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ARTICLE

Spatial effects of oxovanadium-immobilized mesoporous silica on racemization of alcohols and application in lipase-catalyzed dynamic kinetic resolution

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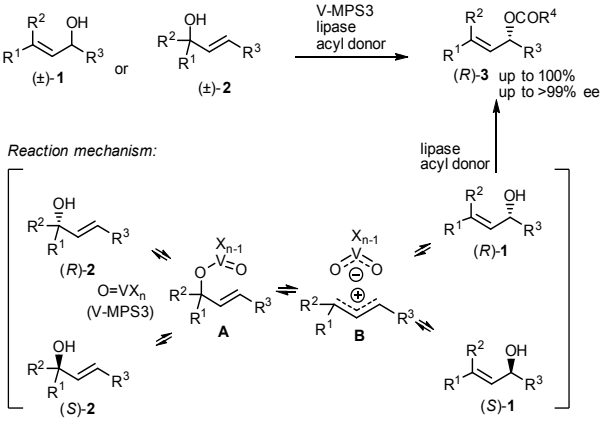
We recently reported a new dynamic kinetic resolution (DKR) method based on the combination of lipase-catalyzed kinetic resolution of racemic alcohols and the V-MPS3-catalyzed in situ racemization of less reactive alcohol enantiomers. In V-MPS3, oxovanadium moieties were covalently bound to the inner surface of mesoporous silica (MPS) with a pore size of about 3 nm. The catalytic activity of V-MPS3 was much higher than that of related vanadium compounds; however, we could neither explain its unusually high activity nor confirm that the racemization predominantly occurred inside the V-MPS pores. Therefore, in this study, we prepared V-MPS2 and V-MPS4 from the corresponding MPS with pore diameters of approximately 2 nm and 4 nm, respectively and compared their racemization activities with that of V-MPS3 using some optically active alcohols with different molecular sizes and polarities. We discovered a positive correlation between the pore size of V-MPS and substrate racemization rate as well as the high polarity of the MPS pores. The results suggested that the racemization predominantly occurs in the pores of V-MPS and that a small pore size (2–4 nm) is essential to generate the polar environment of V-MPS, which probably accelerates the racemization by facilitating the C–O bond cleavage of the vanadate intermediates. Using V-MPS with a pore size suitable for each substrate, lipase/oxovanadium combo-catalyzed DKR could be applied to a wider range of alcohols including allyl alcohols, benzylic alcohols, and propargyl alcohols to give the corresponding esters in excellent isolated yields and enantioselectivities.

Introduction

The enzymatic dynamic kinetic resolution (DKR) of racemic secondary alcohols has gained much attention because it is a simple method to obtain optically pure esters in quantitative yields.[1] DKR is typically performed using a combination of hydrolase-catalyzed kinetic resolution and ruthenium-catalyzed in situ continuous racemization of less reactive alcohol enantiomers via a redox process. The efficiency of the strategy is demonstrated by its applicability to a wide range of alcohols.[2,3] However, some issues ensue when the strategy is applied to allyl alcohols, including the formation of significant amounts of side-products.[1c]

Recently, we have developed a new DKR method, which is particularly useful for allyl alcohols, based on the combined use of lipases and oxovanadium catalysts. In this method, racemization occurs along with the 1,3-migration of hydroxyl groups and enables the use of regioisomeric allyl alcohols (**1** and **2**) as equivalent substrates (Scheme 1),[4] which are very different from the ruthenium-catalyzed DKR. Accordingly, we developed a new racemization catalyst, V-MPS3, in which oxovanadium moieties are covalently bound to the inner surface of mesoporous silica (MPS) with a pore size of about 3 nm (Figures 1A and 1B).[4c,5] MPS is a rigid, well-ordered hexagonal material with uniform pore size, large surface area (averaging 1000 m^2/g or more), and mild acidity. Various kinds of MPS with different pore sizes (ranging from 2 nm to 50 nm) are



Scheme 1 Dynamic kinetic resolution of racemic alcohols (**1** and **2**) by V-MPS3/lipase combo catalysis.

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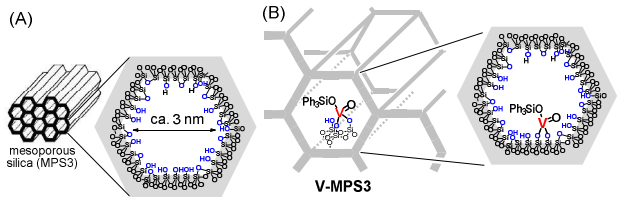

Figure 1 Structure of MPS3 (A) and estimated structure of V-MPS3 (B).[4c]

readily available.[6] The combined use of lipases and V-MPS3 significantly increased the chemical and optical yields of the products, (*R*)-**3**, as compared to our previous DKR methods, in which a homogenous catalyst $O=V(OSiPh_3)_3$[4a] and a polymer-supported oxovanadium compound[4b] were used. One of the most outstanding improvements of V-MPS3 was the excellent compatibility with lipases, because the combined use of lipases and our previous catalysts, such as $O=V(OSiPh_3)_3$[4a] and a polymer-supported oxovanadium compound,[4b] resulted in a loss of their catalytic activities owing to mutual interaction. The compatibility of V-MPS3 and lipases was supposed to be due to the narrow pores of MPS3, which effectively separated the vanadium moiety and lipases and completely suppressed the mutual inactivation. However, we had no evidence to confirm that the racemization predominantly occurred inside the pores of MPS. In addition, V-MPS3 exhibited the highest racemization activity among several oxovanadium compounds, including $O=V(OSiPh_3)_3$,[4a] a polymer-supported oxovanadium compound,[4b] and oxovanadium moieties covalently immobilized on the pore surface of macroporous silica with a pore size of either 100 nm or 400 nm.[4c] These results were especially surprising because polymer supported catalysts are often less reactive than homogeneous catalysts and also because the relatively narrow pore size of V-MPS3 was thought to prevent alcohols from rapidly coming in and out of the pores. The abovementioned unexpectedly high racemization activities of V-MPS3 suggested that the nanosized pores of MPS3 exhibited unknown chemical as well as physical effects on the racemization. We speculated that the small pores of MPS3, whose surface was covered with silanols, created a polar environment[7] that accelerated the racemization by facilitating the C–O bond cleavage of the vanadate **A** and stabilizing ionic intermediate **B**, although we had no evidence to support this hypothesis.

Since its discovery in the early 1990s,[6] MPS has found widespread application in catalysis,[8] carriers,[9] adsorption,[7,10] sensing,[11] and chromatography[12] among other areas.[13] On the contrary, there are limited reports on the use of MPS pores in transformations of organic molecules, which include acetalization reactions,[14] porphyrin synthesis,[15] Friedel–Crafts reactions,[16] metathesis,[17] DKR,[2f,2k] and polymerization.[18] Among the available reports, the active use of pore size effects of MPS were studied in very few cases,[14,15] and most studies used MPS with a single pore size.

In this study, we prepared V-MPS2 and V-MPS4, with pore sizes of approximately 2 and 4 nm, respectively, and compared their racemization activities with that of V-MPS3. We observed some characteristic effects of V-MPS on the racemization of several optically active secondary alcohols with different molecular sizes and/or polarities and on lipase-catalyzed DKR. We also obtained strong evidences for our hypotheses that the racemization predominantly occurred inside the pores of V-MPS and that the polarity of the V-MPS pores accelerated the racemization. Notably, by choosing V-MPS with a suitable pore size for each substrate, the scope of viable substrates for DKR was expanded.

Results and discussion

Preparation of V-MPS with different pore sizes and their application in the racemization of various alcohols.

We prepared V-MPS2 and V-MPS4 by the silanol-exchange reaction of the corresponding MPS2 and MPS4 with $O=V(OSiPh_3)_3$, in a manner similar to that described for V-MPS3.[4c] The structures of V-MPS2 and V-MPS4 were determined by Brunauer–Emmett–Teller (BET), Barrett–Joyner–Halenda (BJH), inductively coupled plasma (ICP), and elemental analyses (Table 1). The average pore sizes of V-MPS2 and V-MPS4, as measured by BET, were 1.7 nm and 3.3 nm, respectively (for reference, the average pore size of V-MPS3 is 2.6 nm). The loading of the vanadium component of V-MPS4, as measured by ICP, was 0.20 mmol/g and was almost the same as that of V-MPS3 (0.20–0.22 mmol/g). On the other hand, the loading of the vanadium component of V-MPS2 was 0.02 mmol/g, and such a low vanadium loading is probably due to the narrow pore of MPS2, which might hamper the incorporation of $O=V(OSiPh_3)_3$ into MPS2. The similarity of the solid-state ^{13}C NMR data (δ 135.0, 130.3, 128.0) of V-MPS4 to those of $O=V(OSiPh_3)_3$ and the elemental analysis indicated that the immobilized vanadium of V-MPS4 had a single $OSiPh_3$ group, similar to V-MPS3 (Figure 1B) [for more information about the synthesis of V-MPS2 and V-MPS4 and the solid-state ^{13}C NMR spectra, see Electronic Supplementary Information (ESI)].

Insert **Table 1**

The catalytic activities of V-MPS2, V-MPS3, and V-MPS4 (1.0 mol% of the amount of vanadium in each case) were evaluated in the racemization of (*S*)-**1a** (>99% ee) in CH_3CN at 35 °C as a model case (Scheme 2); the time course for each reaction is shown in Figure 2A. Both V-MPS3 and V-MPS4 showed similar activities and the racemization was complete within 2 h; however, V-MPS2 showed much lower activity. At the same time, a mixture of two diastereomers of dimeric ethers **4a**, generated by the reaction of cationic intermediate **B** and **1a**, was formed,[19] and the formation rate was dependent on the pore size of V-MPS (Figure 2B).

We next investigated the efficiency of V-MPS2, V-MPS3, and V-MPS4 with larger substrates. For example, alcohol (*S*)-**1b** (>99% ee) with a length of about 1.4 nm was evaluated (Figure 3).20 Racemization proceeded when V-MPS3 and V-MPS4 were used, although 5.0 mol% of V-MPS was required at slightly higher

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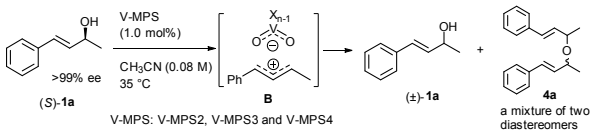

Scheme 2 Racemization of optically pure (*S*)-**1a** with V-MPS with different pore sizes.

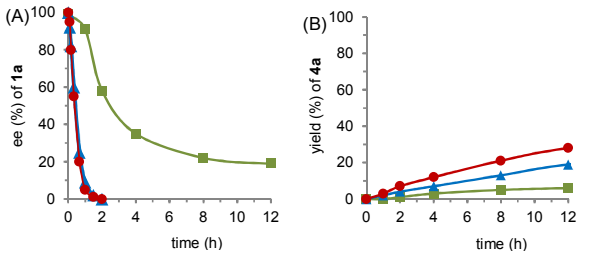

Figure 2 Racemization of optically pure (*S*)-**1a** catalyzed by V-MPS2 (–■–), V-MPS3 (–▲–), and V-MPS4 (–●–) (1.0 mol% of the amount of vanadium). (A) Change in optical purity (ee %) of (*S*)-**1a** over time. (B) Formation of **4a** over time.

temperature such as 50 °C because of the decreased catalytic activity with such a bulky alcohol. Racemization by V-MPS4 was much faster than that by V-MPS3, probably due to the better mobility of **1b** into and out of V-MPS4. On the other hand, racemization by V-MPS2 was very slow. These results give good evidence for our hypothesis that the racemization predominantly occurred inside the pores of V-MPS.

Next the effect of substrate polarity on the racemization was examined to prove the polarity of the MPS pores. Thus, the racemization of a 1:1 mol mixture of optically pure (*S*)-**1c** and (*S*)-**1d**, each of which has a side chain of almost the same length but with different polarity, was examined in the presence of V-MPS2, V-MPS3, and V-MPS4 (1.0 mol% vanadium each for the total amount of **1c** and **1d**) under identical reaction conditions. Notably, the racemization of (*S*)-**1d** was faster than that of (*S*)-**1c** in all cases (Figures 4A–C). On the other hand, the racemization rate of (*S*)-**1c** and (*S*)-**1d** using a homogenous catalyst $O=V(OSiPh_3)_3$[21] (10 mol% vanadium) was almost the same, although 10 times the amount of $O=V(OSiPh_3)_3$ was needed to obtain similar activity (Figure 4D). In addition, the racemization activity of V-MPS was dependent on the pore size, viz., V-MPS2 (Figure 4A) < V-MPS3 (Figure 4B) ≅ V-MPS4 (Figure 4C). The difference between the racemization by V-MPS and that of $O=V(OSiPh_3)_3$ unambiguously demonstrates that the majority of racemization by V-MPS occurs in the narrow pores of the MPS and that there is a positive correlation between the polarity of the substrate and the racemization rate by V-MPS.

The racemization of bulky alcohols (*S*)-**1e** (>99% ee) and (*S*)-**1f** (>99% ee), each of which has two side chains of almost the same length but different polarities, was also compared using either V-MPS3 or V-MPS4 (each 5.0 mol% vanadium) under identical conditions. The racemization of (*S*)-**1f** was faster than that of (*S*)-**1e** when using either V-MPS3 or V-MPS4. In addition, the racemization using V-MPS4 was faster than that using V-MPS3 for both (*S*)-**1e** and (*S*)-**1f** (Figure 5).

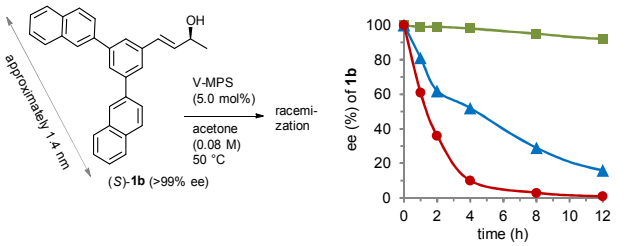

Figure 3 Racemization of optically pure (*S*)-**1b** catalyzed by V-MPS2 (–■–), V-MPS3 (–▲–), and V-MPS4 (–●–) (5.0 mol% of the amount of vanadium).

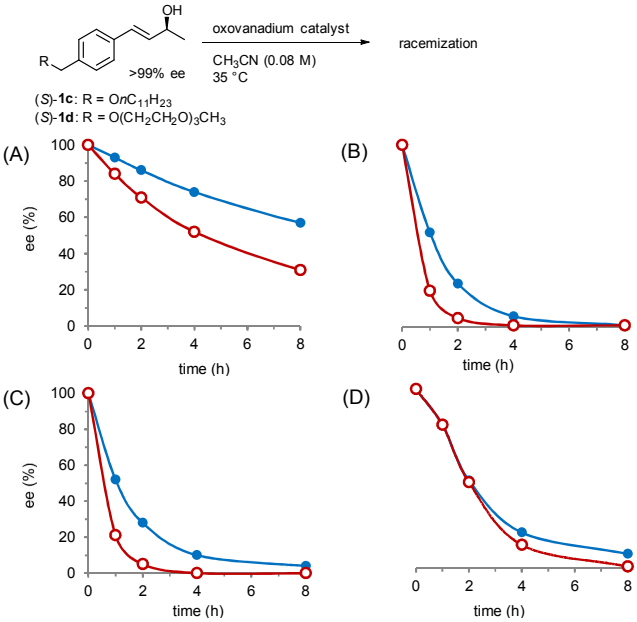

Figure 4 Racemization of optically pure (*S*)-**1c** (–●–) and (*S*)-**1d** (–○–) catalyzed by V-MPS. (A) V-MPS2 (1.0 mol% for total amount of **1c** and **1d**); (B) V-MPS3 (1.0 mol% for total amount of **1c** and **1d**); (C) V-MPS4 (1.0 mol% for total amount of **1c** and **1d**); (D) by $O=V(OSiPh_3)_3$ (10 mol% for total amount of **1c** and **1d**).[21]

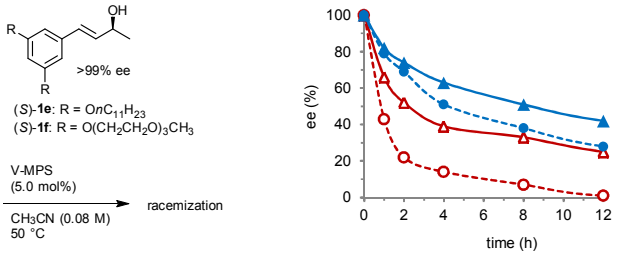

Figure 5 Racemization of optically pure (*S*)-**1e** and (*S*)-**1f** catalyzed by V-MPS (5.0 mol% vanadium for each alcohol). (*S*)-**1e** with V-MPS3 (–▲–), (*S*)-**1e** with V-MPS4 (- -●- -), (*S*)-**1f** with V-MPS3 (–△–), and (*S*)-**1f** with V-MPS4 (- -○- -).

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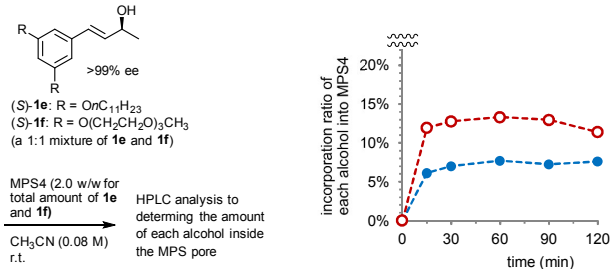

Figure 6 Incorporation of (*S*)-**1e** and (*S*)-**1f** into MPS4 (twice the amount by weight of **1e** + **1f**). (*S*)-**1e** (- -●- -) and (*S*)-**1f** (- -o- -).

To obtain further information about the polarity of the MPS pores, we investigated the incorporation rate of **1e** and **1f** into MPS4 (not V-MPS4). Thus, a 1:1 mol mixture of (*S*)-**1e** and (*S*)-**1f** (100 mg total) was mixed with MPS4 (200 mg; twice the amount by weight of **1e** + **1f**) in CH_3CN, and the mixture was stirred at room temperature. The amount of alcohol inside the MPS pores was determined via HPLC analysis of the alcohols in the supernatant. The time-course of the experiment shown in Figure 6 reveals that both **1e** and **1f** were incorporated in the pores, and that the incorporation ratio of **1f** was about 1.5 times that of **1e**.

The aforementioned results (Figures 2–6) generated the following discussion about the characteristic effects of V-MPS as well as MPS on the racemization: (1) The racemization predominantly proceeds inside the pores of V-MPS, which is quite reasonable because the majority of vanadium moieties should be immobilized on the inner surface of the MPS (870–1200 m^2/g); (2) more polar substrates (**1d** and **1f**) tend to go into the MPS pores more and racemize faster than less polar substrates such as **1c** and **1e**; and (3) a polar environment is generated inside pores of V-MPS as well as MPS. In our previous studies, we observed that the use of highly polar solvents significantly accelerated the racemization of optically active alcohols using either the polymer supported oxovanadium compound[4b] or V-MPS3.[4c,22] These solvent effects on the racemization are accountable by the acceleration of the C–O bond cleavage of vanadate **A** and by the stabilization of ion pair intermediate **B** (see Scheme 1) in highly polar media. It is also reported that the inner surface of MPS pores is locally polar due to the silanols (Figure 1A).[7] Therefore, we assume that the small pore size of V-MPS generates the polar environment in the whole pore space, which should be the most plausible reason why the racemization by V-MPS is much faster than that by homogeneous catalyst $O=V(OSiPh_3)_3$,[4a] a polymer supported oxovanadium compound,[4b] and related oxovanadium species covalently immobilized on the pore surface of macroporous silica with a pore size of either 100 nm or 400 nm.[4c] In addition, for the racemization to occur in unsymmetrically substituted substrates (see Scheme 1), the allyl cation has to leave the oxovanadium anion to change face, for which the pore size as well as the polar environment should also have some significant effects.

From another mechanistic view point, it is worth noting that the incorporation of both **1e** and **1f** into MPS4 reached a steady state within 15 min (Figure 6). Thus, the mobility of alcohols into and out of the pores is sufficiently high compared with the racemization rate.

We also observed the positive correlation between the sizes of the MPS pores and those of the substrates which strongly affects the racemization rate. Among some reports on the use of MPS pores in selective transformations of organic molecules,[2f,2k,14-18] the pore size effects of MPS were studied in only acetalization reactions[14] and porphyrin synthesis,[15] and most studies used MPS with a single pore size. In the present work, we found that the pore size of V-MPS can differentiate the molecular size of substrates.

V-MPS/lipase combo-catalyzed DKR

V-MPS2, V-MPS3, and V-MPS4 were combined with commercially available immobilized lipases, such as *Candida antarctica* lipase B (CAL-B) and *Burkholderia cepacia* lipase (PS-IM), and used for the DKR of alcohols (±)-**1** and (±)-**2**.

First, (±)-**2a** was treated with CAL-B in the presence of V-MPS4 (1.0 mol%) in CH_3CN at 35 °C for 24 h to give (*R*)-**3a** (98% ee) in 95% isolated yield (Table 2, entry 3), which was very similar to the result obtained with V-MPS3 (entry 2).[4c] On the other hand, with V-MPS2, (*R*)-**3a** (98% ee) was obtained in a lower yield (74% yield), and optically pure (*S*)-**2a** was recovered in 24% yield. This was due to the lower racemization activity of V-MPS2 (see Figure 2A). Despite the yields, the formation of (*R*)-**3a** with excellent optical purity (98–99% ee) in all cases demonstrated the outstanding compatibility of V-MPS with lipase. Although the use of V-MPS4 (1.0 mol%) alone afforded dimer **4a** in 28% yield after 12 h (see Figure 2B), the combined use of V-MPS4 and lipase dramatically suppressed the formation of **4a** to 5% even after 24 h (entry 3). A 50% reduction in the amount of V-MPS4 (0.5 mol%) sufficiently diminished the yield of **4a** to 1% and improved the yield of (*R*)-**3a** to 98% with an optical purity of 98% ee (entry 4). Notably, a similar reation using 0.10 mol% of V-MPS4 also produced (*R*)-**3a** (98% ee) in 94% yield, although it took 5 days (entry 5).

Insert **Table 2**

The DKR of various (±)-**1** and (±)-**2** is summarized in Table 3. The effects of the pore size of V-MPS can be summarized as follows: (1) with bulky alcohols (±)-**2b**, (±)-**2e**, and (±)-**2f**, V-MPS4 gave optically pure esters (*R*)-**3b**, (*R*)-**3e**, and (*R*)-**3f** in better yields than those with V-MPS3 (entries 1–6). These results reflect the faster racemization by V-MPS4. (2) DKR of (±)-**2c**, (±)-**2d**, (±)-**2g**, (±)-**1h–j**, and (±)-**1m**, which have moderate molecular sizes, by V-MPS4 and V-MPS3 afforded the corresponding esters (*R*)-**3** in nearly identical chemical and optical yields (entries 7–20, and 26). (3) When V-MPS2 was used at a slightly elevated temperature (50 °C), the chemical and optical yields of (*R*)-**3** were similar to those obtained with V-MPS3 and V-MPS4 (entries 9–14). (4) On the other hand, the efficient DKR of compact and unstable alcohols such as (±)-**2l**[23] could only be achieved with V-MPS2 (entries 23–25).[24] In this case, the racemization by V-MPS3 or V-MPS4 caused gradual decomposition of **2l**, whereas that with V-MPS2 did not.

Furthermore, V-MPS4 could be used in the DKR of alcohols having a cyano (±)-**1m** or terminal alkynyl group (±)-**1n** to give optically pure (*R*)-**3m** and (*R*)-**3n** in excellent chemical yields (entries 26 and 27). The successful DKR of **1n** is notable, because while the reaction of **1n** and V-MPS4 gave an *E/Z* mixture of 3-(4-methoxyphenyl)propenal via Meyer-Schuster rearrangement, such

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products were not observed in the presence of the lipase and vinyl acetate (entry 27).

Insert **Table 3**

To summarize the V-MPS/lipase combo-catalyzed DKR of alcohols **1** and **2**, the viable substrate scope was expanded by choosing suitable pore size of V-MPS. Both V-MPS3 and V-MPS4 showed similar activity for medium-sized substrates (e.g., MW < ca. 400 and/or the shorter lengh < ca. 0.7 nm), while V-MPS4 was particularly beneficial for larger substrates such as **2b**, **2e**, and **2f**. When dimeric ethers such as **4a** were formed as byproducts, a reduction in the amount of V-MPS4 suppressed the formation of the dimeric ethers and improved the yields of **3** while maintaining their optical purities (e.g., Table 1, entry 4). The excellet availability of the alchols, such as **1j**, **1m** and **1n**, possessing a functional group at the terminal position will extend the practical utility of this DKR for further modification of the products.

Conclusions

We previously reported a new DKR method based on the combination of lipase-catalyzed kinetic resolution of racemic alcohols and the V-MPS3-catalyzed in situ racemization of less reactive enantiomers.[4c] In V-MPS3, oxovanadium moieties were covalently bound to the inner surface of MPS with a pore size of about 3 nm. Although the catalytic activity of V-MPS3 was much higher than that of related vanadium compounds, we had no evidence to confirm that the racemization occurred inside the pores of MPS or to explain its unusually high activity. In this study, we prepared V-MPS2 and V-MPS4 from the corresponding MPS with pore diameters of approximately 2 and 4 nm, respectively, and compared their racemization activities using some optically active alcohols with different molecular sizes and polarities with the activity of V-MPS3. We discovered unique features of V-MPS, such as a positive correlation between the pore size of V-MPS and substrate racemization rate. The high polarity of the MPS pores possibly accelerates the racemization by facilitating the C–O bond cleavage of the vanadate **A** and stabilizing ion pair intermediate **B**; a small pore size (2–4 nm) efficiently functions to generate this polar environment in the entire pores, while macroporous silica with a pore size of 100–400 nm does not exhibit similar effects. These results demonstrated that the racemization predominantly occured in the pores of V-MPS. We expect that the unique polarity of MPS and their ability to distinguish substrate sizes will be useful in the development of new MPS-immobilized catalysts.

From the synthetic point of view, V-MPS4 catalyzed the racemization of various-sized alcohols, and the combination of V-MPS4 and lipases enabled highly effective DKR to afford optically active esters in excellent chemical and optical yields. In some cases, V-MPS2 was more suitable. Therefore, appropriate selection of V-MPS based on pore size enables the efficient DKR of a wide range of alcohols. The combination of hydrolase-catalyzed kinetic resolution and racemization using porous materials, such as mesoporous silica and zeolites, has garnered considerable attention during the last several years from the viewpoints of reaction site separation, bifunctional proximal catalysis, and reuse.[2,3] The synergistic effect of enzymes and mesoporous materials will stimulate new avenues of research into enantioselective transformations.

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Notes and references

1 For the first enzymatic DKR of secondary alcohols, see (*a*) J. V. Allen, J. M. Williams, *Tetrahedron Lett.* **1996**, *37*, 1859–1862. For some recent reviews, see (*b*) C. A. Denard, J. F. Hartwig, H. Zhao, *ACS Catal.* 2013, **3**, 2856–2864. (*c*) D. Zell, P. R. Schreiner, In *Comprehensive Organic Synthesis,* 2nd Edition, P. Knochel, G. A. Molander, Eds,; Elsevier: Oxford, 2014, vol. 6, pp 296–354. (*d*) S. Akai, *Chem. Lett.* 2014, **43**, 746–754. (*e*) S. Takizawa, H. Gröger, H. Sasai, *Chem. Eur. J.* 2015, **21**, 8992–8997. (*f*) O. Verho, J.-E. Bäckvall, *J. Am. Chem. Soc*. 2015, **137**, 3996–4009. (*g*) L. Otto, S. Tiina, Y. M. Dmitry, L. Reko, *ChemCatChem*, 2015, **7**, 4004–4015.

2 For some recent examples of DKR by the combination of hydrolases and redox catalysts, see (*a*) A. Träff, R. Lihammer, J.-E. Bäckvall, *J. Org. Chem.* 2011, **76**, 3917–3921. (*b*) H. Kim, Y. K. Choi, J. Lee, E. Lee, J. Park, M.-J. Kim, *Angew. Chem. Int. Ed.* 2011, **50**, 10944–10948. (*c*) K. Engström, M. Vallin, P.-O. Syrén, K. Hult, J.-E. Bäckvall, *Org. Biomol. Chem.* 2011, **9**, 81–82. (*d*) K. Engström, M. Shakeri, J.-E. Bäckvall, *Eur. J. Org. Chem*. 2011, **10**, 1827–1830. (e) M. C. Warner, A. Nagendiran, K. Bogár, J.-E. Bäckvall, *Org. Lett*. 2012, **14**, 5094–5097. (*f*) K. Engström, E. V. Johnston, O. Verho, K. P. J. Gustafson, M. Shakeri, C.-W. Tai, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* 2013, **52**, 14006–14010. (*g*) M. C. Warner, G. A. Shevchenko, S. Jouda, K. Bogár, J.-E. Bäckvall, *Chem. Eur. J.* 2013, **19**, 13859–13864. (*h*) R. Lihammar, R. Millet, J.-E. Bäckvall, *J. Org. Chem.* 2013, **78**, 12114−12120. (*i*) C. Kim, J. Lee, J. Cho, Y. Oh, Y. K. Choi, E. Choi, J. Park, M.-J. Kim, *J. Org. Chem.* 2013, **78**, 2571−2578. (*j*) S. Kim, Y. K. Choi, J. Hong, J. K. Park, M.-J. Kim, *Tetrahedron Lett.* 2013, **54**, 1185–1188. (*k*) K. P. J. Gustafson, R. Lihammar, O. Verho, K. Engström, J.-E. Bäckvall, *J. Org. Chem*. 2014, **79**, 3747–3751. (*l*) H. Cao, X.-H. Zhu, D. Wang, Z. Sun, Y. Deng, X.-F. Hou, D. Zhao, *ACS Catal.* 2015, **5**, 27–33. (*m*) J. Lee, Y. Oh, Y. K. Choi, E. Choi, K. Kim, J. Park, M.-J. Kim, *ACS Catal.* 2015, **5**, 683−689. (*n*)

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DOI: 10.1039/C6CY00257A

J. Cho, J. Lee, J. Park, M.-J. Kim, *Tetrahedron: Asymmetry*, 2015, **26**, 840–845.

3 For some recent examples of related DKR, see (*a*) Y. Zhu, K.-L. Fow, G.-K. Chuah, S. Jaenicke, *Chem. Eur. J.* 2007, **13**, 541–547. (*b*) C. M. Sapu, T. Görbe, R. Lihammar, J.-E. Bäckvall, J. Deska, *Org. Lett.* 2014, **16**, 5952−5955. (*c*) W. Wang, X. Li, Z. Wang, Y. Tang, Y. Zhang, *Chem. Commun.* 2014, **50**, 9501–9504. (*d*) R. Nieguth, J. ten Dam, A. Petrenz, A. Ramanathan, U. Hanefeld, M. B. Ansorge-Schumacher *RSC Adv*., 2014, **4**, 45495–45503. (*e*) A. Petrenz, P. Domínguez de María, A. Ramanathan, U. Hanefeld, M. B. Ansorge-Schumacher, S. Kara, *J. Mol. Catal. B: Enzymatic* 2015, **114**, 42–49. (*f*) K.-I. Shimomura, H. Harami, Y. Matsubara, T. Nokami, N. Katada, T. Itoh, *Catalysis Today*, 2015, **255**, 41–48.

4 (*a*) S. Akai, K. Tanimoto, Y. Kanao, M. Egi, T. Yamamoto, Y. Kita, *Angew. Chem. Int. Ed.* 2006, **45**, 2592–2595. (*b*) S. Akai, R. Hanada, N. Fujiwara, Y. Kita, M. Egi, *Org. Lett.* 2010, **12**, 4900–4903. (*c*) M. Egi, K. Sugiyama, M. Saneto, R. Hanada, K. Kato, S. Akai, *Angew. Chem. Int. Ed.* 2013, **52**, 3654–3658.

5 In our previous paper, we used MPS with a pore size of approximately 2.7 nm to synthesize V-MPS.[4c] In this paper, we called it V-MPS3 in order to differentiate it with other V-MPS with different pore sizes.

6 (*a*) T. Yanagisawa, T. Shimizu, K. Kuroda, C. Kato, *Bull. Chem. Soc. Jpn.* 1990, **63**, 988–992. (*b*) C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* 1992, **359**, 710–712. (*c*) S. Inagaki, Y. Fukushima, *J. Chem. Soc., Chem. Commun.* 1993, 680–682. For some recent reviews: (*d*) Y. Wan, D. Zhao, *Chem. Rev.* 2007, **107**, 2821–2860. (*e*) B. Naik, N. N. Ghosh, *Recent Pat. Nanotechnol.* 2009, **3**, 213–224. (*f*) F. Hoffmann, M. Fröba, *Chem. Soc. Rev.* 2011, **40**, 608–620. (*g*) N. Mizoshita, T. Tani, S. Inagaki, *Chem. Soc. Rev.* 2011, **40**, 789–800.

7 For related studies on the hydrophilicity of mesoporous materials and their pore surface structure, see (*a*) E.-P. Ng, S. Mintova, *Micropor. Mesopor. Mater.* 2008, **114**, 1–26. (*b*) S. Maaz, M. Rose, R. Palkovits, *Micropor. Mesopor. Mater.* 2016, **220**, 183–187.

8 M. M. Heravi, K. Bakhtiari, H. Alinejhad, M. Saeedi, R. Malakooti, *Chin. J. Chem.* 2010, **28**, 269–272.

9 (*a*) J. Mondal, A. Modak, A. J. Bhaumik, *Mol. Catal. A: Chem.* 2011, **335**, 236–241. (*b*) S. Kawamori, T. Miyazaki, H. Ohmiya, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.* 2011, **133**, 19310–19313. (*c*) Si-H. Wu, Y. Hung, C.-Y. Mou, *Chem. Commun.* 2011, **47**, 9972–9985. (*d*) S. Jana, S. Haldar, S. Koner, *Tetrahedron Lett.* 2009, **50**, 4820–4823. (*e*) K. M. Parida, S. S. Dash, S. Singha, *Appl. Catal. A* 2008, **351**, 59–67. (*f*) S. Samanta, N. K. Mal, A. Bhaumik, *J. Mol. Catal. A; Chem.* 2005, **236**, 7–11. (*g*) S. Xiang, Y. Zhang, Q. Xin, C. Li, *Angew. Chem. Int. Ed.* 2002, **41**, 821–824. (*h*) T. Ookoshi, M. Onaka, *Chem. Commun.* 1998, 2399–2400.

10 (*a*) M. H. Lim, A. Stein, *Chem. Mater.* 1999, **11**, 3285–3295. (*b*) D. Chandra, S. K. Das, A. Bhaumik, *Micropor. Mesopor. Mat.* 2010, **128**, 34–40.

11 K. Sarkar, K. Dhara, M. Nandi, P. Roy, A. Bhaumik, P. Banerjee, *Adv. Funct. Mater.* 2009, **19**, 223–234.

12 C. Thoelen, J. Paul, I. F. J. Vankelecom, P. A. Jacobs, *Tetrahedron: Asymmetry*, 2000, **11**, 4819–4823.

13 Al-MPS, in which silicon was partly replaced with aluminum, have also been used for various reactions. See (*a*) C.-H. Lee, H.-C. Lin, S.-H. Cheng, T.-S. Lin, C.-Y. Mou, *J. Phys. Chem. C* 2009, **113**, 16058–16069. (*b*) M. Onaka, N. Hashimoto, Y. Kitabata, R. Yamasaki, *Appl. Catalysis Gen.* 2003, **241**, 307–317.

14 M. Iwamoto, Y. Tanaka, N. Sawamura, S. Namba, *J. Am. Chem. Soc.* 2003, **125**, 13032–13033.

15 T. Shinoda, Y. Izumi, M. Onaka, *J. Chem. Soc., Chem. Commun.* 1995, 1801–1802.

16 J. L. Gu, X. Dong, S. P. Elangovan, Y. Li, W. Zhao, T. Iijima, Y. Yamazaki, J. L. Shi, *J. Solid State Chem.* 2012, **186**, 208–216.

17 (*a*) R. Ji, K. Yu, L.-L. Lou, Z. Gu, S. Lie, *J. Inorg. Organomet. Polym.* 2010, **20**, 675–683. (*b*) T. Shinde, N. Žilková, V. Hanková, H. Balcar, *Catalysis Today*, 2012, **179**, 123–129. (*c*) M. Bru, R. Dehn, J. H. Teles, S. Deuerlein, D.-I. M. Danz, I. B. Müller, M. Limbach, *Chem. Eur. J.* 2013, **19**, 11661–11671. (*d*) J. Pastva, K. Skowerski, S. J. Czarnocki, N. Žilková, J. Čejka, Z. Bastl, H. Balcar, *ACS Catal.* 2014, **4**, 3227–3236.

18 S. Deng, J. Zhi, X. Zhang, Q. Wu, Y. Ding, A. Hu, *Angew. Chem. Int. Ed*. 2014, **53**, 14144–14148.

19 Similar formation of dimeric ethers from allyl alcohols was reported previously. see, C. Morrill, G. L. Beutner, R. H. Grubbs, *J. Org. Chem.* 2006, **71**, 7813–7825.

20 Due to the poor solubility of (*S*)-**1b** in CH_3CN, the racemization of (*S*)-**1b** was examined in acetone.

21 The data of Figure 4D were obtained using a 300:1 mol ratio of water and amount of $O=V(OSiPh_3)_3$. After the publication on the use of V-MPS3[4c] we found that the addition of a range of water [ca. 10–300:1 mol ratio of water and amount of $O=V(OSiPh_3)_3$] to the reaction mixture was very important to exhibit catalytic activity of the racemization and also to obtain good reproducibility. Investigation to clarify the role of water in these reactions is in progress in our laboratory.

22 The racemization in CH_3CN was faster than that in acetone[4b] and heptane.[4c]

23 Alcohol **2l** was reported to be very sensitive to acid and readily decomposes under acidic conditions. See A. A. McCubbin, S. Voth, O. V. Krokhin, *J. Org. Chem.* 2011, **76**, 8537–8542.

24 The use of V-MPS2 under the standard reaction conditions generated (*R*)-**3l** in poor chemical and optical yields. After screening of various conditions by changing the amounts of V-MPS2, lipase, and acyl donors, as well as solvents, we found the use of 2,2,2-trifluoroethyl docosanate (0.30 equiv x 3), 0.20 w/w of CAL-B, iPr$_2$O produced (*R*)-**3l** in the better chemical and optical yields. In particular, the portion-wise addition of the acyl donor was the key for the high optical purity as shown in Table 2, entry 23, and the use of a slightly less amount of the acyl donor made the purification of the product easier.

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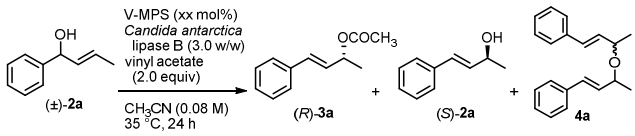
Table 1. Analytical data of MPSs and V-MPSs

	vanadium content	average pore size (nm)	surface area (m^2/g)	pore volumn (cm^3/g)	elemental analysis carbon (%)	hydrogen (%)
MPS2		1.7	0.87 x 10^3	0.41	6.7	1.2
V-MPS2	0.1 w/w% (0.02 mmol/g)	1.7	0.86 x 10^3	0.40	8.3	1.2
MPS2 – (V-MPS2)		0.0	0.01 x 10^3	0.01	–1.6	0.0
MPS3[a]		2.8	1.02 x 10^3	1.04	2.5	0.7
V-MPS3[a]	1.0 w/w% (0.20 mmol/g)	2.6	0.94 x 10^3	0.90	7.3	1.0
MPS3 – (V-MPS3)		0.2	0.08 x 10^3	0.14	–4.8	–0.3
MPS4		3.7	0.92 x 10^3	1.17	1.6	0.5
V-MPS4	1.0 w/w% (0.20 mmol/g)	3.3	0.86 x 10^3	1.02	6.8	0.9
MPS4 – (V-MPS4)		0.4	0.06 x 10^3	0.15	–5.2	–0.4

a) Cited from ref. 4c.

Table 2 Comparison of three different V-MPS on lipase-catalyzed DKR of (±)-**2a**.



entry	V-MPS [mol equiv]	(*R*)-**3a** yield (%)[a]	(*R*)-**3a** ee (%)	(*S*)-**2a** yield (%)[a]	(*S*)-**2a** ee (%)	yield of **4a** (%)[b]
1	V-MPS2 [1.0 mol%]	74	98	24	>99	—
2[c]	V-MPS3 [1.0 mol%]	99	99	—		—
3	V-MPS4 [1.0 mol%]	95	98	—		5
4	V-MPS4 [0.50 mol%]	98	98	—		1
5[d]	V-MPS4 [0.10 mol%]	94	98	6	99	—

a) Isolated yield. b) Based on ^{1}H NMR analysis of a crude product. c) Cited from ref. 4c.
d) The reaction was conducted for 120 h.

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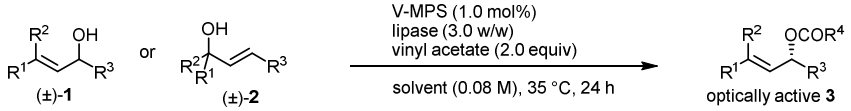
Table 3 DKR of alcohols (±)-**1** and (±)-**2** by lipases and V-MPS with different pore sizes.[a]



entry	substrate		conditions[b]	V-MPS	product		yield (%)	ee (%)
1[c,d,e]	R = 2-naphthyl	(±)-**2b**	A	V-MPS3	R = 2-naphthyl	(*R*)-**3b**	91	>99
2[c,d,e]		(±)-**2b**	A	V-MPS4		(*R*)-**3b**	>99	>99
3[c,e]	R = O*n*C$_{11}$H$_{23}$	(±)-**2e**	A	V-MPS3	R = O*n*C$_{11}$H$_{23}$	(*R*)-**3e**	77	>99
4[c,e]		(±)-**2e**	A	V-MPS4		(*R*)-**3e**	91	>99
5[c,e]	R = O(CH$_2$CH$_2$O)$_3$CH$_3$	(±)-**2f**	A	V-MPS3	R = O(CH$_2$CH$_2$O)$_3$CH$_3$	(*R*)-**3f**	90	98
6[c,e]		(±)-**2f**	A	V-MPS4		(*R*)-**3f**	>99	99
7[f]	R = Cl	(±)-**2g**	A	V-MPS3	R = Cl	(*R*)-**3g**	96	97
8		(±)-**2g**	A	V-MPS4		(*R*)-**3g**	97	98
9[c,g]	R = CH$_2$O*n*C$_{11}$H$_{23}$	(±)-**2c**	A	V-MPS2	R = CH$_2$O*n*C$_{11}$H$_{23}$	(*R*)-**3c**	95	97
10[c,g]		(±)-**2c**	A	V-MPS3		(*R*)-**3c**	>99	95
11[c,g]		(±)-**2c**	A	V-MPS4		(*R*)-**3c**	92	95
12[c,g]	R = CH$_2$O(CH$_2$CH$_2$O)$_3$CH$_3$	(±)-**2d**	A	V-MPS2	R = CH$_2$O(CH$_2$CH$_2$O)$_3$CH$_3$	(*R*)-**3d**	95	98
13[c,g]		(±)-**2d**	A	V-MPS3		(*R*)-**3d**	93	98
14[c,g]		(±)-**2d**	A	V-MPS4		(*R*)-**3d**	90	98
15[f]		(±)-**1h**	A	V-MPS3		(*R*)-**3h**	94	95
16		(±)-**1h**	A	V-MPS4		(*R*)-**3h**	94	98
17[f]		(±)-**1i**	B	V-MPS3		(*R*)-**3i**	90	97
18		(±)-**1i**	B	V-MPS4		(*R*)-**3i**	87	96
19[f,h]		(±)-**1j**	B	V-MPS3		(*S*)-**3j**	96	>99
20[h]		(±)-**1j**	B	V-MPS4		(*S*)-**3j**	94	>99
21[f]		(±)-**1k**	A	V-MPS3		(*R*)-**3k**	100	99
22		(±)-**1k**	A	V-MPS4		(*R*)-**3k**	99	>99
23[i]		(±)-**2l**	A	V-MPS2		(*R*)-**3l**	79	94
24[i]		(±)-**2l**	A	V-MPS3		(*R*)-**3l**	decomp.	
25[i]		(±)-**2l**	A	V-MPS4		(*R*)-**3l**	decomp.	
26[j]		(±)-**1m**	B	V-MPS4		(*R*)-**3m**	81	>99
27[k]		(±)-**1n**	A	V-MPS4		(*R*)-**3n**	92	97

a) Unless otherwise noted, reactions were carried out using 0.1–0.3 mmol of substrates. b) A: *Candida antarctica* lipase B (CAL-B) in CH_3CN, B: *Burkholderia cepacia* lipase (PS-IM) in heptane. c) A 1:1 mixture of (*E*)- and (*Z*)-**2** was used. d) Acetone was used instead of CH_3CN. e) Performed using 5.0 mol% of V-MPS at 50 °C for 72 h (entries 1–4) or at 35 °C for 24 h (entries 5 and 6). f) Cited from ref. 4c. g) Conducted at 50 °C. h) Vinyl decanoate was used instead of vinyl acetate. i) 2,2,2-Trifluoroethyl docosanate (0.30 equiv), 0.20 w/w of CAL-B, *i*Pr$_2$O were used instead of vinyl acetate, 3.0 w/w of CAL-B, and CH_3CN, respectively. Additional 2,2,2-trifluoroethyl docosanate (0.30 equiv) was added after 12 and 24 h, and the reaction mixture was stirred tor total 36 h. The isolated yield of (*R*)-**3l** was based on (±)-**2l**. j) Vinyl butyrate and toluene were used instead of vinyl acetate and heptane, respectively. k) Vinyl butyrate was used instead of vinyl acetate at 50 °C.

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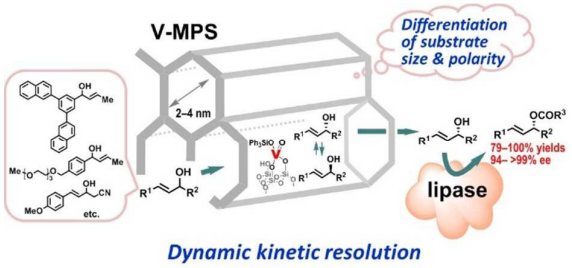

The nano-scale pores of mesoporous silica and their polar environment accelerate the racemization to make the lipase/oxovanadium combo-catalysed DKR applicable to a wider range of alcohols.