone that coordinates to ruthenium atom can be rotated freely, so the chiral alcohol could be racemized by unselective ruthenium hydrogen insertion. In addition to our above experimental observations, other chiral alcohol, including some racemized alcohol will replace the racemic alcoholic minus-ion to proceed the catalytical cycle. Affected by the increasing racemic alcohol, the racemization process of chiral alcohol will be slower (as shown in Fig. 2–4); however, the rate of intramolecular hydrogen transfer process of alcohols keeps unchanged. In DKR, when the alcohol is transformed to corresponding acetate, the hydrogen transfer process catalyzed by ruthenium complex **3** will be terminated and the ruthenium complex **3** could be recycled.

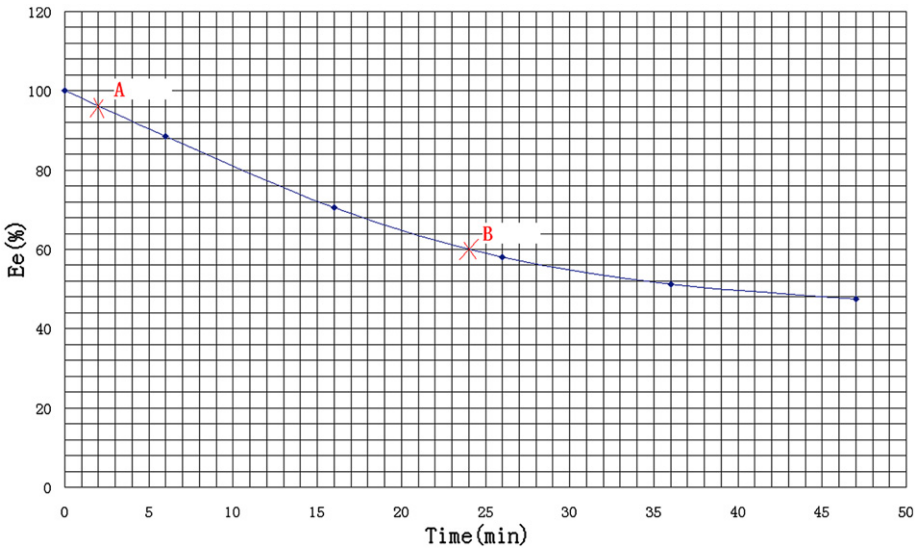
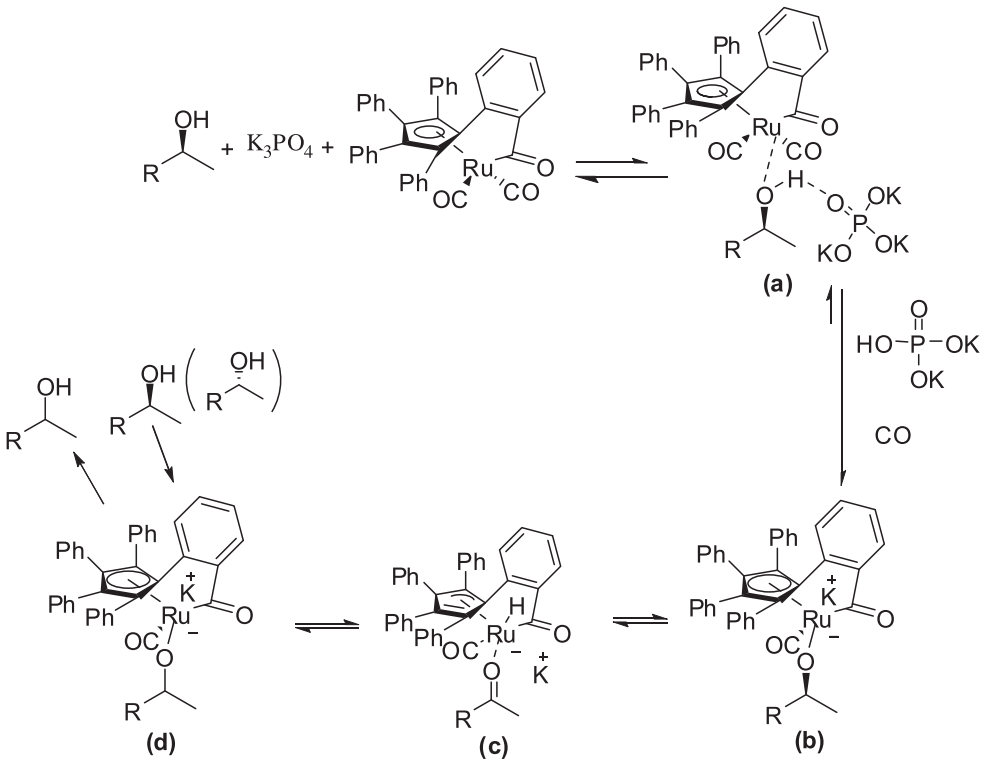


Figure 5. Calculation of the value of *k* catalyzed by 0.5% ruthenium **3** and *t*-BuOK.

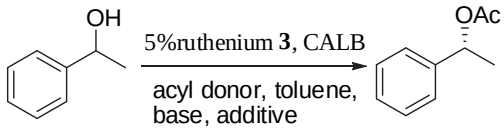
2.3. Dynamic kinetic resolution of secondary alcohols by catalyst 3 and CALB

Although many metals have been used to racemize chiral alcohols,[2a,12] only a few of them accord with the enzymatic kinetic resolution very well.[4,6–9] Our initial attempts to combine enzymatic kinetic resolution with our racemization system were not successful until we reduced the amount of lipase and added some 4 Å Molecular Sieves as shown in Scheme 10. In our first trial, 50 mg CALB was used with different acyl donors, but only less satisfactory results were obtained (Table 1, entries 1–2). Introduction of equivalent Na_2CO_3 and catalytical amount of *t*-BuOK, the base system used in Bäckvall and Park's work,[6,7] also proved ineffective (Table 1, entry 3). Considering trace water contaminated in CALB might affect the racemization, we added some 4 Å MS in our DKR system, and the product was obtained with 99% yield and 59% ee (Table 1, entry 4). Although it still seemed not very satisfactory, we ensured that partial racemization of chiral phenylethanol was accompanied with the kinetic resolution catalyzed by CALB. Reduction of CALB (8 mg) to diminish the water amount led to the total loss of optical activity (Table 1, entry 5). The reason may be that subtle water comprised in lipase was absorbed by 4 Å Molecular Sieves, and then directly catalyzed by *t*-BuOK, 1-phenylethanol was rapidly converted to



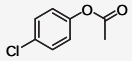
Scheme 9. A possible mechanism for racemization of chiral secondary alcohol.

corresponding acetate, so the product without optical activity was obtained. After many trials, a new system of dynamic kinetic resolution of 1-phenylethanol was developed using molecular sieve as an additive and K_3PO_4 as the base, and an excellent result with 97% yield and 99% ee was achieved as shown in entry 6, Table 1.



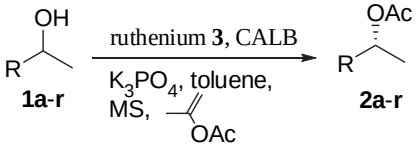
Scheme 10. Dynamic kinetic resolution of 1-phenylethanol.

Table 1
Some tries about dynamic kinetic resolution of 1-phenylethanol

Entry	CALB(mg)	Base	Acyl donor	Additive	Time (h)	Yield (%)	ee (%)
1	50	K_3PO_4		—	20	55[c]	—
2	50	K_3PO_4		—	20	50[c]	—
3	100	Na_2CO_3/^{t}BuOK		—	20	50[c]	—
4	100	Na_2CO_3/^{t}BuOK		MS[a]	12	99[b]	59[b]
5	8	Na_2CO_3/^{t}BuOK		MS[a]	10	99[b,d]	0[b,d]
6	10	K_3PO_4		MS[a]	10	97[b]	99[b]

[a] 170 mg 4 Å Molecular Sieves was added.
[b] Determined by GC with RT BDEXM column.
[c] Determined by ^{1}H NMR of the reaction mixture.
[d] Directly transesterification catalyzed by *t*-BuOK was also observed in our laboratory.

When the optimization of the DKR reaction of typical secondary alcohol was established, a series of secondary alcohols bearing various functional groups was examined under similar conditions. (Scheme 11). The results as displayed in Table 2, This DKR system seems not only accord with simple secondary alcohols, such as aromatic alcohols and aliphatic alcohols; but also with more complicated secondary alcohols with various functional groups, such as sulfonyl group, ester, phosphonate. 1-Phenylethanol could be transformed to its corresponding acetate with 94% yield (isolated yield) and 99% ee within 10 h (Table 1, entry 1). For other substituted phenylethanols, whether with electron-donating group, 1-(4-methylphenyl) ethanol or with electron-withdrawing group, 1-(4-fluorophenyl) ethanol, both gave chiral products with high chemical yield and excellent enantioselectivity. (Table 2, entries 2–3). As substituted phenylethanols, a naphthyl derivative also gave excellent result with longer reaction time up to 20 h (Table 2, entry 4). Since chiral aliphatic alcohols are usually not easy to be prepared by asymmetric hydrogenation,[13] consequently,



Scheme 11. 11DKR of various secondary alcohols.

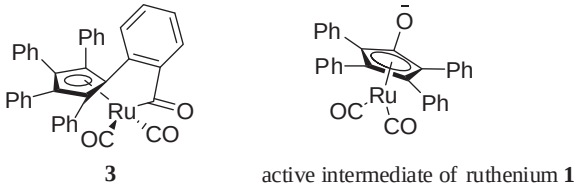
Table 2
DKR of various secondary alcohols

Entry	Substrates (**1a–r**)	CALB [mg]	t [h]	T [°C]	Products (**2a–r**)	Yield[a] [%]	ee[b] [%]
1		10	10	25		94 (97)	99
2		10	10	25		92 (96)	98
3		10	10	25		90 (90)	99
4		10	20	25		95 (99)	99
5		6	20	50		90 (92)	99
6		4	20	50		92 (95)	96
7		6	20	50		92 (95)	92
8		20	20	25		99	97[c]
9		50	20	25		94	94
10		25	20	25		85[f]	95
11		25	20	25		86[f]	93
12		25	20	25		95[f]	95
13		25	20	25		83[f]	92
14		80	20	25		80[e]	92
15		30	20	25		85[e,f]	90[d]
16		30	20	25		70[e,f]	>95[d]
17		30	20	25		75[e,f]	92[d]
18		80	20	25		88[e]	>95[d]

[a] All numbers were isolated yields, Some numbers in parentheses were determined by GC or HPLC.
[b] Unless otherwise noted, all the enantiomeric excess values were determined by GC or HPLC with chiral columns, for more detailed information, you can see experimental section.
[c] The product was firstly deacetylated with the solution (K_2CO_3 and (H_2O/MeOH=1:4)), and then the enantiomeric excess value was determined by GC with RT BDEXM column.
[d] These products were firstly hydrolyzed by NH_3/MeOH solution, and then those ee values were determined by ^{31}P NMR of their hydrolyzation mixed with quinine.
[e] The amount of K_3PO_4 was reduced to 10% and the mount of catalyst up to 9%.
[f] These reactions were carried out on 0.5 mmol scale.

dynamic kinetic resolution of aliphatic alcohols turns up more important. Compared to aromatic alcohol, the acidity of hydroxyl function of aliphatic alcohol is markedly weaker, so more harsh reaction conditions (higher reaction temperature, up to 50 °C) was

needed (Table 2, entries 5–6). For 4-phenylbut-3-en-2-ol, the expected product could be obtained with 95% chemical yield and 92% ee (Table 1, entry 7). β-Hydroxyl ester is a class of important synthon, and a typical 3-hydroxybutyric acid *tert*-butyl ester was examined in our system, we were pleased to find that a product with 99% chemical yield and 97% ee was isolated (Table 2, entry 8). Chiral β-hydroxyalkyl sulfones have been widely used as key synthons in organic synthesis due to their specific characteristics: the sulfonyl group is not only capable to stabilize an adjacent carbanionic center, but also can be easily reduced. So far, many methods have been developed for their preparation, for example, enantioselective reduction of β-ketosulfones catalyzed by yeast, kinetic resolution of racemic β-hydroxyalkyl sulfones by using lipase, asymmetric hydrogenation of β-ketosulfones.[5p,14] Preparation of chiral β-hydroxyalkyl sulfones based on DKR was first reported by the Rutjes group, however, their DKR system was time-consuming and less effective.[5p] Therefore, a series of β-hydroxyalkyl sulfones were investigated in our DKR system. As shown in entries 9–13, of Table 2, all substituted phenylsulfonyl-2-propanols were successfully converted to corresponding acetates smoothly with high yield and excellent enantioselectivity. These results clearly indicated that β-hydroxyalkyl sulfones may coordinate to ruthenium atom. Chiral hydroxyalkylphosphonates have attracted increasing attentions due to their potential bioactivity and widely application in organic synthesis. Many protocols including asymmetric reduction of ketophosphonates, kinetic resolution of racemic hydroxyalkylphosphonate, have been developed for their synthesis in past years.[5i,15] To the best of our knowledge, only one dynamic kinetic resolution system catalyzed by ruthenium **1** has been used to catalyze DKR of hydroxyalkylphosphonate, however, to carry on such reaction, harsh conditions are usually required and the reaction products are contaminated by oxidation side-products. Furthermore, this system is less effective with β-hydroxyalkylphosphonates, probably due to their easily coordination to ruthenium atom.[5i] Some β-hydroxyalkylphosphonates have also been synthesized and examined (Table 2, entries 14–17). More amount of ruthenium **3** and less amount of K_3PO_4 will make these reactions more fluently and satisfactory. Compared to other alcohols studied in this paper, the yields and ee values of the products of this system are a less satisfactory. A possible explanation was given in Scheme 12, β-hydroxyalkylphosphonates usually exists in form of i, in which the phosphorus atom connects with the oxygen through d–pπ bond, however due to the oxygen shows stronger electronegativity than the phosphorus atom, its resonance structure ii is therefore well-known, while the oxygen atom and phosphorous atom are bonded ionic in nature (Scheme 12). In our DKR system, existence of various species (iii–v) is possible. For example, intramolecular hydrogen bond caused by former iii will increase the acidic activity of hydroxyl of β-hydroxyalkylphosphonates, and in presence of the base (K_3PO_4), β-hydroxyalkylphosphonate can react with isopropenyl acetate and be converted to the corresponding acetate. So in our DKR system, only a small amount of K_3PO_4 was needed, and the enantioselectivity seemed lower than other alcohols. When β-hydroxyalkylphosphonate coordinates to ruthenium atom in type of iv or v, this coordination will reduce the efficiency of racemization catalyzed by ruthenium complex **3**, so the yield is lower. For the α-hydroxylalkylphosphonate, the corresponding acetoxyphosphonate was obtained in higher chemical yield and more excellent enantioselectivity, and this may be due to the increasing hindrance, which makes it hard to coordinate to ruthenium atom. Furthermore, the steric hindrance around the ruthenium atom in ruthenium **3** seems stronger than active intermediate of ruthenium **1** as shown in Scheme 13, so our DKR system shows more suitable for substrates, which easily coordinate to ruthenium atom.[5i,p]



Scheme 13. Comparison with ruthenium **3** and ruthenium **1**.

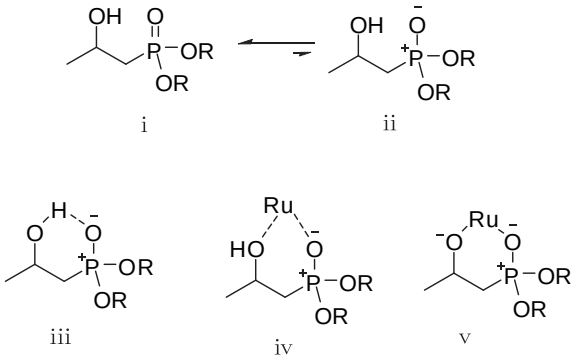
3. Conclusions

In summary, the ruthenium catalyst **3** has been conveniently synthesized from pentaphenylcyclopenta-2, 4-dienol and $Ru_3(CO)_{12}$. A plausible pathway involving ruthenium mediated C–H activation was proposed and a key intermediate **c** in this pathway was captured by reacting with 4-methoxyphenylisocyanide. One comparative experiment using pentaphenylcyclopentaienyl ruthenium(II) chloride and Cs_2CO_3 also led to the formation of catalyst **3**, which strongly supported our proposed pathway. The above mechanistic study shed light on the future improvement of catalyst **3**, which shows high efficiency in racemization of chiral secondary alcohols. The kinetic study of the racemiation, the observation of color change and an ^1H NMR study of the substrate's change in racemization supported a reversible intramolecular hydrogen transfer mechanism, as shown in Scheme 9. In combination with CALB, our catalyst system provides high activity and selectivity in dynamic kinetic resolution of a wide range of secondary alcohols, rendering it an important alternative to currently used DKR catalysts.

4. Experimental section

4.1. General

Toluene was dried over CaH_2 overnight, distilled under argon, and stored over 4-Å molecular sieves. Isopropenyl acetate was washed with saturated K_2CO_3, dried over $CaCl_2$, and distilled under argon. IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A massspectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AM 330 (300 MHz) or Bruker AM-400 (400 MHZ) spectrometer in $CDCl_3$ and chemical shifts were reported in part per million downfield relative to TMS (internal standard); ^{31}P NMR was reported on a Bruker AM-400 (400 MHZ) spectrometer with $CDCl_3$ as the solvent and H_3PO_4 as the external standard. Elemental analysis values were detected on Heraeus Rapid-CHNO apparatus. The enantiomeric excess values of products were determined by GC (HP 6890) with chiral columns (RT BDEXM and J-W CYCLOSIL-B) or HPLC (Waters) with chiral columns (CHIRALPAK AD-H and



Scheme 12. Some possible formers of β-hydroxyalkylphosphonate in DKR.

CHIRALPAK OD, and CHIRALPAK AS). The optical rotation values were determined by polarimeter (J-S P-1030).

4.2. Synthesis of cyclopentadienyl benzoyl ruthenium(II) complex 3

I: $Ru_3(CO)_{12}$ (213 mg, 0.3 mmol) and 1,2,3,4,5-pentaphenyl-cyclopenta-2,4-dienol (462 mg, 1 mmol) were placed in a schlenk tube. Toluene (5 mL) was added and the mixture was flushed with argon 5 min before the system was closed. The reaction was stirred at 150 °C (bath temperature) for 24 h, then cooled down to remove the carbon monoxide in solution. The system was closed and stirred at the same temperature for additional 48 h. The reaction was cooled down again, and the resulting solution was concentrated and chromatographed on aluminum oxide column to give a pale yellow solid 260 mg, yield: 41%. (When molecular sieve was added to this reaction, 360 mg ruthenium complex **3** was obtained, chemical yield was increased to 57%).

II: $Ru_3(CO)_{12}$ (71 mg, 0.11 mmol) and 1,2,3,4,5-pentaphenyl-cyclopenta-2, 4-dienyl chloride (160 mg 0.3 mmol), and 100 mg Cs_2CO_3were placed in a schlenk tube, toluene (5 mL) was added and the mixture was flushed with argon 5 min before the system was closed. The reaction was stirred at 150 °C (bath temperature) during 24 h, then cooled down to removed the carbon monoxide in solution. The system was closed and stirred at the same temperature for additional 48 h. The reaction was cooled down once more, the resulting solution was concentrated and chromatographed on aluminum oxide column to give a pale yellow solid 19 mg, yield: 10%.

Ruthenium complex **3**, mp: 285 °C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (1H, d, J=7 Hz), 7.43 (1H, d, J=7 Hz), 7.27 (1H, t, J=7 Hz), 6.99–7.17 (21H, m).

4.3. Synthesis of ruthenium(II) complex 4

$Ru_3(CO)_{12}$ (213 mg, 0.33 mmol) and 1,2,3,4,5-pentaphenyl-cyclopenta-2, 4-dienol (462 mg 1 mmol) were placed in a schlenk tube, toluene (5 mL) was added and the mixture was flushed with argon 5 min before the system was closed. The reaction was stirred at 150 °C (bath temperature) during 24 h, then cooled down, and removed the carbon monoxide in solution, after the 4-methoxyphenylisocyanide (150 mg) was added, then the system was closed and stirred at the same temperature for additional 48 h. The reaction was cooled down once more, the resulting solution was concentrated and chromatographed on aluminum oxide column (PE/CH2Cl2=2/1–0/1) to give a brown solid 83 mg, yield: 11%, mp: 237 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 (1H, m), 7.34 (1H, m), 7.16–7.19 (2H, m), 6.99–7.12 (16H, m), 6.87–6.92 (6H, m), 6.65 (2H, m), 3.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.92, 184.79, 162.66, 154.89, 150.44, 132.95, 131.00, 130.94, 129.50, 128.18, 127.44, 127.01, 126.69, 126.66, 126.64, 126.54, 123.67, 122.76, 119.74, 113.36, 110.85, 109.67, 106.08, 54.52; IR: 2015, 1962, 1603, 1580, 1500, 1444, 1240, 1179, 1030, 877, 755, 734, 696, 587, 572 cm^{-1}; MALDI-MS (m/z): $(M+H)^+$ 735; HRMS-MALDI: calcd for $C_{45}H_{32}NO_3Ru^{96+}$ $(M+H)^+$ 730.1465; found: 730.1465.

4.4. Procedures for racemization of (*S*)-1-phenylethanol

I: Racemization of 1 mmol (*S*)-1-phenylethanol catalyzed by 5% ruthenium **3** and K_3PO_4: (Fig. 2). In a 25 mL absolute dry schlenk flask, 220 mg dry potassium phosphate and 30 mg ruthenium **3** were placed in, the Schlenk flask was evacuated and filled with argon another three times, then toluene (3 mL) and (*S*)-1-Phenylethanol (120 μL, 1 mmol) were injected; keep the reaction under argon atmosphere. About 15 min later, the racemization system turns to pale red. The ee values were determined by GC with RT BDEXM column: Samples of 20 μL were withdrawn from the reaction mixture by means of a syringe, diluted to 1 mL with CH_2Cl_2/MeOH (1:1). After reaction, 27 mg ruthenium **3** was recovered.

II: Racemization of 1 mmol (*S*)-1-phenylethanol catalyzed by 0.5% ruthenium **3** and K_3PO_4: (Fig. 3). In a 25 mL absolute dry schlenk flask, 220 mg dry potassium phosphate and 3 mg ruthenium **3** were placed in, the Schlenk flask was evacuated and filled with argon another three times, then toluene (3 mL), and (*S*)-1-Phenylethanol (120 μL, 1 mmol) were injected; keep the reaction under argon atmosphere. The ee values were determined by GC with RT BDEXM column until the reaction ended.

III: Racemization of (*S*)-1-phenylethanol catalyzed by 0.5% ruthenium **3** and 0.5% *t*-BuOK (Fig. 4): in a 25 mL absolute dry schlenk flask, 3 mg ruthenium **3** was added, the Schlenk flask was evacuated and filled with argon another three times, then toluene (3 mL) and *t*-BuOK in THF solution (5 μL, 1.0 M) were injected, this solution immediately turns to pale red, after 5 min, (*S*)-1-Phenylethanol (120 μL, 1 mmol) was also injected. Keep the reaction under argon atmosphere. The ee values were determined by GC with RT BDEXM column.

4.5. Calculation of the value of *k* catalyzed by 0.5% ruthenium 3 and 0.5% *t*-BuOK (Fig. 5)

In the racemization system as shown in Scheme 7, the concentration of active ruthenium complex is a constant determined by the amount of ruthenium **3**, so v=dc/dt=k [chiral alcohols], when t=t_A, the concentration of chiral alcohol is determined by the ee% (t_A)×0.33 mol/L, the value of v_A is the slope of point A, which can be calculated by drawing the tangent through the point of A in the curve of AB. Finally, we find that k_A=0.021 min^{-1}. In the same way, we also can find that k_B=0.019 min^{-1}.

4.6. General procedure for dynamic kinetic resolution of secondary alcohols

Dynamic kinetic resolution of 1-phenylethanol: in a 25 mL dry schlenk flask, 220 mg potassium phosphate, and 170 mg molecular sieve 4 Å were placed in. The Schlenk flask was evacuated and filled with argon, CALB 10 mg and Ru catalyst **3** (32 mg 0.05 mmol) were quickly added, then toluene (3 mL) was added, and the mixture was stirred for 5 min, 1-phenylethanol 1a (120 μL, 1 mmol) was then added, and after 5 min isopropenyl acetate (200 μL, 1.8 mmol) was added. Argon atmosphere was maintained throughout the reaction. Yield and ee value were determined by GC: Samples of 20 μL were withdrawn from the reaction mixture by means of a syringe, diluted to 1 mL with CH_2Cl_2/MeOH (1:1), and filtered through a pad of cotton. The solution was filtered and washed with EtOAc, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel with petroleum ether/CH_2Cl_2 (1:1 to 1:10). The product **2a** was obtained as a colorless liquid (151 mg, yield: 94%, ee: 99%).

*4.6.1. Compound **2a**.* (*R*)-acetic acid 1-phenyl-ethyl ester, obtained as a colorless liquid, 151 mg, yield: 94%, 97% (GC), ee: 99% (using RT BDEXM column), $[\alpha]_D^{27}$ +104 (c 0.60, $CHCl_3$); lit.[16]: $[\alpha]_D^{25}$ +106 (c 1.00, Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25–7.36 (5H, m), 5.85–5.92 (1H, m), 2.07 (3H, s), 1.53 (3H, d, J=6 Hz).

*4.6.2. Compound **2b**.* (*R*)-acetic acid 1-*p*-tolyl-ethyl ester, obtained as a colorless liquid, 161 mg, yield: 92%, 96% (GC), ee: 98% (using RT BDEXM column), $[\alpha]_D^{26}$ +113 (c 0.87, $CHCl_3$); lit.[17]: $[\alpha]_D^{25}$ +94.6 (c 5.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (2H, d, J=8 Hz), 7.15 (2H, d, J=8 Hz), 5.82–5.89 (1H, m), 2.33 (3H, s), 2.05 (3H, s), 1.52 (3H, d, J=6 Hz).

*4.6.3. Compound **2c**.* (*R*)-Acetic acid 1-(4-fluoro-phenyl)-ethyl ester, obtained as a colorless liquid, 160 mg, yield: 90%, 90% (GC), ee: 99% (using RT BDEXM column), $[\alpha]_D^{26}$ +89 (c 0.98, $CHCl_3$); $[\alpha]_D^{26}$ +113

(c 0.87, $CHCl_3$); lit.[18]: $[\alpha]_D^{32}$ +92.8 (c 3.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.35 (2H, m), 6.99–7.05 (2H, m), 5.82–5.89 (1H, m), 2.06 (3H, s), 1.52 (3H, d, J=6 Hz).

4.6.4. Compound ***2d***. (*R*)-Acetic acid 1-naphthalen-2-yl-ethyl ester, obtained as a colorless liquid, 200 mg, yield: 95%, 99% (HPLC), ee: 99% (using OD column, hexane/^{i}PrOH=95/5, 0.8 mL/min), $[\alpha]_D^{29}$ +46 (c 0.88, $CHCl_3$); lit.[19]: $[\alpha]_D^{20}$ +33 (c 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.08 (1H, d, J=8 Hz), 7.84–7.88 (1H, m), 7.79 (1H, d, J=8 Hz), 7.43–7.61 (4H, m), 6.65 (1H, t, J=6 Hz), 2.11 (3H, s), 1.70 (3H, d, J=6 Hz).

4.6.5. Compound ***2e***. (*R*)-Acetic acid 1-cyclohexyl-ethyl ester, obtained as a colorless liquid, 150 mg, yield: 90%, 92% (GC) ee: 99% (using RT BDEXM column), $[\alpha]_D^{27}$ +7.2 (c 0.77, $CHCl_3$); lit.[20]: $[\alpha]_D^{24}$ +6.6 (c 2.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.69–4.74 (1H, m), 2.02 (3H, s), 1.65–1.76 (5H, m), 1.12–1.43 (4H, m), 1.16 (3H, d, J=6 Hz), 0.93–1.01 (2H, m).

4.6.6. Compound ***2f***. (*R*)-Acetic acid 1-methyl-heptyl ester, obtained as a colorless liquid, 155 mg, yield: 92%, 95% (GC), ee: 96% (using RT BDEXM column), $[\alpha]_D^{27}$ −2.3 (c 0.73, $CHCl_3$); lit.[21]: $[\alpha]_D^{25}$ −1.9 (c 1.50, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.86–4.92 (1H, m), 2.03 (3H, s), 1.45–1.59 (2H, m), 1.28–1.33 (8H, m), 1.20 (3H, m), 0.88 (3H, t, J=6 Hz).

4.6.7. Compound ***2g***. (*R*)-Acetic acid 1-methyl-3-phenyl-allyl ester, obtained as a colorless liquid, 174 mg, yield: 92%, 95% (GC) ee: 92% (using RT BDEXM column), $[\alpha]_D^{27}$ +130 (c 0.73, CHCl3); lit.[22]: $[\alpha]_D^{20}$ +80 (c 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.24–7.39 (5H, m), 6.60 (1H, d, J=11 Hz), 6.15–6.22 (1H, m), 5.51–5.55 (1H, m), 2.07 (3H, s), 1.41 (3H, d, J=6 Hz).

4.6.8. Compound ***2h***. (*R*)-3-Acetoxy-butyric acid *tert*-butyl ester, obtained as a colorless liquid, 195 mg, yield: 99%, ee: 97% (determined by its deacetylation by using RT BDEXM column), $[\alpha]_D^{27}$ +5.5 (c 1.06, $CHCl_3$); lit.[5m]: $[\alpha]_D^{25}$ +7.59 (c 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 5.15–5.32 (1H, m), 2.35–2.55 (2H, m), 1.99 (3H, s), 1.41 (9H, s), 1.24 (3H, d, J=6 Hz).

4.6.9. Compound ***2i***. (*R*)-Acetic acid 2-(4-chlorophenyl)sulfonyl-1-methyl-ethyl ester, obtained as a colorless liquid, 250 mg, yield: 94%, ee: 94% (using AD-H column, hexane/^{i}PrOH=95/5, 0.7 mL/min), $[\alpha]_D^{26}$ +1.4 (c 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.85 (2H, d, J=9 Hz),7.56 (2H, d, J=9 Hz), 5.27–5.30 (1H, m), 3.46–3.54 (1H, m), 3.20–3.27 (1H, m), 1.82 (3H, s), 1.34 (3H, d, J=6 Hz).

4.6.10. Compound ***2j***. (*R*)-Acetic acid 2-phenylsulfonyl-1-methyl-ethyl ester, obtained as a white solid, mp: 87–89 °C, 85 mg, yield: 85%, ee: 95% (using AS column, hexane/^{i}PrOH=60/40, 0.7 mL/min), $[\alpha]_D^{26}$ +0.24 (c 1.00, $CHCl_3$); lit.[5p]: $[\alpha]_D$ +0.6 (c 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.89 (2H, d, J=7 Hz), 7.64–7.66 (1H, m), 7.56 (1H, d, J=7 Hz), 5.28–5.29 (1H, m), 3.46–3.54 (1H, m), 3.20–3.25 (1H, m), 1.75 (3H, s), 1.32 (3H, d, J=6 Hz).

4.6.11. Compound ***2k***. (*R*)-Acetic acid 2-(4-methylphenyl)sulfonyl-1-methyl-ethyl ester, obtained as a white solid, mp: 64–65 °C,102 mg, yield: 86%, ee: 93% (using AD-H column, hexane/^{i}PrOH=95/5, 0.7 mL/min), $[\alpha]_D^{26}$ +0.10 (c 1.32, $CHCl_3$); lit.[5p]: $[\alpha]_D$ +0.6 ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.77–7.80 (2H, m), 7.36–7.39 (2H, m), 5.26–5.28 (1H, m), 3.44–3.53 (1H, m), 3.18–3.25 (1H,m), 2.46 (3H, s), 1.80 (3H, s), 1.34 (3H, d, J=6 Hz).

4.6.12. Compound ***2l***. (*R*)-Acetic acid 2-(4-bromophenyl)sulfonyl-1-methyl-ethyl ester, obtained as a colorless liquid, 115 mg, yield: 95%, ee: 95% (using AD-H column, hexane/^{i}PrOH=95/5, 0.7 mL/min. Retention time: (*R*)-enantioisomer, 51.38 min; (*S*)-enantioisomer, 47.88 min), $[\alpha]_D^{26}$ +2.4 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.72–7.79 (4H, m), 5.26–5.30 (1H, m), 3.47–3.53 (1H, m), 3.22–3.27 (1H, m), 1.82 (3H, s), 1.34 (3H, d, J=6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.52, 138.42, 132.53, 129.65, 129.13, 64.90, 60.61, 20.67, 20.14; IR (film): 3090, 2983, 2936, 1741, 1576, 1473, 1390, 1374, 1317, 1238, 1153, 1129, 1086, 1069, 1044, 1011, 782, 570 cm^{-1}; ESIMS (m/z): 338 $(M+NH_4)^+$; Anal. Calcd for $C_{11}H_{13}BrO_4S$: C, 41.54; H, 4.40. Found: C, 41.13; H, 4.08.

4.6.13. Compound ***2m***. (*R*)-Acetic acid 2-(4-methoxylphenyl)sulfonyl-1-methyl-ethyl ester, obtained as a pale yellow liquid, 96 mg, yield: 83%, ee: 92% (using AD-H column, hexane/^{i}PrOH=90/10, 0.7 mL/min. Retention time: (*R*)-enantioisomer, 34.19 min; (*S*)-enantioisomer, 32.60 min), $[\alpha]_D^{26}$ +0.33 (c 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.83 (2H, d, J=9 Hz),7.30 (2H, d, J=9 Hz), 5.25–5.28 (1H, m), 3.89 (3H, s), 3.43–3.51 (1H, m), 3.17–3.24 (1H, m), 1.84 (3H, s), 1.33 (3H, d, J=6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.70, 163.89, 131.12, 130.37, 114.50, 65.25, 61.04, 55.72, 20.86, 20.27; IR (film): 2983, 2937, 2845, 1741, 1596, 1499, 1374, 1318, 1299, 1260, 1237, 1145, 1089, 1043, 838, 815, 804, 772, 573 cm^{-1}; ESIMS (m/z): 290 $(M+NH_4^+)$, 295 $(M+Na^+)$. Anal. Calcd for $C_{12}H_{16}O_5S$: C, 53.04; H, 6.03. Found: C, 52.93; H, 5.92.

4.6.14. Compound ***2n***. (*R*)-Acetic acid 2-(diethoxy-phosphoryl)-1-methyl-ethyl ester, obtained as a pale yellow liquid, 180 mg, yield: 80%, ee: 92% (using J-W CYCLOSIL-B column), $[\alpha]_D^{26}$ +8.92 (c 1.00, $CHCl_3$); lit.[23]: $[\alpha]_D^{25}$ +9.7 (c 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.17–5.21 (1H, m), 4.08–4.15 (4H, m), 1.99–2.21 (5H, m), 1.32–1.39 (9H, m); ^{31}P NMR (121.5 MHz, $CDCl_3$, H_3PO_4) δ: 27.07.

4.6.15. Compound ***2o***. (*R*)-Acetic acid 2-(dipropoxy-phosphoryl)-1-methyl-ethyl ester, obtained as a pale yellow liquid, 108 mg, yield: 85%, ee: 90% (determined by ^{31}P NMR), $[\alpha]_D^{27}$ +9.37 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.18–5.22 (1H, m), 3.97–4.03 (4H, m), 1.99–2.21 (5H, m), 1.67–1.72 (4H, m), 1.38 (3H, d, J=6 Hz), 0.96 (6H, t, J=7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.00, 67.14–67.23 (m), 66.19, 33.26, 31.87, 23.78–23.84 (m), 21.02–21.15 (m), 9.97; ^{31}P NMR (121.5 MHz, $CDCl_3$, H_3PO_4) δ: 27.12; IR (film): 3469, 2969, 2880, 1739, 1373, 1243, 995, 556 cm^{-1}; ESIMS (m/z): 267.0 $[M+H]^+$; HRMS-ESI: calcd for $C_{11}H_{24}O_5P(M+H)^+$: 267.1357; found: 267.1356.

4.6.16. Compound ***2p***. (*R*)-Acetic acid 2-(diisopropoxy-phosphoryl)-1-methyl-ethyl ester, obtained as a pale yellow liquid, 70 mg, yield: 70%, ee: >95% (determined by ^{31}P NMR), $[\alpha]_D^{27}$ +10.39 (c 0.60, $CHCl_3$); lit.[24]: $[\alpha]_D^{20}$ +11.1 (c 1.80, acetone); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.16–5.20 (1H, m), 4.68–4.73 (2H, m), 1.89–2.21 (5H, m), 1.26–1.37 (15H, m); ^{31}P NMR (121.5 MHz, $CDCl_3$, H_3PO_4) δ: 25.34.

4.6.17. Compound ***2q***. (*R*)-Acetic acid 2-(dibutoxy-phosphoryl)-1-methyl-ethyl ester, obtained as a pale yellow liquid, 85 mg, yield: 75%, ee: 92% (determined by ^{31}P NMR), $[\alpha]_D^{27}$ +9.34 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.18 (1H, m), 4.00–4.07 (4H, m), 1.95–2.24 (5H, m), 1.62–1.69 (4H, m), 1.37–1.46 (7H, m), 0.94 (6H, t, J=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.96, 66.16, 65.37 (q, J=4 Hz), 33.19, 32.40–32.47 (m), 31.79, 20.99–21.15 (m), 18.64, 13.50; ^{31}P NMR (121.5 MHz, $CDCl_3$, H_3PO_4) δ: 27.44; IR (film): 3468, 2960, 2935, 2875, 1740, 1459, 1373, 1243, 1031, 979, 956, 902, 556 cm^{-1}; ESIMS (m/z): 295.0 $(M+H)^+$; HRMS-ESI: calcd for $C_{13}H_{28}O_5P(M+H)^+$: 295.1670; found: 295.1669.

4.6.18. Compound ***2r***. (*R*)-Acetic acid 1-(diisopropoxy-phosphoryl)-ethyl ester, obtained as a pale yellow liquid, 215 mg, yield: 88%, ee: >95% (Determined by ^{31}P NMR), $[\alpha]_D^{27}$ +17.4 (c 0.92, $CHCl_3$); lit.[23]: $[\alpha]_D^{25}$ +20.1 (c 1.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ:

5.13–5.21 (1H, m), 4.69–4.79 (2H, m), 2.09 (3H, s), 1.38–1.45 (3H, m), 1.23–1.33 (12H, m); ^{31}P NMR (121.5 MHz, $CDCl_3$, H_3PO_4) δ: 20.28.

Acknowledgements

We appreciate kind suggestions from Prof. J.-B. Chen, and Dr. Y.-H. Zhang. This Project was financially supported by the National Natural Science Foundation of China (Grant No. 20872125 and 20672132).

References and notes

1. (a) *Organic Synthesis with Enzymes in Non-Aqueous Media*; Carrea, G., Riva, S., Eds.; Wiley-VCH: Weinheim, Germany, 2008; (b) *Asymmetric Organic Synthesis with Enzymes*; Gotor, V., Alfonso, I., Garcı′a-Urdiales, E., Eds.; Wiley-VCH: Weinheim, Germany, 2008.
2. (a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321; (b) Kim, M.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578; (c) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247; (d) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291; (e) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226; (f) Ahn, Y.; Ko, S.; Kim, M.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647.
3. Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *42*, 7623.
4. (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem.* **1997**, *109*, 1256; *Angew. Chem. Int. Ed.* **1997**, *36*, 1211; (b) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.
5. (a) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037; (b) Huerta, F. F.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 1209; (c) Runmo, A.-B. L.; Pàmies, O.; Faber, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 2983; (d) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1261; (e) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2001**, *343*, 726; (f) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2002**, *344*, 947; (g) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 4022; (h) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 9006; (i) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 4815; (j) Persson, B. A.; Huerta, F. F.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 5237; (k) Edin, M.; Steinreiber, J.; Bäckvall, J.-E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5761; (l) Martín-Matute, B.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, *69*, 9191; (m) Kim, M.-J.; Choi, Y. K.; Choi, M. Y.; Kim, M. J.; Park, J. *J. Org. Chem.* **2001**, *66*, 4736; (n) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 409; (o) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 2487; (p) Kiełbasiński, P.; Rachwalski, M.; Mikołajczyk, M.; Moelands, M. A. H.; Zwanenburg, B.; Rutjes, F. P. J. T. *Tetrahedron: Asymmetry* **2005**, *16*, 2157.
6. (a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M. J.; Park, J. *Angew. Chem.* **2002**, *114*, 2479; *Angew. Chem., Int. Ed.* **2002**, *41*, 2373; (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M. J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972.
7. (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem.* **2004**, *116*, 6697; *Angew. Chem., Int. Ed.* **2004**, *43*, 6535; (b) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817; (c) Träff, A.; Bogaćr, K.; Warner, M.; Bäckvall, J.-E. *Org. Lett.* **2008**, *10*, 4807.
8. (a) Kim, N.; Ko, S. B.; Kwon, M. S.; Kim, M. J.; Park, J. *Org. Lett.* **2005**, *7*, 4523; (b) Ko, S. B.; Baburaj, B.; Kim, M. J.; Park, J. *J. Org. Chem.* **2007**, *72*, 6860; (c) Kim, M. J.; Choi, Y. K.; Kim, S.; Kim, D.; Han, K.; Ko, S. B.; Park, J. *Org. Lett.* **2008**, *10*, 1295.
9. Chen, Q. H.; Yuan, C. Y. *Chem. Commun.* **2008**, 5333.
10. The chemical shift of OH of 1-phenylethanol is about 1.61 ppm, however, its value is only about 1.23 ppm in the racemization system, which may indicate that when 1-phenylethanol coordinates to the ruthenium catalyst, the original hydrogen bond between two 1-phenylethanols disappears. Record on ^{1}H NMR of racemization system: in a 25 mL absolute dry schlenk flask, 50 mg dry potassium phosphate and 15 mg ruthenium **3** were placed in, the Schlenk flask was evacuated and filled with argon another three time, then toluene-d_8 (0.75 mL) and (*S*)-1-Phenylethanol (12 μL, 0.1 mmol) were injected; keep the reaction under argon atmosphere. Two hours later, the racemization system was terminated and detected by Bruker AM-400 (400 MHZ) spectrometer.
11. (a) Nyhlén, J.; Privalov, T.; Bäckvall, J.-E. *Chem.—Eur. J.* **2009**, *15*, 5220; (b) Åberg, J. B.; Nyhlén, J.; Martín-Matute, B.; Privalov, T.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 9500.
12. (a) Xi, Q.; Zhang, W.; Zhang, X. *Synlett* **2006**, 945; (b) Csjernyik, G.; Bogar, K.; Bäckvall, J. E. *Tetrahedron Lett.* **2004**, *45*, 6799; (c) Kim, W.-H.; Karvembu, R.; Park, J. *Bull. Korean Chem. Soc.* **2004**, *25*, 931; (d) Ito, M.; Osaku, A.; Kitahara, S.; Hirakawa, M.; Ikariya, T. *Tetrahedron Lett.* **2003**, *44*, 7521; (e) Pàmies, O.; Bäckvall, J.-E. *Chem.—Eur. J.* **2001**, *7*, 5052; (f) Koh, J. H.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545.
13. (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40; (b) Sarvary, I.; Almqvist, F.; Frejd, T. *Chem.—Eur. J.* **2001**, *7*, 2158.
14. (a) Hiraoka, C.; Matsuda, M.; Suzuki, Y.; Fujieda, S.; Tomita, M.; Fuhshuku, K.; Obata, R.; Nishiyama, S.; Sugai, T. *Tetrahedron: Asymmetry* **2006**, *17*, 3358; (b) Wan, X.; Meng, Q.; Zhang, H.; Sun, Y.; Fan, W.; Zhang, Z. *Org. Lett.* **2007**, *9*, 5613; (c) Zhang, H.; Hou, X.; Dai, L.; Luo, Z. *Tetrahedron: Asymmetry* **2007**, *18*, 224; (d) Chen, Q. H.; Wang, K.; Yuan, C. Y. *New J. Chem.* **2009**, *33*, 972.
15. (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931; (b) Żymańczyk-Duda, E.; Klimek-Ochab, M.; Kafarski, P.; Lejczak, B. *J. Organomet. Chem.* **2005**, *690*, 2593; (c) Zhang, Y. H.; Li, J. F.; Yuan, C. Y. *Tetrahedron* **2003**, *59*, 473.
16. Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531.
17. Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346.
18. Naemura, K.; Murata, M.; Tanaka, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3285.
19. Bakker, M.; Spruijt, A. S.; Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1801.
20. Naemura, K.; Fukuda, R.; Murata, M.; Konishi, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2385.
21. Kato, K.; Irimescu, R.; Saito, T.; Yokogawa, Y.; Takahashi, H. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 203.
22. Kenyon, J.; Partridge, S. M.; Phillips, H. *J. Chem. Soc.* **1936**, 85.
23. Zhang, Y. H.; Yuan, C. Y.; Li, Z. Y. *Tetrahedron* **2002**, *58*, 2973.
24. Woschek, A.; Lindner, W.; Hammerschmidt, F. *Adv. Synth. Catal.* **2003**, *345*, 1287.