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Asymmetric Aerobic Oxidation of α-Hydroxy Acid Derivatives Catalyzed by Reusable, Polystyrene-Supported Chiral *N*-Salicylidene Oxidovanadium *tert*-Leucinates

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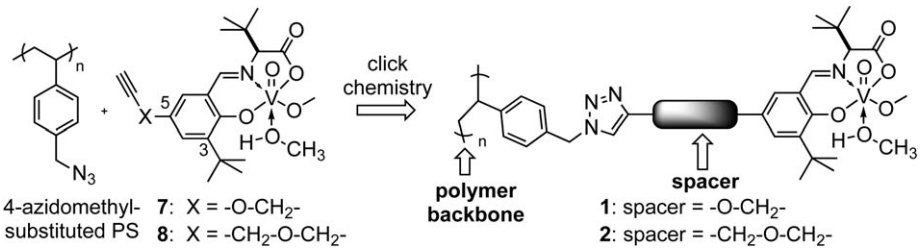
Abstract: The direct immobilization of two different C-5-propargyl ether-modified, chiral *N*-salicylidene vanadyl(V) *tert*-leucinates onto 4-azidomethyl-substituted polystyrene by click chemistry was examined. Among the eight different solvents investigated, the resulting polystyrene-supported catalysts promote the asymmetric, aerobic oxidation of α-hydroxy (thio)esters and amides with enantioselectivities of up to 99% *ee* (selectivity factor up to 41) in chloroform. These polystyrene-supported catalysts can be readily recovered by filtration and reused for at least four consecutive runs without discernible loss of reactivity and enantioselectivity.

Keywords: click chemistry; direct immobilization; enantioselective aerobic oxidation; recyclable catalysts; vanadyl compounds

Transition metal complex-catalyzed asymmetric aerobic oxidations[1] have recently emerged as highly efficient methods to obtain optically pure alcohols along with kinetic resolution, especially in cases where asymmetric reduction of ketones could not provide sufficiently high enantioselectivity. Significant progress in this area has been made with a variety of chiral metal catalysts.[2] In particular, enantiomerically pure α-hydroxy carboxylic acid and mandelic acid derivatives are ubiquitous building blocks in enantioselective synthesis and the synthesis of biologically active compounds such as semi-synthetic penicillin, cephalosporin, anti-thrombotic and anti-obesity agents.[3] With the extension of interest in new organic transformations by using vanadyl species,[4,5] we and Toste's group have developed highly enantioselective aerobic oxidations catalyzed by chiral *N*-salicylidene vanadyl(V) carboxylates[6] and alocholates,[7] respectively, for the preparation of optically enriched α-hydroxy carboxylic acid derivatives. The oxidative kinetic resolution strategy has also shown its potential in the syntheses of biologically relevant α-hydroxy phosphonates,[8] α-hydroxy ketones[9], enantioenriched cyclic ethers[10] and an antitumor agent – octalactin A.[11] Moreover, chiral vanadyl(V) complexes are also an effective catalysts in asymmetric sulfide oxidation[12] and oxidative coupling of 2-naphthols.[13] In addition, these complexes acts as a DNA photocleavage agent[14] and metal ion-specific (e.g., K^+ and Ag^+) transporters.[15]

Although these homogenous transition metal complexes offer high levels of reactivity and enantioselectivity, their applications in the chemical and pharmaceutical industry remain somewhat limited due to their relatively high cost, difficulties in separation and contamination of metal complexes or metal salts either in waste or the end products. Consequently, their immobilization on solid supports has attracted enormous interest, as this allows for facile separation of the heterogeneous catalysts from products, enables efficient recovery and reuse of catalysts and minimizes pollution occurring from metal complexes.[16] Despite these options and numerous applications of chiral vanadium complexes, only a few approaches for their immobilization have been described.[17] Among these, the Jones group reported polymer-supported, tridentate vanadyl complexes derived from salicylaldehydes and optically active α-amino alcohols.[17d] Preimmobilization of the Schiff base ligands by a copolymerization method followed by *in-situ* introdcution of the vanadyl(V) units led to the resulting heterogeneous catalysts for oxidative kinetic resolution of α-hydroxy esters with good to moderate enantioselectivities albeit with a somewhat limited substrate scope.

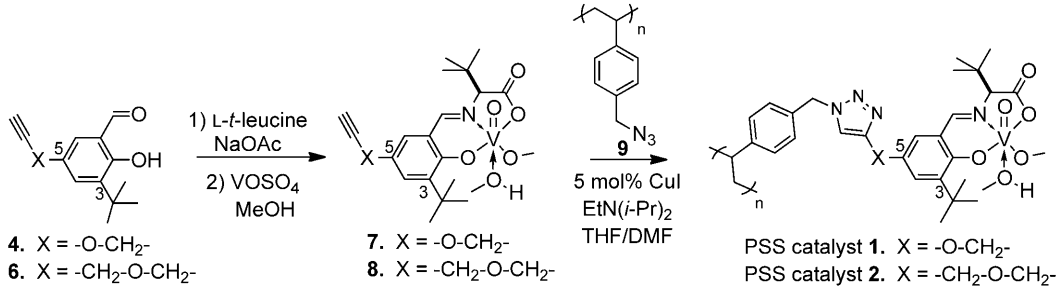


Scheme 1. Synthetic design of heterogeneous, PS-supported chiral vanadyl catalysts **1** and **2** by click chemistry.

We report here for the first time, the *direct immobilization* of chiral vanadyl(V) *tert*-leucinates on a polystyrene (PS) support through the copper(I)-catalyzed azide-alkyne cycloaddition[18] reaction (i.e., click chemistry[19]) and their applications in the heterogeneous asymmetric aerobic oxidation of α-hydroxy acid derivatives. We envisaged that click chemistry, an efficient and mild immobilization technique,[20] should lead to economical, eco-friendly and recyclable polymer-supported vanadyl catalysts (**1** and **2**) without any freely dissociated metal complexes. In addition, the anchoring of an azido-bearing polymer at the C-5 position of the catalysts **7** or **8** through an ether spacer should avoid any interference of the polymer backbone with the catalytic site (Scheme 1).

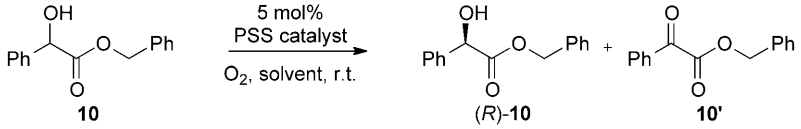
Propargyl ether-modified salicylaldehydes **4** and **6** were readily prepared in two steps from 2-*tert*-butylbenzene-1,4-diol and 3-*tert*-butyl-2-hydroxybenzaldehyde, respectively, in good yields.[21] They can be transformed into the corresponding chiral vanadyl(V) complexes **7** and **8** by using our own protocol as described previously with L-*tert*-butylglycine and $VO(SO_4)$. Conversely, azido-substituted resin **9** was prepared by treating chloromethyl-polystyrene with sodium azide. Alkyne-modified chiral oxidovanadium complexes were then grafted onto the azido functionalized resin by a copper(I)-catalyzed cycloaddition, affording the immobilized catalysts **1** and **2** (Scheme 2). Notably, they can also be prepared by first carrying out the click chemistry followed by vanadyl complex formation with similar efficiency. Complete consumption of the azido-functionalized resin during the cycloaddition with alkyne-modified catalysts was confirmed by the complete disappearance of the typical azide N≡N stretching band at 2082 cm^{-1} on IR spectroscopy, along with the formation of new characteristic bands at 1619–1623 cm^{-1} (C=N), 1548–1550 cm^{-1} (COO) and 982–995 cm^{-1} (V=O) in **1** and **2**. The vanadium loadings in catalyst **1** and **2** were found to be 0.74 mmol g^{-1}(3.74 wt%) and 0.78 mmol g^{-1}-(3.98 wt%), respectively, as determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES).[21] Binding energies of V $2p_{3/2}$ for the PSS catalysts **1** and **2** were determined to be 517.3 eV and 518.8 eV, respectively, by X-ray photoelectron spectroscopy (XPS), which are attributed to V(V) species.[13d,22]

By following our optimal homogeneous catalytic asymmetric aerobic oxidation protocol,[6] we tested the newly developed heterogeneous PSS catalysts **1** and **2** for the kinetic resolution of racemic benzyl mandelate **10** as a model substrate by using molecular oxygen as an oxidant, Table 1. The aerobic oxidation of **10**, catalyzed by PSS catalyst **1**, was completed in 60 h at 57% conversion (entry 1, Table 1). In marked contrast, the corresponding analoguous PSS catalyst **2** is more reactive, which effects 51% conversion of the same substrate within 40 h (entry 2, Table 1). In addition, the enantioselectivity for the asymmetric oxidation of *O*-benzyl mandelate catalyzed by **2** ($k_{rel}=10$) is significantly higher than that catalyzed by **1** ($k_{rel}=6$). Since the extent of resin swelling highly depends on solvent attributes, we paid much more attention to identify an optimal solvent for this reaction by using PSS catalyst **2**. After screening several polar coordination (TBME, CH_3CN, and THF) and non-polar



Scheme 2. Preparation of PSS catalysts **1** and **2**.

Table 1. Effect of PSS catalysts **1** or **2** and solvents on the asymmetric aerobic oxidation of racemic benzyl mandalate **10**.



Entry	Catalyst/Solvent	Time [h]	Conversion [%][a]	% *ee*[b] (Yield[c] [%])	k_{rel}[d]
1	**1**/toluene	60	57	68 (40)	6
2	**2**/toluene	40	52	70 (45)	10
3	**2**/TBME	80	51	65 (46)	8
4	**2**/CH_3CN	168	44	29 (53)	3
5	**2**/THF	80	trace	n.d.	n.d.
6	**2**/C_6H_5Cl	48	55	82 (42)	13
7	**2**/CCl_4	112	63	75 (34)	6
8	**2**/CH_2Cl_2	26	56	90 (40)	17
9	**2**/$(CH_2Cl)_2$	50	55	79 (42)	11
10	**1**/$CHCl_3$	34	56	88 (41)	16
11	**2**/$CHCl_3$	22	57	96 (41)	24

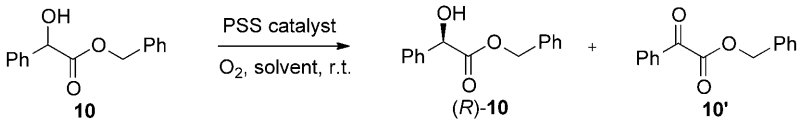
[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Determined by HPLC analysis on a Chiralcel AD-H column.
[c] Isolated, purified material for the alcohol by column chromatography.
[d] $k_{rel}=\ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where C is conversion and *ee* is enantiomeric excess.

(chlorobenzene and haloalkanes) solvents, a significant improvement in asymmetric induction was observed in chloroform ($k_{rel}=24$, entry 11 in Table 1). Under the optimal reaction conditions, PSS catalyst **1** was found to be less enantioselective ($k_{rel}=16$, entry 10 in Table 1) in comparison with PSS catalyst **2**.

The effect of catalyst loadings on enantioselectivity (Table 2) was further evaluated. It was found that catalyst loading of **2** at 2 mol% can still promote the aerobic oxidation of **10** without significant loss in reactivity and selectivity (entry 4, Table 2). Further decrease in catalyst loading to 1 mol% led to a sluggish reaction (80 h) and moderate enantioselectivity (69% *ee*, entry 5 in Table 2).

The substrate scopes for the kinetic resolution of mandelates by heterogeneous catalyst **2** with varying ester appendages were further examined (Table 3). The beneficial effect of an *O*-benzyl substituent ($k_{rel}=24$) over *O*-methyl (**11**, $k_{rel}=12$), *O*-ethyl (**12**, $k_{rel}=9$), and *O*-isopropyl (**13**, $k_{rel}=11$) substituents was observed. This finding prompted us to subsequently resolve *S*-benzyl and *N*-benzyl mandelates, **14** and **15**, under the optimal conditions. It was found that *N*-benzylmandelamide is more enantioselective towards asymmetric oxidation for catalyst **2** ($k_{rel}=41$) followed by *O*-benzyl mandelate, whereas *S*-benzyl thiomandelate was found to be the least enantioselective ($k_{el}=17$). Notably, oxidation of *N*-benzylmandelamide proceeded to 55% conversion, providing the (*R*)-enantio-

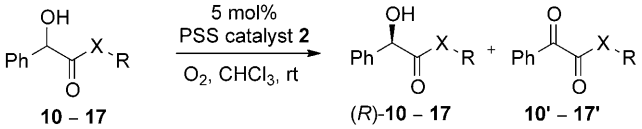
Table 2. Effect of catalyst loadings on kinetic resolution of **10**.



Entry	Catalyst Loading [mol%]	Time [h]	Conversion [%][a]	% *ee*[b] (Yield[c] [%])	k_{rel}[d]
1	5	22	57	96 (41)	24
2	4	22	56	94 (42)	23
3	3	23	55	91 (42)	21
4	2	27	53	83 (43)	17
5	1	80	51	69 (46)	10

[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Determined by HPLC analysis on a Chiralcel AD-H 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 is conversion and *ee* is enantiomeric excess.

Table 3. Effects of *O*-, *N*-, or *S*-substituents on the asymmetric aerobic oxidation of racemic mandelates by PSS catalyst **2**.



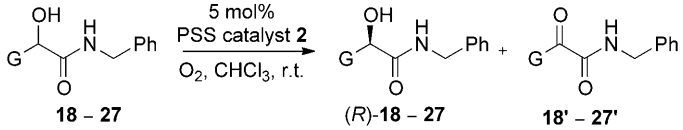
X-R	Time [h]	Conversion [%][a]	% *ee*[b] (Yield[c] [%])	k_{rel}[d]
OCH_2Ph (**10**)	22	57	96 (41)	24
OCH_3 (**11**)	28	58	87 (38)	12
OCH_2CH_3 (**12**)	28	61	87 (35)	9
O*i*Pr (**13**)	30	62	92 (34)	11
SCH_2Ph (**14**)	24	58	93 (39)	17
$NHCH_2Ph$ (**15**)	27	55	98 (43)	41
$NHCH(Ph)_2$ (**16**)	52	55	64 (42)	6
NH*i*Pr (**17**)	29	59	94 (38)	16

[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Determined by HPLC analysis on a Chiralcel AD-H 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 is conversion and *ee* is enantiomeric excess.

mer of **15** in 43% yield and 98% *ee* along with *N*-benzyl-benzoyl-formamide in 53% isolated yield. In marked contrast, substrates **16** ($k_{rel}=6$) and **17** ($k_{rel}=16$) bearing *N*-diphenylmethyl and *N*-isopropyl appendages are less reactive and selective than **15** towards asymmetric oxidation under optimal reaction conditions.

To probe further the substrate scope catalyzed by PSS catalyst **2**, a series of benzyl α-hydroxyamides bearing different α-aryl and alkyl groups was examined under the optimal aerobic oxidation conditions (Table 4). Among the three *para*-substituted phenyl derivatives examined, the substrate bearing an electron-donating *para*-methyl group **18** ($k_{rel}=19$) is slightly more selective than those with electron-withdrawing groups, *para*-chloro **19** ($k_{rel}=15$) and *para*-CF_3 **20** ($k_{rel}=13$). Substrates bearing *ortho*-methyl **21** ($k_{rel}=9$) and *ortho*-chloro **22** ($k_{rel}=17$) groups are less reactive (112 and 88 h) than the corresponding *para*-substituted counterparts. The kinetic resolution process also works well in the cases of α-1-naphthyl- and α-2-thiophenyl-containing analogues, leading to recovery of the (*R*)-enantiomers **23** and **24** in 90% *ee* ($k_{rel}=13$) and 91% *ee* ($k_{rel}=14$), respectively. The oxi-

Table 4. Effects of α-substituents on the asymmetric aerobic oxidation of racemic *N*-benzyl α-hydroxy-amides by catalyst **2**.



G/substrate	Time [h]	Conversion [%][a]	% *ee*[b] (Yield[c] [%])	k_{rel}[d]
4-$CH_3C_6H_4$/**18**	36	60	97 (37)	19
4-ClC_6H_4/**19**	30	62	97 (35)	15
4-$CF_3C_6H_4$/**20**	32	56	85 (42)	13
2-$CH_3C_6H_4$/**21**	112	58	80 (39)	9
2-ClC_6H_4/**22**	88	64	99 (33)	17
1-naphthyl/**23**	38	59	90 (39)	13
2-thiophenyl/**24**	22	59	91 (35)	14
(*E*)-PhCH=CH/**25**	8	56	86 (41)	14
cyclopropyl/**26**[e]	90	57	91 (40)	17
$(CH_3)_2CH$/**27**[e]	95	60	44 (38)	3

[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Determined by HPLC analysis on a Chiralcel AD-H 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 is conversion and *ee* is enantiomeric excess.
[e] Reactions are conducted at 40 °C.

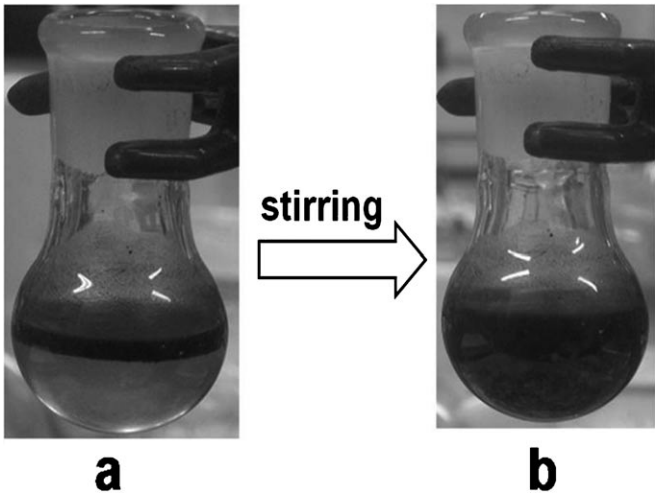


Figure 1. Photos for mixture containing (**a**) only PSS catalyst **2** and (**b**) PSS catalyst **2** and substrate **10** in $CHCl_3$ with stirring.

dation of substrate **25** possessing a *trans*-cinnamyl group ($k_{rel}=14$) proceeded at a significantly faster rate (8 h) than those (30–112 h) of α-aryl analogues without any intervening epoxidation at the alkene moiety. Conversely, substrates bearing α-alkyl groups like **26** and **27** are somewhat inert at ambient temperature under the standard conditions. Nevertheless, the desired process can be effected at slightly elevated temperatures, albeit with prolonged reaction times (90–95 h). Notably, the selectivity factors of their oxidations catalyzed by **2** highly hinge on the steric effects of the α-alkyl groups. In comparison, the substrate **26** bearing a 2° α-cyclopropyl group ($k_{rel}=17$) is highly enantioselective as compared to that bearing an α-isopropyl group **27** ($k_{rel}=3$).

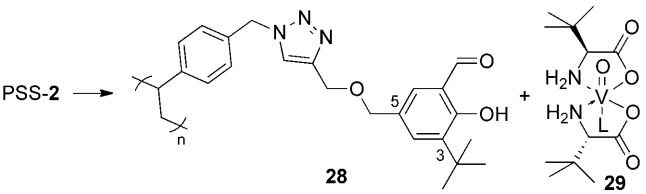
To demonstrate the recyclability and reusability of PSS catalyst **2**, the aerobic oxidation reactions of **10** by recovered catalyst were tested. Notably, PSS catalyst **2** is completely insoluble and floats on the surface of $CHCl_3$ (Figure 1, **a**). Nevertheless, it can be fully dispersed into $CHCl_3$ upon stirring with substrate **10** (Figure 1, **b**).

After completion of each cycle, the catalyst **2** was filtered, washed with $CHCl_3$, and dried under vacuum. Notably, the recycled catalyst **2** was reused for four consecutive runs on three representative substrates (**10**, **15**, and **23**) without significant erosion in reactivity and selectivity (Table 5). The vanadium loading of the recovered catalyst **2** after the 4th cycle was then checked again by ICP-AES MS. About 9% loss of vanadium from PSS catalyst **2** was observed in the recycling experiments. In principle, the hydrolysis of PSS catalyst **2** would lead to PSS salicylaldehyde **28** and *tert*-leucine-based vanadyl complex **29** (Scheme 3). Nevertheless, **28** can be readily converted back to PSS-**2**. Notably, a control experiment using

Table 5. Recycling experiments for enantioselective aerobic oxidations of racemic substrates **10**, **15** and **23** by PSS-**2**.

Entry	Cycle	Substrate	Time [h]	Conversion [%][a]	% *ee*[b] (yield[c] [%])	k_{rel}[d]
1	1	**10**	22	57	96 (41)	24
2	2[e]	**10**	23	55	92 (42)	23
3	3[e]	**10**	26	59	97 (38)	21
4	4[e]	**10**	27	54	89 (42)	21
5	1	**15**	27	55	98 (43)	41
6	2[e]	**15**	30	56	99 (42)	41
7	3[e]	**15**	29	53	94 (45)	39
8	4[e]	**15**	30	54	96 (44)	39
9	1	**23**	38	59	90 (39)	13
10	2[e]	**23**	37	54	81 (43)	13
11	3[e]	**23**	44	58	86 (38)	11
12	4[e]	**23**	47	61	88 (36)	10

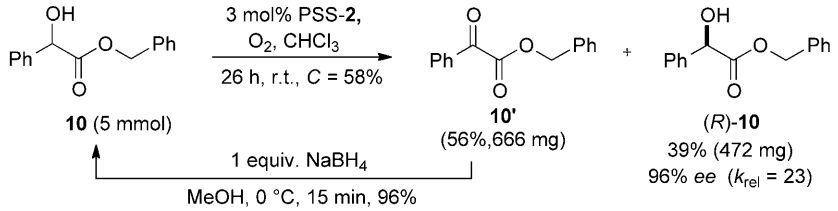
[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Determined by HPLC analysis on a Chiralcel AD-H column.
[c] Isolated, purified material for the alcohol by column chromatography.
[d] $k_{rel}=\ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where C is conversion and *ee* is enantiomeric excess.
[e] Recycled PSS catalyst **2** from the previous run was used.



Scheme 3. Potential leaching of vanadium by hydrolysis of PSS-**2**.

authentic complex **29** (5 mol%) for the aerobic oxidation of **10** was found to be completely inactive in $CHCl_3$ for 3 days, thus excluding its potential interference.

To demonstrate the synthetic utility of this protocol, a practical scale experiment (5 mmol) was performed (Scheme 4). With 3 mol% of PSS **2**, the desired (*R*)-benzyl mandelate **10** was obtained in 39% yield (472 mg) and 96% *ee* ($k_{rel}=23$). The oxidized product **10'** (56% yield) was then converted back to racemic **10** in 96% yield by treatment with a solution of $NaBH_4$ in MeOH at 0 °C in 15 min. Repetition of the sequences allowed the preparation of optically pure (*R*)-**10** in a reasonable quantity. Previously, we[6,13] and others[1] have demonstrated that during the aerobic oxidation event the molecular oxygen ultimately leads to water which has a negligible effect on the reaction rate. Therefore, the catalytic protocol can be carried out under an oxygen atmosphere on a practically large scale.



Scheme 4. Practical scale synthesis of (*R*)-**10** by kinetic resolution of **10** and the recycle of **10** by reduction of **10′**.

In conclusion, we have documented the first efficient immobilization of C-5-propargyl ether-modified chiral *N*-salicylidene vanadyl(V) *tert*-leucinates onto azido-functionalized PS by click chemistry. In addition, we have demonstrated for the first time that the resulting PSS catalysts promote aerobic oxidations of a broad range of α-hydroxy carboxylic acid derivatives smoothly with excellent enantioselectivities in $CHCl_3$. A practical scale synthesis of optically pure, mandelic acid derivatives can be made with 3 mol% loading of PSS-**2** in $CHCl_3$. Furthermore, the PSS-based catalysts can be readily recovered by filtration and reused without discernible loss of reactivity and enantioselectivity. The partially hydrolyzed catalyst observed after four runs can be readily converted back to the original entity.

Experimental Section

General Procedure for the Synthesis of Polystyrene-Supported (PSS) Vanadyl Catalysts 1 and 2

(Azidomethyl)polystyrene resin **9** (estimated loading of azide = 1.07 mmol g^{-1}, 935 mg, 1 mmol, 1 equiv.) was placed in 1:1 mixture of anhydrous DMF:THF (20 mL). To this suspension was added propargyl ether-modified vanadyl(V) methoxide complex **7** or **8** (1.5 mmol, 1.5 equiv.) followed by *N,N*-diisopropylethylamine (1.04 mL, 774 mg, 6 mmol, 6 equiv.) and copper(I) iodide (9.5 mg, 0.05 mmol, 0.05 equiv.). The resulting mixture was vigorously stirred at ambient temperature and the progress of the reaction was monitored by IR spectroscopy. After having been stirred for 68–70 h, the typical azide band at 2082 cm^{-1} in the IR spectrum had completely disappeared. The heterogeneous reaction mixture was then filtered and the solid was sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF:MeOH (1:1, 250 mL), MeOH (250 mL) and THF (250 mL). The solid was then placed in air-saturated MeOH (20 mL) and the mixture was refluxed under an oxygen atmosphere for 12 h and then gradually cooled to ambient temperature. The solid was filtered and dried under vacuum overnight to afford polystyrene supported chiral vanadyl(V) methoxide complex **1** or **2** (i.e., PSS catalyst **1** or **2**).

Data for PSS catalyst **1**: FT-IR (KBr): ν = 3384 (br), 1658, 1622 (C=N), 1599, 1547 (COO), 1420, 1338, 1202, 1153, 1045, 982 (V=O), 903, 757 cm^{-1}; elemental analysis (%) found: C 66.51, H, 6.65, N 5.35; ICP-AES MS (%): V, 3.71; catalyst loading = 0.95 mmol g^{-1} of resin; vanadium loading = 0.73 mmol g^{-1} of resin.

Data for PSS catalyst **2**: FT-IR (KBr): ν = 3336 (br), 2906, 2850, 1658, 1619 (C=N), 1548 (COO), 1452, 1334, 1206, 1167, 1077, 995 (V=O), 908, 841 cm^{-1}; elemental analysis (%) found: C 69.33, H 7.33, N 5.49; ICP-AES MS (%): V, 3.98; catalyst loading = 0.98 mmol g^{-1} of resin; vanadium loading = 0.78 mmol g^{-1} of resin.

Representative Procedure for the Asymmetric Aerobic Oxidation of Racemic α-Hydroxy Carboxylic Acid Derivatives by PSS-2

Into a 5-mL, two-necked, round-bottomed flask was placed PSS catalyst **2** (25.5 mg, 0.025 mmol, 5 mol%) in oxygen-saturated $CHCl_3$ (0.25 mL). A solution of α-hydroxy carboxylic acid derivative (0.5 mmol, 1 equiv.) in oxygen-saturated $CHCl_3$ (0.25 mL) was added and the resulting heterogeneous mixture was vigorously stirred at ambient temperature under an oxygen atmosphere. The reaction progress was monitored by ^1H NMR spectroscopy for percent conversion. Upon reaching 55–64% conversion, the reaction mixture was filtered through a sintered-glass funnel and the insoluble PSS catalyst **2** was washed with $CHCl_3$ (2 × 0.5 mL). The combined filtrates were 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 (EtOAc/hexanes). The enantiomeric excess of the pure, resolved α-hydroxy carboxylic acid derivative was analyzed by chiral HPLC analysis.

General Procedure for the Recovery of PSS Catalyst 2

Upon reaching 53–56% conversion, the reaction mixture was filtered through a sintered-glass funnel and the insoluble PSS catalyst **2** was washed with $CHCl_3$ (2 × 0.5 mL). The recovered PSS catalyst **2** was dried under vacuum overnight and then placed in MeOH (1.0 mL). The resulting suspension was purged with oxygen gas for 30 min. The insoluble catalyst was filtered, dried under vacuum for 30 min and used for the next run.

Acknowledgements

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