ORGANIC LETTERS

2000
Vol. 2, No. 8
1037−1040

Dynamic Kinetic Resolution of α-Hydroxy Acid Esters

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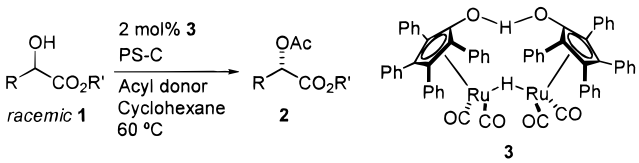
Received January 20, 2000

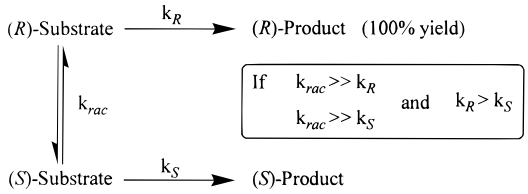
ABSTRACT



Enzymatic resolution in combination with ruthenium-catalyzed racemization of the substrate led to dynamic kinetic resolution of α-hydroxy esters in good yields and excellent ee's. Studies of different parameters showed that the best results were obtained using *Pseudomonas cepacia* lipase, ruthenium catalyst 3, and 4-chlorophenyl acetate as acyl donor in cyclohexane.

Since 1987, "the enzymatic second-order asymmetric transformation of different compounds" or *dynamic kinetic resolution* (DKR) has been the focus of many studies.[1] This is due to the fact that, with this new methodology, the main drawback of the traditional kinetic resolution (maximum 50% yield) is overcome. With DKR the unreactive enantiomer is continuously racemized and the product can be obtained optically pure in 100% yield (Scheme 1).

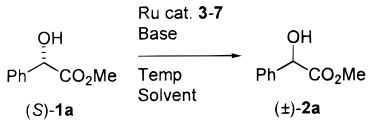
Scheme 1. Dynamic Kinetic Resolution (DKR)



In connection with our work on the combination of enzyme and transition metal catalysis in organic synthesis,[2] we recently reported on the dynamic kinetic resolution (DKR) of secondary alcohols[3] and diols.[4] In these reactions a ruthenium catalyst racemizes a secondary alcohol during enzymatic esterification. Here, we report our results on the dynamic resolution of α-hydroxy esters, applying this racemization−esterification methodology.

We first investigated the racemization[5] of (*S*)-methyl mandelate[6] [(*S*)-**1a**] with different ruthenium catalysts, **3**−**7** (Scheme 2). The best results in the racemization were obtained with ruthenium complexes **3** and **4**. Complex **3** has been successfully used previously for the racemization of

Scheme 2. Racemization of (*S*)-Methyl Mandelate



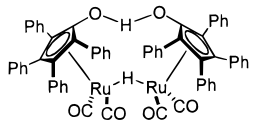
(1) Caddick, S.; Jenkis, K. *Chem. Soc. Rev.* **1996**, 447−456. (b) Stecher, H.; Faber, K. *Synthesis* **1997**, 1−16. (c) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (d) Stürmer, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1173−1174.

(2) Bäckvall, J. E.; Gatti, R.; Schink, H. E. *Synthesis* **1993**, 343−348. (b) Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 577−584.

(3) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J. E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211−1212. (b) Persson, B. A.; Larsson, A. L.; LeRay, M.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 1645−1650.

(4) Persson, B. A.; Huerta, F. F.; Bäckvall, J. E. *J. Org. Chem.* **1999**, *64*, 5237−5249.

10.1021/ol000014+ CCC: $19.00
Published on Web 03/28/2000



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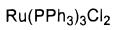

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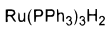

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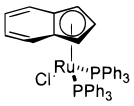

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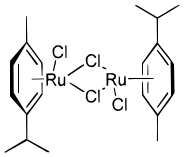

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secondary alcohols in toluene at 70 °C. This procedure was initially used for the racemization of (*S*)-**1a**. However, low solubility of the catalyst in this solvent together with low conversions made it necessary to change solvent. The use of cyclohexane as the solvent and employing 20 mol % of methyl 2-oxo-2-phenylacetate as ketone led to substantial racemization. Thus, with enantiomerically pure (*S*)-**1a**, 82% racemization had occurred after 24 h (Table 1, entry 2).

Table 1. Racemization of (*S*)-Methyl Mandelate[a]

entry	Ru cat.[b]	base[c]	solvent	temp (°C)	ee[d] (%)
1	**3**		$PhCH_3$	70	60
2	**3**[e]		C_6H_{12}	60	18
3	4	Et_3N (4 mol %)	$PhCH_3$	50	0
4	**4**	Et_3N (2 mol %)	*i*-C_8H_{18}	60	68
5	**5**[f]		C_6H_{12}	60	80
6	**6**	Et_3N (2 equiv)	CH_2Cl_2	40	100
7	**7**	Et_3N (3 equiv)	CCl_4	60	100

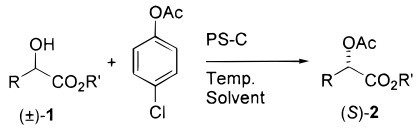
[a] All the reactions were run for 24 h. [b] Unless otherwise noted, 2 mol % of catalyst was used without added ketone. [c] Unless otherwise noted, 1 equivof base was used. [d] The ee was determined by HPLC on a Chiralcel OD-H column. [e] Methyl 2-oxo-2-phenylacetate (20 mol %) was used as ketone. [f] Methyl 2-oxo-2-phenylacetate (1 equiv) was used as ketone.

As was known from previous work in this field,[3,4] ruthenium complex **4** showed a higher rate than **3**, and complete racemization was achieved after 24 h (Table 1, entry 3). However, the use of complex **4** requires a base, which might interfere with the enzyme. Ruthenium dihydride complex **5** has recently been found to be responsible for the reduction of ketones to secondary alcohols under hydrogen transfer conditions.[7] Unfortunately this complex did not work in our system. Complexes **6** and **7** have been used recently for the racemization of secondary alcohols,[8] but with hydroxy acid ester **1a** we could not obtain any racemization.

The racemization mechanism has been studied extensively, and it was shown to proceed via a hydrogen transfer pathway.[7,9] This is confirmed by the fact that in the (*S*)-methyl mandelate racemization the presence of the corresponding ketone[10] accelerates the reaction rate. However, in some cases there was no significant effect by the use of added ketone and therefore it was omitted (Table 1, entries 1, 3, and 4). Further experiments revealed that for some α-hydroxy esters the use of added ketone has a significant influence, vide infra.

For the kinetic resolution of hydroxy esters,[11] *Pseudomonas cepacia* lipase (PS-C, type II from Amano) was employed. 4-Chlorophenyl acetate was used as acyl donor because, after the acyl transfer process, the resulting chlorophenol does not interfere with the ruthenium catalyst.[3] The use of vinyl acetate as acyl donor would result in the formation of acetaldehyde, which interferes with the metal complex employed. Different conditions, such as temperature, solvent, substrate concentration, etc. were screened under kinetic resolution conditions (Scheme 3, Table 2).

Scheme 3. Kinetic Resolution of Hydroxy Acid Esters



1a: R = Ph; R' = Me
1b: R = Ph; R' = Et
1c: R = *p*-MeOPh; R' = Me
1d: R = *p*-BrPh; R' = Me
1e: R = Cy; R' = Me
1f: R = $PhCH_2CH_2$; R' = Me
1g: R = *n*-Bu; R' = Me

The choice of the proper solvent is critical, because selectivity and especially reaction times may change significantly (Table 2, entry 3 versus entries 4 and 5). According to the results in Table 2, it seems to be a requirement that the β-carbon of the α-hydroxy acid ester is a secondary

Table 2. Kinetic Resolution of Compounds **1**[a]

entry	enzyme	substr	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	N-435	**1a**	$PhCH_3$	70	48	0	
2	PS-D	**1a**	$PhCH_3$	50	48	40	92
3	PS-C	**1a**	$PhCH_3$	50	100	40	99
4	PS-C	**1a**	*i*-C_8H_{18}	60	24	49	99
5	PS-C	**1a**	C_6H_{12}	60	24	44	96
6	PS-C	**1b**	C_6H_{12}	60	28	42	99
7	PS-C	**1c**	C_6H_{12}	60	24	46	99
8	PS-C	**1d**	C_6H_{12}	60	24	39	99
9	PS-C	**1e**	C_6H_{12}	60	24	49	99
10	PS-C	**1f**	C_6H_{12}	60	24	48	18
11	PS-C	**1g**	*i*-C_8H_{18}	40	24	47	62

[a] Unless otherwise noted, all the reactions were performed on a 0.25 mmol scale with 15 mg of enzyme and 2 equiv of the acyl donor (4-Cl-C_6H_4OAc) in 1.25 mL of the corresponding solvent. [b] Yield determined by ^1H NMR. [c] The ee was determined on the acetate **2** by HPLC using a Chiralcel OD-H column.

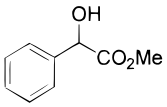
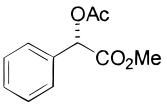
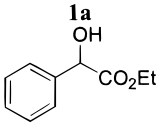
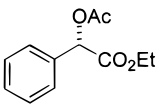
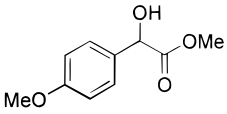
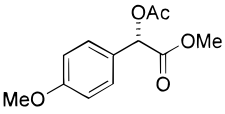
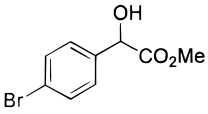
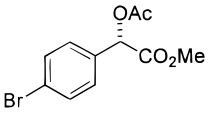
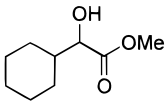
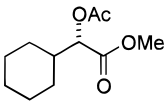
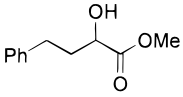
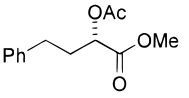
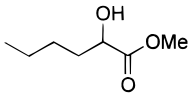
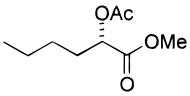
(5) For a review on racemization of optically active compounds, see: Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417−9476.

(6) Previous experiments showed that the presence of a carboxylic acid functionality is not compatible with the ruthenium complexes for racemization purposes.

(7) Aranyos, A.; Csjernyik, G.; Szabó, K. J.; Bäckvall, J. E. *Chem. Commun.* **1999**, 351−352.

(8) Koh, J. H.; Jung, H. M.; Kim, M.-J.; Park, J. *Tetrahedron Lett.* **1999**, *40*, 6281−6284. (b) Koh, J. H.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545−5548.

Table 3. Dynamic Kinetic Resolution of α-Hydroxy Acids with PS-C and Ru Catalyst **3**[a]

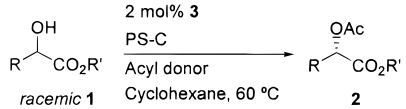
entry	substrate	product	time (h)	yield (%)[b]	ee (%)[c]
1[d]	 **1a**	 **2a**	48	80	94
2[d]	 **1b**	 **2b**	72	74	96
3	 **1c**	 **2c**	48	76 (73[e])	94
4	 **1d**	 **2d**	72	69	98
5	 **1e**	 **2e**	48	80 (70[e])	98
6	 **1f**	 **2f**	48	62	30
7[f]	 **1g**	 **2g**	24	60	80

[a] Unless otherwise noted, all the reactions were performed on a 0.25 mmol scale with 2 mol % of Ru catalyst **3**, 15 mg of PS-C, and 2 equiv of acyl donor (4-Cl-C_6H_4OAc) in 1.25 mL of cyclohexane under argon at 60 °C. [b] Unless otherwise noted, yield calculated by ^{1}H NMR. [c] The ee was determined on the acetate **2** by HPLC using a Chiralcel OD-H column. [d] 20 mol % of the corresponding ketone was used. [e] Isolated yield. [f] The reaction was performed in isooctane at 40 °C.

carbon for a good kinetic resolution to occur. Substrates **1f** and **1g** (Table 2, entries 10 and 11) with a primary β-carbon atom show very poor ee's. Since this study is aimed at dynamic kinetic resolution, some of the parameters such as solvents and temperature have to fit the optimal function of the Ru catalyst (Table 1), where higher temperatures imply faster racemization. The temperature in the kinetic resolution was set at the high-temperature limit for the enzyme. Above this temperature the selectivity of the enzyme drops dramatically. For *P. cepacia* lipase (PS-C (type II) from Amano), this limit was at 60 °C under the conditions described above.

In general, good results were obtained with the traditional kinetic resolution of compounds **1a**−**e** (Table 2, entries 3−9), and conversions in the range of 40−50% with high ee's were obtained. The next step was to combine the racemization and the enzymatic transformation and run the reaction in one pot (Scheme 4).

Scheme 4. Dynamic Kinetic Resolution of Hydroxy Acid Esters



In Table 3, our preliminary results are summarized. An efficient dynamic kinetic resolution was achieved for substrates **1a**−**e** with goods yields and high ee's. Mandelic acid ester **1a** gave an 80% yield of **2a** in 94% ee and ester **1b** afforded **2b** in 74% yield and 96% ee (Table 3, entries 1 and 2). Ring-substituted mandelic acid ester derivatives (**1c** and **1d**) showed high efficiency in these reactions, proving

(9) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Takehera, J.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (b) Santosh Laxmi, Y. R.; Bäckvall, J. E. *Chem. Commun.* **2000**, 611−612.

(10) Methyl 2-oxo-2-phenylacetate was used as ketone.

(11) Ebert, C.; Ferluga, G.; Gardossi, L.; Gianferrara, T.; Linda, P. *Tetrahedron: Asymmetry* **1992**, *3*, 903−912.

that the presence of electron-withdrawing or -donating groups in the ring does not affect the DKR process (Table 3, entries 3 and 4). The nonaromatic, cyclohexyl analogue (**1e**) worked even better under the same reaction conditions (Table 3, entry 5), giving **2e** in 80% yield and 98% ee. Thus, the scope of this methodology is not restricted to aromatic hydroxy acids. For substrates **1f** and **1g**, less efficient reactions were obtained (Table 3, entries 6 and 7), which reflects the poor results for these substrates in the kinetic resolution (Table 2, entries 10 and 11).

The reaction of **1g** under DKR conditions (Table 3, entry 7) demonstrates the efficiency of the dynamic process compared to the kinetic resolution of this compound. Whereas kinetic resolution gave **2g** in only 47% yield with 62% ee (Table 2, entry 11), DKR gave **2g** in 60% yield with 80% ee. When this reaction was run longer (48 h instead of 24 h, Table 3, entry 7), the small gain in yield produced a negative effect on the ee (66% yield, 60% ee). These results indicate that for substrates **1f** and **1g** further experiments are needed in order to find the proper reaction conditions for a successful dynamic kinetic resolution.

Recently, Faber et al. developed a method for deracemization of mandelic acid based on enzymatic resolution and subsequent biochemical racemization.[12] When this one-pot sequence was repeated four times, the α-acetoxy acid was obtained in 80% yield and 98% ee.

In summary, we have shown that dynamic kinetic resolution of different α-hydroxy esters was carried out successfully to give enanitomerically pure compounds in good yields and in one single step. It was demonstrated that the high enantioselectivity of the enzyme is compatible with the ruthenium-catalyzed racemization of α-hydroxy esters. The racemization process takes place via a hydrogen transfer pathway involving dehydrogenation of the alcohol to ketone and readdition of hydrogen. This methodology is applicable to a variety of substrates, although substrates with a primary carbon at the *β*-position of the α-hydroxy ester gave poor results.

Supporting Information Available: Shvo catalyst preparation details and HPLC and GC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000014+

(12) Strauss, U. T.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4079−4081.