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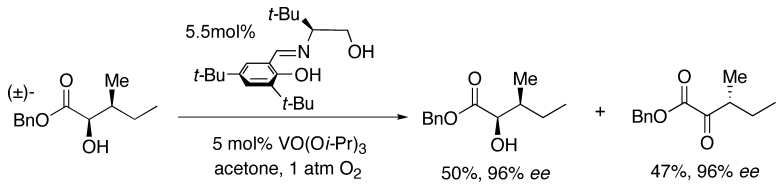

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Vanadium-Catalyzed Asymmetric Oxidation of α-Hydroxy Esters Using Molecular Oxygen as Stoichiometric Oxidant

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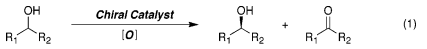
Secondary alcohols of defined absolute stereochemical configuration are key components for enantioselective synthesis. Kinetic resolution[1] of racemic secondary alcohols represents an attractive catalytic route to these optically pure building blocks, especially in cases where other methods[2] are not possible or provide insufficient enantiocontrol. Pioneering work by Rychnovsky demonstrated the utility of employing a catalytic asymmetric oxidant to effect the kinetic resolution of alcohols (eq 1).[3] More recently, the palladium(II)/(−)-sparteine system developed independently by Stoltz[4] and Sigman[5] has helped fuel interest in the field of asymmetric oxidation. Clearly, the ability to harvest atmospheric oxygen as a stoichiometric oxidant has extraordinary practical advantages.



(1)

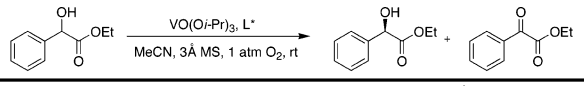
During the development of a Re(V)-catalyzed propargylic etherification, we noted the aerobic oxidation of a propargylic alcohol under the action of catalytic $VO(acac)_2$.[6,7] Given the wealth of coordination chemistry literature for vanadium, we became interested in exploring the possibility of employing chiral ligands to render the oxidation asymmetric. We now report our initial findings regarding a vanadium-catalyzed oxidative kinetic resolution of α-hydroxy esters using molecular oxygen as the terminal oxidant.

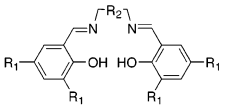
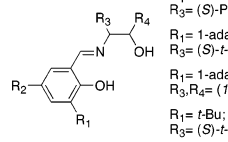
We began our investigation with α-hydroxy acid derivatives as substrates for kinetic resolution due to their importance in enantioselective synthesis.[2,8] Analytical experiments showed that catalyst systems based on tetradentate salen-type ligands failed to produce either efficient or selective oxidation catalysts (Table 1, entries 1−2). Moving to a tridentate ligand[9] with an *O,N,O*-binding motif produced a marked increase in stereoselectivity. Tuning of the steric and electronic parameters led to the selection of ligand **1**, derived from 3,5-di-*tert*-butylsalicylaldehyde and (*S*)-*tert*-leucinol (entry 7).

Optimization of the reaction conditions for the asymmetric oxidation allowed for further increases in stereoselectivity (for details see Supporting Information). Specifically, distilled solvent and molecular sieves were found to be unnecessary for efficient reactivity and selectivity. The best results were observed using acetone as solvent at ambient temperature without addition of molecular sieves, giving selectivity factors exceeding the accuracy of our analytical assay. Interestingly, our attempts to employ vanadium sources other than $VO(O\textit{i}\text{-}Pr)_3$ as catalyst precursors were met with unsatisfactory results. Particularly surprising in this regard was the poor performance of $VO(acac)_2$, a commonly used precatalyst for oxovanadium(V)-catalyzed transformations.[10]

Preparative-scale experiments were conducted to probe the scope of the vanadium-catalyzed asymmetric oxidation. The reaction of racemic ethyl mandelate under the optimized reaction conditions proceeded to 51% conversion after 10 h at ambient temperature, providing (*R*)-ethyl mandelate in 49% yield and 99% ee along with ethyl benzoylformate in 46% yield (Table 2, entry 1). Additionally, mandelate derivatives bearing electron-donating (entry 2) and electron-withdrawing (entry 3) para substituents are well tolerated.

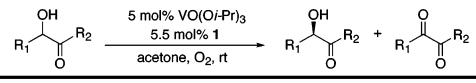
Table 1. Ligand Effects on the V-Catalyzed Resolution of Ethyl Mandelate[a]



entry	ligand (L*)	conversion[b]	ee ROH	s[c]
1	 R_1= *t*-Bu; R_2= (*1R,2R*)-1,2-diphenylethylenediamine	< 2	--	--
2	R_1= H; R_2= (*R*)-BINAM	30	0	1
3	 R_1= 1-adamantyl; R_2= Me; R_3= (*S*)-Ph; R_4= (*R*)-Ph	7	5	4
4	R_1= 1-adamantyl; R_2= Me; R_3= (*S*)-*t*-Bu; R_4= H	35	46	21
5	R_1= 1-adamantyl; R_2= Me; R_3,R_4= (*1S,2R*)-1-amino-2-indanol	51	86	33
6	R_1= *t*-Bu; R_2= NO_2; R_3= (*S*)-*t*-Bu; R_4= H	45	63	15
7	R_1= *t*-Bu; R_2= *t*Bu; R_3= (*S*)-*t*-Bu; R_4= H (1)	50	86	40

[a] Conditions: 8 mol % $VO(O\textit{i}Pr)_3$, 10 mol % ligand, 1 atm O_2, 4 h. [b] Conversion and ee determined by chiral GC analysis of crude reaction mixture. See Supporting Information for details. [c] $s = k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.

Table 2. Kinetic Resolution of α-Hydroxy Esters[a]



entry	R_1	R_2	time (h)	conversion	isolated yield[b]	ee[c]	*s*
1	Ph–	OEt	10	51%	49% (95%)	99% (*R*)	> 50
2	*p*-$MeOC_6H_4$–	OMe	5.5	62%	38% (69%)	95% (*R*)	13
3	*p*-$CF_3C_6H_4$–	OMe	4.0	57%	35% (88%)	98% (*R*)	29
4		OBn	16	57%	45% (90%)	92% (*R*)	18
5	 TMS	OEt	16	47%	53% (85%)	50% (*R*)	6
6		O*i*-Pr	90	55%	37% (86%)	98% (*R*)	30
7	 TBSO	OMe	144	51%	48% (95%)	90% (*R*)	42
8	 C_6H_5	OEt	72	48%	48% (88%)	90% (*R*)	34
9[d]	Ph–	NH*t*Bu	12	52%	48% (97%)	72% (*R*)	12

[a] Conditions: 5 mol % $VO(O\textit{i}\text{-}Pr)_3$, 5.5 mol % ligand, 1 atm O_2, 0.2 M substrate in acetone. [b] Isolated yield of enantioenriched alcohol after silica gel chromatography. Number in parentheses is the total combined yield of alcohol and ketone. [c] For determination of conversion, ee, and absolute configuration assignment, see Supporting Information. [d] Reaction conducted at 40 °C.

Efficient kinetic resolution is also possible with nonbenzylic substrates. Although increased reaction times are required, both simple alkyl substrates (entry 6) and those bearing pendant silyl ethers (entry 7) are smoothly resolved with good selectivity. Additionally, α-hydroxy amides are also viable substrates for resolution albeit at slightly elevated reaction temperatures (entry

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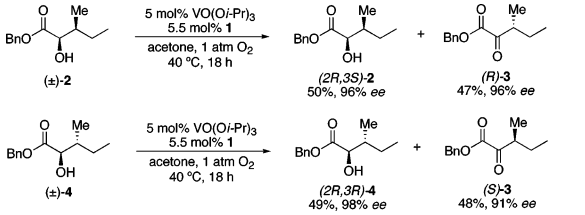
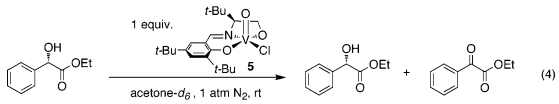
9).[11] Mindful of the known catalytic activity of vanadium−oxo complexes for alkene epoxidations,[12] we examined the performance of the vanadium-catalyzed asymmetric oxidation with regard to substrates bearing proximal olefins. Notably, both allylic and homoallylic substrates showed good stereoselectivity in the resolution event, demonstrating excellent chemoselectivity for alcohol oxidation over olefin epoxidation (entries 4, 8). Furthermore, alkynyl substituents allow for the resolution of a propargyl alcohol (entry 5) albeit with decreased selectivity.

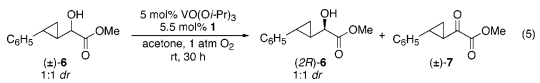
A kinetic resolution of α-hydroxy esters bearing multiple stereocenters can also be conducted using the current asymmetric oxidation methodology. For example, diastereomeric substrates (±)-**2** and (±)-**4** resolve cleanly under the reaction conditions providing both the alcohol and the ketone with high enantioselectivity (eqs 2, 3).



In an attempt to gain insight into the mechanism of the oxidation event, we conducted an initial experiment with chlorovanadate **5**, which demonstrates a singlet ^{51}V NMR resonance at δ −438 ppm. Reaction of equimolar amounts of (*S*)-ethyl mandelate and homochiral chlorovanadate **5** under anaerobic conditions results in approximately 50% oxidation of the organic substrate (eq 4), at which time the ^{51}V NMR spectrum of the reaction mixture shows no signals in the range +2500 to −2000 ppm. EPR spectroscopy of the same mixture exhibits an eight-line profile, which we attribute to an intermediate vanadium(IV) species (^{51}V, $I = {}^{7}/_{2}$). In the absence of molecular oxygen, this species is stable in solution indefinitely. However, upon introduction of an oxygen atmosphere, the ^{51}V NMR resonance for **5** is regenerated. Moreover, the oxidation of (*S*)-ethyl mandelate then continues cleanly and completely to ethyl benzoylformate.



Alerted by the formation of vanadium(IV) compounds under the reaction conditions, we sought to identify whether single-electron-transfer processes were operative. Consequently, cyclopropyl substrate (±)-**6** was subjected to the asymmetric oxidation reaction (eq 5). We observed that oxidative resolution proceeded uneventfully without the formation of any products derived from ring scission of the 2-phenylcyclopropane.[13] This result strongly disfavors an oxidation mechanism that requires generation of a radical at the carbinol carbon in this system.[14,15]



In summary, we have developed an efficient asymmetric oxidation reaction catalyzed by vanadium(V) using molecular oxygen as the stoichiometric oxidant. The ligand architecture allows access to both enantiomers of a secondary alcohol by choice of ligand stereoisomer. The mild reaction conditions and chemoselectivity of the catalyst system provide access to a range of α-hydroxy esters in high yield and excellent enantioselectivity. Additionally, preliminary mechanistic investigations suggest molecular oxygen in the reaction manifold functions solely to reoxidize vanadium(IV) intermediates to the catalytically active vanadium(V) species, and its presence is not necessary for initial alcohol oxidation. Efforts are currently underway to provide detailed mechanistic insight into the catalytic cycle and to expand the scope and synthetic utility of the asymmetric oxidation.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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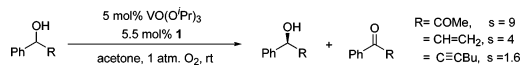
(11) Other secondary alcohols gave moderate selectivities (see below), while less activated alcohols (e.g., α-methylbenzyl alcohol) gave poor reactivity.



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(15) A mechanism that proceeds via initial two-electron reduction of V(V) to V(III), followed by rapid redox reaction with a second equivalent of V(V) to give two equivalents of V(IV) is most consistent with the observed spectral and product-distribution data.

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