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Highly Enantioselective Aerobic Oxidation of α-Hydroxyphosphonates Catalyzed by Chiral Vanadyl(V) Methoxides Bearing *N*-Salicylidene-α-aminocarboxylates

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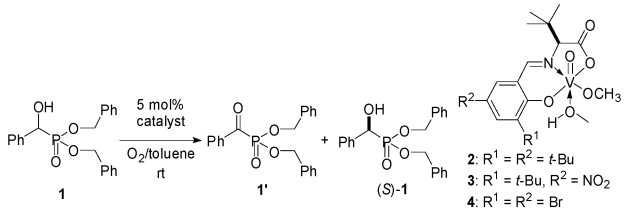
For the past decade, the syntheses of chiral α-hydroxyphosphonates have caught fascinating attention,[1] particularly in connection with the searches for bioactive isosters of the corresponding α-hydroxycarboxylic acids.[2] Consequently, these α-hydroxyphosphonic acid derivatives constitute attractive targets in subsequent biomedicinal studies.[3] Some α-hydroxyphosphonates have also shown excellent inhibitory activities toward HIV protease[4] and tyrosine specific kinase.[5] Racemic α-hydroxyphosphonates have been conventionally synthesized through base-catalyzed hydrophosphonylation (i.e., Pudovik reaction) of aldehydes with dialkyl or aryl phosphites. Significant advances have been achieved in the asymmetric variants[6] of the Pudovik reaction by the uses of La−Li−BINOL complexes (LPB),[7] Al−Li−BINOL/Al(salalen) complexes,[8] and complexes from a combination of Ti(O*i*-Pr)$_4$ and cyclohexane-1,2-diol or tartrate.[9]

As part of our ongoing projects by using vanadyl and oxometallic species in catalyzing C−C and C−X bond formation,[10] aerobic oxidative coupling,[11] and photoinitiated DNA cleavage[12] events, we and Toste have recently independently reported highly enantioselective kinetic resolution of α-hydroxyesters and α-hydroxyamides by respective *N*-salicylidene vanadyl(V) alcoholates[13] and carboxylates[14] under aerobic oxidation conditions. In view of the unprecedented asymmetric aerobic catalytic process with α-hydroxy acid derivatives, we thought to examine the feasibility of the direct asymmetric aerobic oxidation of α-hydroxyphosphonates at ambient temperature by chiral vanadyl complexes.[15] Herein we report our preliminary results in that aspect.

By following our optimal catalytic asymmetric aerobic oxidation protocol on the kinetic resolution of benzyl mandelates by our vanadyl(V) complexes, we began by applying the newly developed strategy onto the aerobic oxidation of a test dibenzyl phenylhydroxymethylphosphonate **1** with varying C3- and C5-substituents in the *N*-salicylidene template of catalysts, Table 1. In marked contrast to the asymmetric oxidation process of α-hydroxyesters, the enantioselectivity for the kinetic resolution of the current test phosphonate **1** increases with reduced steric bulk of the C3 substituent in the catalysts. Vanadyl(V) complexes **2** and **3** bearing a 3-*tert*-butyl group are less enantioselective (k_{rel} = 7) than 3,5-dibromo-substituted complex **4** (k_{rel} > 99) toward the kinetic resolution process. On the other hand, the C5-substituent in the catalysts only serves to alter the reactivity of the catalysts, where the electron-withdrawing Br or NO_2 facilitates the catalytic efficiency of the oxidation (reaction time: 30 and 40 h, respectively).[16]

The versatility of the new catalytic protocol by the optimal vanadyl(V) methoxide-**4** was illustrated by its application to a wide range of α-aryl-α-hydroxyphosphonates (Table 2). For 4-substituted-phenyl derivatives **5**−**11**, the selectivity factors (k_{rel}) in the kinetic resolution process range from 81 to >99, which are slightly higher than the parent system from **1**. With varying functionalities of electronic attributes at the 4-position of the α-phenyl ring in **5**−**9**, the oxidation reactions proceed cleanly in 6−40 h. Notably, the catalytic processes proceed similarly for the electron-donating 4-methoxy and 4-*N*,*N*-dimethylamino cases (**6** and **7**, 34−36 h) as the corresponding 4-methyl and 4-chloro (**5** and **8**, 40 h) analogues. Conversely, excellent reaction rates and selectivity factors (k_{rel} >

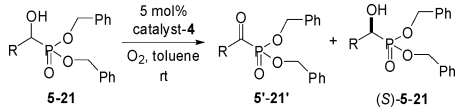
Table 1. Effects of Catalysts on the Asymmetric Aerobic Oxidation of Racemic Dibenzyl Phenylhydroxymethylphosphonate-**1**



catalyst	time, h	% conversion[a]	%ee,[b] (yield,[c] %)	k_{rel}[d]
2	45	51	60 (48)	7
3	40	51	60 (48)	7
4	30	51	99 (48)	>99

[a] Determined by ^{1}H and ^{31}P NMR analysis of the reaction mixture. [b] Determined by HPLC analysis on Chiralcel 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.

Table 2. Effects of α-Aryl, Alkenyl, and Alkynyl Groups on the Asymmetric Aerobic Oxidation of Racemic Dibenzyl α-hydroxyphosphonates **5**−**21** by Catalyst **4**[e]



R	time, h	% conversion[a]	%ee,[b] (yield,[c] %)	k_{rel}[d]
C_6H_5 (**1**)	30	51	99 (47)	>99
4-$CH_3C_6H_4$ (**5**)	40	49	96 (46)	>99
4-$CH_3OC_6H_4$ (**6**)	36	50	99 (49)	>99
4-$Me_2NC_6H_4$ (**7**)	34	50	97 (50)	>99
4-ClC_6H_4 (**8**)	40	49	96 (49)	>99
4-$NO_2C_6H_4$ (**9**)	6	50	99 (49)	>99
4-CNC_6H_4 (**10**)	18	51	95 (47)	81
4-MeOC(O)C_6H_4 (**11**)	13	50	>99 (49)	>99
3-HOC_6H_4 (**12**)	48	50	99 (46)	>99
3-$MeOC_6H_4$ (**13**)	40	50	>99 (48)	>99
2-$CH_3OC_6H_4$ (**14**)	90	50	99 (49)	>99
2-BrC_6H_4 (**15**)	150	49	33 (47)	3
1-Np (**16**)	60	50	99 (46)	>99
2-furanyl (**17**)	50	49	90 (47)	95
2-thiophenyl (**18**)	14	50	99 (49)	>99
trans-PhCH=CH (**19**)	90	49	95 (47)	>99
trans-CH_3CH=CH (**20**)	18	49	96 (49)	>99
PhC≡C (**21**)	24	50	68 (49)	11

[e] Superscripts a−d are the same as those in Table 1.

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99) were observed in the cases of the most electron-withdrawing 4-nitro and 4-carbomethoxy systems **9** and **11**. The reactions were complete at 50% conversion in 6−13 h, leading to recovery of the (*S*)-enantiomers **9** and **11** in ≥99% ee, respectively

To elucidate the effect of functional group compatibility, 3-methoxy and 3-hydroxyphenyl analogues **12** and **13** were also examined. It was found that both the asymmetric oxidations work well with excellent enantioselectivity (≥99% ee, k_{rel} > 99) albeit with slightly prolonged reaction time (40−48 h). In addition, no discernible oxidation or homocoupling of the phenolic moiety was observed. To gain further insights into the steric and electronic factors of the substrates bearing ortho substituents in the α-aryl groups, 2-methoxy- and 2-bromophenylmethyl-α-hydroxyphosphonates **14** and **15** were chosen as representative examples. The oxidations proceeded at significantly slower rates (90 and 150 h) in both cases. In the former case, the reaction was stopped at 50% conversion (90 h), leading to the recovery of (*R*)-**14** in 99% ee (k_{rel} >99). In marked contrast, a very poor reaction rate and selectivity factor resulted from the 2-bromophenyl analogue **15** (33% ee, k_{rel} = 3) at 49% conversion. The severe Coloumbic repulsion between the lone pair electrons on both Br groups (i.e., 2-BrC_6H_4 in the substrate and the C3−Br group in the catalyst template) may be responsible for the erosion of enantiocontrol.

Upon changing the nature of the α-aryl groups from phenyl, 1-naphthyl, to 2-thiophenyl, we observe increasing enantiocontrols (k_{rel} > 99) in the aerobic oxidation processes except in the 2-furanyl case (k_{rel} = 95) presumably due to the competing coordination of the oxygen in the 2-furanyl group. Notably, the 1-naphthyl analogue **16** is the slowest-reacting substrate (60 h) among the four cases. Furthermore, substrates bearing allylic α-substituted systems such as **19** (R = *trans*-cinnamyl) and **20** (R = *trans*-crotonyl) were also examined. Notably, the alkene moieties in **19** and **20** remain intact without any intervening epoxidation. Both the reactions were complete in less than 90 h at 49% conversion, leading to (*S*)-**19** and (*S*)-**20** in 95−96% ee (k_{rel} > 99). The slower oxidation rate in **19** may be due to the larger steric effect of the phenyl group in the cinnamyl moiety as compared to methyl group in the crotonyl moiety of **20**. On the other hand, the substrate bearing α-phenylethynyl group (i.e., **21**) is also fairly reactive, and the selectivity factor for its asymmetric oxidation is 11.

The substrate class was further extended to dibenzyl α-hydroxyphosphonates possessing α-alkyl groups of varying steric demands. Unfortunately, our preliminary study showed that negligible asymmetric inductions were effected for the substrates bearing α-methyl, benzyl, *i*-propyl, and *tert*-butyl groups at 50% conversion. Nevertheless, the facile conversion of **19** and **20** to the corresponding saturated analogues by chemoselective hydrogenation[8a] allows one to access optically pure α-hydroxyphosphonates possessing α-alkyl groups.

On the basis of the structural study of an *N*-benzylmandelamide catalyst adduct in the asymmetric oxidation of α-hydroxyamides,[14] we propose that the thermodynamically more stable diastereomeric adduct **22** as shown in Figure 1 is a slower-reacting species toward oxidation. On the contrary, the sterically more encumbered diastereomeric adduct **22′** is faster reacting for the subsequent α-proton elimination process leading to α-ketophosphonate-**1′** with concomitant reduction of the vanadyl(V) species to the corresponding vanadium(III)OH.

In conclusion, we have documented a new kinetic resolution process for α-hydroxyphosphonates with the assistance of *N*-salicylidene-L-*tert*-leucine-based vanadyl(V) methoxide complexes, effecting highly enantioselective and chemoselective aerobic oxidations at ambient temperature. Judicious selection of the C3,C5 substituents in the template allows us to access the optimal vanadyl(V) methoxide as the 3,5-dibromo analogue **4**. The current protocol works well for a diverse array of α-aryl- and α-heteroaryl-α-hydroxyphosphonates, auguring well for its potential applications in biomedicinal chemistry.

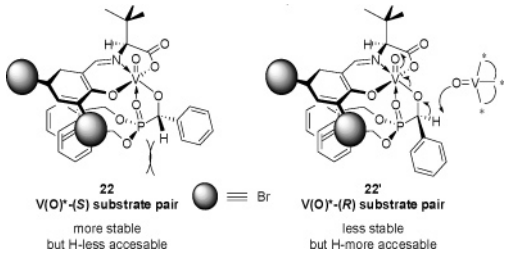

Figure 1. Proposed reactivity difference for the diastereomeric adducts **22** and **22′** formed between vanadyl(V) methoxide **4** and racemic **1**.

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Supporting Information Available: Characterization data for the vanadyl(V) methoxide complexes **2**−**4**, kinetic resolution products **1** and **5**−**21**, and oxidation products **5′**−**21′**. This material is available free of charge via the Internet at http://www.acs.org.

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(16) The asymmetric oxidations of the corresponding dimethyl- and diethyl phenylhydroxymethylphosphonates by catalyst **4** led to lower selectivities (k_{sel} = 49 and 41).

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