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Dynamic Kinetic Resolution of Primary Alcohols with an Unfunctionalized Stereogenic Center in the β-Position†

Dirk Strübing,[a] Patrik Krumlinde,[a] Julio Piera,[a] and Jan-E. Bäckvall[a,*]

[a] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, 10691 Stockholm, Sweden
Fax: (+46)-8-154-908; e-mail: jeb@organ.su.se

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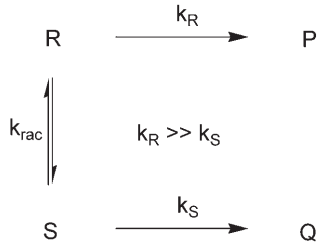
Abstract: Primary alcohols with an unfunctionalized stereogenic center in the β-position undergo an enzyme- and metal-catalyzed dynamic kinetic resolution (DKR). The *in situ* racemization of the primary alcohol, required for the DKR, takes place *via*: (i) ruthenium-catalyzed dehydrogenation of the alcohol, (ii) enolization of the aldehyde formed, and (iii) ruthenium-catalyzed readdition of hydrogen to the aldehyde. The present method widens the scope of metal- and enzyme-catalyzed DKR, which has so far been limited to α-chiral alcohol and amine derivatives.

Keywords: dynamic kinetic resolution; enzyme catalysis; metal catalysis; primary alcohols

The development of efficient protocols for the synthesis of optically active compounds has attracted major attention in organic chemistry, because of the increasing demand for such compounds as building blocks in the pharmaceutical or agrochemical industry.[1] The most common way to prepare enantiomerically pure compounds in the chemical industry is still *via* resolution and separation of enantiomers from racemic mixtures.[2] In this respect, enzymatic resolution plays an important and dominant role[3] and a number of multi-ton industrial processes are based on enzymatic resolution.[4] A drawback with these kinetic resolutions (KR) is the maximum theoretical yield of 50% leading to waste of half of the material. A solution to this problem is dynamic kinetic resolution (DKR),[5] which takes advantage of an *in situ* racemization of the remaining substrate enantiomer (Scheme 1). In this way a yield of up to 100% of enantiopure material can be achieved.

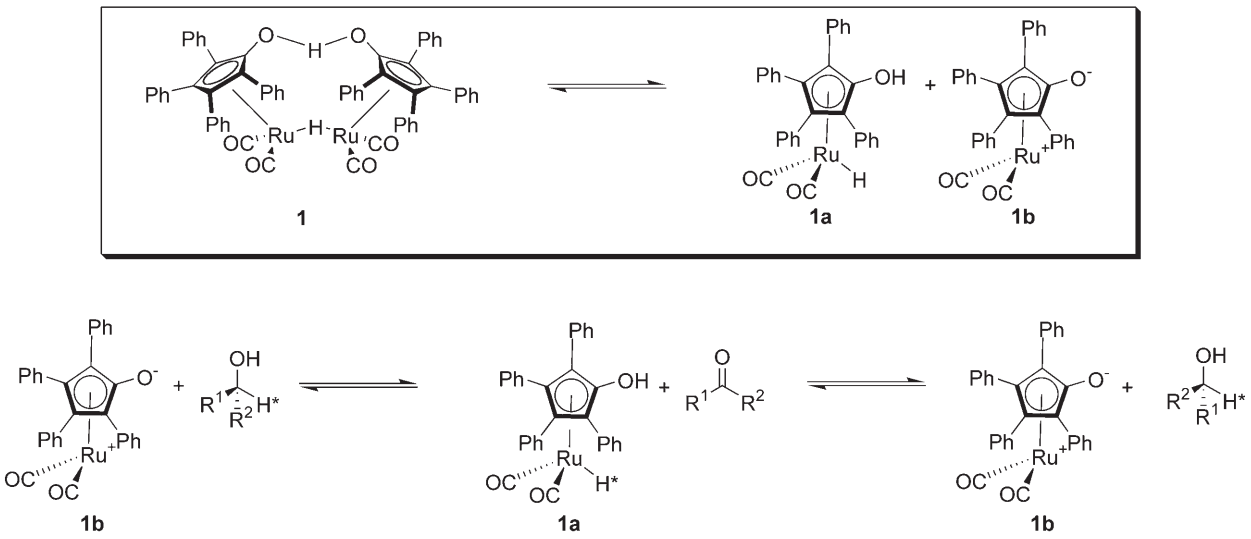


Scheme 1. Principle of a dynamic kinetic resolution (DKR).

During the past decade, various DKR methods based on the combination of an enzyme and an additional racemization catalyst have been developed.[5d,6] In particular, the combination of an enzyme and a transition metal catalyst has proven to be useful for DKR of secondary alcohols.[5d] In the first efficient system developed,[7] Shvo's ruthenium catalyst **1** (Scheme 2) was employed, and this catalyst requires a slightly elevated temperature. This procedure has been successfully applied to the DKR of various substituted secondary alcohols including diols[8] and allylic alcohols.[9] The method was recently extended to amines.[10]

Further developments have led to room temperature procedures for DKR of secondary alcohols that employ a new type of racemization catalyst together with an enzyme.[11–13] In all these applications, the metal catalyst can be compared with the dehydrogenase/hydrogenase activity by enzymes having NAD(P)/NAD(P)H as cofactor.

All of the protocols for chemoenzymatic DKR of alcohols and amines described to date have been limited to substrates that are chiral at the α-carbon (**A**, Figure 1). An extension of chemoenzymatic DKR to alcohols and amines with a non-functionalized chiral carbon, for example, **B** (Figure 1) would significantly broaden the scope of the method.



Scheme 2. Shvo's catalyst **1** and its role in the racemization of secondary alcohols.

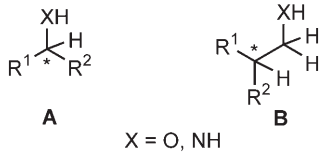
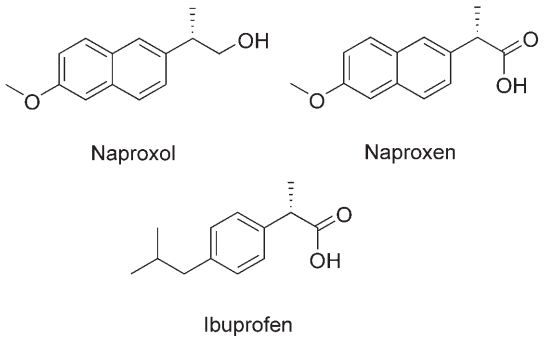


Figure 1. Alcohols and amines for dynamic kinetic resolution.

Compound **B** has a chiral center in the β-position to the alcohol or amine and it is not straightforward to racemize this center, which is a requirement for DKR. A multitude of biologically active compounds are related to structure **B** and in particular β-aryl-substituted alcohols are, either by themselves or after oxidation to the corresponding acid, part of many important non-steroidal anti-inflammatory drugs like Naproxol, Naproxen and Ibuprofen (Scheme 3).[14]

Herein, we report on a DKR of primary alcohols with an unfunctionalized stereogenic center in the β-position, where the *in situ* racemization occurs *via* an indirect pathway in the DKR process.

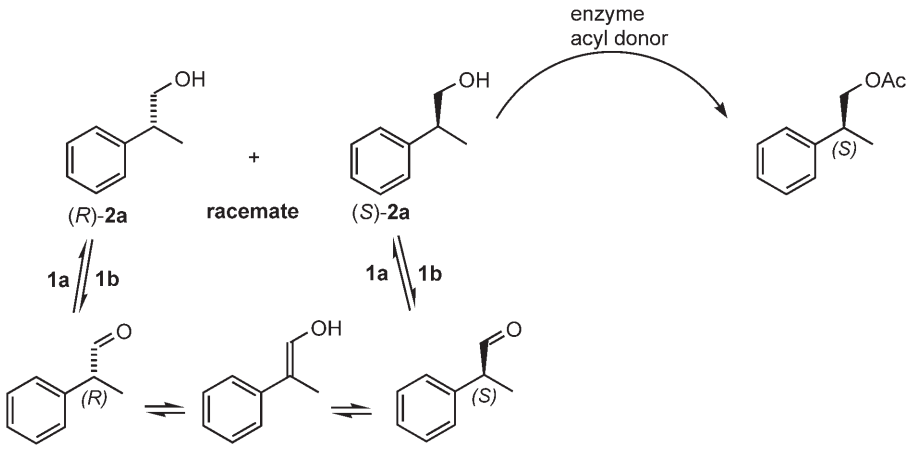


Scheme 3. Some representative examples for β-aryl-substituted alcohols and derived carboxylic acids with anti-inflammatory activity.

As outlined in Scheme 1, a DKR process relies on an *in situ* racemization of the remaining substrate enantiomer by a chosen catalyst. In the case of catalyst **1** and secondary alcohols, this process takes place *via* a reversible oxidation of the unreactive enantiomer of the substrate to the corresponding ketone, which is reduced again by the generated ruthenium hydride **1a** (Scheme 2). Since the hydrogenation of the prochiral ketone by **1a** can occur from either face, this process leads to racemization of the remaining starting material.

In contrast to secondary alcohols, the racemization of β-branched primary alcohols by C–H bond cleavage is not straightforward. However, an indirect method for racemization of alcohol **2a** would be to utilize the dehydrogenase/hydrogenase activity of metal catalyst **1** to create an equilibrium between primary alcohol and aldehyde, where the latter can undergo enolization (Scheme 4). Enolization of the aldehyde, which can be facilitated by elevated temperature or acid/base catalysis, would lead to racemization. In contrast to the racemization of secondary alcohols, it is important to note that catalyst **1** serves only as an indirect racemization catalyst for the primary alcohols.

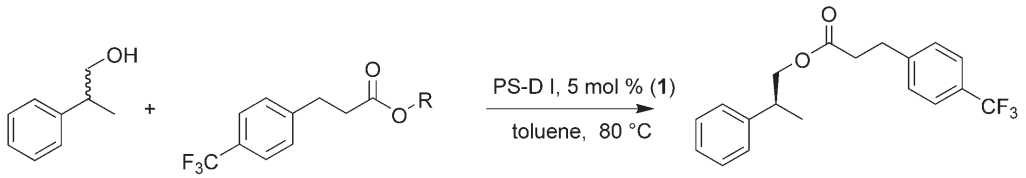
In addition to the choice of a suitable metal catalyst **1**, a highly enantioselective enzyme is required for the esterification of β-branched primary alcohols. Kawasaki et al. have reported a highly efficient kinetic resolution protocol for various primary alcohols.[15] A KR system incorporating a lipase from *Burkholderia cepacia* in the presence of differently substituted vinyl 3-phenylpropanoates as acyl donors was found to be the most selective. Encouraged by their findings, we investigated the DKR of the chosen model substrate



Scheme 4. Proposed mechanism for the DKR of the primary alcohol **2a** as model substrate.

2a in an initial screening. Hereby, the influence of various solvents, reaction temperatures and reaction times, vinyl 3-arylpropanoates and different preparations of immobilized *Burkholderia cepacia* lipases were investigated (data not shown). As a result, a combination of Amano Lipase PS-D I and vinyl 3-[4-(trifluoromethyl)phenyl]propanoate (**3**) as acyl donor[16] afforded the desired product in good yield in high enantioselectivity (92% *ee*, 79% yield, entry 1, Table 1). However, as we have already reported in our previous work on the DKR of secondary alcohols[7b], the nature of the acyl donor also plays an important role in the selectivity of the reaction. Therefore, we studied the influence of different acyl donors more carefully. As depicted in Table 1, the use of isopropenyl- (**4**) and 2,2,2-trifluoroethyl- (**5**) substituted

Table 1. Optimization of reaction conditions.[a]



2a

3 R = vinyl
4 R = isopropenyl
5 R = 2,2,2-trifluoroethyl
6 R = *p*-NO_2-phenyl
7 R = *p*-Cl-phenyl

8a

Entry	Acyl donor	Time [h]	Conversion [%]	Yield [%][f]	*ee* [%]
1	**3**	24	>99	79	92
2	**4**	24	60	39	91
3	**5**	24	85	83	66
4	**6**	24	>99	92	84
5	**7**	24	>99	89	81
6[b]	**3**	24	>99	80	74
7[c]	**6**	24	83	78	93
8[c]	**6**	36	87	80	92
9[c,d]	**6**	24	>99	79	93
10[c,e]	**6**	36	>99	93	93

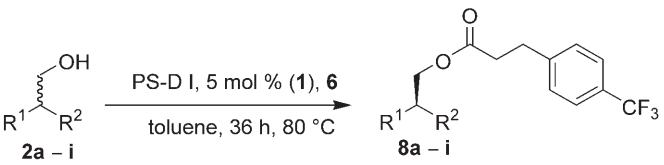
[a] *Reaction conditions:* unless otherwise noted 0.1 mmol **2a**, 0.15 mmol acyl donor, 5 mg PS-D I, 5 mol% **1**, 80°C, toluene.
[b] Reaction was run under one atmosphere of hydrodrogen.
[c] 3 mg PS-D I.
[d] 10 mol% **1**.
[e] 1 mg PS-D I added after 24 h, reaction went to completion after additional 12 h.
[f] Yield determined by HPLC.

acyl donors resulted either in lower yield or decreased enantiomeric excess (*ee*) of the desired product (entries 2 and 3, Table 1). However, the employment of 4-nitrophenyl- (**6**) or 4-chlorophenyl 3-[4-(trifluoromethyl)phenyl]propanoates (**7**) as acyl donors furnished the model product in very good yield but in slightly decreased enantioselectivities (entries 4 and 5, Table 1). Therefore, we decided to investigate the use of acyl donor **6** in detail. A significant improvement in enantioselectivity was achieved by lowering the amount of the enzyme, which was also accompanied by a lower conversion (93% *ee*, 83% conversion, entry 7, Table 1). Most probably, the latter observation can be rationalized by a deactivation of the enzyme, since prolonging the reaction time to 36 h did not lead to full conversion (entry 8, Table 1). To increase the concentration of the intermediate aldehyde species, which would presumably increase the reaction rate, the amount of ruthenium catalyst **1** was raised to 10 mol%. Unfortunately, this resulted in a lower yield at full conversion, which made this approach unfeasible (entry 9, Table 1). However, the best results were achieved by simply adding fresh enzyme to the reaction mixture after 24 h. Using this approach, the desired product was obtained in very good yield and enantioselectivity (93% *ee*, 93% yield, entry 10, Table 1).

After determining the optimized DKR conditions, the scope of the method was investigated. Hence, we subjected various racemic primary alcohols with a chiral center at the β-carbon to the reaction conditions developed. As shown in Table 2, the chosen catalytic system was suitable for a wide range of primary alcohols. For instance, varying the alkyl part towards ethyl- and *n*-propyl-subtituents afforded the corresponding products in good yields and enantiomeric excess (70–80% yield, 78–86% *ee*, entries 2 and 3, Table 2). Furthermore, different aryl-substituted alcohols were tested as well. The desired products were generally isolated in good to high yields (70–85%) with *ee*s up to 99% (entries 4–8, Table 2). Importantly, the method developed is not only limited to β-aryl-substituted primary alcohols, since also the cyclohexyl-derived alcohol **2i** was converted successfully to the enantiomerically enriched ester (84% *ee*, 84% yield, entry 9, Table 2).

In conclusion, we have shown that DKR of primary alcohols with an unfunctionalized stereogenic center at the β-carbon can be achieved *via* combined enzyme and metal catalysis. The *in situ* generation of an α-branched aldehyde is of vital importance for the DKR process, since this intermediate can be racemized by means of a straightforward enolization reaction. Various β-racemic primary alcohols were converted to the enantiomerically enriched alcohol esters in good to high yields and with a good to high optical purity (up to 99% *ee*).

Table 2. Scope of the method.[a]



Entry	Product	R^1/R^2	Yield [%][b]	ee [%]
1	**8a**	Ph/Me	87	93
2	**8b**	Ph/Et	80	78[c]
3	**8c**	Ph/*n*-Pr	70	86[c]
4	**8d**	2-MeO-C_6H_4/Me	72	>99[c]
5	**8e**	3-MeO-C_6H_4/Me	85	83[c]
6	**8f**	4-MeO-C_6H_4/Me	70	71[c]
7[d]	**8g**	4-O_2N-C_6H_4/Me	85[e]	67[c]
8[d]	**8h**	4-Br-C_6H_4/Me	81	70[c]
9[d]	**8i**	cyclohexyl/Me	84	84[c]

[a] *Reaction conditions:* unless otherwise noted 0.5 mmol alcohol, 0.6 mmol **6**, 15 mg PS-D I, 5 mol% **1**, 80°C, 5 mL toluene for 24 h, then 5 mg PS-D I to complete reaction after additional 12 h.
[b] Isolated yield.
[c] Determined after hydrolysis to the corresponding alcohol.
[d] 48 h.
[e] Yield determined by ^{1}H NMR.

Experimental Section

Representative Procedure for the DKR of Primary Alcohols 2a–i: DKR of 2a to 8a

A flame-dried Schlenk tube was charged under Ar with 0.5 mmol **2a**, 0.6 mmol 4-nitrophenyl 3-[4-(trifluoromethyl)-phenyl]propanoate (**6**), 5 mol% Shvo catalyst **1**, 15 mg PS-D "Amano" I and toluene (5 mL). The mixture was stirred for 24 h at 80°C. Afterwards 5 mg of fresh PS-D "Amano" I were added and the reaction was allowed to continue for additional 12 h at 80°C. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-pentane/EtOAc) afforded **8a** as a colorless oil; yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$ (d, $J =$ 8.1 Hz, 2H), 7.33–7.17 (m, 7H), 4.20 (dd, $J = 10.8$ Hz, 7.1 Hz, 1H), 4.13 (dd, $J = 10.8$ Hz, 7.0 Hz, 1H), 3.06 (m, 1H), 2.94 (t, $J = 7.6$ Hz, 2H), 2.60 (t, $J = 7.6$ Hz, 2H), 1.26 (d, $J = 7.0$ Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 172.3$, 144.5, 143.0, 128.6, 128.5, 127.2, 126.7, 125.4 (q, $^3J_{CF} =$ 3.7 Hz), 69.5, 38.9, 35.3, 30.6, 18.0; HR-MS (ESI): $m/z =$ 359.1229, calcd. for $C_{19}H_{19}F_3O_2Na$ $[M+Na]^+$: 359.1234.

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