An unexpected ruthenium complex and its unique behavior as catalyst in dynamic kinetic resolution of secondary alcohols†‡

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A ruthenium complex was accidentally synthesized and its unique catalytic behavior in dynamic kinetic resolution of various types of secondary alcohols, particularly for those bearing additional functional groups, is described.

Enantiomerically pure compounds are of great importance in pharmaceutical, agrochemical and other fine chemical industries. In the last decades, many asymmetric transformations have been developed for the preparation of enantiomerically pure compounds by employing chiral transition-metal complexes, enzymes or organocatalysts.[1] However, direct resolution of racemic mixtures is still the most popular method to prepare enantiomerically pure compounds in industry.[2] Enzymatic kinetic resolutions are usually very efficient in stereoselectivity, but they have an intrinsic limitation: not more than 50% of the enantiomer could be resolved. Dynamic kinetic resolution (DKR), in which an *in situ* racemization of an undesired enantiomer is coupled with kinetic resolution (KR), may be the best way to overcome this limitation.[3] A number of Rh, Ir, and Ru complexes have been studied for the racemization of secondary alcohols.[4] However, only very few of them have been successfully incorporated in chemoenzymatic kinetic resolution (Fig. 1).[5] In 1997, the Backvall group first reported an efficient process for DKR by combining ruthenium complex **1** with *Candida antarctica* lipase B (CALB).[5a] Later, the Park and Kim group developed a new type of ruthenium complex **2a**, which substantially improved the efficiency of DKR.[5b,c] A very active racemization catalyst **2b** which remarkably reduced the reaction time of DKR was introduced by the Backvall group.[5d,e] Recently, the Park and Kim group has initiated a mild and reusable system of DKR with catalysts **2c** and **2d**.[5f,g] However, to the best of our knowledge, catalyst **1** needs harsh conditions, while catalyst **2a** and **2b** require strong base *t*BuOK, in addition, catalysts can not be reused; catalysts **2c** and **2d** make the DKR more smoothly, however, only secondary alcohols without functional groups have been studied. Furthermore, for catalysts **2a** to **2d**, a good leaving group such as a chlorine atom is usually essential, which can easily provide a coordination site. Additionally, for these secondary alcohols bearing sulfonyl or phosphonate moiety, they easily coordinate to ruthenium, therefore, none of the reported catalysts can operate smoothly and efficiently.[6] For these reasons, synthesis of a novel and more effective and highly compatible racemization catalyst for the DKR process is a major challenge. Herein we wish to report a synthetic protocol leading to cyclopentadienyl benzoyl ruthenium(II) complex **3**, which bears a unique metallic spiro structure. It is interesting to note that, with the aid of this complex, some optically active secondary alcohols were racemized smoothly. In the meantime, while the reaction system was coupled with lipase, a typical and effective DKR of various type of secondary alcohols was achieved.

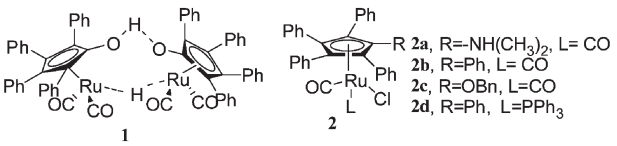
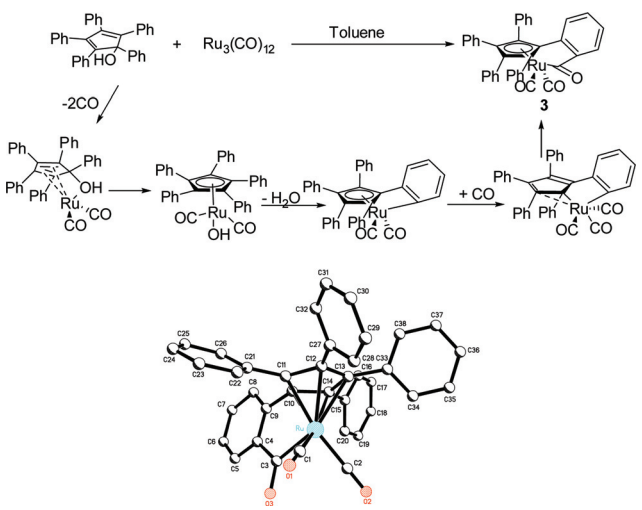


Fig. 1 Ruthenium complexes used in racemization during DKR.

Cyclopentadienyl benzoyl ruthenium(II) complex **3**‡ was accidentally synthesized by the reaction of $Ru_3(CO)_{12}$ with pentaphenylcyclopenta-2,4-dienol with 41% yield. This reaction incredibly includes oxidative addition and activation of a carbon–hydrogen bond, as well as functionalization of the benzene ring. A tentative mechanism is postulated as shown in Scheme 1.[7] The structure of ruthenium complex **3** was confirmed by an X-ray diffraction study. A detailed study of this reaction mechanism is being carried out in our group. The reaction involved in the preparation of ruthenium complex **3** is interesting



Scheme 1 Synthesis of ruthenium complex **3**.

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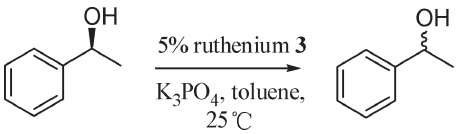
‡ Moiety formula: $C_{38}H_{24}O_3RuC_7H_8$, formula weight: 721.78, space group: $P2_1/c$, cell: a = 11.9868(19), b = 16.875(3), c = 17.706(3), β = 104.126(3), temperature: 293 K, D_c: 1.380 g cm^{-3}, Z: 4. Data completeness = ratio = 0.997, θ(max) = 26.000, R (reflections) = 0.0714 (3636), $wR2$ (reflections) = 0.2022 (6797), S = 0.950.

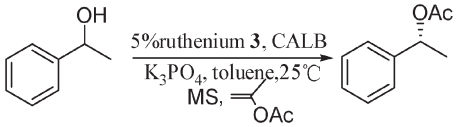
because it may include a novel method to functionalize the carbon–hydrogen bond that is a topic of current interest in organometallic chemistry.

As far as we are aware, most reported ruthenium complexes used in the DKR process, as a rule, contain a good leaving group such as a chloride or bromide,[5b–g] or appear unstable and lead to an activated ruthenium intermediate that contains 16 coordinated electrons.[5a] Our experimental results on ruthenium complex **3** are very intriguing, since it does not meet with the general structural requirements of previous reported racemization catalysts. Additionally, complex **3** is stable in air until the temperature reaches 285 °C. However, as we have found even at room temperature, a mixture of 5% ruthenium complex **3** and one equivalent of potassium phosphate was sufficient to racemize (*S*)-1-phenylethanol within 6 h (Scheme 2). After racemization, the catalyst can be recovered and reused.[8]

We were surprised by this unusual racemization catalysis, which encouraged us to study what would happen when



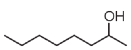
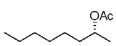
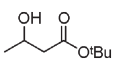
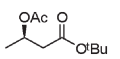
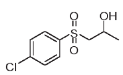
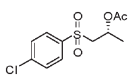
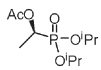
Scheme 2 Racemization of (*S*)-1-phenylethanol.



Scheme 3 DKR of 1-phenylethanol.

ruthenium complex **3** was allowed to couple with CALB in the presence of an alcohol and an acyl donor. We are aware that many metal complexes are known to catalyze fast racemization of alcohols, but upon their combination with an enzyme, catalytic kinetic resolutions are usually not trivial.[4,5] Our initial attempts to

Table 1 DKR of various secondary alcohols

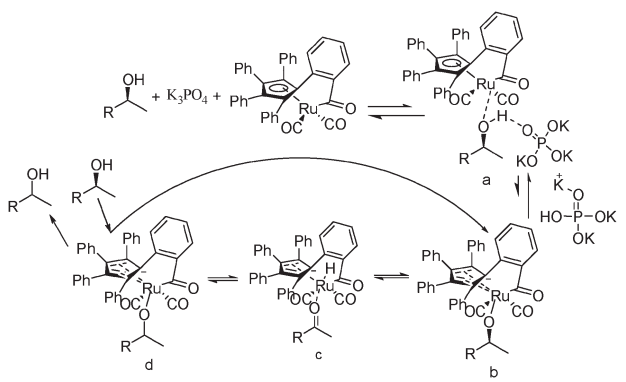
Entry	Substrate (**1a–11a**)	CALB/mg	Time/h	Temp./°C	Product (**1b–11b**)	Yield (%)[ab]	ee (%)
1		10	10	25		94 (97)	99[c]
2		10	10	25		92 (96)	98[c]
3		10	10	25		90 (90)	99[c]
4		10	20	25		95 (99)[d]	99[d]
5		6	20	50		90 (92)	99[c]
6		4	20	50		92 (95)	96[c]
7		6	20	50		92 (95)	92[c]
8		20	20	25		99[f]	97[e]
9		50	20	25		94[f]	94[d,i]
10		80	20	25		80[f,g]	92[c]
11		80	20	25		88[f,g]	>95[h]

[a] Isolated yield. [b] Numbers in parentheses were determined by GC or HPLC. [c] Determined by GC with chiral column. [d] Determined by HPLC with chiral column. [e] From GC with chiral column of the hydrolyzed product. [f] The amount of catalyst was increased to 9%. [g] The amount of K_3PO_4 was reduced to 10%. [h] From the ^{31}P NMR of the hydrolyzed product. [i] The absolute configuration of 9b was determined by comparison of ref. 6*a*.

combine ruthenium complex **3** with an enzymatic kinetic resolution were unsuccessful. It was supposed that these unsuccessful trials might be due to the presence of a trace amount of water in this system. As expected, after addition of 4 Å molecular sieves to the reaction system, an acetate of 1-phenylethanol was obtained in 10 h with 97% yield and 99% ee (Scheme 3).

To study the scope of the application of this unusual ruthenium complex **3**, a variety of substrates was prepared and examined (Table 1). As indicated in Table 1, our catalyst system displayed a high efficiency towards benzylic alcohols (Table 1, entries 1–4), 1-phenylethanol, 1-(4-methylphenyl)ethanol, and 1-(4-fluorophenyl)ethanol. These alcohols were successfully converted to (*S*)-aceta-tes in 10 h with high chemical yields and excellent enantioselectivities (Table 1, entries 1–3). Besides, the electronic effect on the reaction involving benzylic alcohols was not obvious. A naphthyl derivative also gave excellent results, but a longer reaction time (up to 20 h) was needed (Table 1, entry 4). For aliphatic alcohols, heating at 50 °C and a lesser amount of CALB were required for satisfactory results concerning both yields and enantioselectivities (Table 1, entries 5–6). Hydroxyl compounds bearing an additional functional group worked very well with this complex **3**. For 4-phenylbut-3-en-2-ol, with less CALB and higher temperature, the expected product was obtained with 95% chemical yield and 92% ee. (Table 1, entry 7). 3-Hydroxybutyric acid *tert*-butyl ester was successfully transformed to the corresponding (*S*)-acetate with high yield and excellent enantioselectivity (Table 1, entry 8). The (*S*)-acetate of *p*-chlorophenylsulfonylpropan-2-ol was obtained in 94% chemical yield and 94% ee (Table 1, entry 9). As for α-hydroxylalkylphosphonate and β-hydroxylalkylphosphonate, the corresponding acetoxyphosphonates were also obtained in high chemical yields and excellent enantioselectivities (Table 1, entries 10–11). Overall, our catalyst works well with those secondary alcohols that contain additional functional groups. It is worthy to note that, for substrates **7a**, **9a**, **10a**, it was reported that when catalyst **1** or **2b** was used, oxidation usually occurred;[5e,6] while our catalyst had not such drawbacks.

There is no good leaving group coordinated to ruthenium in our catalyst **3**, so an alternative hydrogen transfer was involved in racemization. As shown in Scheme 4, a mechanism of racemization was tentatively proposed, that was supported by followed experimental evidence: the catalyst is reusable; the K_3PO_4 is not active enough to produce alcoholic minus-ion directly; only a catalytic amount of K_3PO_4 is needed to catalyze DKR of alcohols with phosphonate; acetone achieved by DKR does not interfere with the racemization process, this is probably due to the presence of an intramolecular hydrogen transfer in racemization.[5e]



Scheme 4 A tentative mechanism for racemization.

In summary, we have introduced a new ruthenium complex **3** that bears a unique metallic spiro structure. This new ruthenium complex was successfully used as a powerful catalyst in DKR of secondary alcohols under mild conditions in a short reaction time, particularly for those alcohols that had additional functional groups. In these reactions, higher chemical yields and excellent enantioselectivities were achieved. Further detailed investigations in connection to the reaction mechanism of this catalytic racemization process will be undoubtedly helpful to the design of new and more effective ruthenium complexes as powerful catalysts in the DKR processes in the quest for optically pure compounds.

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7 When 4 Å molecular sieve was added to the reaction, the yield was increased dramatically up to 16% in general. It is indirect experimental evidence showing that water molecules were formed in this reaction.

8 Catalyst can be recovered with 90% yield after racemization and the recovered catalyst can be used with same activity.