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Readily Available Ruthenium Complex for Efficient Dynamic Kinetic Resolution of Aromatic α-Hydroxy Ketones

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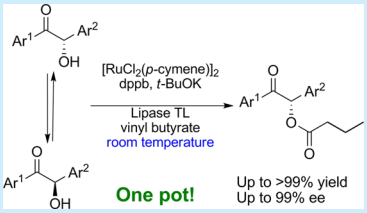
Supporting Information

ABSTRACT: A ruthenium complex formed from commercially available [Ru(*p*-cymene)Cl_2]$_2$ and 1,4-bis(diphenylphosphino)butane catalyzes the racemization of aromatic α-hydroxy ketones very efficiently at room temperature. The racemization is fully compatible with a kinetic resolution catalyzed by a lipase from *Pseudomonas stutzeri*. This is the first example of dynamic kinetic resolution of α-hydroxy ketones at ambient temperature in which the metal and enzyme catalysts work in concert in one pot at room temperature to give quantitative yields of esters of α-hydroxy ketones with very high enantioselectivity.



Dynamic kinetic resolutions (DKRs) are powerful synthetic tools for synthesizing single-enantiomer products from racemic mixtures. By using a DKR, it is possible to circumvent the 50% theoretical maximum yield of kinetic resolutions (KRs). The principle governing this procedure is the combination of an *in situ* racemization of the substrate with a kinetic resolution process in one pot. Thus, the racemization occurs simultaneously with the KR, and 100% of a racemic mixture can be converted into a single enantiomer of the product.[1] In the past decade, DKRs have been widely used for the preparation of enantiopure esters from *sec*-alcohols by combining transition-metal-catalyzed racemizations with enzyme-catalyzed kinetic resolutions.[1,2] Finding reaction conditions under which both catalysts, with their quite different natures, work efficiently in the same reaction mixture is a major challenge that must be overcome for every single combination of transition metal catalyst and enzyme. Ruthenium(II) complexes containing substituted cyclopentadienyl ligands (**1** and **2a**,**b** in Figure 1) are well-known for their excellent activity in combination with lipases and proteases for the DKRs of *sec*-alcohols.[1,2b−j]

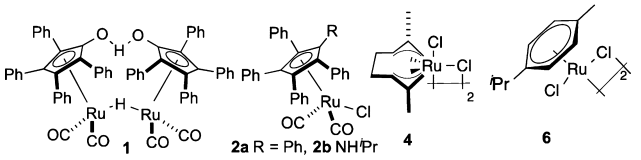
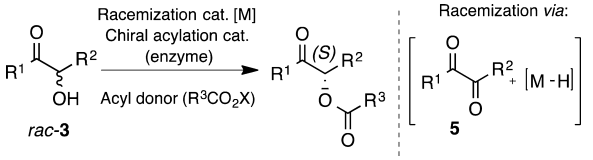


Figure 1. Ruthenium complexes used in the racemization of *sec*-alcohols.

α-Hydroxy ketones are a very special group of *sec*-alcohols (Scheme 1). They are important building blocks that are used in the synthesis of a wide range of biologically active molecules.[3] Current methods for their preparation include asymmetric benzoin condensations,[4] asymmetric reductions of α-diketones,[5] and enzyme-catalyzed kinetic resolutions.[6,7]

Scheme 1. DKR of α-Hydroxy Ketones



Dynamic kinetic resolution is an alternative method to obtain enantiopure α-hydroxy ketones in high yields (Scheme 1).[7,8] However, although they are *sec*-alcohols, the DKR of α-hydroxy ketones is challenging. The presence of the carbonyl and alcohol functionalities in close proximity enables coordination of the substrate to the metal center in a bidentate fashion, which can affect the catalytic activity of the metal complex. Also, the racemization of *sec*-alcohols[9] involves formation of carbonyls and metal hydride intermediates. In the case of α-hydroxy ketones (**3**), 1,2-diketones are formed. The hydride can be delivered back to either of the two carbonyl groups. This results in the formation of a mixture of α-hydroxy ketones during the racemization process, except in those cases in which the two substituents, R^1 and R^2 (Scheme 1), are identical or when these impart a large steric and/or electronic differentiation that results in a selective reduction of one of the carbonyls. Additionally, the optimal enzyme for the KR of α-hydroxy ketones with two aromatic substituents is lipase TL (from *Pseudomonas stutzeri*). The optimal temperature for activity with this enzyme is room temperature, and thus it is incompatible with several racemization catalysts that require elevated temperatures. Efficient DKRs of α-hydroxy ketones with one aromatic and one aliphatic substituent have been achieved with CALB.[8] CALB is a thermostable enzyme, and therefore racemization can be performed at high temperatures without compromising the enzyme activity. However, this

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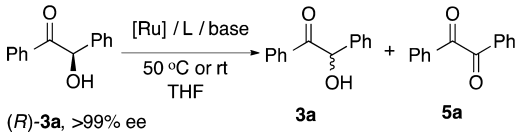
reaction is limited to those substrates with either a methyl or an ethyl substituent at the alcohol carbon.

DKRs of aromatic α-hydroxy ketones (R^1 and R^2 = Ar) have been carried out using Shvo's dimeric ruthenium complex (**1**) in combination with lipase TL.[7] Complex **1** is activated by heat (ideally >80 °C), resulting in the formation of two monomeric species, both of which are catalytically active.[9] This Ru complex can be used at slightly lower temperatures, but it then requires rather long reaction times. In combination with lipase TL, Shvo's catalyst was used at 50 °C in the DKR of aromatic α-hydroxy ketones.[7]

Due to the low activity of the enzyme at this temperature, the DKR had to be carried out in several steps: first the substrate was exposed exclusively to the enzyme catalyst (KR), which resulted in the formation of up to 50% of the ester product. This was followed by the addition of Shvo's complex and more of the enzyme catalyst. This sequence gave good results, but currently, there are no efficient catalytic enzyme/transition metal combinations working simultaneously in one pot for the DKR of aromatic α-hydroxy ketones that do not require very long reaction times. In this paper, we report the first example of a metal catalyst that can racemize these substrates at ambient temperature. This makes the catalytic racemization fully compatible with lipase TL, allowing the first efficient DKR of aromatic α-hydroxy ketones in which both catalysts work in concert under the same reaction conditions and are present in the reaction flask from the start, avoiding the need for successive additions of catalysts.

We started our study by searching for a metal complex that could racemize (*R*)-benzoin **3a** (>99% ee) at 50 °C in THF. The results are summarized in Table 1. Ru(II) complex **2a**, which is a highly active catalyst for the racemization of *sec*-alcohols,[2e,f] and Ru(IV) complex **4**, excellent for the isomerization of allylic alcohols,[10] were chosen for the initial screening. Neither complex **2a** nor complex **4** was effective for the racemization of **3a** (Table 1, entries 1 and 2). The activity of complex **4** slightly improved in the presence of Cs_2CO_3 to give a product with 75% ee after 1 h, along with 16% of unwanted diketone **5a** (Table 1, entry 3). *p*-Cymene Ru(II) complex **6** has been used successfully in DKRs of *sec*-alcohols,[11] and complexes formed from complex **6** and chiral bidentate ligands have been widely studied in asymmetric transfer hydrogenation.[12] However, complex **6** had little activity in the racemization of α-hydroxy ketones (Table 1, entry 4). When a base was added, the racemization slightly improved, albeit with concomitant formation of diketone byproduct **5a** (Table 1, entry 5). We then investigated a variety of ligands (Figure 2) in combination with complex **6**. Monodentate

Table 1. Racemization of Benzoin 3a[a]



(*R*)-**3a**, >99% ee **3a** **5a**

	Ru/ligand/base	*t* (h)	ee of **3a** (%)[b]	**5a**[c]
1	**2a**/−/*t*-BuOK	2	99	
2	**4**/−/−	1	94	14
3	**4**/−/Cs_2CO_3	1	75	16
4	**6**/−/−	2	95	4
5	**6**/−/*t*-BuOK	2	70	10
6	**6**/**7**/*t*-BuOK	2	77	28
7	**6**/**8**/*t*-BuOK	2	91	9
8	**6**/**9**/*t*-BuOK	2	90	7
9	**6**/**10**/*t*-BuOK	2	46	9
10	**6**/**11**/*t*-BuOK	2	37	13
11	**6**/**12**/*t*-BuOK	2	37	14
12	**6**/**13**/*t*-BuOK	2	6	12
13	**6**/**14**/*t*-BuOK	2	1	11
14[d]	**6**/**14**/*t*-BuOK	2	0.5	8
15[e]	**6**/**14**/*t*-BuOK	2	1	10
16	−/−/*t*-BuOK	2	99	2

[a]All reactions were carried out using (*R*)-**3a** (0.05 mmol, 10.5 mg), Ru (5 mol %) at 50 °C in dry THF (0.5 mL) under an argon atmosphere. [b]Determined by HPLC using a Chiralpak IC column. [c]Determined by ^{1}H NMR spectroscopy. [d]At rt. [e]With 2.5 mol % of Ru at rt.

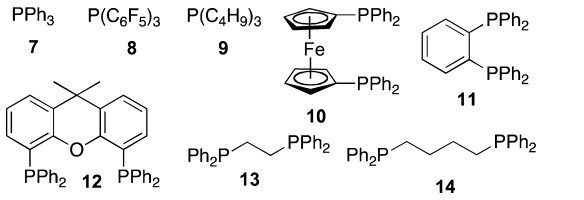


Figure 2. Ligands tested.

phosphines (**7**−**9**, Figure 2) did not perform well in the racemization (Table 1, entries 6−8). On the other hand, the racemization rate increased significantly in the presence of bidentate phosphines **10**−**14** (Table 1, entries 9−13). In particular, with 1,4-bis(diphenylphosphino)butane (dppb, **14**), complete racemization occurred within 2 h (Table 1, entry 13). Furthermore, the temperature could be decreased to rt (Table 1, entry 14), and the catalyst loading decreased to 2.5 mol % of Ru (Table 1, entry 15). A control experiment in the presence of *t*-BuOK (without Ru catalyst and ligand) resulted in no racemization (Table 1, entry 16). To test the scope of this catalytic system, we also investigated the racemization of (*S*)-1-phenylethanol using the same conditions as in Table 1, entry 15. However, no racemization occurred.

Encouraged by the excellent results obtained for the racemization of α-hydroxy ketone **3a** at room temperature, we next attempted to combine the racemization with a KR catalyzed by lipase TL (from *Pseudomonas stutzeri*). The compatibility of the two processes in one pot was surprisingly good; the metal complex and the enzyme could both be present in the reaction mixture from the start; that is, successive catalyst additions and/or successive KR/DKR were not required (Scheme 2). Importantly, under the DKR conditions, the formation of undesired diketone **5** was minimized, and only in certain cases was it formed in up to 6−7%. The DKR of benzoin **3a** gave enantiopure ester **15a** in 91% isolated yield with 99% ee. Aromatic α-hydroxy ketones with substituents in the *para* or *meta* positions were good substrates and afforded esters **15b**−**15f** and **15h** in excellent yields and enantioselectivities. However, a limitation was found for substrates with substituents in the *ortho* positions (e.g., **3g**); such substrates were not acylated by the enzyme. α-Hydroxy ketones bearing heteroaromatics such as thiophene and furans underwent the DKR to give excellent yields of the products (**15i**−**j**) with excellent enantioselectivities. When the two aryl substituents on the substrates were not identical, the DKR gave a mixture of constitutional isomeric products. This is due to the mechanism of racemization, which involves the formation of unsymmetrical diketone intermediates (vide

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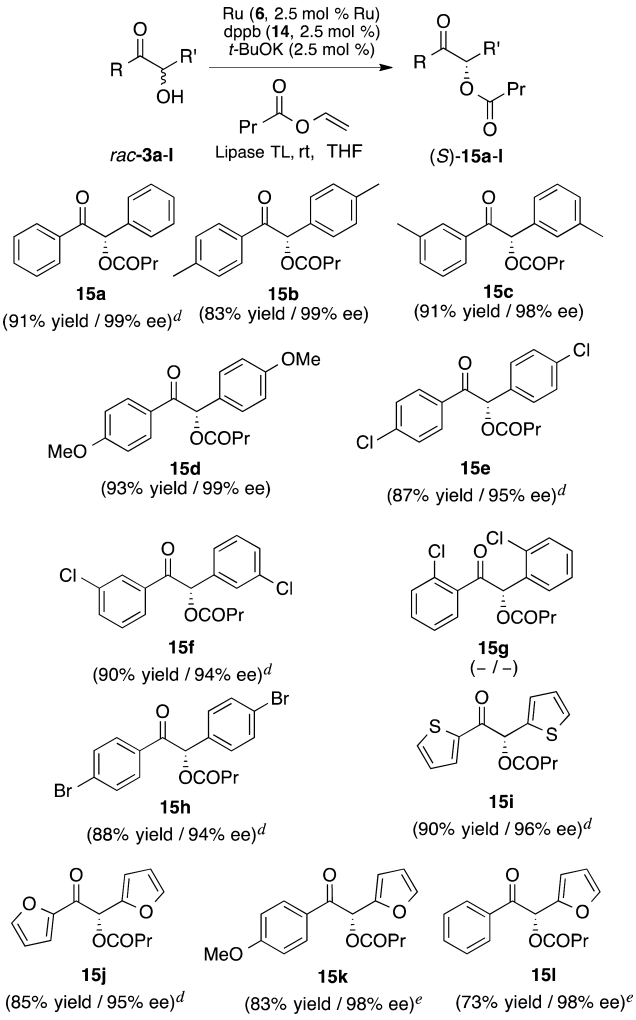
Scheme 2. DKR of a Variety of *rac*-α-Hydroxy Ketones 3[a,b,c]



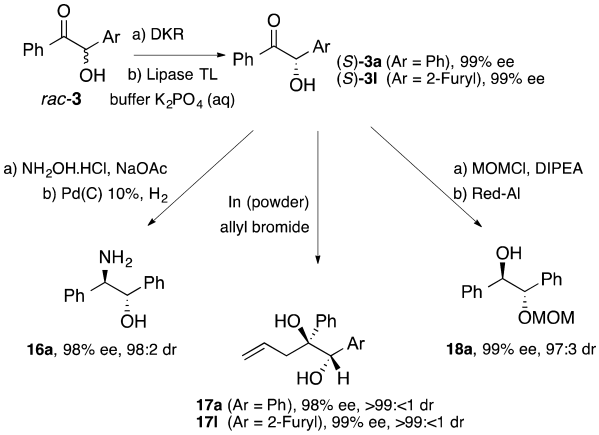
[a]Lipase LT (40 mg), *rac*-**3** (0.2 mmol), vinyl butyrate (0.6 mmol, 76 μL), Ru (**6**, 0.0025 mmol, 1.6 mg, 2.5 mol % of Ru), dppb (**14**, 0.005 mmol, 2 mg, 2.5 mol %), *t*-BuOK (0.5 M in anhydrous THF, 10 μL, 0.0025 mmol, 2.5 mol %) in dry THF (2 mL), at rt under an Ar atmosphere for 24 h. [b]Isolated yields. [c]Enantioselectivities were determined by HPLC (see Supporting Information). [d]With 6–7% of diketone **5** formed. [e]Diketone **5** and isomeric acetates (see Scheme S1) were observed in the ^{1}H NMR spectrum of the crude mixture.

supra, Scheme 1). In certain cases, for substrates whose aryl functionalities had sufficiently different electronic properties (a higher electronic density on the aryl substituent next to the carbonyl functionality), a selective DKR was achieved. Two examples that gave reasonably high yields of single constitutional isomers are shown in Scheme 2, **15k–l**. Lipase TL has very low activity in the KR of α-hydroxy ketones bearing alkyl substituents at the alcohol carbon,[13] thus these types of substrates were not investigated.

To evaluate the scalability of the reaction, the DKR of **3a** was conducted on a 2 mmol scale. The catalyst loading could be lowered to 1 mol % of Ru (0.5 mol % of dimer **6**) (See Supporting Information). After 24 h, ester **15a** was obtained in 97%, along with diketone **5a** in only 3%, as determined by ^{1}H NMR spectroscopy of the crude mixture. After purification, **15a** was isolated in 94% yield with >99% ee. This experiment demonstrates the simplicity of this DKR procedure and, therefore, its potential to be used for the synthesis of enantiopure esters of α-hydroxy ketones on a large scale.

α-Hydroxy ketones are important synthetic intermediates in organic chemistry.[3] This DKR method can be used as the key step in the preparation of a variety of functionalized molecules, such as enantiopure amino alcohols (**16a**)[3b] and diols (**17a**, **17l**) or diol derivatives (**18a**)[3e–g] (Scheme 3).

Scheme 3. α-Hydroxy Ketones as Synthetic Intermediates



In conclusion, we have developed the first highly efficient protocol for the DKR of α-hydroxy ketones in a one-pot procedure. Commercially available $[Ru(p\text{-cymene})Cl_2]_2$ and 1,4-bis(diphenylphosphino)butane allowed the racemization to occur at room temperature, which is the optimal reaction temperature for the enzyme used. With this DKR procedure, esters of α-hydroxy ketones are obtained in high yields with high enantioselectivities. Their versatility as synthetic intermediates in organic synthesis has been shown by synthesizing a variety of diols and amino alcohols in a diastereo- and enatioselective manner.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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