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Authors: Jan-E. Bäckvall, Tamas Gorbe, and Richard Lihammar

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Heterogeneous Acid-Catalyzed Racemization of Tertiary Alcohols

Tamás Görbe,[a] Richard Lihammar,[a] and Jan-E. Bäckvall*[a]

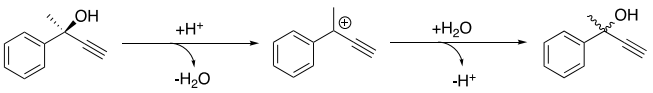
Abstract: Tertiary alcohols are important structural motifs in natural products and building blocks in organic synthesis but only few methods are known for their enantioselective preparation. Chiral resolution is one of these approaches which leaves one enantiomer (50% of the material) unaffected. An attractive method to increase the efficiency of those resolutions is to racemize the unaffected enantiomer. In the present work we have developed a practical racemization protocol for tertiary alcohols. Five different acidic resin materials were tested. The Dowex 50WX8 was the resin of choice since it was capable of racemizing tertiary alcohols without any byproduct formation. Suitable solvents and a biphasic system were investigated, and the optimized system was capable of racemizing differently substituted tertiary alcohols.

The stereoselective synthesis of organic molecules is of a high demand in the pharmaceutical and agrochemical industry. Three strategies are presently used for the preparation of enantiomerically pure compounds, one of them being the chiral pool synthesis, where chiral natural products are used as building blocks for the synthesis of complex molecules.[1] The other two strategies include resolution of racemates [2] and asymmetric synthesis, where in the latter case chiral reagents or catalysts are used.[3] Although asymmetric synthesis based on catalysis, i.e. asymmetric catalysis, is a very powerful method for obtaining enantiomerically pure compounds, the most common method used in chemical industry for obtaining such compounds is still via resolution. In a resolution, which could be crystallization, chiral chromatography, or kinetic resolution, two enantiomers are separated and the desired enantiomer is collected. The drawback of the resolution strategy is that only 50% of the material is used, and the unwanted enantiomer is discarded. A solution of this problem is to racemize the unwanted enantiomer and to recirculate the racemic mixture, which increases efficiency. Therefore, there is a high demand of efficient racemization methods in industrial applications.

Racemization can be achieved by a variety of techniques: thermal racemization, enzyme-catalyzed racemization, racemization *via meso*-intermediates, racemization by nucleophilic substitution, racemization via radical and redox reactions, photochemical racemization, and acid or base-catalyzed racemization.[4] The most common racemization catalysts for secondary alcohols are transition metal-based hydrogen transfer catalysts, which racemize the alcohol via a dehydrogenation-hydrogenation (oxidation-reduction) pathway.[5] When such a racemization catalyst is combined with a kinetic resolution catalyst (e.g. an enzyme) a so called "dynamic kinetic resolution" (DKR) can be achieved.[6]

Tertiary alcohols and their esters are important compounds, which are found in a number of natural products.[7] These compounds are also important building blocks in synthetic chemistry.[8] The synthesis of optically pure tertiary alcohols is still a challenging problem in organic chemistry, not only in the field of biocatalysis, but also in classical asymmetric synthesis.[9] The chemical or enzymatic resolution of tertiary alcohols have been reported for a few different types of compounds.[10,11] The chemical resolution of 3-hydroxy-3-substituted oxindoles was studied by Zhao and coworkers.[10] In their procedure they used N-heterocyclic carbene (NHC) catalysis to obtain the enantiomerically pure alcohols, and within the applied method it was found that the protocol is highly substrate specific.[10] Within the field of biocatalysis, Bornscheuer and his research group have studied different types of hydrolase enzymes for the resolution of tertiary alcohols.[11] They discovered that a specific amino acid motif (GGGX-motif, where G denotes glycine and X denotes any amino acid) located in the oxyanion hole of lipases and esterases show activity towards tertiary alcohols. The ester hydrolysis protocols reported provided the possibility to produce enantiomerically enriched tertiary alcohols.[11] However the transesterification with the same enzyme is extremely slow.[12]

As mentioned above, resolution methods for tertiary alcohols are known to some extent in the literature, although they are limited; however racemization processes that can be combined with kinetic resolution are unknown. Unfortunately, metal-catalyzed racemization of tertiary alcohols via a redox reaction is not possible. The only way to racemize tert-alcohols would seem to be via cleavage of the C-O bond. This may occur via protonation and formation of a carbocation, which is quenched by water (Scheme 1). This pathway has been demonstrated for racemization of secondary alcohols.[13,14] In this communication, we report a method for racemization of tertiary alcohols that is based on the use of an acidic resin.



Scheme 1. Acid catalyzed racemization of our model tertiary alcohols.

The Brønsted acid-catalyzed racemization via a carbocation is associated with alkene formation, which is a problematic side reaction. If the reaction is performed in a water-rich environment, elimination to alkene is suppressed. Acidic zeolites are heterogeneous catalysts, which can racemize secondary alcohols, however, with moderate success since alkene side products were formed leading to a decrease in yield.[14] Acidic resins have proven to be excellent racemization catalysts and are commercially available at low cost.[14,15] Our research group has already applied the acid-catalyzed racemization technique

[a] T. Görbe, Dr. R. Lihammar, Prof. Dr. J.-E. Bäckvall
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University
SE-106 91, Stockholm (Sweden)
E-mail: jeb@organ.su.se

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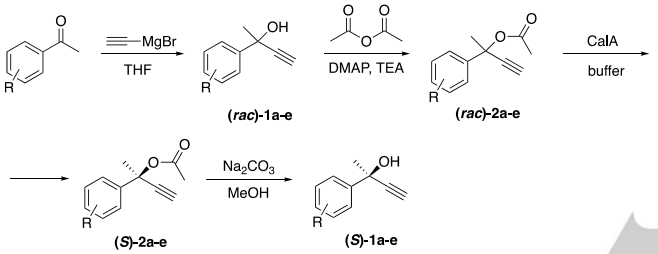
to a migratory DKR protocol, where we were able to use the acidic resins in an isomerization step of a cyclic allylic alcohol.[16] This racemization was combined with a resolution using *Candida antarctica* lipase B (CalB).

Our model substrate, 2-phenylbut-3-yn-2-ol **(1a)**, was chosen based on the previous studies of kinetic resolution of tertiary alcohols with *Candida antarctica* lipase A (CalA).[11] The alcohol substrate was synthesized by Grignard reaction of the corresponding acetophenone compound. The racemic 2-phenylbut-3-yn-2-ol derivatives (*rac*)-**1a**-**e** were chemically acylated with acetic anhydride in a Biotage® microwave reactor to produce 2-phenylbut-3-yn-2-yl acetate (*rac*)-**2a**-**e** products. The racemic acetate derivatives (*rac*)-**2a**-**e** were hydrolyzed enzymatically towards the enantiomerically enriched alcohol products. The applied enzyme, CalA wild type, was immobilized by adsorption on the hydrophobic support Accurel MP-1001. The enzymatic hydrolysis was performed in pH 7.6 phosphate buffer solution.

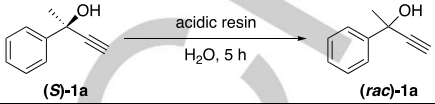


Scheme 2. Synthesis of enantiomerically enriched 2-phenylbut-3-yn-2-ol derivatives **(*S*)-1a-e**.

The synthesized tertiary ester compounds are not highly stable; chemical hydrolysis can occur in solution and the CalA enzyme reacts rapidly with the substrate ester molecules. Because of this high reactivity, the substrates **2a**-**e** were over-hydrolyzed. Afterwards, the enantiomerically enriched acetates (*S*)-**2a**-**e** were separated by column chromatography and chemically hydrolyzed to (*S*)-**1a**-**e** by a 4:1 mixture of MeOH and an aqueous saturated solution of Na_2CO_3. In this way, the desired enantiomerically enriched tertiary alcohols (*S*)-**1a**-**e** required for the racemization studies, were obtained.

Five different types of acidic resins were studied. These resins are based on a styrene-divinylbenzene (gel) polymer functionalized either with carboxylic acid or sulfonic acid groups (Table 1). The heterogeneous acids were investigated in water as solvent. The model reaction was done on a 0.1 mmol scale using substrate (*S*)-**1a** in 1 mL of water with 40 mg of acid catalyst. The racemization of benzylic alcohols requires an acid of sufficient strength, and the weaker carboxylic acid-based Amberlite 120 resulted in a moderate rate for racemization of alcohol (*S*)-**1a** (Table 1, entry 1). Amberlyst 15 showed very good capability of the racemization (Table 1, entry 2). Three differently cross-linked Dowex resins (2, 4 and 8% cross-linkage) were next examined (Table 1, entry 3, 4 and 5). The amount of cross-linking is very important for the activity of the catalyst, and 8% cross-linking led to the highest activity. Although, fewer acidic groups are introduced into a higher cross-linked resin, these functional groups are spaced closer together on a volume basis, and the volume of water is reduced by the additional cross-linking. Due to these facts only Dowex 50WX4 and Dowex 50WX8 are enough acidic to be able to racemize alcohol substrate (*S*)-**1a** (Table 1, entry 4, 5).

Table 1. The screening of the acidic resins.

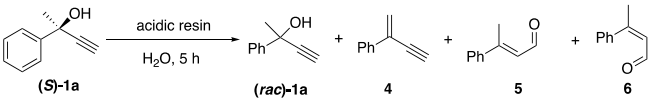


Entry[a]	Resin	Acidic group	Capacity [meq/mL]	*ee* [%]
1	Ambelite 120	–COOH	1.0	13
2	Amberlyst 15	$–SO_3H$	1.7	<1
3	Dowex 50WX2	$–SO_3H$	0.6	23
4	Dowex 50WX4	$–SO_3H$	1.1	<1
5	Dowex 50WX8	$–SO_3H$	1.7	2

[a] 0.1 mmol substrate was solved in 1 mL of water, 40 mg of acidic resin was added and stirred at room temperature for 5 h. 0.05 mL of samples were taken, extracted with EtOAc. The organic phase was analyzed by chiral-GC.

During the racemization, the reaction mixtures were also analyzed by ^{1}H-NMR spectroscopy, with the aim to detect the possible elimination products. It is known in the literature that propargylic alcohols can undergo a Mayer-Schuster rearrangement, where (*E*)- and (*Z*)-unsaturated aldehydes are formed. We identified (*E*)-3-phenylbut-2-enal (**4**) and (*Z*)-3-phenylbut-2-enal (**5**) as byproducts from such a rearrangement (Table 2).

Table 2. By-product formation during the acidic resin screening.



Entry[a]	Resin	**1a** [%][b]	**3** [%][b]	**4** [%][b]	**5** [%][b]
1	Amberlite 120	81	0	10	9
2	Ambelyst 15	53	29	10	8
3	Dowex 50WX2	100	0	0	0
4	Dowex 50WX4	100	0	0	0
5	Dowex 50WX8	100	0	0	0

[a] 0.1 mmol substrate was solved in 1 mL of water, 40 mg of acidic resin was added and stirred at room temperature for 5 h. 0.05 mL of samples were taken, extracted with EtOAc. The organic phase was collected and the solvent was evaporated. The samples were dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy. [b] Conversions based on ^{1}H NMR.

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The results in Table 2 shows that Dowex resins (entries 3-5) are the most selective catalysts without any formation of by-products **3-5**. Of these three resins the Dowex 50WX8 was chosen for further studies since it was also the most effective resin (Table 1). Five different solvents were studied for the racemization of (*S*)-**1a** using Dowex 50WX8, and the reactions were run for 5 h (Figure 1). As expected, for this type of racemization, water is the best solvent, which led to good reaction rate with no side products. Also, isooctane gave a good reaction rate of the racemization, but unfortunately, 8% of **3** and 33% of **4-5** byproducts were formed with this solvent. However, for Dowex 50WX8 in toluene and in acetonitrile racemization was slower and after 5 h of reaction the alcohol **1a** was of 54% *ee* and 40% *ee*, respectively. The *i*-octane/water 1:1 system was also examined, and this two-phase-system worked almost as well as that with water as solvent and gave **1a** with 9% *ee* without any byproduct formation. This two-phase-system should be suitable for applications that require an organic solvent.

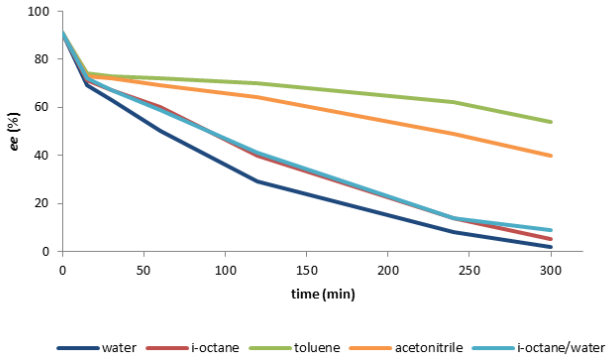

Figure 1. Solvent screening. Reaction conditions: 0.1 mmol of substrate **(*S*)-1a** was dissolved in 1 mL of solvent, 40 mg of Dowex 50WX8 resin was added and stirred at room temperature. 0.05 mL of samples were taken, extracted with EtOAc. The organic phase was analyzed by chiral-GC and by ^{1}H NMR spectroscopy.

With the optimized reaction conditions in hand differently substituted tertiary alcohols were tested in the racemization (Figure 2.). The Dowex 50WX8 resin was capable of racemizing alcohols (*S*)-**1a-b** within 5 h of reaction time. The process was tested with electron-withdrawing groups on the aromatic ring as well. Whereas *p*-fluorophenyl derivative **1c** was racemized within 5 h, the corresponding *p*-chlorophenyl compound **1d** required 8h to be racemized. For the *p*-nitro substrate **1e** 120 mg of Dowex 50WX8 at 70 ºC had to be used for 52 h. In the latter case the formation of the carbocation is much slower, then for the other substrates. We tried to use the electron-donating 2-(4-methoxyphenyl)but-3-yn-2-ol substrate. Unfortunately, the synthesized acetate was too unstable, and it was self-hydrolyzed during the work up of the reaction.

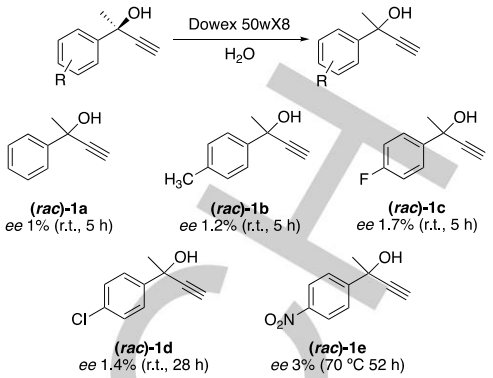

Figure 2. Substrate scope. The racemic alcohols were recovered in >95% yield according to ^{1}H NMR spectroscopy. Compound (***rac*)-1a** was also obtained in 96% isolated yield. The half-life time for substrate **(*S*)-1a** is about 1 h and for substrates (*S*)-**1b** and (*S*)-**1c** it is almost identical. The half times for (*S*)-**1d** and (*S*)-**1e** are 5 h and 12 h, respectively.

A practical and easy-to-use racemization of tertiary alcohols has been developed. Several acidic resins with different acidity were screened for the activity of the racemization. Dowex 50WX8 was found to be the optimal resin for racemization of tertiary alcohols and it was tested in a few different solvents. Water was found to be the best solvent giving excellent results without any formation of byproducts. Tertiary alcohols were racemized within 5-8 h at room temperature. Only in one case, it was necessary to use more acid, elevated temperature and longer reaction time. This new method would be useful in combination with various resolution processes of tertiary alcohols.

Experimental Section

General racemization protocol of (*S*)-2-phenylbut-3-yn-2-ol derivatives ((*S*)-1a-e)

The alcohol **(*S*)-1** (0.1 mmol) was placed in a vial, and 1 mL of water or another solvent was added (see Figure 1. for solvent). The corresponding acidic resin (40 mg) was added to the solution, and the mixture was stirred at room temperature for the given times (see Figure 2.). Samples (0.05 mL) were taken and added to 2 mL 1:1 EtOAc/water mixture. The organic phase was separated and analyzed by chiral-GC or chiral-HPLC and ^{1}H NMR.

Acknowledgements

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Keywords: racemization • tertiary alcohols • heterogeneous catalysis • acidic resins

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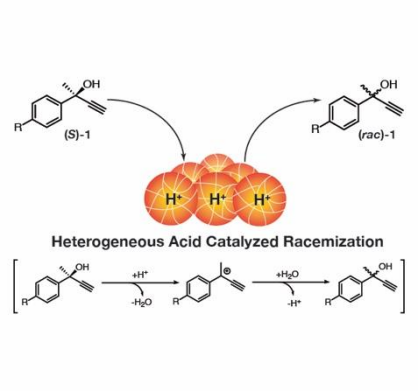

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Page No. – Page No.

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Layout 2:

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Page No. – Page No.

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Text for Table of Contents