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Highly efficient dynamic kinetic resolution of secondary aromatic alcohols at low temperature using a low-cost sulfonated sepiolite as racemization catalyst



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ABSTRACT

A highly efficient dynamic kinetic resolution system for secondary aromatic alcohol using low-cost sulfonated sepiolite as a racemization catalyst has been developed. The system operates at 25 °C, achieves good ee_p (>99%) and substrate conversion ratio (>99%), is applicable to a variety of substrates and can be reused more than 10 times.

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Introduction

Dynamic kinetic resolution (DKR) is a widely researched method for the preparation of optically pure chiral secondary alcohols. By combining enzyme-catalyzed kinetic resolution (KR) with an in situ racemization, normally catalyzed by chemical catalyst, DKR increases the maximum yield of enantiopure product of a KR process from 50% to 100%.¹ The key aspect of a successful and practical DKR system is a highly efficient and low cost racemization catalyst capable for mild reaction conditions that an enzyme requires.² However, currently available racemization catalysts are either difficult to synthesize homogeneous metal complexes or supported transition metals, which typically require either high temperature or the presence of high-pressure hydrogen.³

Here, we report a highly efficient DKR system for chiral aromatic alcohols that works at a quite mild temperature (25 °C) using low-cost sulfonated sepiolite as the racemization catalyst. The system was applied to a variety of substrates, all achieving both high ee_p (>99%) and substrate conversion (>99%).

Results and discussion

In our previous research, acidic resins (CD550 and CD8604, entries 1 and 2 in Table 1)⁴ and solid super acids $(TiO_2/SO_4^{2-}, entry)$

3 in Table 1)⁵ performed well in organic media as racemization catalysts of optically pure enantiomer of aromatic secondary alcohols. Their catalytic activity is derived from their sulfuric acid groups (–SO₃H). DKR systems of aromatic *sec*-alcohols have been well established by coupling these racemization catalysts with Novozym 435 (immobilized *Candida antarctica* lipase B), and when the acylation reaction was carried out at 40 °C using *p*-chlorophenyl valerate as acyl donor, both ee_p and substrate conversion were greater than 99%.^{5,6}

However, 40 °C, which the acidic resin and solid super acid require to racemize chiral aromatic sec-alcohols, is still not low enough for most commercially available lipases other than Novozym 435 (which is known to be pretty thermally stable). Therefore, the racemization catalyst needed further improvements for even higher efficiency, so as to build truly enzyme-compatible for use in a practical DKR system. Because solid super acid displayed higher stability than the acidic resins in the very reaction condition of aromatic alcohol resolution in organic media, this catalyst was targeted for enhancement. Nano-scaling is a widely accepted approach for the activation of catalysts, so large specific surface area nanosized materials with different microstructures with large specific surface areas, such as SBA-15, nanosized SiO₂, and SBA-3 were prepared according to the literature,⁷ and then sulfonated to make the corresponding nanosized super acids (entries 4, 5, and 6 in Table 1). These catalysts did have higher catalytic activity than the previously synthesized catalysts (entries 1, 2, and 3 in Table 1), but unfortunately, they also produced significant





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Table 1

Racemization performance of nanosized super acids and sulfonated natural minerals as compared with other acidic catalysts



^a Reaction conditions for racemization (Reaction I): toluene (1 mL), (S)-1-phenylethanol (100 mmol L⁻¹), and catalyst (10 mg) were mixed in a 2 mL tube, reacted for 6 h at 40 °C, and agitated at 200 rpm.

^b Non-enzymatic acylation (Reaction II) is a side reaction in which acidic catalyst might catalyze during DKR process. This side reaction lowers the overall ee_p of DKR and should be avoided. In the table, higher conversion ratio of Reaction II indicates a poorer specificity of the catalyst. Reaction conditions for the non-enzymatic acylation (Reaction II): toluene (1 mL), *rac*-1-phenylethanol (100 mmol L⁻¹), *p*-chlorophenyl valerate (300 mmol L⁻¹), and catalyst (10 mg) were mixed in a 2 mL tube, reacted for 6 h at 40 °C, and agitated at 200 rpm.

^c Sulfonation conditions for entries 3, 4, 5, 6, 7, and 8: the solid was impregnated in H_2SO_4 (0.5 mol L⁻¹) for 4 h and then heated at 400 °C for another 4 h.

 $^{d}\,$ The standard crystallochemical formula of halloysite is $Al_{2}O_{3}\cdot 2SiO_{2}\cdot 4H_{2}O.$

^e The standard crystallochemical formula of sepiolite is Mg₈(H₂O)₄[Si₆O₁₆]₂(OH)₄·8H₂O.

Table 2 Racemization performance of the sulfonated sepiolite at different temperatures

Entry	Temperature (°C)	Time (h)	ee (%)	Styrene (mmol·L ⁻¹)	
1	40	4	0	0	
2	35	6	0	0	
3	30	12	0	0	
4	25	24	0	0	

amounts of side-products in the non-enzymatic acylation of aromatic *sec*-alcohol (reaction II in Table 1). Of these three spherical nanosized catalysts, the porous SBA-15/SO₄^{2–} had the lowest side reactions.

From this, it can be inferred that the large specific surface area of nanosized material tend to over-activate the catalyst, lowering their specificity. The porous microstructure, however, was able to inhibit the non-enzymatic acylation side reaction. Working from this, and the complexity of the preparation and higher cost of the

Table 3

DKR of various sec-alcohols with p-chlorophenyl valerate as the acyl donor





Entry	Substrate	Product	ee _p (%)	Conversion ^b (Yield ^c) (%)
6	СН ЗОН	Ly lon	>99	>99 (92)
7	ОН	Long Contraction	>99	>99 (90)
8	CI OH		>99	>99 (88)
9	CI	ci jo	>99	>99 (90)
10	CI CI CI CI		>99	>99 (92)
11	Br	Br Louis	>99	>99 (89)
12	OH SOH		>99	>99 (92)
13	O O O		>99	>99 (88)
14	OH C		>99	>99 (90)
15	о Г С Т С Т С Н		>99	>99 (92)
16	ОН		>99	>99 (90)

^a Reaction conditions: toluene (1 mL), racemic aromatic *sec*-alcohol (100 mmol L^{-1}), *p*-chlorophenyl valerate (300 mmol L^{-1}), Novozym 435 (10 mg), and sepiolite/SO₄²⁻ (10 mg) were mixed in a 2 mL tube, reacted at 25 °C for 24 h, and agitated at 200 rpm.

^b Conversion ratio (%) = [converted substrate (mol)]/[total initial substrate (mol)] × 100%.

^c Isolated yield (%) = [isolated product (mol)]/[total initial substrate (mol)] \times 100%. The enantiomerically pure DKR products were isolated from the reactant by column chromatography using *n*-hexane/ethyl acetate = 10:1 (v/v) as a developing agent.

nanosized catalysts, we decided to synthesize a super acid based on low cost natural minerals with a porous microstructure and a

Table 3 (continued)



Figure 1. Operational stability of the DKR system in a series of batch reactions. After a batch of reaction, the catalysts (sepiolite/SO₄⁻ and Novozym 435) were separated by centrifugation (12,000 rpm for 5 min using a Sigma 3-18K centrifuge). The recycled catalysts were then washed by toluene 3 times and stored at 25 °C for the next batch of use.

specific surface area between those of common catalysts (CD550, CD8604, and TiO_2/SO_4^{2-}) and nanosized catalysts (SBA-3/SO₄²⁻, nanosized SiO_2/SO_4^{2-} , and $SBA-15/SO_4^{2-}$). Sepiolite and halloysite are among those cheapest minerals with the largest specific surface areas.⁸ After sulfonation, they displayed higher catalytic activity in the racemization of (S)-1-phenylethanol than CD-550, CD-8604, and the TiO_2/SO_4^{2-} , and better specificity than SBA-15/SO₄²⁻, nanosized SiO₂/SO₄²⁻, and SBA-3/SO₄²⁻. The racemization temperature of sepiolite/ SO_4^{2-} was investigated further (Table 2), indicating that this newly developed catalyst performed well at temperatures as low as 25 °C. At 25 °C, sulfonated sepiolite was then employed as the racemization catalyst in the DKR of several chiral aromatic sec-alcohols, coupled with Novozym 435 as the resolution catalyst and all achieved ee_p >99% and conversions >99% (Table 3). This DKR system could be reused more than 10 times without any decrease in ee_p and conversion (Fig. 1).

Conclusions

In summary, a low-cost racemization catalyst based on sulfonated sepiolite was developed and employed in the DKR of secondary aromatic alcohols, achieving good ee_p and substrate conversion ratios at 25 °C, which was the lowest reported DKR temperature.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07. 102.

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