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Highly efficient dynamic kinetic resolution of secondary aromatic alcohols using a low-cost solid super acid as a racemization catalyst

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ABSTRACT

A new, efficient dynamic kinetic resolution (DKR) of secondary aromatic alcohols using self-made solid super acid TiO_2/SO_4^{2-} as a racemization catalyst was developed. Low-cost and easily produced TiO_2/SO_4^{2-} showed excellent racemization activity. When coupled with the lipase, Novozym 435, good biocompatibility was observed, and optically pure aromatic acetate (>99%) was obtained with a high yield. It is noteworthy that the system could be reused more than 10 times with little loss of yield or reduction in the enantiomeric excess (*ee*) value of product.

Introduction

Dynamic kinetic resolution (DKR) is a kinetic resolution (KR) coupled with in situ racemization of the slow-reacting enantiomer. The DKR approach could overcome the limitation of KR and increase the theoretical maximum yield from 50% to 100%, thus avoiding separation of the unwanted enantiomer from the reaction system.[1] According to previous studies, for successful chemo-enzymatic DKR, a highly selective KR catalyst, an efficient racemization catalyst, and the compatibility between them are essential.[2] To date, many reported lipases meet the necessary selectivity of KR, whereas only two main types of racemization catalysts have been shown to be effective for DKR of *sec*-alcohols.[3] Transition metal catalysts are one type of racemization catalyst reported to be involved in the hydrogen-transfer mechanism and are called pentaphenylcyclopentadienyl ruthenium complexes.[4] An excellent enantiomeric excess (*ee*) value and a high yield have been obtained by coupling this catalyst type with lipase; however, the high cost of the ruthenium complexes, the complexity of the preparation process, the difficulty of the ruthenium complexes to be recycled, and in some cases, the requirement of rigorous reaction conditions may prevent the use of ruthenium complexes in further applications.[5] Acid racemization catalysts are another type of racemization catalyst that is involved in the transfer of hydrogen protons and the formation of carbenium ions. Acid zeolite, a common acid racemization catalyst, was first used in DKR of *sec*-alcohols.[6] Because of a non-selective transesterification reaction, a high yield and excellent *ee* value could not be obtained simultaneously. A high racemization temperature, 60 °C, produced poor biocompatibility with lipase, and byproducts of styrene and ether were produced in the DKR process.[7] In our previous study, CD 8604 and CD 550, which are two types of cation exchange resins with large pore polyethylene-divinylbenzene copolymer as vector and $-SO_3H$ as the catalytic functional group, were found to be very efficient and more compatible with lipase in the DKR of secondary alcohols.[8] A high yield (>99%) and excellent *ee* (>99%) were obtained.[9] However, one limitation of the latter study was that the catalysts gradually dissolved in the solvent, and the solved acid group $-SO_3H$ reduced the lipase activity. Furthermore, it also makes the separation process more difficult.

Herein, we develop a new type of acid racemization catalyst, a nano solid super acid, which showed high efficient racemization capability. When coupling this new racemization catalyst with the lipase, Novozym 435, good biocompatibility was demonstrated, and optically pure aromatic acetate was obtained.

Results and discussion

Several solid super acid catalysts were synthesized smoothly and screened for their racemization activity to (*S*)-1-phenylethanol (Table 1).[10] Additionally, the racemization activity of other catalysts is also summarized in Table 1.

We were intrigued to find that all the new racemic catalysts, TiO_2/SO_4^{2-}, Al_2O_3/SO_4^{2-}, and Fe_2O_3/SO_4^{2-}, showed efficient racemization, and (*S*)-1-phenylethanol was almost completely racemized after 6 h (Table 1, entries 1–3). The acid resin CD 8604 and CD 550 were two types of efficient racemization catalysts according to our previous report (entries 4 and 5).[8] The racemization of three solid super acid catalysts with H_0s of -12 to -14[10c] was slightly more efficient

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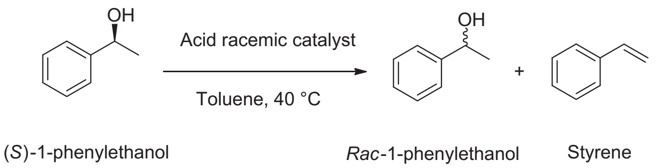
Table 1

The racemization of (*S*)-1-phenylethanol with different racemic catalysts



Entry	Catalyst	Acid group	Reaction time (h)	ee_S (%)	Styrene (%)
1	TiO_2/SO_4^{2-}	$-SO_3H$	6	6.4	0
2	Al_2O_3/SO_4^{2-}	$-SO_3H$	6	9.5	0
3	Fe_2O_3/SO_4^{2-}	$-SO_3H$	6	10.8	0
4	CD 8604	$-SO_3H$	6.5	12.5	0
5	CD 550	$-SO_3H$	6.5	16.3	0
6	HY-zeolite	Al^{3+}	6	28	15
7	D 113	–COOH	6	>99	0
8	116	–COOH	6	>99	0

Reactions: 2 mL toluene, 100 mmol/L (*S*)-1-phenylethanol, 80 mg racemic catalyst, at 40 °C and 200 rpm.

ee_s is the enantiomeric excess value of substrate, D 113 and 116 are two types of cation exchange resins with large pore acrylic acid copolymer as vector and –COOH as catalytic functional group.

than racemization with CD 8604 and CD 550, and the byproduct styrene was not detected in the reaction system. Although (*S*)-1-phenylethanol was racemized under Al^{3+}, which is a medium strong acid with an H_0 of approximately −9,[11] the side reaction was not successfully inhibited, and 15% byproduct was obtained (Table 1, entry 6). Carboxylic acid is a weak acid; thus, (*S*)-1-phenylethanol was barely racemized (Table 1, entries 7 and 8). Taken together, racemization capacity was enhanced and byproduct was reduced with the increasing of acid strength, these results proved that these three solid super acids with $-SO_3H$ were effective racemic catalysts. With the best racemization activity, TiO_2/SO_4^{2-} was chosen as our racemization catalyst in the present study.

The as-prepared solid super acid TiO_2/SO_4^{2-} was characterized by FT-IR, BET, and SEM.

Figure 1 illustrates the FT-IR spectra of TiO_2/SO_4^{2-} in the region of 400–4000 cm^{-1}. Two bands at 1125 and 1138 cm^{-1} were characteristic of asymmetric and symmetric stretching of S=O vibrations, respectively.[10d,e] The band at 1383 cm^{-1} was related to the S=O stretching vibration from the sulfate ion on the surface of the solid. The bending and stretching vibrations of OH produced the band at 1633 cm^{-1}, and the band at 3404 cm^{-1} represented the surface hydroxyl group of TiO_2. Thus, the racemization catalyst TiO_2/SO_4^{2-} with a strong acid group and a polarity vector was successfully synthesized. Based on the mechanism of acid racemization, (*S*)-1-phenylethanol could be racemized under acid conditions, and the reaction to styrene was reversible. Additionally, this reversible reaction had difficulty producing byproducts under strong acid conditions. Thus, the byproduct was effectively inhibited when TiO_2/SO_4^{2-} was used as the racemization catalyst (Table 1, entry 1).

Table 2

Physical properties of racemization catalysts

Entry	Catalyst	*d* (nm)	*S* (m^2 g^{-1})
1	TiO_2/SO_4^{2-}	8.5	92
2	CD 8604	39.4	31.46
3	CD 550	35.7	31.15

d Stands for the pore size calculate from the adsorption branch by the BJH method, *S* is the BET surface area.

The physicochemical parameters of TiO_2/SO_4^{2-} are summarized in Table 2. The BET surface area of TiO_2/SO_4^{2-} was much larger than that of CD 8604 and CD 550, providing much more loading sites for $-SO_3H$. Thus, (*S*)-1-phenylethanol could be racemized more rapidly with TiO_2/SO_4^{2-}.

The N_2 adsorption–desorption isotherm of TiO_2/SO_4^{2-} exhibited a typical IUPAC type IV pattern with the presence of a H2 hysteresis loop and is presented in Figure 2. The hysteresis loop is a typical

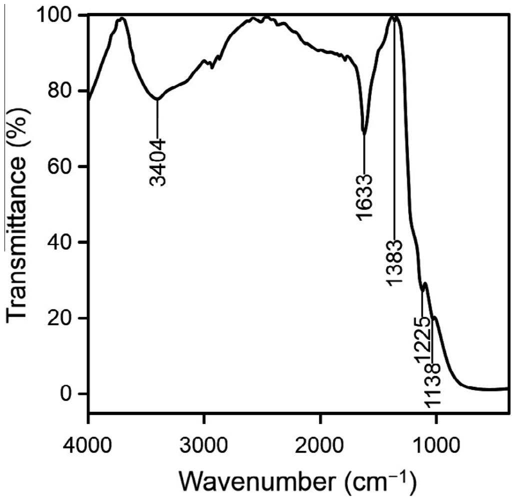


Figure 1. FTIR spectrometer of TiO_2/SO_4^{2-}.

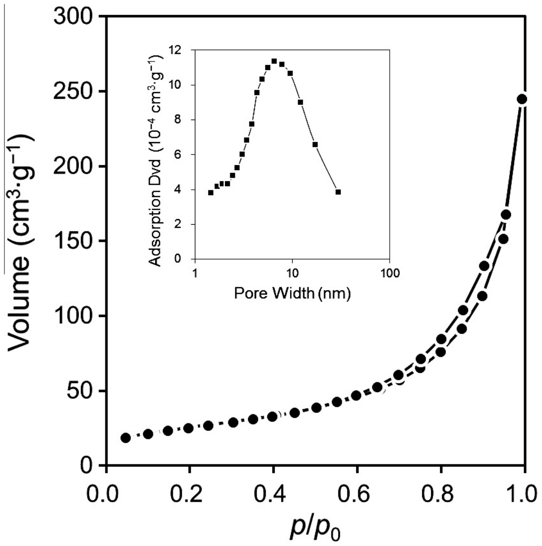


Figure 2. N_2 adsorption–desorption isotherm and pore size distribution of TiO_2/SO_4^{2-}.

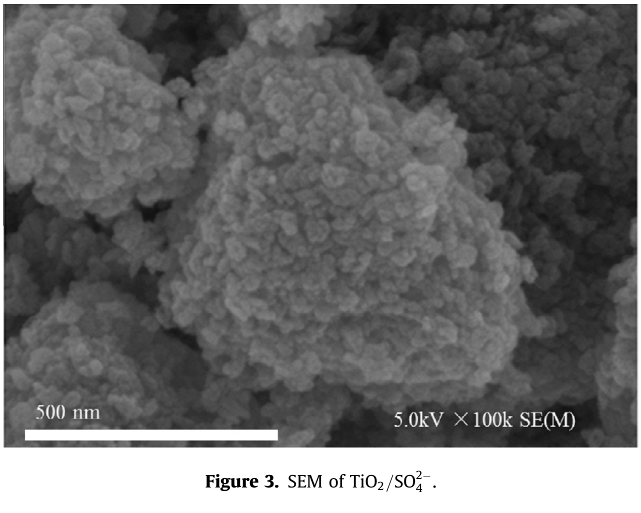


Figure 3. SEM of TiO_2/SO_4^{2-}.