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Highly Efficient Route for Enantioselective Preparation of Chlorohydrins via Dynamic Kinetic Resolution

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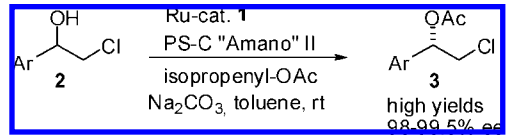
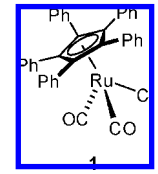
ABSTRACT



Dynamic kinetic resolution (DKR) of various aromatic chlorohydrins with the use of *Pseudomonas cepacia* lipase (PS-C "Amano" II) and ruthenium catalyst 1 afforded chlorohydrin acetates in high yields and high enantiomeric excesses. These optically pure chlorohydrin acetates are useful synthetic intermediates and can be transformed to a range of important chiral compounds.

Enantiomerically pure chlorohydrins are versatile synthetic intermediates and can be used in asymmetric synthesis of epoxides,[1] β-aminoalcohols,[2] pyrrolidines,[3] and functionalized cyclopropanes.[4] Various methods have been reported for the enantioselective preparation of chlorohydrins, and methods that provide high enantiomeric excess include asymmetric hydroboration,[2,3,5] (transfer) hydrogenation,[1,6,7] and biocatalytic reduction of α-chloroketones.[8] Other methods are kinetic[1b,9,10] and dynamic kinetic resolution[1b] of halohydrins.

Dynamic kinetic resolution (DKR) of secondary alcohols has emerged as a powerful and efficient method for the preparation of enantiomerically pure alcohols.[11−13] In this respect, hydrolases have been found to be useful enzymes for resolution.[14] Successful DKR protocols involve a ruthenium catalyst for the racemization and a lipase for enzymatic resolution. In 2004, we reported on a new efficient racemization catalyst, Ru complex **1**, which led to a highly efficient DKR system with fast reactions at room temperature.[15] This new system has been applied to various secondary alcohols[16] and can be run on large scale (100 g to 1 kg).[17] In this communication, we have applied this new DKR system to chlorohydrins, which leads to high yields and unusually high ee's.



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(1) (a) Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373–4376. (b) Pàmies, O.; Bäckvall, J. E. *J. Org. Chem.* **2002**, *67*, 9006–9010.

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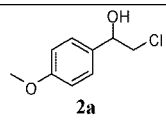
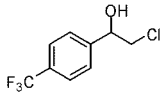
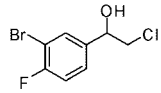
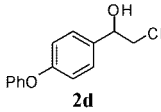
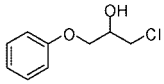
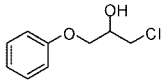
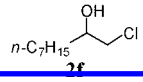
Enzymatic resolution of aromatic chlorohydrins is known to work very well with *Pseudomonas cepacia* lipase.[1,9] For these chlorohydrins, *Candida antarctica* lipase B also gives good results albeit slower.[1b] Our choice of enzyme was therefore the former lipase, and the selectivity of this enzyme with the acyl donor isopropenyl acetate in toluene was determined for a few substrates (Table 1). The kinetic resolution reactions were run at room temperature (except entry 6). As can be seen from Table 1, aromatic chlorohydrins give excellent enantioselectivity with E values >300, whereas aliphatic chlorohydrins give very poor results (entry 7). The presence of different substituents on the aromatic ring does not seem to influence the enantioselectivity of the enzyme. For substrate **2e**, we also carried out the kinetic resolution at an elevated temperature (80 °C) since the racemization of this substrate is slow at room temperature (vide infra). At 80 °C, the E value for **2e** dropped to 81.

For the aliphatic substrate **2f**, the enzyme showed poor selectivity (entry 7, Table 1). PS-C "Amano" I and PS-D "Amano" II were also tested in a kinetic resolution of this substrate but showed low selectivity as well.

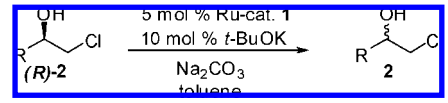
Table 1. Kinetic Resolution of Chlorohydrins[a]

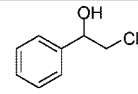
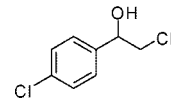
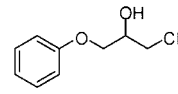
entry	substrate[a]	convn[b] (%)	ee[c] (%) acetate	ee[c] (%) alcohol	E
1	 **2a**	42	99	71	>300
2	 **2b**	44	>99	77	>300
3	 **2c**	32	>99	47	>300
4	 **2d**	40	>99	65	>300
5	 **2e**	33	>99[d]	48[d]	>300
6[e]	 **2e**	46	94[d]	81[d]	81
7	 **2f**	40	42	28	3.2

[a] With 0.5 mmol Na_2CO_3, 25 mg of PS-C "Amano" II, 1 mL of dry toluene, 0.5 mmol β-chloroalcohol, and 1.0 mmol isopropenyl acetate. [b] Calculated value. [c] The enantiomeric excess of (*S*)-acetate and (*R*)-alcohol was determined by chiral GC, and from these figures, the E value was calculated. [d] Determined by HPLC. [e] With 2.5 mg of PS-C "Amano" II at 80 °C.

The racemization was investigated for a few substrates. The results are shown in Table 2. As can be seen from Table 2, 1-aryl-2-chloroethanols are racemized fast at room temperature whereas chloroalcohol **2e** is racemized slow under these conditions. For a good dynamic kinetic resolution, the racemization should be at least 10 times faster than the conversion of the slow-reacting enantiomer in the kinetic resolution. For the aromatic alcohols (arylalcohols), the racemization is fast so this requirement will be fulfilled with the enzyme amounts used in Table 1.

Table 2. Racemization of Enantiopure (*R*)-β-Chloroalcohols[a]



entry	substrate	t (min)	T (°C)	ee (%)[b,c]
1	 **2g**	5	rt	0
2	 **2i**	5	rt	0
3	 **2e**	120	rt	30[d]
		30	60	5[d]
		5	80	5[d]

[a] 0.015 mmol $RuCl(CO)_2(\eta^5C_5Ph_5)$ and 0.3 mmol Na_2CO_3 were mixed in 0.3 mL of toluene, and 0.03 mmol *t*-BuOK (dissolved in 30 μL of dry THF) was added. After 6 min, 0.3 mmol substrate (dissolved in 0.3 mL of dry toluene and dried over molecular sieves) was added. [b] Determined by chiral GC. [c] Enantiomeric excess of (*R*)-alcohol. [d] Determined by chiral HPLC.

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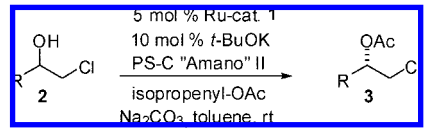
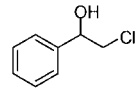
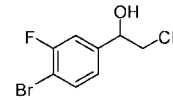
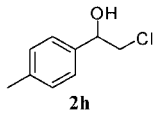
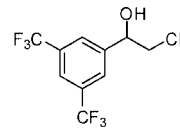
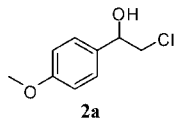
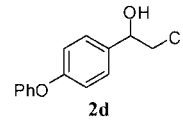
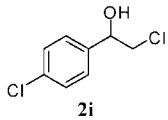
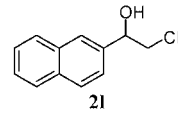
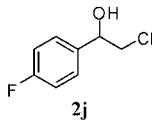
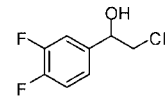
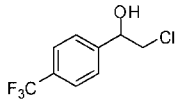
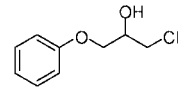
Table 3. DKR of β-Chloroalcohols[a]



entry	substrate	t (h)	yield[b,c] (%)	ee[b,d] (%)	entry	substrate	t (h)	yield[b,c] (%)	ee[b,d] (%)
1	 **2g**	13 24	98 >99 (95)	99.5 >99	7	 **2c**	26 60 °C	>99	98
2	 **2h**	24	97 (90)	99.3	8	 **2k**	24 80 °C	>99	98
3	 **2a**	22	>99	>99	9	 **2d**	24	87	>99
4	 **2i**	22	97 (89)	>99	10	 **2l**	24	99 (93)	99.1
5	 **2j**	24	>99	>99	11[f]	 **2m**	30 80 °C	99 (86)	98
6	 **2b**	48 60 °C	>99	98	12[g]	 **2e**	48 90 °C	84[e]	92[e]

[a] 0.025 mmol $RuCl(CO)_2(\eta^5C_5Ph_5)$, 0.5 mmol Na_2CO_3, and 25 mg of PS-C "Amano" II were mixed in 0.5 mL of dry toluene; 0.05 mmol *t*-BuOK (dissolved in 50 μL of dry THF) was added. After 6 min, 0.5 mmol substrate was added (dissolved in 0.5 mL of dry toluene and after an additional 4 min, 1.0 mmol isopropenyl acetate was added. [b] Determined by chiral GC. [c] Determined by chiral HPLC. [d] Enantiomeric excess of (*S*)-acetate. [e] Isolated yield in parentheses. [f] 0.05 mmol $RuCl(CO)2(\eta^5C_5Ph_5)$ (0.5 mol %), 2 mmol Na_2CO_3, and 120 mg of PS-C "Amano" II were mixed in 5 mL toluene; 0.05 mmol *t*-BuOK (dissolved in 100 μL of dry THF) was added. After 6 min, 10 mmol substrate was added, and after an additional 4 min, 15 mmol isopropenyl acetate was added. [g] 2.5 mg/mmol PS-C "Amano" II.

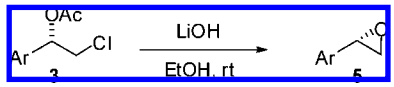
We observed that the racemization of 1-chloro-3-phenoxyisopropanol (**2e**) is much slower than that for the arylethanols, and the combination of ruthenium-catalyzed racemization with enzymatic resolution for this substrate was too slow at room temperature. At elevated temperature, the rate of racemization is significantly increased, and at 80 °C, **2e** was completely racemized within 5 min (cf. Table 2).

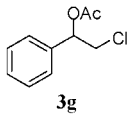
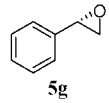
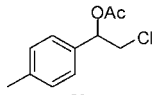
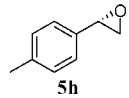
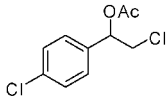
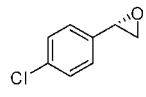
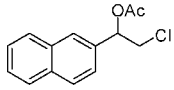
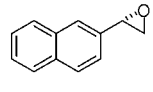
By optimizing the enzyme loading and increasing the amount of base and isopropenyl acetate, DKR of **2g** can now run to 98% conversion with 99.5% ee in 13 h. Full conversion was obtained after 24 h at room temperature (entry 1, Table 3). With these optimized conditions, DKR was run for a variety of β-chlorohydrins with different aromatic groups.

As can be seen from Table 3, the DKR works very well for different aromatic chlorohydrins, both with activating and deactivating groups. For the chlorohydrins in entries 1−5, 9, and 10, the chloroacetates were obtained in ee's exceeding 99%. For chlorohydrins with highly electron-withdrawing groups on the aromatic ring, elevated temperature was required to make the racemization faster (entries 6−8 and 11). The selectivity of the enzyme at this temperature is still high and gives the products in 98% ee. The reaction conditions for 1-chloro-3-phenoxy-2-propanol (entry 12) were optimized based on the results of the separate racemization and kinetic resolution. When this substrate was run at room temperature, the racemization was too slow (Table 2) compared to the kinetic resolution. At elevated temperature, the racemization rate increased. As shown in Table 1 the selectivity for the enzyme at 80 °C is good. The reaction was run at elevated temperature, and it was found that the best results concerning yield and ee values were obtained at 90 °C (entry 12).

DKR of chlorohydrin **2m** was run on a 10 mmol scale to afford synthetic intermediate **3m** in 99% yield and 98%

Table 4. Ring Closing to Epoxide[a]



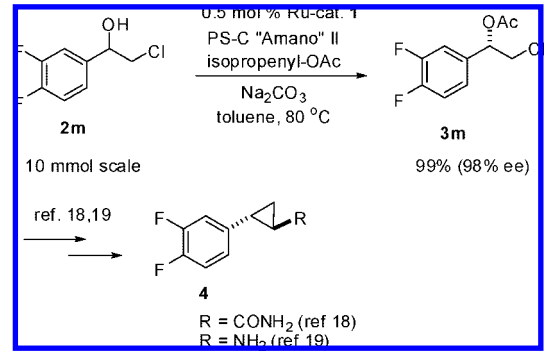
entry	substrate	product	yield[b] (%)	ee[c] (%)
1	 **3g**	 **5g**	87	>98
2	 **3h**	 **5h**	96	99
3	 **3i**	 **5i**	97	>98
4	 **3l**	 **5l**	95	>95

[a] The substrate (1.0 mmol) was dissolved in 10 mL of EtOH (95%). LiOH (3 mmol) was added. The reaction was quenched by addition of $NaHCO_3$ (6 mmol). [b] Isolated yields. [c] Determined by chiral HPLC.

ee with 0.5 mol % of Ru catalyst **1**. Compound **3m** has previously been used for the transformation to pharmaceutically important cyclopropanes **4** (Scheme 1).[18,19]

(18) Dejonghe, J.-P.; Peeters, K.; Renard, M. WO 2008018822 A1, 2008.
(19) Mitsuda, M.; Moroshima, T.; Tsukuya, K.; Watabe, K.; Yamada, M. WO 2008018823 A1, 2008.

Scheme 1



The chiral chlorohydrins in Table 3 are important precursors for chiral epoxides. To demonstrate this point, a few of the chlorohydrin acetates were transformed to enantiomerically pure epoxides (Table 4). This approach provides styrene oxides with high ee. The DKR protocol combined with epoxide formation should be one of the best methods to prepare these enantiomerically pure epoxides.

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Supporting Information Available: Synthesis and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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