



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



Jian-Ping Wu, Xiao Meng, Liang Wang, Gang Xu*, Li-Rong Yang

Institute of Biological Engineering, Department of Chemical and Biological Engineering, Zhejiang University, 310027 Hangzhou, China

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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

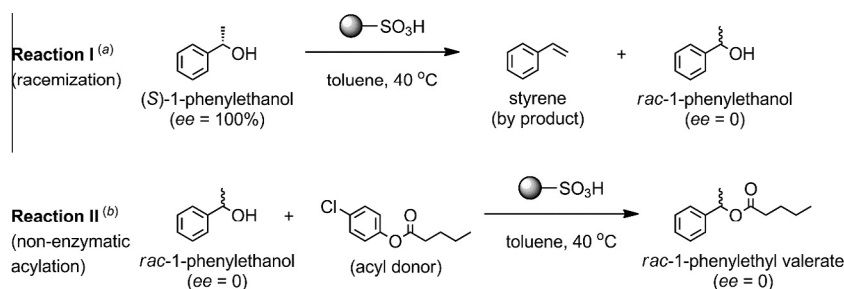
In our previous research, acidic resins (CD550 and CD8604, entries 1 and 2 in Table 1)⁴ and solid super acids (TiO_2/SO_4^{2-} , entry

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 ($-SO_3H$). 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 SiO_2 , 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

* Corresponding author.

Table 1
Racemization performance of nanosized super acids and sulfonated natural minerals as compared with other acidic catalysts



Entry	Catalyst	Microscopic structure	Average pore size (nm)	Specific surface area (m ² g ⁻¹)	Reaction I ^a		Reaction II ^b
					<i>ee</i> (%)	Styrene (mmol L ⁻¹)	Conversion (%)
1	CD550	Porous	35.7	31	16.3	0.0	0.0
2	CD8604	Porous	39.4	31	12.5	0.0	0.0
3	TiO ₂ /SO ₄ ²⁻ -c	Spherical	—	92	6.4	0.0	0.0
4	SBA-15/SO ₄ ²⁻ -c	Porous	4.0	534	9.5	0.0	13.3
5	Nanosized-SiO ₂ /SO ₄ ²⁻ -c	Spherical	—	1015	7.7	0.0	32.6
6	SBA-3/SO ₄ ²⁻ -c	Spherical	—	1266	3.9	0.0	33.3
7	Halloysite/SO ₄ ²⁻ -c,d	Porous	16.2	87	5.5	0.0	0.0
8	Sepiolite/SO ₄ ²⁻ -c,e	Porous	12.0	154	0.4	0.0	0.0

^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 H₂SO₄ (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 Al₂O₃·2SiO₂·4H₂O.

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

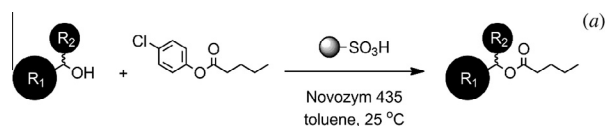
Table 2
Racemization performance of the sulfonated sepiolite at different temperatures

Entry	Temperature (°C)	Time (h)	<i>ee</i> (%)	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/SO₄²⁻ 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	<i>ee</i> _p (%)	Conversion ^b (Yield ^c) (%)
1			>99	>99 (95)
2			>99	>99 (95)
3			>99	>99 (95)
4			>99	>99 (95)
5			>99	>99 (94)

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