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# Asymmetric Aerobic Oxidation of α-Hydroxy Acid Derivatives by $C_4$-Symmetric, Vanadate-Centered, Tetrakisvanadyl(V) Clusters Derived from *N*-Salicylidene-α-aminocarboxylates

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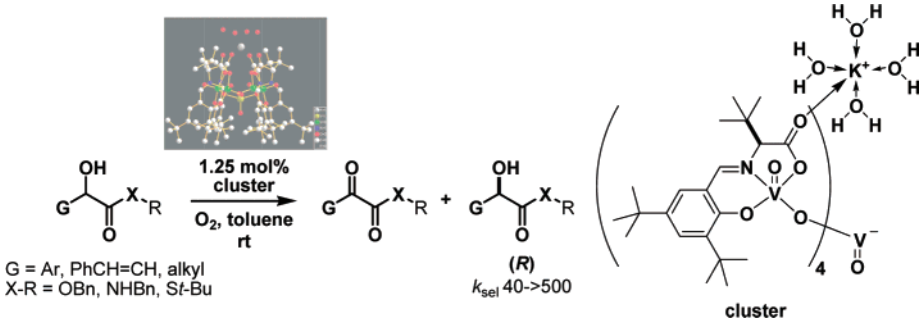


A series of chiral vanadyl(V) methoxides bearing 3-*t*-butyl-5-substituted *N*-salicylene-L-valinate and L-*t*-leucinate as chiral auxiliaries has been prepared. In all cases except the 3,5-di-*t*-butyl analogue, they exist as monomers both in solution and in the single crystal state. In the case of the 3,5-di-*t*-butyl analogue, the architectural nature of the vanadyl(V) complex highly depends on the base used during the complex formation event. A pentanuclear $C_4$-symmetric complex was formed when potassium salts were employed instead of the corresponding sodium salts. A central vanadate(V) unit serves to grip four identical chiral monomeric vanadyl(V) units together, by which a potassium ion sits on top of the four flanking units through carbonyl coordinations and serves to hold the whole cluster by cooperation with the central vanadate(V) unit. In comparison with the corresponding monomeric vanadyl(V) methoxide complex, the cluster complex was utilized to facilitate the asymmetric aerobic oxidations of various racemic α-hydroxyesters, -amides, and -thioesters with excellent selectivity factors ($k_{rel}$ 40 to >500).

## Introduction

It is well-documented that vanadyl(V) complexes normally exist as monomers, $\mu$-oxo-bridged dimers, and tetramers in the solid state.[1] Dependent on solvent polarity, these species may become monomers and dimers in solution. On the other hand, to fulfill penta- or hexavalency requirements, the corresponding vanadyl(IV) complexes may adopt monomeric, dimeric, and even polymeric frameworks.[2] Chiral organometallic complexes possessing unique $C_2$- and $C_3$-symmetry have been extensively examined for asymmetric catalysis and molecular recognition.[3] In most cases, $C_2$- and $C_3$-symmetric ligands were employed to capture metal ion centers. Furthermore, several $C_3$-symmetric prosthetic groups have been utilized as receptors for chiral molecular recognition. In marked contrast, $C_4$-symmetric ligands are relatively unexplored except in the synthetic study of calix-[4]arenes.[4] To date, artificial $C_4$-symmetric oligonuclear organometallic assemblies that exhibit specific molecular recognition, biological functions, or asymmetric catalysis have not been reported.[5] As part of our ongoing programs by using vanadyl and oxometallic species in catalyzing C−C and C−X bond

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formation,[6] asymmetric aerobic oxidative dehydrogenation[7] and coupling,[8] and photoinitiated DNA cleavage,[9] we recently discovered that a given vanadyl(V) alkoxide complex may self-assemble into a $C_4$-symmetric pentanuclear cluster under a special type of *N*-salicylidene-*t*-leucinate template and well-defined complex formation conditions.[10] More importantly, the resultant cluster displays an unprecedented, highly enantioselective asymmetric aerobic oxidation behavior toward a wide variety of α-hydroxy esters, amides, and thioesters.[11] We report herein our complete results of this finding.

## Results and Discussion

**Catalyst Preparation.** A series of 3-*t*-butyl-5-substituted *N*-salicylidene vanadyl(IV) complexes bearing L-*t*-leucine or L-valine can be readily prepared by treatment of in situ generated *N*-salicylidene-L-*t*-leucinate or -L-valinate with NaOAc (2 equiv) followed by vanadyl(IV) sulfate (1 equiv) in warmed, oxygen-free MeOH. The respective vanadyl(IV) complexes were collected from the precipitates by filtration (Figure 1).

**Catalyst Crystallographic Analysis.** After having been recrystallized from oxygen-saturated methanol, all the vanadyl-(IV) centers in the complexes were oxidized to individual vanadyl(V) methoxides **1**−**4** (or **1′**−**4′**) bearing a neutral methanol ligand. The resulting vanadyl(V) complexes as represented by **1′** and **4′** exhibit a slightly distorted octahedral geometry (Figure 2). The vanadyl(V) center is configurationally

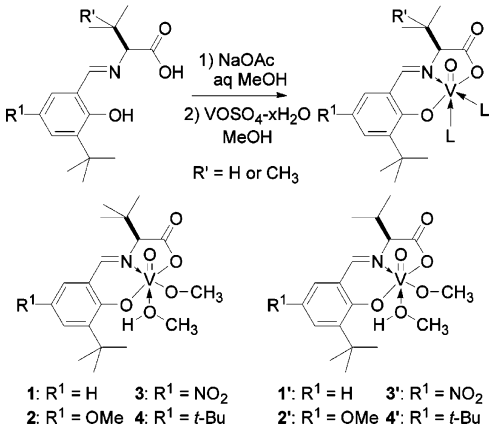


**FIGURE 1.** Preparation conditions for complexes **1**−**4** and **1′**−**4′**.

uniform and is positioned cis to the pendant, pseudo-axial *i*-propyl group in the chiral tridentate *N*-salicylidene-L-valinate template. The covalently bound methoxide unit is located trans to the Schiff base imine nitrogen. Coordinated neutral MeOH is placed trans to the vanadyl oxygen (i.e., V═O).

**Cluster Catalyst Structure.** In marked contrast, the complex generated from the corresponding 3,5-di-*t*-butyl analogue **4** by using KOH or KO*t*-Bu as a base led to an unprecedented $C_4$-symmetric cluster **5**. The pentanuclear cluster **5** shows several unique structural features (see Figure 3 and Table 1). There exists a $C_4$-symmetric negatively charged vanadate center that holds four chiral L-*t*-leucine-based 3,5-di-*t*-butyl *N*-salicylidene vanadyl(V) alkoxides. Four V−O fragments (average length: 1.876 Å, see Table 1) of the central vanadate serve as alkoxides for covalent attachment to the four peripheral chiral vanadyl-(V) units and are positioned trans to the respective Schiff base nitrogens. On the other hand, the lone pair electrons on the four respective alkoxide oxygens serve to coordinate anti to the next V═O unit in a counter-clockwise fashion as viewed from the potassium ion. The average distance for coordination to the adjacent V═O (i.e., O → V) is 2.454 Å, which is significantly longer (by ca. 0.10−0.11 Å) than distances in monomers **1′** and **4′** (O → V: 2.342 and 2.351 Å), allowing for better accommodation of the central vanadate unit. Notably, the central V═O unit (1.547 Å) is pointed away from all four carboxyl units in the four chiral vanadyl(V) templates (Figure 3a,c).

Intriguingly, the negative charge in the central $C_4$-symmetric vanadate is balanced by the potassium ion that is situated right on top of the vanadate center and cooperated with the vanadate center to stabilize the whole $C_4$-symmetric structure. Moreover, the potassium ion is sandwiched between the four top water molecules ($H_2O$ → K: 2.76 Å) and the four bottom carbonyl units (C═O → K av length: 2.40 Å) in the chiral vanadyl(V) templates in a fashion similar to a 1:2 complex from $K^+$ and two 12-crown-4 units.[12] The $C_4$-symmetry of the pentanuclear cluster **5** can be visualized by the relative orientation of the four axially disposed *t*-butyl groups in the chiral appendages and the eight C3 and C5 *t*-butyl groups in the salicylidene templates (Figure 3b,c). Surprisingly, only the monomeric vanadyl(V) complex **4** can be utilized for the assembly of the pentanuclear cluster **5**. Other monomeric complexes including

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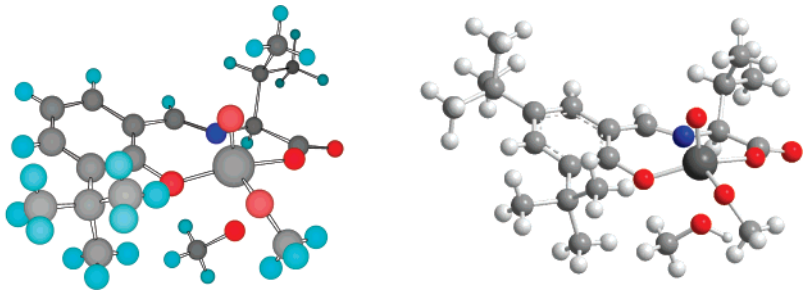


**FIGURE 2.** Chem-3-D presentation for X-ray crystal structures of **1′** and **4′**.

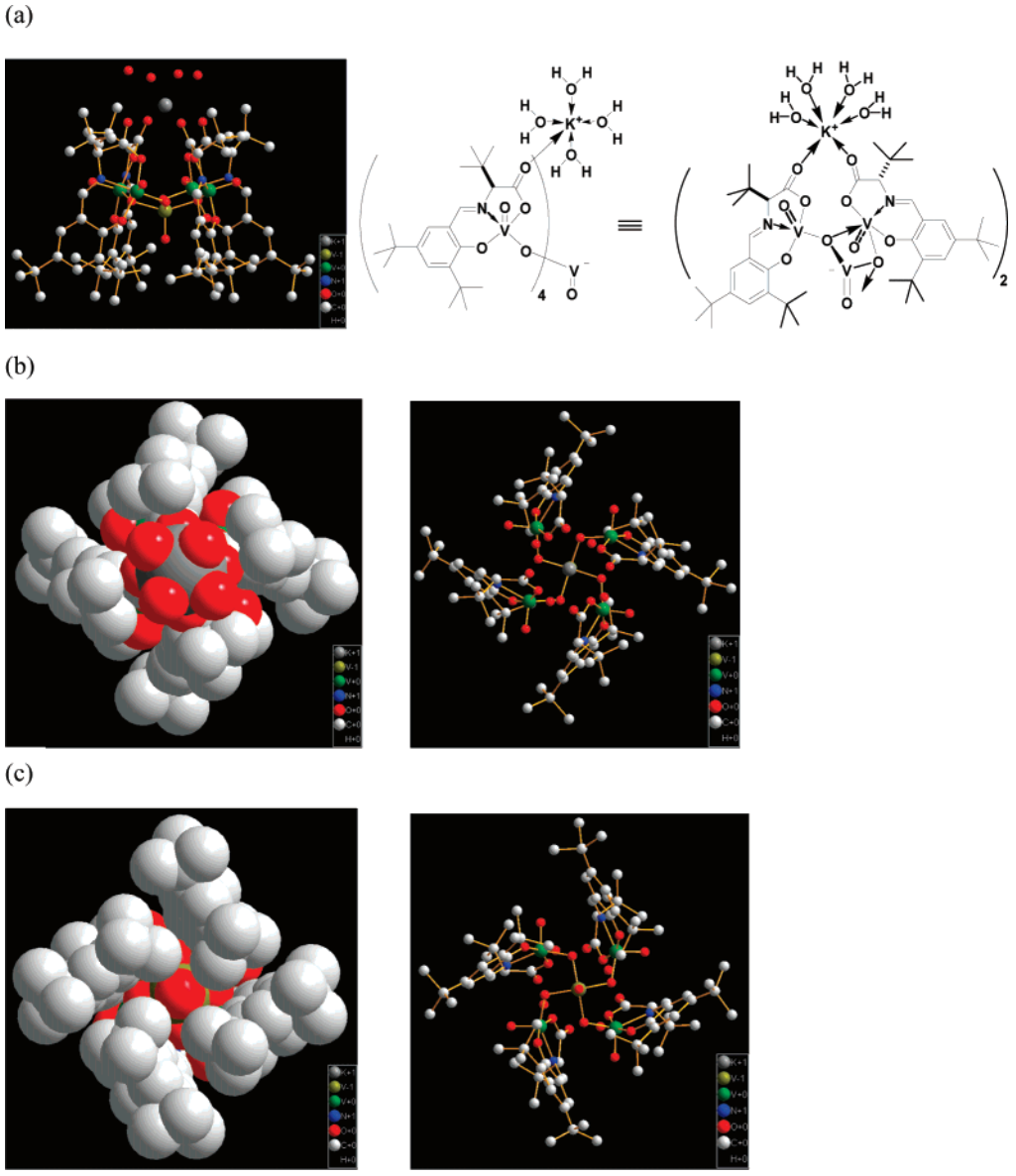



**FIGURE 3.** Diamond and ChemDraw presentations for X-ray crystal structure of the $C_4$-symmetric pentanuclear cluster **5** (hydrogens omitted for clarity): (a) side view, (b) top view, and (c) bottom view.

**4′** do not exert any aggregation effects even when potassium salts were employed during complex formation. More importantly, the cluster behavior of **5** remains intact in organic solvents as evidenced by its $^{51}V$ NMR spectrum in $CDCl_3$, which shows two peaks at −536.1 and −609.6 ppm in a 1:4 ratio, respectively, for the central vanadate and the four flanking chiral vanadyl complexes. Therefore, the vanadyl cluster **5** can be visualized as a tetravalent receptor or template for the encapsulation of potassium vanadate. Furthermore, the central potassium vanadate can be visualized as an unprecedented $C_4$-symmetric vanadate base.

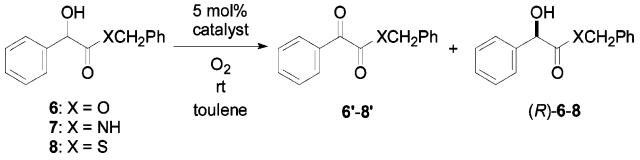
**Comparison of Monomer and Cluster Catalysts in Aerobic Oxidation Reactivity and Selectivity.** Both monomers **1**−**4** (or **1′**−**4′**) and cluster **5** are readily soluble in toluene and can

**TABLE 1. Selected Bond Lengths (Å) for Monomers 1′ and 4′ and Cluster 5**

| | V=O | V−O[a] | O → V[b] | N → V | C=O → K |
|---|---|---|---|---|---|
| V/**1** | 1.600 | 1.778 | 2.342 | 2.098 | |
| V/**4** | 1.589 | 1.770 | 2.351 | 2.101 | |
| V(**1**)[c]/**5** | 1.547 | 1.876[d] | | | |
| V(**2**)/**5** | 1.579 | 1.792 | 2.421 | 2.100 | 2.374 |
| V(**3**)/**5** | 1.551 | 1.788 | 2.456 | 2.086 | 2.423 |
| V(**4**)/**5** | 1.581 | 1.772 | 2.432 | 2.083 | 2.393 |
| V(**5**)/**5** | 1.586 | 1.800 | 2.507 | 2.097 | 2.410 |
| Σ(V(**2** → **5**))/**4**[e] | 1.574 | 1.788 | 2.454 | 2.092 | 2.400 |

[a] V−O represents the bond trans to the N → V bond. [b] O → V represents the bond trans to the V=O unit. [c] Central vanadate. [d] Data represent the av value of all four V−O bonds in the central vanadate. [e] Av value of all four identical peripheral vanadyl complexes.

**TABLE 2. Effects of Catalysts on Asymmetric Aerobic Oxidation of Racemic X-Benzyl Mandelate, Mandelamide, and Thiomandelate 6−8**

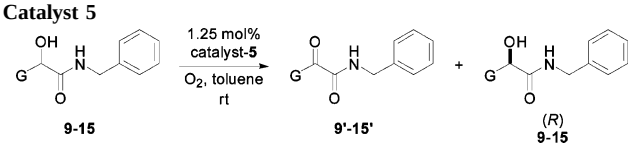



| entry | substrate (catalyst) | time (h) | % conversion[a] | % ee[b] (yield[c] %) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 1 | **6** (**1**) | 14.5 | 52 | 97 (46) | 76 |
| 2 | **6** (**1′**) | 20 | 53 | 97 (42) | 55 |
| 3 | **6** (**2**) | 124 | 52 | 97 (45) | 76 |
| 4 | **6** (**3**) | 14.5 | 50.5 | 97 (50) | 167 |
| 5 | **6** (**3′**) | 9 | 47.5 | 78 (48) | 32 |
| 6 | **6** (**4**) | 19 | 50 | 98 (46) | 458 |
| 7 | **6** (**4′**) | 19 | 50.5 | 92 (46) | 63 |
| 8 | **6** (**5**[e]) | 19 | 50 | 96 (46) | 194 |
| 9 | **7** (**1**) | 20 | 50 | 98 (48) | 458 |
| 10 | **7** (**1′**) | 20 | 50 | 98 (48) | 458 |
| 11 | **7** (**2**) | 60 | 50 | 98 (50) | 458 |
| 12 | **7** (**3**) | 13 | 52 | 93 (43) | 44 |
| 13 | **7** (**3′**) | 11 | 52 | 80 (43) | 16 |
| 14 | **7** (**4**) | 25 | 50 | 99 (47) | >500 |
| 15 | **7** (**4′**) | 20 | 51 | 98 (43) | 153 |
| 16 | **7** (**5**[e]) | 23 | 50 | 99 (47) | >500 |
| 17 | **8d** (**4**) | 7 | 51 | 78 (47) | 16 |
| 18 | **8d** (**5**[e]) | 5 | 51 | 95 (46) | 82 |

[a] Determined by $^1$H NMR analysis of the reaction mixture. [b] Determined by HPLC analysis on a Chiralpak AD-H or AS column. [c] Isolated, purified material for the alcohol by column chromatography. [d] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where $C$ = conversion and ee = enantiomeric excess. [e] 1.25 mol % catalyst was used.

catalyze the asymmetric aerobic oxidation of X-benzyl mandelate, mandelamide, and thiomandelate **6**−**8**. In general, the vanadyl(V) complexes **1′**−**4′** derived from L-valine are less enantioselective than those from the corresponding L-*t*-leucine (Table 2). The vanadyl(V) complex **3** bearing an electron-withdrawing nitro group at the C5 position is the most reactive catalyst. The aerobic oxidations of **6** and **7** catalyzed by **3** can be completed in 13−14.5 h at about 50% conversion (entries 4 and 12 in Table 2). In marked contrast, the corresponding C5-methoxy (an electron-donating group) analogue **2** is the least reactive, which effects 50% conversion of **6** and **7** in 60−124 h (entries 3 and 11 in Table 2). The reactivity profiles (14.5−25 h) for the vanadyl(V) complexes bearing C5-H (i.e., **1**) or C5-*t*-butyl groups (i.e., **4** and **5**) lie in between those of **2** and **3**. Among all the catalysts examined, both **4** and **5** led to the best selectivity factors in the kinetic resolution process ($k_{rel}$ 194 to >500; entries 6, 8, 14, 16, and 18 in Table 2). In comparison

**TABLE 3. Effects of α-Aryl Groups on Asymmetric Aerobic Oxidations of Racemic *N*-Benzyl-mandelamide 9−15 by Cluster Catalyst 5**




| entry | G | time (h) | conversion (%)[a] | % ee[b] (yield[c] %) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ (**7**) | 23 | 50 | 99 (47) | >500 |
| 2 | 4-$CF_3C_6H_4$ (**9**) | 16 | 48 | 92 (47) | 40 |
| 3 | 4-C1$C_{66}H_4$(**10**) | 62 | 48 | 87 (46) | 57 |
| 4 | 2-$CH_3C_6H_4$ (**11**) | 81 | 52 | 96 (44) | 65 |
| 5 | 2-C1$C_6H_4$ (**12**) | 18 | 50 | 92 (47) | 79 |
| 6 | 1-Np (**13**) | 122 | 54 | 99 (45) | 61 |
| 7 |  (**14**) | 4 | 51 | 99 (46) | 211 |
| 8 | *trans*-PhCH =CH(**15**) | 76 | 50 | 99 (46) | >500 |

[a] Determined by $^1$H NMR analysis of the reaction mixture. [b] Determined by HPLC analysis on a Chiralpak AD-H or AS column. [c] Isolated, purified material for the alcohol by column chromatography. [d] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where $C$ = conversion and ee = enantiomeric excess.

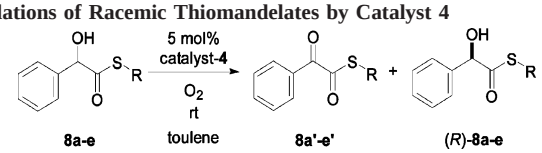
with monomer **4**, cluster **5** shows essentially similar or better reactivity and selectivity profiles toward the oxidations of **6**−**8**. In general, *N*-benzyl-mandelamide **7** (entries 9−16 in Table 2) is the most enantioselective substrate for a given catalyst followed by *O*-benzyl mandelate **6** (entries 1−8 in Table 2). On the other hand, *S*-benzyl thiomandelate **8** (entries 17 and 18 in Table 2) is the least enantioselective.

Notably, complex **5** can be generated in situ by direct addition of potassium metavanadate ($KVO_3$, 1.25 equiv) to the freshly made *N*-salicylidene-L-*t*-lencine in oxygen-saturated MeOH. The resulting complex **5** can be isolated as a dark brown solid after concentration of the methanol solution to half of its original volume. ESI-MS analysis of the solid shows only the signal arising from the pentanuclear complex **5**.[10] It was also found that the resulting cluster can be used directly for asymmetric aerobic oxidation chemistry with intact selectivity profiles.

**Cluster Catalyst 5 in Asymmetric Aerobic Oxidation of α-Hydroxyamides.** To probe the substrate scope, we have selected six different *N*-benzyl-α-aryl-α-hydroxyacetamides for further catalytic studies in the presence of **5** (1.25 mol %) (Table 3). Substrates bearing α-phenyl (i.e., **7** in entry 1 in Table 3) and α-2-thiophenyl (i.e., **14** in entry 7 in Table 3) are the most selective followed by those bearing the α-2-substituted phenyl (i.e., **11**−**13** in entries 4−6 in Table 3) groups. On the other hand, substrates bearing α-4-substituted phenyl groups are the least enantioselective ($k_{rel}$ 40−57 in entries 2 and 3 in Table 3). As represented in **15** (entry 8 in Table 3), substrates bearing α-alkenyl groups are also ideal cases for the new asymmetric aerobic oxidation protocol.

**Cluster Catalyst 5 in Asymmetric Aerobic Oxidation of α-Hydroxythioesters.** Since there have not been any studies on the asymmetric aerobic oxidations of α-hydroxythioesters, we sought to extend the applications of catalyst **4** and cluster **5** toward resolving this substrate class. As illustrated in entry 17 of Table 2, *S*-benzyl-thiomandelate **8d** is the least-selective substrate for monomer catalyst **4**. By a systematic survey of five different *S*-appendages with thiomandelates (G = Ph) for their asymmetric aerobic oxidation profiles, we found that *S*-ethyl-, isopropyl-, and *t*-butyl thiomandelates **8a**−**c** are the most selective substrates by using monomer **4** as the catalyst

**TABLE 4. Effects of *S*-Pendent Groups on Asymmetric Aerobic Oxidations of Racemic Thiomandelates by Catalyst 4**




| entry | R/catalyst | time (h) | conversion (%)[a] | % ee[b] (yield[c] %) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 1 | $CH_2CH_3$ (**8a**)/**4** | 6 | 51 | 99 (48) | 211 |
| 2 | $CH(CH_3)_2$ (**8b**)/**4** | 6 | 51 | 99 (47) | 211 |
| 3 | $C(CH_3)_3$ (**8c**)/**4** | 6 | 50.5 | 98 (48) | 230 |
| 4 | $CH_2C_6H_5$ (**8d**)/**4** | 7 | 51 | 78 (47) | 16 |
| 5 | $C_6H_5$ (**8e**)/**4** | 9 | 52 | 47 (48) | 4 |
| 6 | $C_6H_5$ (**8e**)/cluster **5** | 7 | 53 | 64 (45) | 7 |

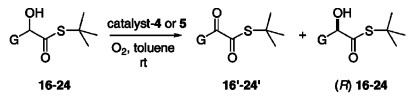
[a] Determined by $^1$H NMR analysis of the reaction mixture. [b] Determined by HPLC analysis on a Chiralpak AD-H or AS column. [c] Isolated, purified material for the alcohol by column chromatography. [d] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where $C$ = conversion and ee = enantiomeric excess.

(entries 1−3 in Table 4). On the other hand, the asymmetric oxidation for *S*-phenyl-thiomandelate **8e** is less selective than that for *S*-benzyl-thiomandelate **8d** (entries 4 and 5 in Table 4). In addition, the enantioselectivity for the asymmetric oxidation of *S*-phenyl-thiomandelate (**8e**) catalyzed by cluster **5** ($k_{rel}$ 7, entry 6 in Table 4) is significantly higher than that catalyzed by monomer complex **4** ($k_{rel}$ 4, entry 5 in Table 4).

*t*-Butylthioesters are popular derivatives of protected acids. Their *t*-butyl moiety can be readily unmasked by treatment with polymer-supported $SO_3H$,[13a] $Br_2$/aq THF,[13b] or in aqueous $LiOH/H_2O_2$.[14] In addition, *t*-butylthioesters can be readily functionalized into amides,[15] esters,[16] and thioacids.[17] Therefore, a series of α-substituted *S*-*t*-butyl α-hydroxythioesters was further examined in view of their versatility and to fully grip their kinetic resolution profiles by monomer **4** and cluster **5**, respectively.

Despite that cluster **5** ($k_{rel}$ 82) is a better catalyst than monomer **4** ($k_{rel}$ 16) for the kinetic resolution of *S*-benzylmandelate **8d** (entries 17 and 18 in Table 2), similarly effective resolutions can now be achieved for both catalysts for the corresponding *S*-butyl analogue **8c** (entries 1 and 2 in Table 5). Furthermore, *S*-*t*-butyl α-hydroxythioesters bearing electron-withdrawing and -donating α-aryl ($k_{rel}$ 94 to >500, entries 3−12 in Table 5), -naphthyl ($k_{rel}$ 81/146, entries 13 and 14 in Table 5), -heteroaryl ($k_{rel}$ 458/81, entries 15 and 16 in Table 5), -alkenyl ($k_{rel}$ > 500, entries 17 and 18 in Table 5), and -alkyl ($k_{rel}$ 230/116, entries 19 and 20 in Table 5) are all amenable to aerobic oxidative processes with high to excellent selectivity factors by using both monomer **4** and cluster **5**, respectively. Consequently, the kinetic resolutions for these *S*-*t*-butyl α-hydroxythioesters can now be as efficient as those for the corresponding *N*/*O*-benzyl analogues as shown in Table 3.

**TABLE 5. Effects of α-Substituents on Asymmetric Aerobic Oxidations of Racemic *S*-*t*-Butyl α-Hydroxythioesters 16−24 by Catalyst 4 or Cluster 5**




| entry | G/catalyst | time, h | conversion, % [a] | %ee,[b] (yield,[c] %) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ (**8c**)/**4** | 6 | 50.5 | 98 (48) | 230 |
| 2 | $C_6H_5$ (**8c**)/**5** | 7.5 | 50 | 98 (46) | 458 |
| 3 | 4-$NO_2C_6H_4$ (**16**)/**4** | 60 | 50 | 99 (48) | >500 |
| 4 | 4-$NO_2C_6H_4$ (**16**)/**5** | 82 | 51 | >99 (46) | >211 |
| 5 | 4-$ClC_6H_4$ (**17**)/**4** | 80 | 50 | 98 (48) | 458 |
| 6 | 4-$ClC_6H_4$ (**17**)/**5** | 87 | 51 | 98 (48) | 153 |
| 7 | 4-$CH_3C_6H_4$ (**18**)/**4** | 90 | 50 | 93 (48) | 94 |
| 8 | 4-$CH_3C_6H_4$ (**18**)/**5** | 115 | 50 | 93 (47) | 94 |
| 9 | 2-$ClC_6H_4$ (**19**)/**4** | 94 | 51 | 99 (47) | 211 |
| 10 | 2-$ClC_6H_4$ (**19**)/**5** | 106 | 49 | 96 (49) | >500 |
| 11 | 2-$CH_3OC_6H_4$ (**20**)/**4** | 150 | 50 | 99 (47) | >500 |
| 12 | 2-$CH_3OC_6H_4$ (**20**)/**5** | 132 | 52 | 99 (46) | 116 |
| 13 | 1-Np (**21**)/**4** | 160 | 51 | 95 (49) | 81 |
| 14 | 1-Np (**21**)/**5** | 165 | 50 | 95 (48) | 146 |
| 15 |  (**22**)/**4** | 30 | 50 | 98 (48) | 458 |
| 16 |  (**22**)/**5** | 41 | 51 | 95 (47) | 81 |
| 17 | *trans*-PhCH=CH (**23**)/**4** | 24 | 50 | 99 (49) | >500 |
| 18 | *trans*-PhCH=CH (**23**)/**5** | 32 | 50 | 99 (48) | >500 |
| 19 | $PhCH_2CH_2$ (**24**)/**4** | 24 | 51 | 97 (48) | 230 |
| 20 | $PhCH_2CH_2$ (**24**)/**5** | 35 | 52 | 99 (46) | 116 |

[a] Determined by $^1$H NMR analysis of the reaction mixture. [b] Determined by HPLC analysis on Chiralpak AD-H or AS column. [c] Isolated, purified material for the alcohol by column chromatography. [d] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where $C$ = conversion and ee = enantiomeric excess.

**Rationalization on Enantiocontrol.** On the basis of the structural study of an adduct between *N*-benzyl-mandelamide and catalyst **2** in the asymmetric oxidation of α-hydroxyamides,[7] we have proposed that the facile perpendicular $\pi-\pi$ interaction between the salicylidene template and the phenyl group in the *N*/*O*-$CH_2$Ph unit plays the dominant role in inducing exclusive enantiocontrol for the corresponding *N*/*O*-benzyl systems **6** and **7**. Therefore, it is suggested that the thermodynamically more stable diastereomeric adduct **25′** as shown in Figure 4 is a

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(15) For deprotective amidations by Hg(II), Ag(I), and Cu(I) species, see: (a) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145. (b) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 3019. (c) Schmidt, U.; Steindl, F. *Synthesis* **1978**, 544. (d) Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531. (e) Poncet, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *J. Org. Chem.* **1989**, *54*, 617. For amidation to primary amides by $NH_3$, see: (f) Otsuka, M.; Narita, M.; Yoshida, M.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 520. (g) Kittaka, A.; Sugano, Y.; Otsuka, M.; Ohno, M. *Tetrahedron* **1988**, *44*, 2811.

(16) For deprotective esterifications by Ag(I) species, see: (a) Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *Synthesis* **1998**, *2*, 186. (b) Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *Tetrahedron Lett.* **2001**, *42*, 4479. (c) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Usui, T.; Ueda, K.; Osada, H. *J. Med. Chem.* **2001**, *44*, 3216. (d) Clive, D. L. J.; Hisaindee, S. *J. Org. Chem.* **2000**, *65*, 4923. By $Tl(ONO_2)_3$, see: (e) Mukai, C.; Kim, I. J.; Furu, E.; Hanaoka, M. *Tetrahedron* **1993**, *49*, 8323. (f) Mukai, C.; Kim, I. J.; Hanaoka, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1007. By $Hg(NO_3)_2$, see: (g) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909.

(17) Bekker, R. A.; Rozov, L. A.; Popkova, V. Y.; Knunyants, I. L. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1982**, *31*, 2123.

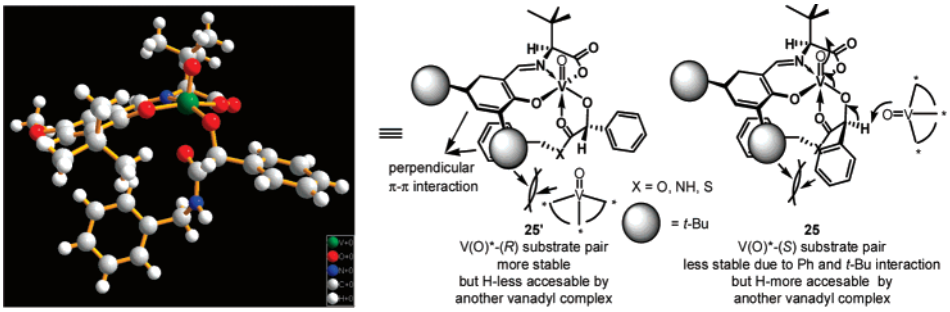
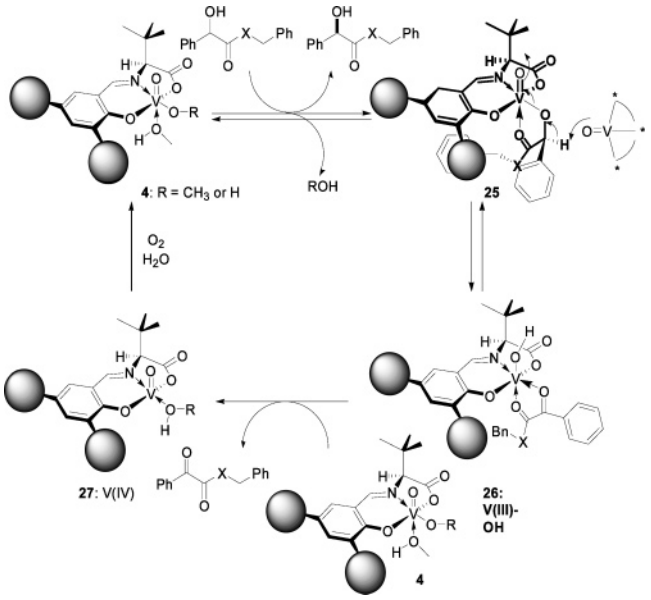



**FIGURE 4.** 4. Proposed two diastereomeric assemblies between catalyst **4** and racemic X-benzyl mandelate.

**SCHEME 1**




slower-reacting species toward deprotonative oxidation since the α-proton in the substrate is less accessible by another vanadyl complex due to the proximal C3-*t*-butyl group in the salicylidene template. On the contrary, the less stable, sterically more encumbered diastereomeric adduct **25** is faster reacting for the subsequent α-proton elimination process via a two-electron oxidation process leading to α-ketothioester **8d′** with concomitant reduction of the vanadyl(V) species to the corresponding vanadium(III)OH **26** (Scheme 1).

The vanadium(III) hydroxide **26** may disproportionate with the original vanadyl(V) methoxide **4** catalyst to give two molecules of vanadyl(IV) complex **27** with the release of *N*-benzyl benzoyl-thioformate **8d′** and $CH_3OH$. The vanadyl-(IV) complex **27** would be oxidized in the presence of oxygen atmosphere to regenerate the original catalyst **4**, thus completing the catalytic cycle.

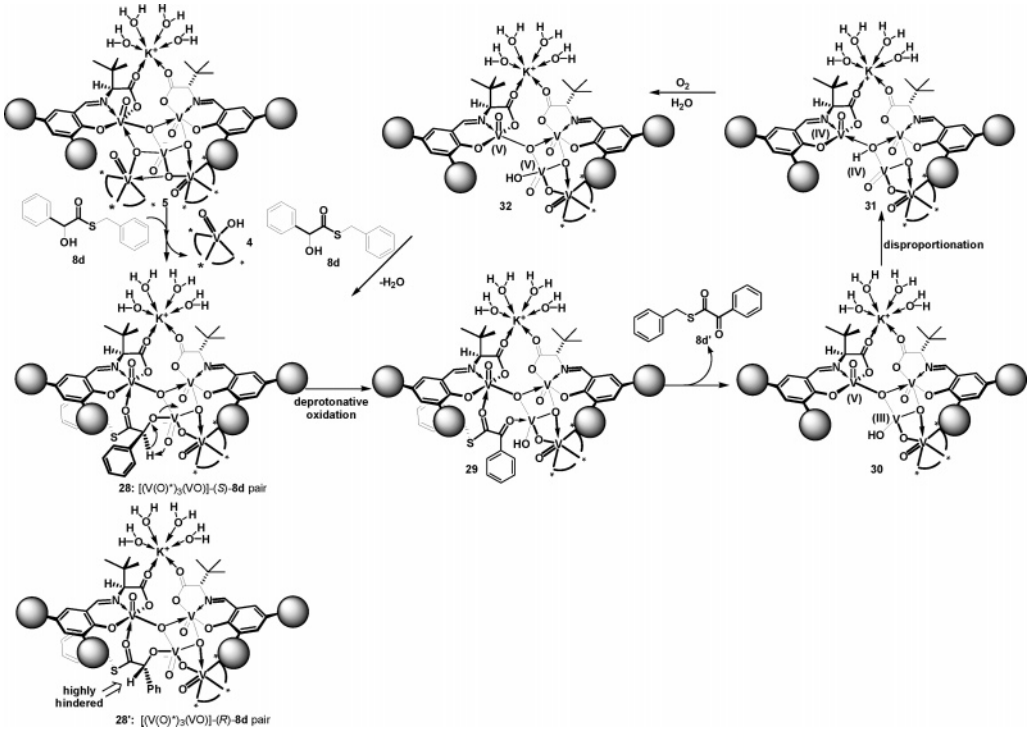
In marked contrast, *S*-ethyl-, isopropyl-, and *t*-butyl thiomandelates **8a**−**c** are the most selective substrates instead of the corresponding *S*-benzyl and -phenyl systems **8d** and **8e** by using monomer **4** as the catalyst. The longer S−C(O) bond and less rigid conformation in the *S*-benzyl and -phenyl thioesters reduce the stabilization effect of the perpendicular $\pi-\pi$ interaction between the salicylidene template and the phenyl group in the *S*-$CH_2$Ph or *S*-Ph unit, resulting in diminished enantiocontrol in the asymmetric oxidations of *S*-benzyl- and *S*-phenyl-thiomandelates **8d** and **8e** by catalyst **4.**

Since the enantioselectivities for the asymmetric oxidations of *S*-benzyl- and *S*-phenyl thiomandelates by cluster **5** are significantly higher ($k_{rel}$, 82 and 7) and faster (5−7 h) than those exerted by the corresponding monomer **4** ($k_{rel}$, 16 and 4; time, 7−9 h), there exists a synergistic effect for the cluster during the asymmetric aerobic oxidation event. One can envisage that cluser **5** acts like a space station with a central potassium vanadate core and four docked homochiral, monomer catalysts **4**. Upon initial ligand exchange of *S*-benzyl-thiomandelate **8d** with **5** by nucleophilic attack of (*S*)-**8d** to the central vanadate, one vanadyl(V) hydroxide **4** would dissociate with concomitant docking of **8d** to the vanadate center of the cluster station (Scheme 2). (*S*)-**8d** fits nicely into the chiral pocket that is created after the departure of one vanadyl(V) hydroxide **4** from the cluster **5**. The docking would involve a seven-membered chelation of (*S*)-**8d** to both a nearby docked monomer unit and the central vanadate, leading to adduct **28**. Subsequent deprotonation of the docked (*S*)-**8d** by the central V═O with its concomitant reduction would generate adduct **29** with a reduced V(III)−OH center. The resulting oxidation product, *S*-benzyl benzoyl-thioformate **8d′**, would dissociate from **29** to give **30**. A facile disproportionation between either the flanking vanadyl-(V) unit or the central V(III)−OH in **30** would lead to **31**, which bears one flanking vanadyl(IV) unit and one central vanadyl-(IV)−OH. These two vanadyl(IV) units in **31** would undergo spontaneous oxidation in the presence of an oxygen atmosphere to give a turnover catalyst **32**, which possesses recovered vanadyl(V) states, thus completing the catalytic cycle.

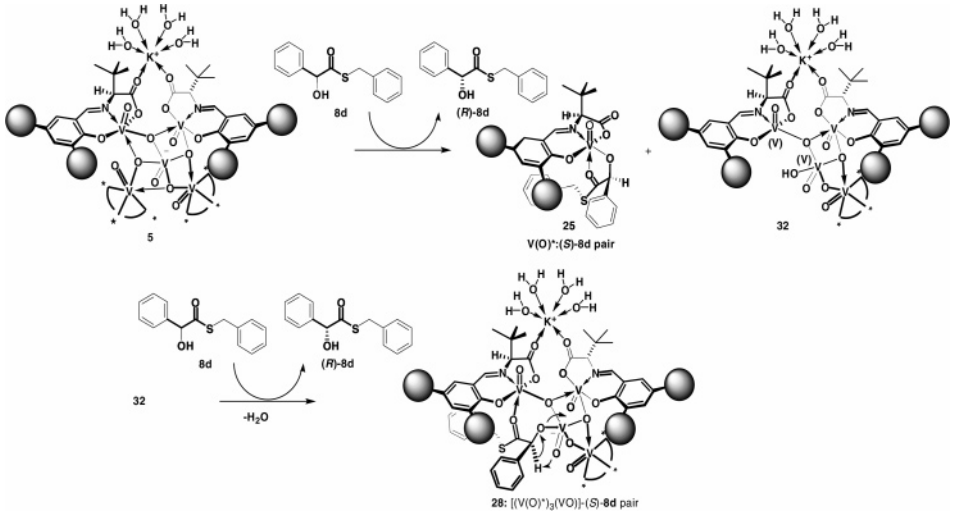
On the other hand, the ligand exchange reaction of cluster **5** by (*R*)-**8d** would produce the alternative epimeric adduct **28′**. Subsequent deprotonative oxidation in **28′** would be highly hindered due to the inaccessibility of the benzylic proton in docked (*R*)-**8d** either by the central vanadate or by prior-dissociated vanadyl(V) hydroxide **4**. The higher oxidation enantioselectivity with cluster **5** indicates that there exists a better defined asymmetric environment in the chiral pocket in **32** as compared to that in **4**. In addition, the key deprotonative oxidation is intramolecular in **28** rather than intermolecular when the reaction is catalyzed by monomer **4**, which would secure a faster reaction and a better enantioselectivity by cluster **5**.

At the current stage, we can ignore the possibility of double or triple ligand exchange between the cluster **5** and the given substrate (*S*)-**8d** since the central vanadate is the only vanadyl-(V) unit that can participate in the subsequent deprotonative oxidation. In addition, a loose asymmetric environment would result from multiple ligand exchange. Therefore, complete dissociation of all four monomer units from the central potassium vanadate through quadrupole ligand exchange with the substrate is unlikely since this event would lead to a random

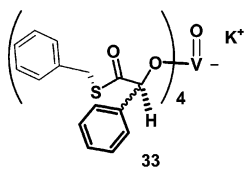
**SCHEME 2**




**SCHEME 3**




unselective attachment of either enantiomeric **8d** to the central vanadate, leading to **33**.



**33**

An alternative ligand exchange mechanism between cluster **5** and (*S*)-**8d** by nucleophilic attack of (*S*)-**8d** to either flanking vanadyl(V) unit would generate the diastereomeric adduct **25** as in Scheme 1 and the same turnover catalyst **32** as in Scheme 2 (Scheme 3). Under such circumstances, the faster deprotonative oxidation and better enantioselectivity by cluster **5** remain secured. In addition, to completely shut down the catalytic pathway mediated by cluster **5** would require a quadrupole ligand exchange for the alternative mechanism and would result in the precipitation of $K^+V(O)(OH)_4^-$ from toluene due to its insolubility in organic solvents, which was not observed during the reaction. A similar mechanistic principle would also hold for the corresponding *S*-phenyl thioester case.

Last, the uniformly high enantioselectivities and divergent relative rates observed for the asymmetric oxidations of *S*-*t*-butyl thioesters by both catalyst **4** and cluster **5** (Table 5) indicate that both the freely dissociated vanadyl(V) hydroxide **4** and the turnover cluster catalyst **32** may be operative at the same time

due to the increased steric bulk of the substrates, which might hinder their dockings to the chiral pocket in **32**.

## Conclusion

We have documented a unprecedented $C_4$-symmetric pentanuclear vanadyl(V) cluster **5** bearing one central vanadate and four identical vanadyl(V) 3,5-di-*t*-butyl *N*-salicylene-L-*t*-leucinates as chiral peripheral units as evidenced by X-ray crystallographic, ESI-MS, and $^{51}$V NMR spectroscopic analyses. The cluster was best produced when potassium *t*-butoxide was used as the base instead of NaOAc or NaO*t*-Bu during the complex formation. The negative charge in the central vanadate(V) unit is compensated by a potassium ion sitting on top of the four flanking units through carbonyl coordinations. Like monomer **4**, cluster **5** exhibits a high reactivity and enantioselectivity profiles toward the asymmetric aerobic oxidations of various racemic α-aryl- and α-alkenyl-α-hydroxyesters and -amides with excellent selectivity factors. In the case of *S*-benzyl- and *S*-phenyl-thiomandelates, cluster **5** shows even higher enantiocontrols than those exerted by monomer **4**, indicating a potential cooperative effect[18] between three of the four docked vanadyl(V) alkoxide units and the central $K^+V(O)O_4^-$ in the cluster **5** during the kinetic resolution event. Conversely, *S*-*t*-butyl α-hydroxythioesters were found to be the best thioester substrates. Uniformly excellent selectivity factors ($k_{rel}$ 45 to >200) were achieved for their asymmetric aerobic oxidations catalyzed both by monomer **4** and by cluster **5**. A handy one-pot recipe for the preparation of cluster **5** is also established, arguing well for its practical applications in the kinetic resolution of α-hydroxy acid derivatives. Investigations on its potential use as a $C_4$-symmetric chiral vanadate base in asymmetric catalysis are underway.

## Experimental Section

**Representative Preparation Procedure and Analytical Data for Vanadyl(V) Methoxide (or Hydroxide) Complexes 1−4.** In a 50 mL, two-necked, round-bottomed flask was placed L-*t*-leucine (5 mmol) and NaOAc-5$H_2O$ (1.17 g, 10 mmol) in degassed water (10 mL). After having been stirred at 60 °C for 10 min to effect their complete dissolution, the reaction mixture was treated dropwise with a solution of respective 2-hydroxybenzaldehyde derivatives (5 mmol) in degassed EtOH (12.5 mL). The reaction mixture became homogeneous by heating at 80 °C for 15 min and then gradually cooled to ambient temperature for 2 h. To the resultant Schiff base was added a solution of vanadyl(IV) sulfate trihydrate (1.08 g, 5 mmol) in degassed water (5 mL). The dark green complex started crashing out in 15 min. The reaction mixture was stirred for 2 h and then concentrated to half of the original solvent volume. The crude vanadyl(IV) complex collected by filtration was washed sequentially with water (5 × 25 mL) and cold ether (5 × 25 mL) and then dried in vacuo to furnish the pure vanadyl(IV) catalyst. The corresponding analytically pure vanadyl(V) methoxide (or hydroxide) complexes were obtained by recrystallization from oxygen-saturated MeOH and were used for asymmetric aerobic oxidation experiments. Data for **4:** yield: 75%; $M_w$ (**M**: $C_{21}H_{31}NO_4V$) 412; MS (ESI) 881 ($M_2O + H_2O + Na^+$, 6), 460 ($MOCH_3 + H_2O^+$, 77), 444 ($M + CH_3OH^+$, 13), 413 ($M + H^+$, 100); $^{51}$V NMR ($CDCl_3$) $\delta$ −583.38; IR (KBr) $\nu$ 3322 (br, w), 2959 (m), 2908(w), 2871 (w), 1698 (m), 1613 (s, C═N), 1557 (w, COO), 1477 (w), 1462 (m), 1436 (w), 1414 (w), 1392 (w), 1362 (w), 1322 (w), 1300 (w), 1274 (w), 1252 (w), 1211 (w), 1182 (w), 1078 (w), 982 (w, V═O) cm$^{-1}$; $[\alpha]_D^{25}$ +36.02 (*c* 1.0, $CH_2Cl_2$); TLC $R_f$ 0.37 (MeOH/$CH_2Cl_2$, 1:8); Anal. calcd For [($H_2O$)**M**OH]: C, 56.37; H, 7.66; N, 3.13. Found: C, 55.72; H, 7.32; N, 2.71.

**Procedure for Preparation of $C_4$-Symmetric Pentanuclear Vanadyl(V) Cluster 5**. In a 50 mL, round-bottomed flask was placed L-*t*-leucine (131 mg, 1.0 mmol) and 3,5-di-*t*-butyl salicyladehyde (234 mg, 1.0 mmol) in anhydrous methanol (5 mL) under oxygen atmosphere. After having been refluxed at 80 °C for 12 h, the reaction mixture led to the complete formation of the resultant Schiff base. A solution of potassium *t*-butoxide (258 mg, 2.3 mmol) in anhydrous THF (1 mL) was added dropwise to the Schiff base at ambient temperature. The reaction mixture was then stirred for 1 h, and a solution of $VOSO_4$-*x*$H_2O$ (203.8 mg, 1.25 mmol) in anhydrous THF (1 mL) was added gradually. A dark green species was formed immediately and precipitated out completely in 20 min. After having been stirred under oxygen atmosphere for an additional 24 h, the dark green reaction mixture was concentrated in vacuo to half of the original volume. The crude pentanuclear cluster was collected by filtration and washed sequentially with water (5 × 25 mL) and cold diethyl ether (5 × 25 mL) and then dried under vacuum. The pure pentanuclear cluster **5** was obtained by recrystallization from wet MeOH with slow evaporation of MeOH and then used for asymmetric aerobic oxidation experiments. Single crystals suitable for X-ray crystallographic analysis was obtained by recrystallization from MeOH to yield 742 mg (38%) of brown prism: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (s, 1H), 7.82 (d, $J$ = 2.0, 1H), 7.50 (d, $J$ = 2.4, 1H), 4.03 (s, 1H), 1.59 (s, 3H), 1.38 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.2, 143.0, 138.1, 132.9, 128.4, 121.2, 86.9, 38.2, 35.2, 34.9, 31.7, 30.4, 30.3, 28.1; $^{51}$V NMR ($CDCl_3$) $\delta$ −536.14, −609.59; $M_w$ MS (ESI) (**M**: $C_{84}H_{132}KN_4O_{25}V_5$, 1891.74) 1820 (M-4$H_2O$, 100); IR (KBr) $\nu$ 3434 (br, w), 3188 (br, m), 2969 (w), 1619 (s, C═N), 1541 (m, COO), 1510 (m), 1455 (m), 1429 (m), 1390 (m), 1362 (m), 1340 (m), 1309 (m), 1250 (m), 1192 (m), 1164 (m), 1244 (m), 1004 (m, V═O), 979 (bs, V═O) cm$^{-1}$; $[\alpha]_D^{25}$ +66.3 (*c* 1.0, $CH_2Cl_2$); Anal. calcd for **M** + 2MeOH ($C_{86}H_{140}KN_4O_{27}V_5$): C, 52.81; H, 7.21; N, 2.86. Found: C, 52.37; H, 6.75; N,2.97.; mp 260−262 °C.

**Representative Procedure for Asymmetric Aerobic Oxidation of X-Benzyl α-Hydroxyesters, -Amides, and -Thioesters.** To a 50 mL, two-necked, round-bottomed flask was placed a vanadyl(V) catalyst (0.05 mmol, 5 mol %) in oxygen-saturated toluene (3 mL) under oxygen atmosphere. The reaction flask was vacuum-evacuated at 15 Torr for 20 s and then filled with an $O_2$ balloon (150 mL). A solution of α-hydroxyester, -amide, and -thioester (1 mmol) in oxygen-saturated toluene (2 mL) was added by cannula, and the resulting dark brown mixture was stirred at ambient temperature. The reaction progress was monitored by $^1$H NMR spectroscopy for percent conversion (142 mg; i.e., 1 mmol of 2-methyl-naphthalene was used as an internal standard). The enantiomeric excess of the kinetically resolved product was determined by chiral HPLC analysis after filtration of the reaction aliquot (100 $\mu$L) over a short plug of silica gel ($Et_2O$ or $CH_2Cl_2$ as eluent). Upon reaching optimal resolution of the asymmetric oxidation (50−53% conversion), the reaction was quenched by the addition of silica gel (150 mg), and the mixture was concentrated under reduced pressure. The resulting residue was loaded directly on top of an eluent-filled silica gel column and purified by flash column chromatography. The enantiomeric excess of the pure, resolved α-hydroxyester, -amide, and -thioester was analyzed again by chiral HPLC analysis.

***S*-Benzyl 2-Hydroxy-2-phenyl-thioacetate 8d**. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.37 (m, 5H), 7.30−7.27 (m, 5H), 5.21 (s, 1H), 4.16 (d, $J$ = 13.6, 1H), 4.10 (d, $J$ = 13.6, 1H), 3.57 (bs, 1H, OH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.4, 137.8, 136.7, 128.8, 128.79, 128.7, 128.6, 127.3, 127.0, 79.7, 33.2; MS (EI, 70 eV) ($C_{15}H_{14}O_2S$, 258.3) 259 ($M + 1^+$, 5), 213 (23), 124 (26), 107 (100),

(18) For heterobimetallic Ln and Y complexes in multifunctional asymmetric catalysis, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419.

91 (31), 79 (25), 77 (16); HRMS calcd for ($C_{15}H_{14}O_2S$) 258.0715, found 258.0782; TLC $R_f$ 0.37 (EtOAc/hexane, 1:6); HPLC $t_R$ 19.55 min (*S*), 23.66 min (*R*) (Chiralcel AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda = 254$ nm). After kinetic resolution: 19.75 min (*S*, minor, 2.59%), 23.92 min (*R*, major, 97.41%). $[\alpha]_D^{28}$ −82.32 (*c* 1.0, $CHCl_3$) for 95% ee; $[\alpha]_D^{25}$ +141.9 (*c* 1.0, MeOH) for 78% ee. The absolute configuration was deduced to be *R* according to the sign of optical rotation; mp 83−85 °C.

***S*-Benzyl Oxo-phenyl-thioacetate 8d′.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J = 8.0$, 2H), 7.66 (td, $J = 8.0$, 0.8, 1H), 7.50 (t, $J = 7.6$, 2H), 7.38−7.28 (m, 5H), 4.28 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.1, 186.0, 136.4, 134.9, 131.6, 130.8, 129.0, 128.8, 128.75, 127.6, 33.3; MS (EI, 70 eV) ($C_{15}H_{12}O_2S$, 256) 256 ($M^+$, 3), 228 (53), 105 (100), 91 (17), 77 (29); TLC $R_f$ 0.39 (EtOAc/hexane, 1:28); Anal. calcd for $C_{15}H_{13}O_3S$: C, 70.29; H, 4.72. Found: C, 70.52; H, 4.48.

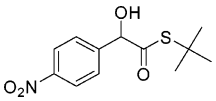
**Representative Procedure for Preparation of *S*-*t*-Butyl α-Hydroxythioesters.** To a solution of a methyl mandelate derivative (5 mmol) in $CH_3CN$ (10 mL) was added $VOCl_3$ (0.09 mL, 0.5 mmol) under oxygen atmosphere. After having been stirred for several hours, the reaction mixture was concentrated under reduced pressure, and the crude ketoester product was purified by column chromatography (eluent: hexane) on silica gel. The purified α-ketoester (2 mmol) was treated with aqueous KOH (4 mmol, 224 mg in 4 mL of $H_2O$) in EtOH (8 mL) to effect saponification. After acidification of the reaction mixture with 1 N HCl (5 mL) at 0 °C, the crude acid mixture was then extracted with ether (3 × 15 mL). The combined organic layers were concentrated, dried ($MgSO_4$), and evaporated. The resultant α-ketoacid (2 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and was then cooled to 0 °C. To this solution was added oxalyl chloride (2.5 mL, 2 mmol) under nitrogen. After having been stirred for 30 min, the reaction mixture was treated with a cooled mixture of anhydrous *t*-butanethiol (1.8 mL, 2 mmol) and dry $Et_3N$ (2.7 mL, 2 mmol) at 0 °C and then gradually warmed to ambient temperature. After completion of the reaction, the mixture was concentrated under reduced pressure, and the crude thioester was taken up by ether (30 mL). The concentrated residue was purified by column chromatography (hexane/EtOAc, 9:1) on silica gel. The purified α-keto-thioesters (2 mmol) were dissolved in THF (2 mL) and then treated with $NaBH_4$ (18.9 mg, 0.5 mmol). After completion of the reaction, the reaction mixture was acidified with 1 N HCl at 0 °C. Ether (15 mL) was added, and the organic layer was collected. The aqueous layer was separated and extracted with ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The crude α-hydroxythioester was purified by column chromatography (hexane/$Et_2O$, 8:2) on silica gel.

**Representative Procedure for Asymmetric Aerobic Oxidation of *S*-*t*-Butyl α- Hydroxythioesters**. To a 50 mL, two-necked, round-bottomed flask was placed monomer catalyst **4** (0.05 mmol, 5 mol %) or cluster **5** (0.0125 mmol, 1.25 mol %) in oxygen-saturated toluene (3 mL) under oxygen atmosphere. The reaction flask was vacuum-evacuated at 15 Torr for 20 s and then filled with an oxygen balloon (150 mL). A solution of a α-hydroxythioester (1 mmol) in oxygen-saturated toluene (2 mL) was added by cannula, and the resulting dark brown mixture was stirred at ambient temperature. The reaction progress was monitored by $^1$H NMR spectroscopy to determine the extent of oxidative conversion. The enantiomeric excess of the kinetically resolved product was determined by chiral HPLC analysis after filtration of the reaction aliquot (100 $\mu$L) over a short plug of silica gel ($Et_2O$ or $CH_2Cl_2$ as eluent). Upon reaching optimal resolution of the asymmetric oxidation (50−51% conversion), the reaction mixture was concentrated under reduced pressure. The resulting residue was loaded directly on top of an eluent-filled silica gel column and purified by flash column chromatography. The enantiomeric excess of the pure, resolved α-hydroxythioester was analyzed again by chiral HPLC analysis.

***S*-*t*-Butyl Hydroxyphenyl-thioacetate 8c.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.35 (m, 5H), 5.10 (s, 1H), 3.54 (s, 1H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.91, 138.5, 128.6, 127.1, 79.9, 48.9, 29.8; MS (EI, 70 eV) ($C_{12}H_{16}O_2S$, 224.3) 224 ($M^+$, 5), 107 (100), 79 (38), 57 (25); High resolution MS calcd for ($C_{12}H_{16}O_2S$) 224.0871, found 224.0944; TLC $R_f$ 0.36 (EtOAc/hexane, 2:8); HPLC $t_R$ 10.5 min (*S*), 12.1 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda = 254$ nm). After kinetic resolution: 10.7 min (minor, 1.38%), 12.2 (major, 98.62%); $[\alpha]_D^{25}$ +48.38 (*c* 1.0, MeOH) for 98% ee; mp 59−61 °C.

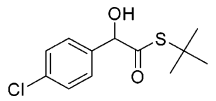
***S*-*t*-Butyl Oxo-phenyl-thioacetate 8c′.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J = 7.2$, 2H), 7.62 (t, $J = 7.4$, 1H), 7.49 (t, $J = 7.6$, 2H), 1.59 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.6, 187.1, 134.6, 131.6, 130.5, 128.7, 49.0, 29.6; MS (EI, 70 eV) ($C_{12}H_{14}O_2S$, 222.3) 222 ($M^+$, 13), 105 (100), 219 (29), 77 (22), 57 (18); TLC $R_f$ 0.45 (EtOAc/hexane, 1:9).

***S*-*t*-Butyl Hydroxy-(4-nitrophenyl)-thioacetate 16.**[19a,b]



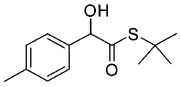

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J = 8.6$, 2H), 7.59 (d, $J = 8.7$, 2H), 5.21 (s, 1H), 1.42 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.4, 147.9, 145.4, 127.8, 123.7, 78.9, 49.5, 29.7 MS (EI, 70 eV) ($C_{12}H_{15}NO_4S$, 269.3) 269 ($M^+$, 4), 153 (100), 57 (85), 136 (30), 106 (20), 77 (15); TLC $R_f$ 0.31 (EtOAc/hexane, 2:8); HPLC $t_R$ 17.2 min (*S*), 20.6 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda = 254$ nm). After kinetic resolution: 17.0 min (minor, 0.88%), 20.4 min (major, 99.12%); $[\alpha]_D^{25}$ −40.8 (*c* 1.0, MeOH) for 98% ee; mp 73−76 °C.

***S*-*t*-Butyl (4-Chlorophenyl)-hydroxythioacetate 17.**[19a,b]




$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53−7.31 (m, 4H), 5.29 (s, 1H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.4, 137.0, 134.5, 128.8, 128.5, 79.2, 49.2, 29.8; MS (EI, 70 eV) ($C_{12}H_{15}ClO_2S$, 258.8) 259 ($M^+$, 4), 141 (100), 57 (38), 143 (34), 77 (36), 113 (12); High resolution MS calcd for ($C_{12}H_{15}ClO_2S$) 258.0481, found 258.0463; TLC $R_f$ 0.29 (EtOAc/hexane, 2:8); HPLC $t_R$ 11.5 min (*S*), 13.4 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda = 254$ nm). After kinetic resolution: 11.0 min (minor, 1.96%), 13.1 min (major, 98.04%); $[\alpha]_D^{25}$ −53.6 (*c* 1.0, MeOH) for 96% ee; mp 88−91 °C.

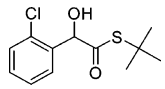
***S*-*t*-Butyl Hydroxy-*p*-tolyl-thioacetate 18.**[19a,b]




$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27−7.17 (m, 4H), 5.07 (s, 1H), 2.35 (s, 3H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.0, 138.4, 135.6, 129.3, 127.1, 79.7, 48.7, 29.8, 21.2; MS (EI, 70 eV) ($C_{13}H_{18}O_2S$, 238.4) 238 ($M^+$, 4), 121 (100), 93 (30), 77 (17), 57 (15); TLC $R_f$ 0.32 (EtOAc/hexane, 2:8); HPLC $t_R$ 12.1 (*S*) min, 15.8 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda = 254$ nm). After kinetic resolution: 11.4 min (minor, 3.28%), 15.8 min (major, 96.71%); $[\alpha]_D^{25}$ −58.6 (*c* 1.0, MeOH) for 93% ee; mp 72−75 °C.

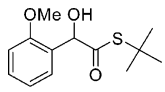
(19) (a) Douglas, K. T.; Demircioglu, H. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1951. (b) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151. (c) Aggarwal, V. K.; Thomas, A.; Franklin, R. J. *J. Chem. Soc., Chem. Commun.* **1994**, *14*, 1653.

***S*-*t*-Butyl (2-Chlorophenyl)-hydroxythioacetate 19.**



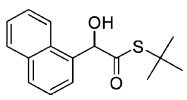
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.35 (m, 2H), 7.29−7.26 (m, 2H), 5.50 (s, 1H), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.0, 136.3, 133.7, 129.9, 129.8, 129.3, 127.2, 76.9, 49.0, 29.7; MS (EI, 70 eV) ($C_{12}H_{15}ClO_2S$, 258.8) 259 ($M^+$, 4), 141 (100), 57 (40), 143 (36), 77 (20), 125 (10); High resolution MS calcd for ($C_{12}H_{15}ClO_2S$) 258.0481, found 258.0470; TLC $R_f$ 0.30 (EtOAc/hexane, 2:8); HPLC $t_R$ 10.4 min (*S*), 12.1 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda$ = 254 nm). After kinetic resolution: 10.5 min (minor, 0.44%), 12.2 min (major, 99.50%); $[\alpha]_D^{25}$ +52.1 (*c* 1.0, MeOH) for 99% ee; mp 67−68 °C.

***S*-*t*-Butyl Hydroxy-(2-methoxy-phenyl)-thioacetate 20.**



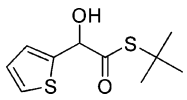
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33−7.27 (m, 2H), 6.99−6.89 (m, 2H) 5.21 (s, 1H), 3.84 (s, 3H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.1, 157.1, 130.0, 129.7, 127.2, 120.8, 111.2, 55.3, 48.0, 29.7; MS (EI, 70 eV) ($C_{13}H_{18}O_3S$, 254.4) 254 ($M^+$, 5), 137 (100), 107 (36), 57 (10); High resolution MS calcd for ($C_{13}H_{18}O_3S$) 254.0977, found 254.1012; TLC $R_f$ 0.33 (EtOAc/hexane, 2:8); HPLC $t_R$ 16.7 min (*S*), 18.8 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda$ = 254 nm). After kinetic resolution: 16.7 min (minor, 0.89%) 18.7 (major, 99.11%); $[\alpha]_D^{25}$ +84.36 (*c* 1.0, MeOH) for 98% ee; mp 56−58 °C.

***S*-*t*-Butyl Hydroxynaphthalen-1-yl-thioacetate 21.**



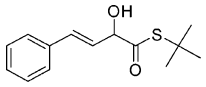
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 7.8, 1H), 7.89−7.86 (m, 2H), 7.55−7.45 (m, 4H), 5.66 (s, 1H), 3.86 (s, 1H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.7, 134.0, 134.1, 131.0, 129.6, 128.7, 127.4, 126.5, 125.8, 125.1, 123.9, 79.0, 48.9, 29.8; MS (EI, 70 eV) ($C_{16}H_{18}O_2S$, 274.4) 274 ($M^+$, 5), 156 (100), 129 (54), 120 (38), 118 (22), 57 (10); High resolution MS calcd for ($C_{16}H_{18}O_2S$) 274.1028, found 274.1020; TLC $R_f$ 0.30 (EtOAc/hexane, 2:8); HPLC $t_R$ 23.0 min (*S*), 26.6 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 4:96, 1.0 mL/min, $\lambda$ = 254 nm). After kinetic resolution: 21.7 min (minor, 2.41%), 24.8 min (major, 97.59%); $[\alpha]_D^{25}$ −100.5 (*c* 1.0, MeOH) for 95% ee; mp 86−89 °C.

***S*-*t*-Butyl Hydroxythiophen-2-yl-thioacetate 22.**



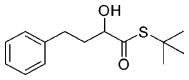
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.31 (dd, $J$ = 4.7, $J$ = 1.0, 1H), 7.21 (d, $J$ = 3.6, 1H), 7.00 (dd, $J$ = 4.9, 3.6, 1H), 5.35 (s, 1H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.6, 141.4, 126.8, 126.5, 126.4, 75.5, 48.9, 29.7 MS (EI, 70 eV) ($C_{10}H_{14}O_2S$, 230.4) 230 ($M^+$, 4), 113 (100), 84 (33), 57 (17); High resolution MS calcd for ($C_{10}H_{14}O_2S_2$) 230.0435, found 230.0432; TLC $R_f$ 0.35 (EtOAc/hexane, 2:8); HPLC $t_R$ 12.3 min (*S*), 16.1 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 6:94, 1.0 mL/min, $\lambda$ = 254 nm). After kinetic resolution: 11.7 min (minor, 0.73%), 15.1 min (major, 99.27%); $[\alpha]_D^{25}$ −47.84 (*c* 1.0, MeOH) for 98% ee; mp 54−55 °C.

***S*-*t*-Butyl 2-Hydroxy-4-phenyl-but-3-enethioate 23.**



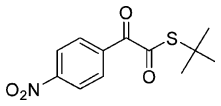
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42−7.27 (m, 5H), 6.77 (d, $J$ = 15.8, 1H), 6.19 (dd, $J$ = 15.8, 6.8, 1H), 4.76 (d, $J$ = 6.8, 1H), 3.41 (bs, 1H), 1.55 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.4, 136.1, 134.0, 128.6, 128.1, 126.8, 125.7, 78.6, 49.0, 29.9; MS (EI, 70 eV) ($C_{14}H_{18}O_2S$, 250.4) 250 ($M^+$, 5), 133 (100), 115 (30), 57 (19), 77 (12); High resolution MS calcd for ($C_{14}H_{18}O_2S$) 250.1028, found 250.1033; TLC $R_f$ 0.34 (EtOAc/hexane, 2:8); HPLC $t_R$ 29.6 min (*S*), 39.9 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 2:98, 1.0 mL/min, $\lambda$ = 254 nm). After kinetic resolution: 36.7 min (major, 99%); $[\alpha]_D^{26}$ +203.4 (*c* 1.0, MeOH) for 99% ee; mp 104−106 °C.

***S*-*t*-Butyl 2-Hydroxy-4-phenyl-thiobutanoate (24).**[20]



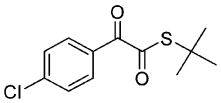
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32−7.18 (m, 5H), 4.19−4.15 (m, 1H), 3.19 (d, $J$ = 5.6, 1H, OH), 2.80−2.76 (m, 2H), 2.18−2.12 (m, 1H), 1.97−1.79 (m, 1H), 1.51 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.9, 141.1, 128.5, 128.4, 126.0, 76.8, 48.3, 37.2, 30.8, 29.9; MS (EI, 70 eV) ($C_{14}H_{20}O_2S$, 252.4) 252 ($M^+$, 100), 225 (18), 197 (20), 147 (10), 116 (10), 90 (15), 56 (10); High resolution MS calcd for ($C_{14}H_{20}O_2S$) 252.1184, found 252.1183; TLC $R_f$ 0.42 (EtOAc/hexane, 2:8); HPLC $t_R$ 19.8 min (*S*), 22.2 min (*R*) (Chiralpak AD-H, *i*-PrOH/hexane, 2:98, 1.0 mL/min, $\lambda$ = 254 nm). After kinetic resolution: 20.3 min (minor, 1.66%), 22.6 (major, 98.34%); $[\alpha]_D^{25}$ +88.38 (*c* 1.0, MeOH) for 97% ee.

***S*-*t*-Butyl (4-Nitrophenyl)-oxo-thioacetate 16′.**



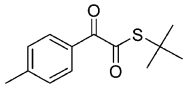
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.33 (d, $J$ = 8.5, 2H), 8.26 (d, $J$ = 8.5, 2H), 1.60 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.3, 185.1, 151.0, 136.5, 131.7, 123.7, 49.5, 29.5; MS (EI, 70 eV) ($C_{12}H_{13}NO_4S$, 267.3) 267 ($M^+$, 4), 57 (100), 150 (57), 104 (25), 76 (21); High resolution MS calcd for ($C_{12}H_{13}NO_4S$) 267.0565, found 267.0582; TLC $R_f$ 0.42 (EtOAc/hexane, 1:9).

***S*-*t*-Butyl (4-Chlorophenyl)-oxo-thioacetate 17′.**[21]



$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 8.6, 2H), 7.46 (d, $J$ = 8.6, 2H), 1.58 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.2, 185.7, 141.4, 132.1, 129.2, 49.1, 29.6; MS (EI, 70 eV) ($C_{12}H_{13}ClO_2S$, 256.8) 256 ($M^+$, 5), 139 (100), 144 (38), 111 (36), 57 (25); TLC $R_f$ 0.41(EtOAc/hexane, 1:9).

***S*-*t*-Butyl Oxo-*p*-tolyl-thioacetate 18′.**[21]



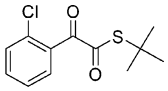
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 8.2, 2H), 7.28 (d, $J$ = 8.1, 2H), 2.42 (s, 3H), 1.58 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$)

(20) For the corresponding *S*-phenyl thioester, see: Berenguer, R.; Cavero, M.; Garcia, J.; Munoz, M. *Tetrahedron Lett.* **1998**, *39*, 2183.

(21) (a) Lapkin, E. A. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 915. (b) Ibid, *Zh. Org. Khim.* **1977**, *13*, 996.

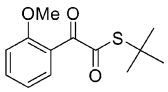
$\delta$ 193.9, 186.8, 145.9, 130.7, 129.5, 129.1, 48.9, 29.7, 21.9; MS (EI, 70 eV) ($C_{13}H_{16}O_2S$, 236.3) 236 ($M^+$, 5), 119 (100), 91 (35), 57 (17), 65 (15); TLC $R_f$ 0.42 (EtOAc/hexane, 1:9).

***S-t*-Butyl (2-Chlorophenyl)-oxo-thioacetate 19′.**



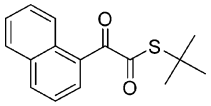
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 7.6, 2H), 7.49−7.42 (m, 1H), 7.39−7.35 (m, 1H), 1.57 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 191.7, 188.8, 133.7, 133.5, 133.2, 131.4, 130.4, 126.9, 49.0, 29.5; MS (EI, 70 eV) ($C_{12}H_{13}ClO_2S$, 256.8) 256 ($M^+$, 5), 139 (100), 144 (38), 57 (35), 75 (16); High resolution MS calcd for ($C_{12}H_{13}ClO_2S$) 256.0325, found 256.0334; TLC $R_f$ 0.41 (EtOAc/hexane, 1:9).

***S-t*-Butyl (2-Methoxyphenyl)-oxo-thioacetate 20′.**[21]



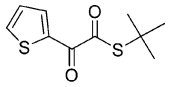
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 7.6, 1H), 7.55 (t, $J$ = 8.2, 1H), 7.06 (t, $J$ = 7.6, 1H), 6.97 (d, $J$ = 8.2, 1H), 3.85 (s, 3H), 1.59 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.3, 189.5, 159.8, 135.6, 131.3, 123.2, 121.1, 112.0, 55.7, 48.7, 29.8; MS (EI, 70 eV) ($C_{13}H_{16}O_3S$, 252.3) 252 ($M^+$, 4), 135 (100), 77 (32), 57 (17); TLC $R_f$ 0.43 (EtOAc/hexane, 1:9).

***S-t*-Butyl Naphthalen-1-yl-oxo-thioacetate 21′.**[21]



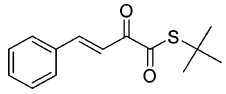
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.78 (d, $J$ = 8.5, 1H), 8.09 (d, $J$ = 8.2, 1H), 8.04 (d, $J$ = 7.2, 1H), 7.90 (d, $J$ = 8.2, 1H), 7.66−7.53 (m, 3H), 1.62 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 194.1, 189.7, 135.1, 133.9, 133.3, 131.1, 128.74, 128.68, 128.0, 126.8, 125.5, 124.1, 49.1, 29.6; MS (EI, 70 eV) ($C_{16}H_{16}O_2S$, 272.4) 272 ($M^+$, 4), 155 (100), 127 (56), 57 (15); TLC $R_f$ 0.42 (EtOAc/hexane, 2:8).

***S-t*-Butyl Oxo-thiophen-2-yl-thioacetate 22′.**[22]



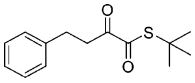
$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13 (d, $J$ = 3.9, 1H), 7.81 (d, $J$ = 3.9, 1H), 7.18 (dd, $J$ = 4.0, 1H), 1.55 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.3, 177.7, 138.0, 137.5, 136.1, 128.5, 48.1, 29.4; MS (EI, 70 eV) ($C_{10}H_{12}O_2S_2$, 228.3) 228 ($M^+$, 15), 111 (100), 57 (35); TLC $R_f$ 0.44 (EtOAc/hexane, 1:9).

***S-t*-Butyl 2-Oxo-4-phenyl-but-3-enethioate 23′.**



$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 16.1, 1H), 7.64 (dd, $J$ = 7.3, 1.3, 2H), 7.44−7.39 (m, 4H), 1.55 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.9, 184.0, 148.4, 134.4, 131.6, 129.1, 117.5, 47.8, 29.5; MS (EI, 70 eV) ($C_{14}H_{16}O_2S$, 284.3) 284 ($M^+$, 4), 131 (100), 103 (35), 77 (15), 57 (10); High resolution MS calcd for ($C_{14}H_{16}O_2S$) 248.0871, found 248.0882; TLC $R_f$ 0.44 (EtOAc/hexane, 1:9).

***S-t*-Butyl 2-Oxo-4-phenyl-thiobutanoate (24′).**[23]



$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30−7.18 (m, 5H), 3.11 (t, $J$ = 7.4, 2H), 2.93 (t, $J$ = 7.5, 2H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.6, 191.3, 140.2, 128.5, 128.4, 126.3, 47.8, 37.8, 29.4, 29.0; MS (EI, 70 eV) ($C_{14}H_{18}O_2S$, 250.4) 250 ($M^+$, 70), 238 (10), 204 (40), 166 (20), 133 (100), 104 (40), 90 (20), 57 (16); TLC $R_f$ 0.49 (EtOAc/hexane, 2:8).

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**Supporting Information Available:** X-ray data for **1′**, **4′**, and **5** and spectroscopic characterization for vanadyl(V) complexes **1**−**4** and **5**, kinetic resolution products **6**−**15**, oxidation products **6′**−**15′**, and HPLC traces of racemic and resolved products **8a**−**e** and **9**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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