Communication

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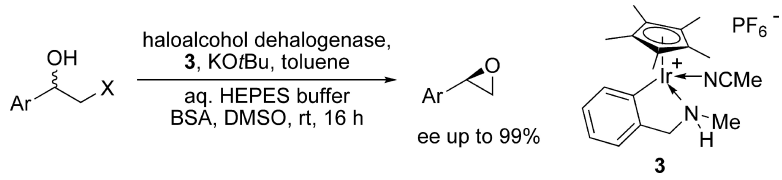

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Dynamic Kinetic Resolution of Racemic β-Haloalcohols: Direct Access to Enantioenriched Epoxides

Robert M. Haak,[†] Florian Berthiol,[†] Thomas Jerphagnon,[†] Arnaud J. A. Gayet,[†] Chiara Tarabiono,[§] Christiaan P. Postema,[§] Vincent Ritleng,[†] Michel Pfeffer,[‡] Dick B. Janssen,*[,§] Adriaan J. Minnaard,[†] Ben L. Feringa,*[,†] and Johannes G. de Vries*[,†,⊥]

Stratingh Institute for Chemistry, University of Groningen, and Department of Biochemistry, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands, Laboratoire de Synthèses Métallo-Induites, Université Louis Pasteur, 4 rue Blaise Pascal, 67000 Strasbourg, France, and DSM Pharmaceutical Products—Innovative Synthesis & Catalysis, P.O. Box 18, 6160 MD Geleen, The Netherlands

Received July 3, 2008; E-mail: D.B.Janssen@rug.nl; B.L.Feringa@rug.nl; Hans-JG.Vries-de@dsm.com

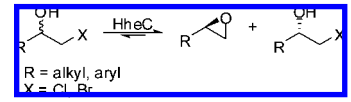
In dynamic kinetic resolution (DKR), a single enantiomer of a racemic starting material is transformed stereoselectively to an enantiomerically enriched product, with concurrent racemization of the remaining starting material. Thus, enantiomerically pure products may be obtained from racemic substrates with complete conversion, overcoming the 50% yield limit of traditional resolution techniques.[1] A common approach to DKR is the combination of stereoselective lipase-catalyzed acylation of a secondary alcohol with transition-metal-catalyzed racemization, introduced in the 1990s.[2] Although many practical examples of DKR are available for a wide variety of substrates, the DKR of β-haloalcohols has been scarcely reported. Bäckvall and Pàmies published the only systematic study so far, showing that it is possible to obtain enantiomerically enriched epoxides from racemic chloroalcohols in a two-step process.[3] Despite this scarce attention, vicinal haloalcohols are highly valuable chiral building blocks in synthesis, for instance as precursors of chiral epoxides or β- and γ-amino alcohols. Herein, we report the first direct chemo-enzymatic DKR of racemic β-haloalcohols to provide the corresponding enantioenriched epoxides.

We recently developed the kinetic resolution of functionalized β-chloroalcohols using haloalcohol dehalogenase HheC, an enzyme catalyzing the interconversion of haloalcohols and epoxides (Scheme 1),[4,5] as well as epoxide ring opening by several nonhalide nucleophiles.[6] In the HheC-catalyzed kinetic resolution of β-chloroalcohols, the *R*-enantiomer of the substrate was converted to the corresponding epoxide. On the basis of these results, we envisioned that the use of a proper racemization catalyst in this system should give access to enantiomerically pure epoxides in a single step.

First, the best catalyst for the racemization of β-haloalcohols was selected. After evaluating a range of metal complexes,[7] it was found that iridacycle **3** was the most active racemization catalyst for β-haloalcohols. Complex **3** was prepared by cycloiridation of the corresponding amine **2** using the commercially available iridium precursor **1** (Scheme 2), following a procedure described for related complexes by the group of Pfeffer.[8,9]

However, the complex turned out to be poorly active for alcohol racemization in toluene. Activation of **3** using 1 equiv of potassium *tert*-butoxide, as employed previously for Ru-based racemization catalysts,[10] led to a new species with high reactivity toward β-haloalcohols. The results of the racemization of alcohols (*R*)-**4**, catalyzed by activated **3**, are shown in Table 1.

Scheme 1. HheC-Catalyzed Ring Closure of Haloalcohols



Scheme 2. Cycloiridation of *N*-Methylbenzylamine

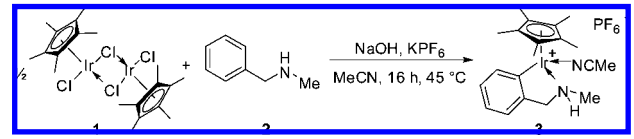
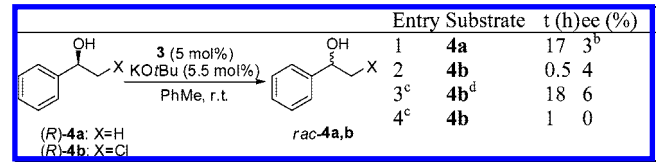


Table 1. Racemization of (*R*)-**4**[a]



Entry	Substrate	t (h)	ee (%)
1	**4a**	17	3[b]
2	**4b**	0.5	4
3[c]	**4b**[d]	18	6
4[c]	**4b**	1	0

[a] Experimental details can be found in the Supporting Information. Quantities used: **3**, 10 μmol; KO*t*Bu, 12 μmol; toluene, 3 mL; (*R*)-**4** (initial ee: > 97%), 200 μmol. [b] In the racemization of (*R*)-**4a**, 13% of acetophenone was formed as a byproduct. [c] Reaction performed in toluene/water 1:1. [d] After 16 h, another 200 μmol of *R*-**4b** was added (ee immediately after addition: 52%) and the reaction was run for an additional 2 h.

A reaction using 5 mol % of **3** resulted in complete racemization of (*R*)-**4a** after 17 h (Table 1, entry 1). Remarkably, **3** is much more active on halohydrins than on simple alcohols, as illustrated by the virtually complete racemization of (*R*)-**4b** after only 30 min (Table 1, entry 2). Furthermore, in the case of alcohol **4a**, 13% acetophenone was formed, whereas using **4b**, no formation of the corresponding chloroketone was observed.[11]

Since HCl or HBr is released upon ring closure of the β-haloalcohols, kinetic resolution using HheC must be performed in a buffered solution, so we investigated the catalyst stability in the presence of water (Table 1, entries 3 and 4). After 16 h, the remaining activity of the catalyst was tested by addition of another equivalent of (*R*)-**4b** to the reaction mixture (Table 1, entry 3), resulting in a decrease of ee from 52% to 6% within 2 h. Subsequent experiments showed that in this biphasic system, racemization of chloroalcohol (*R*)-**4b** is complete after only 1 h (Table 1, entry 4). This compatibility with aqueous conditions is a clear advantage over existing racemization catalysts.

Next, we focused our efforts on finding the best haloalcohol dehalogenase. We selected a variant of HheC incorporating the

[†] Stratingh Institute for Chemistry.
[§] Groningen Biomolecular Sciences and Biotechnology Institute.
[‡] Université Louis Pasteur.
[⊥] DSM Pharmaceutical Products.

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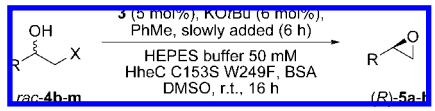
Table 2. DKR of β-Haloalcohols **4**[a]



entry	substrate	R	X	product	convn (%)	ee (%)
1	**4b**	C_6H_5	Cl	**5a**	90	98
2	**4c**	C_6H_5	Br	**5a**	57	56
3	**4d**	4-NO_2−C_6H_4	Cl	**5b**	80 (67)[b]	95 (99)[c]
4[d]	**4d**	4-NO_2−C_6H_4	Cl	**5b**	76	97
5[e]	**4e**	4-NO_2−C_6H_4	Br	**5b**	86	90
6	**4f**	3-NO_2−C_6H_4	Cl	**5c**	75 (65)[b]	97 (94)[c]
7	**4g**	3-NO_2−C_6H_4	Br	**5c**	79	52
8	**4h**	2-NO_2−C_6H_4	Cl	**5d**	28	91
9	**4i**	4-CN-C_6H_4	Cl	**5e**	67 (59)[b]	95 (96)[c]
10	**4j**	4-CN-C_6H_4	Br	**5e**	89	86
11[f]	**4k**	3-MeO-C_6H_4	Cl	**5f**	64 (57)[b]	85 (90)[c]
12[g]	**4l**	4-CF_3−C_6H_4	Cl	**5g**	58 (51)[b]	98 (99)[c]
13	**4m**	C_6H_{11}	Cl	**5h**	50	72

[a] Reactions were performed on 0.2 mmol scale, using 6 U (initial activity) of enzyme. A general procedure can be found in the Supporting Information. [b] Isolated yields in parentheses. [c] ee of the isolated product in parentheses. [d] Run on a 1.0 mmol scale. [e] Reaction performed without BSA. [f] Run using 15 U of HheC (instead of 6 U). [g] Run using 20 vol% of DMSO (instead of 5 vol%); 30 U of HheC was used (instead of 6 U).

mutations Cys153Ser, which increases the enzyme's stability toward oxidation,[12] and Trp249Phe, which increases its enantioselectivity especially for aromatic substrates.[13]

The optimal reaction conditions were determined and DKR was performed as shown in Table 2.

Typically, DKR experiments were performed at 0.2 mmol scale. The reaction is biphasic, using 10 mL of 50 mM aqueous HEPES buffer (pH 7.5 for bromides, pH 8.0 for chlorides) and 3 mL of toluene. The racemization catalyst was activated separately using 1 equiv of KO*t*Bu in freshly distilled toluene under an inert atmosphere. The solution of activated catalyst was then added to the reaction mixture over 6 h using a syringe pump.[14] To solubilize the substrates in the aqueous reaction medium, DMSO (5 vol%) was used as a cosolvent. Finally, the addition of bovine serum albumin (BSA, 3.5 mg/mL)[15] was required to stabilize the enzyme.

The DKR of **4b** gave the expected epoxide **5a** with 90% conversion and 98% ee (Table 2, entry 1).[16] The equivalent bromoalcohol **4c** gave **5a** with only 57% conversion and 56% ee (Table 2, entry 2). The rate of uncatalyzed ring closure of chloroalcohols is lower than that of bromoalcohols, which explains the higher enantioselectivities. Compound **4d** gave an excellent result that could be reproduced on 1.0 mmol scale (Table 2, entries 3 and 4).

As expected, the corresponding bromoalcohol **4e** was converted with lower but still very high enantioselectivity (Table 2, entry 5). A similar halide dependence was observed using 3-nitrophenyl-substituted **4f** and **4g** and 4-cyanophenyl-substituted **4i** and **4j**, as the chlorides could be converted to the epoxides with excellent ee, whereas the bromides led to lower selectivities (Table 2, entries 6 vs 7 and 9 vs 10). The conversion of 2-nitro substituted **4h** was low and in addition its product **5d** was obtained with slightly lower ee (91%) compared to its *meta*- and *para*-substituted equivalents **5c** and **5b** (97% ee, Table 2, entry 8 vs entries 4 and 6). We attribute this to the bulkiness of the *ortho*-substituent. Substrate **4k** was converted with slighly lower conversion and enantioselectivity (Table 2, entry 11). Trifluoromethyl-substituted substrate **4l** was converted to **5g** with an excellent ee of 98%, but HheC seems to be less active toward this substrate and additional enzyme was necessary to obtain a moderate yield (Table 2, entry 12). When cyclohexyl-substituted chloroalcohol **4m** was reacted, racemization did not proceed and static kinetic resolution resulted, giving **5h** with 50% conversion and 72% ee of the epoxide (Table 2, entry 13).

To show the potential of this DKR as a preparative procedure, a number of epoxides were isolated in good yields (entries 3, 6, 9, 11, and 12). The lower isolated yields compared to the GC or HPLC yields, as well as the variations in enantioselectivity, are partly due to the fact that a less active but more enantioselective batch of enzyme was used.

In summary, we developed the first chemo-enzymatic DKR of β-haloalcohols giving the corresponding epoxides in a single step, with good yields and excellent enantioselectivities using a variety of aromatic substrates. This required the development of iridacycle **3**, one of the most effective racemization catalysts to date for β-haloalcohols and compatible with water, and the use of HheC mutant Cys153Ser Trp249Phe.

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

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