Heterogeneous Catalysis

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A Mesoporous-Silica-Immobilized Oxovanadium Cocatalyst for the Lipase-Catalyzed Dynamic Kinetic Resolution of Racemic Alcohols**

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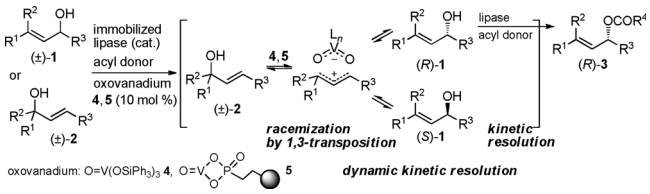
In the last decade, cooperative catalysis has received considerable attention as a powerful synthetic method.[1] Two or more catalysts function simultaneously or sequentially in a single reaction vessel to construct complicated molecules, which provides a means to perform unprecedented syntheses that cannot be achieved by a single catalyst. Various catalytic combinations involving transition metals, organocatalysts, and biocatalysts have been developed thus far.[2]

A typical example is the combined use of lipases and transition metals to attain the dynamic kinetic resolution (DKR) of racemic secondary alcohols for producing single enantiomer products in up to 100% yields,[3] in contrast to the use of lipases alone, which can only achieve maximum yields of 50%. In this DKR process, the enzymatic enantioselective esterification of racemic alcohols is combined with the transition-metal-catalyzed continuous racemization of optically active alcohols, which remain intact during the enzymatic reaction, through a redox process. However, such cooperative cocatalysis often encounters crucial issues of low compatibility between the lipases and the transition metals. Although intense efforts have been devoted to developing highly active racemization catalysts,[4,5] only a few ruthenium complexes have met both the requirement of sufficient compatibility with lipases and high racemization activity.[5]

We recently reported that a combination of oxovanadium compounds (**4** or **5**) with lipases accomplished the efficient and direct conversion of racemic allylic alcohols (±)-**1** and (±)-**2** into optically active allyl esters (*R*)-**3**.[6] This method featured a unique racemization process wherein **4** (or **5**) catalyzed the racemization of (*S*)-**1** with 1,3-transposition of the hydroxy group of **1** or **2**, while the lipases effected chemo- and enantioselective esterification. This is significantly different from the above-mentioned ruthenium-catalyzed DKRs and offered a synthetic advantage in that both (±)-**1** and (±)-**2** were available as equivalent substrates. However, this method required further improvement in both catalytic activity and compatibility of the oxovanadium catalysts with the lipases.[7,8] Herein, we report the preparation of a novel oxovanadium catalyst (V-MPS) immobilized inside mesoporous silica (MPS) with pores of approximately 3 nm in diameter, which enabled a complete division of the racemization site and the enzymatic reaction site. The combined lipase–V-MPS catalyst is reusable and achieved DKR of a wide range of racemic alcohols with excellent chemical and optical yields (Scheme 1).



Scheme 1. Basic concept for DKR by a combination of lipases and oxovanadium compounds.

The immobilization of oxovanadium species inside a solid carrier with microsized pores or multilayered structures[9] enables the minimization of interactions between the oxovanadium species and lipases while maintaining easy access of substrate molecules to the metal center. The solid carrier should be neutral and non-charged in order to exert little adverse effect on the lipases. Among the various potential solid carriers,[10,11] MPS, which is comprised of amorphous silica and has a rigid well-ordered hexagonal structure with uniform pore size,[12] is thought to be one of the best candidates, in particular, MPS with a pore size of 2.7 nm.[13] We therefore prepared a novel vanadium catalyst (V-MPS) by combining $O{=}V(OSiPh_3)_3$ **4** and MPS (pore diameter 2.7 nm)[14] in refluxing benzene for 8 h to anchor vanadium species on the inner surface of the MPS pores.[15,16] The resulting structure was characterized using several techniques and deduced to be as shown in Figure 1, where the oxovanadium moiety covalently bound to the inner surface of MPS possessed a single triphenylsiloxy group on average (see the Supporting Information for details). The loading of the vanadium component onto MPS was determined to be 0.20–0.22 mmol g^{-1} by ICP analysis. For comparison, two other immobilized oxovanadium catalysts, V-MacroPS(100) and

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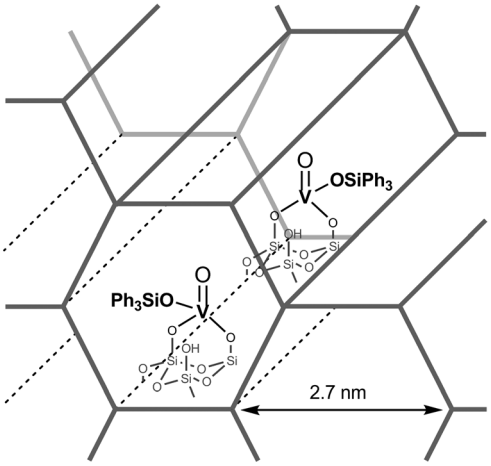


Figure 1. Deduced structure of V-MPS.

V-MacroPS(400), were prepared using macroporous silica (MacroPS), which possesses larger pore sizes of 100 and 400 nm, respectively.

The racemization activities of the immobilized catalysts were evaluated using (*R*)-**1a** (>99% *ee*) in MeCN at 35°C (Figure 2a) to find that the use of either 1 or 2 mol% of V-MPS completed the racemization within 2 h, whereas 2 mol% of V-MacroPS(100) or V-MacroPS(400) was much less reactive. Moreover, the known catalyst V(3)-MPS, which was prepared by the reaction of $O{=}V(O\mathit{i}C_3H_7)_3$ and MPS (2.7 nm), and in which the oxovanadium is immobilized through three V–OSi covalent bonds,[17] was less reactive than V-MPS.[18] These results demonstrate that the mesoporous environment seems to enhance the catalyst activity and that the use of **4** as a precursor is another critical point in producing a highly active catalyst. Furthermore, the racemization activity of V-MPS (1 mol%) was greater than that of **4** and **5** (10 mol% each; Figure 2b). Despite such high activity, V-MPS did not cause the adverse side reaction of **1a** dimerization.[6b,19] The V-MPS-catalyzed racemization proceeded smoothly, even in less polar solvents such as heptane (Figure 2b), which indicates that the V-MPS–lipase cocatalyzed DKR could be conducted in a variety of solvents.

V-MPS also showed excellent catalytic activity in DKR reactions, thus demonstrating its excellent compatibility with lipases. The reaction of (±)-**2a** with commercially available immobilized *Candida antarctica* lipase B (CAL-B; 3.0 w/w), V-MPS (1.0 mol%), and vinyl acetate (2.0 equiv) in MeCN at 35°C, completed within 12 h. After centrifugation, (*R*)-**3a** (99% yield, 99% *ee*) was obtained from the supernatant. As triphenylsilanol was not detected in the crude reaction product, V-MPS appeared to retain its structure after the reaction. The centrifuged deposit containing a mixture of two catalysts was dried under reduced pressure for 10 h at room temperature and reused in the next run.[20] The high catalytic performance of the mixed catalysts was completely sustained up to the sixth run, affording (*R*)-**3a** in quantitative chemical and optical yields. In the seventh run, the DKR reaction provided (*R*)-**3a** (85% yield, 99% *ee*) and (*S*)-4-phenyl-3-buten-2-ol (13% yield, 67% *ee*), which meant that V-MPS lost part of its activity (Scheme 2). The leaching of any vanadium components was evaluated to be < 0.0003% by ICP spectroscopy of the crude products, which indicates that the binding between the vanadium moiety and the silanol of MPS is sufficiently strong.

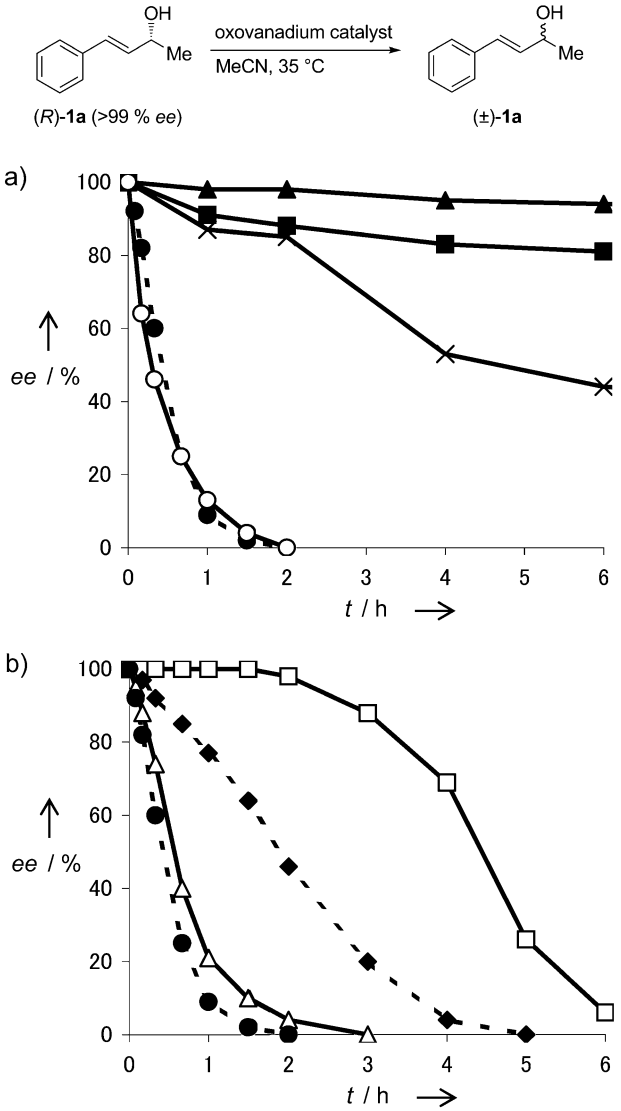
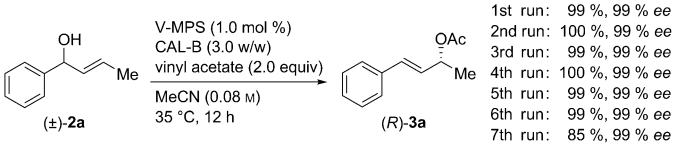


Figure 2. Racemization of (*R*)-**1a** (>99% *ee*) by oxovanadium catalysts. a) Comparison of immobilized catalysts. V-MPS (1 mol%; ●), V-MPS (2 mol%; ○), V-MacroPS(100) (2 mol%; ■), V-MacroPS(400) (2 mol%; ▲), V(3)-MPS (2 mol%; ×). b) Comparison of V-MPS, **4**, and **5**, and that of solvents. V-MPS (1 mol%; ●) in MeCN, V-MPS (1 mol%; ◆) in heptane, **4** (10 mol%; □) in MeCN, **5** (10 mol%; △) in MeCN.



Scheme 2. Reusability of the V-MPS-lipase combo catalyst.

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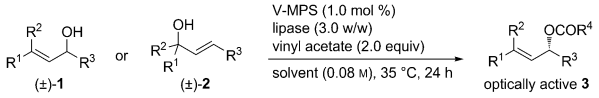
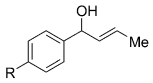
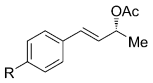
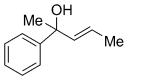
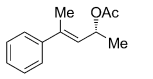
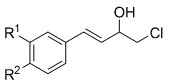
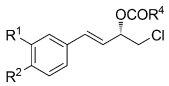
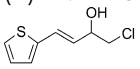
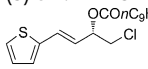
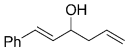
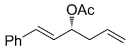
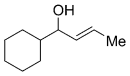
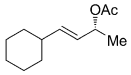
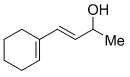
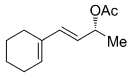
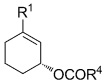
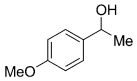
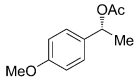
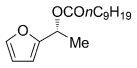
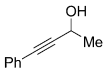
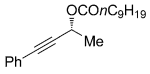
Table 1: Asymmetric synthesis of optically active esters **3** from (±)-**1** or (±)-**2** through lipase–V-MPS cocatalysis.[a]



Entry	Substrate		Lipase/Solvent[b]	Product		Yield [%]	*ee* [%]
1	 (±)-**2a**: R = H		A	 (*R*)-**3a**: R = H		99 98[c] 71[d] 79[e]	99 >99[c] 94[d] 98[e]
2	(±)-**2b**: R = F		A	(*R*)-**3b**: R = F		100 64[d] 64[e]	99 93[d] 80[e]
3	(±)-**2c**: R = Cl		A	(*R*)-**3c**: R = Cl		96 52[d] 74[e]	97 98[d] 94[e]
4		(±)-**2d**	A		(*R*)-**3d**	92 (*E*/*Z*=7:1)	99
5[f,g]	 (±)-**1e**: $R^1 = R^2 = H$		B	 (*S*)-**3e**: $R^1 = R^2 = H$, $R^4 = nC_9H_{19}$		93	>99
6[g]	(±)-**1f**: $R^1 = H$, $R^2 = OMe$		B	(*S*)-**3f**: $R^1 = H$, $R^2 = OMe$, $R^4 = nC_9H_{19}$		96	>99
7[g]	(±)-**1g**: $R^1 = R^2 = OMe$		B	(*S*)-**3g**: $R^1 = R^2 = OMe$, $R^4 = nC_9H_{19}$		97	99
8	(±)-**1h**: $R^1 = OMe$, $R^2 = OTBS$		B	(*S*)-**3h**: $R^1 = OMe$, $R^2 = OTBS$, $R^4 = Me$		98	99
9[g]		(±)-**1i**	B		(*S*)-**3i**	84	>99
10		(±)-**1j**	B		(*R*)-**3j**	98	96
11[f]		(±)-**2k**	A		(*R*)-**3k**	96 68[e]	99 95[e]
12		(±)-**1l**	A		(*R*)-**3l**	94 78[d]	95 92[d]
13[h]	 (±)-**2m**: $R^1 = nC_4H_9$		A	 (*R*)-**3m**: $R^1 = nC_4H_9$, $R^4 = nC_3H_7$		82	>99
14[h]	(±)-**2n**: $R^1 = nC_{11}H_{23}$		A	(*R*)-**3n**: $R^1 = nC_{11}H_{23}$, $R^4 = nC_3H_7$		85 65[e]	>99 96[e]
15	(±)-**2o**: R^1 = Ph		A	(*R*)-**3o**: R^1 = Ph, R^4 = Me		95 78[d]	99 97[d]
16		(±)-**1p**	B		(*R*)-**3p**	90	97
17		(±)-**1q**	A		(*R*)-**3q**	100 97[c] 54[d]	99 >99[c] 97[d]
18[g]		(±)-**1r**	A		(*R*)-**3r**	98	97
19[g]		(±)-**1s**	A		(*R*)-**3s**	96	99

[a] Unless otherwise noted, reactions were carried out using 0.20–1.2 mmol of substrates. [b] A: CAL-B in MeCN was used, B: PS-IM in heptane was used. [c] Performed using 20 mmol of (±)-**2a** or (±)-**1q** for 12 h (entry 1) or for 10 h (entry 17). [d] **4** (10 mol%) was used instead of V-MPS. [e] **5** (10 mol%) was used instead of V-MPS. [f] Conducted at 50 °C. [g] Vinyl decanoate was used instead of vinyl acetate. [h] Vinyl butyrate was used instead of vinyl acetate. TBS = *tert*-butyldimethylsilyl.

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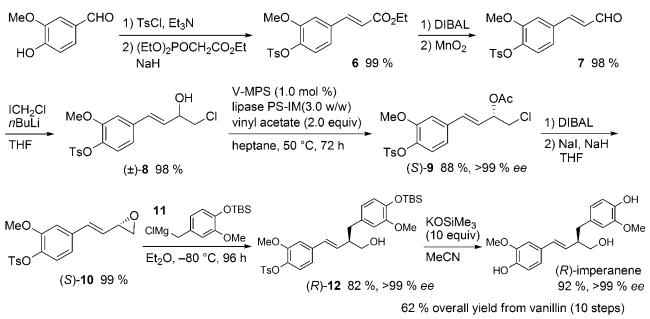
The V-MPS-lipase combo catalysis was applied to allylic alcohols (±)-**1** and (±)-**2**, which were treated with V-MPS (1.0 mol%), an immobilized lipase such as CAL-B or *Burkholderia cepacia* lipase (PS-IM), and vinyl acetate in an organic solvent such as MeCN or heptane, at 35 °C for 24 h to give optically active allylic acetates **3**. The results in Table 1 demonstrate that this method allowed for excellent substrate generality and delivered high product yields and enantioselectivities (**3a–p**; entries 1–16), as well as bringing about significant improvements in the results obtained under our previous conditions using **4** or **5**[6] (entries 1–3, 11, 12, 14, and 15). This method was also applied to a 20 mmol scale reaction without any loss in reactivity or yield (entries 1 and 17). In some cases, the use of acyl donors with a longer alkyl chain, such as vinyl butyrate and vinyl decanoate, produced higher enantioselectivities (entries 5–7, 9, 13, and 14). In the DKRs of **1e–j**, our method provided synthetically useful products, (*S*)-**3e–i** and (*R*)-**3j** containing functional groups as R^3 (entries 5–10). Optically pure (*R*)-**3n**, the key synthetic intermediate of (+)-tanikolide, which employed the less expensive cyclohexenone as the starting material, was produced in twice the previously obtained yield (entry 14).[21] The kinetic resolution of (±)-**1p** using immobilized *Pseudomonas cepacia* (recently classified as *Burkholderia cepacia*) lipase gave (*R*)-**3p** (49%, >99% *ee*) and (*S*)-**1p** (48%, >99% *ee*), which are useful chiral building blocks for the preparation of bioactive aza-sugars.[22] Our DKR method converted (±)-**1p** into (*R*)-**3p** in 90% yield and 97% *ee* (entry 16). Moreover, it was applicable to benzyl **1q**, furyl **1r**, and propargyl alcohols **1s** to give **3q–s** in excellent yield and enantioselectivity, whereas the previous conditions using **4** or **5**[6] were relatively ineffective (entries 17–19). In particular, neither rearrangement nor oxidation was observed in the reaction of **1s**, in contrast to related reactions using other oxometal catalysts.[23]

The efficiency of this method was further demonstrated by the asymmetric synthesis of (*R*)-imperanene (Scheme 3).[24] The combined use of V-MPS and PS-IM for (±)-**8**, which was



Scheme 3. Application of DKR to the synthesis of (*R*)-imperanene.

synthesized from vanillin in 95% overall yield, produced (*S*)-**9** in 88% yield, which was converted into (*S*)-**10**. Treatment of (*S*)-**10** with Grignard reagent **11** at −80 °C in Et_2O led to regio- and stereoselective nucleophilic addition to the oxirane, thus forming (*R*)-**12**. Final deprotection by $KOSiMe_3$ gave optically pure (*R*)-imperanene (62% overall yield from vanillin). The preparation of the naturally occurring *S* isomer through the use of different kinds of hydrolases is now in progress.

In conclusion, we have prepared a new oxovanadium catalyst (V-MPS) immobilized inside mesoporous silica with pores of approximately 3 nm in diameter. V-MPS divides the racemization site and the enzymatic reaction site to achieve excellent compatibility with lipases and effective catalyst sustainability. Furthermore, V-MPS exhibited higher racemization activity on optically active allyl and benzylic alcohols than other oxovanadium compounds (**4** and **5**) or the related oxovanadium catalysts V-MacroPS(100), V-MacroPS(400), and V(3)-MPS. The combination of V-MPS and lipases served as a powerful catalyst for the DKR of various racemic alcohols to give optically active esters in excellent yield and enantioselectivity. The application of this catalyst combination to a wider range of alcohols and the use of other hydrolases as cocatalysts are under investigation in our laboratory.

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[16] Our preliminary studies revealed that $O{=}V(O{i}C_3H_7)_3$ was less reactive for racemization than **4**, and therefore, we chose **4** as the vanadium precursor. The difference in their activity is somewhat attributed to the pK_a value of each ligand (17 for iC_3H_7OH, 13.5 for Ph_3SiOH).

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