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Enantioselective Aerobic Oxidation of α-Hydroxy-Ketones Catalyzed by Oxidovanadium(V) Methoxides Bearing Chiral, *N*-Salicylidene-*tert*-butylglycinates

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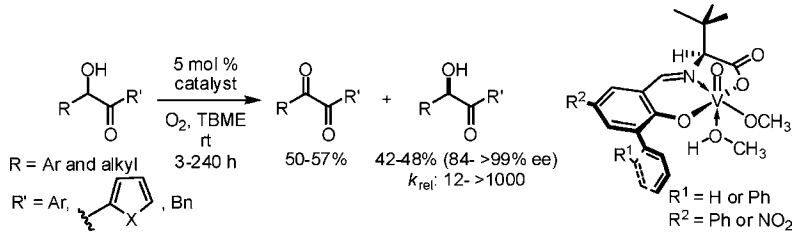
ABSTRACT



Chiral oxidovanadium(V) methoxides prepared from 3,5-disubstituted-*N*-salicylidene-L-*tert*-butylglycines and vanadyl sulfate in air-saturated MeOH serve as highly enantioselective catalysts for asymmetric aerobic oxidations and kinetic resolution of alkyl, aryl, and heteroaryl α-hydroxy-ketones with differed α-substituents at ambient temperature in toluene or TBME (*tert*-butyl methyl ether). The best scenarios involve the use of complexes which bear the tridendate templates derived from 3,5-diphenyl- or 3-*o*-biphenyl-5-nitro-salicyaldehyde. The kinetic resolution selectivities of the aerobic oxidation process are in the range of 12 to >1000 based on the selectivity factors (k_{rel}).

α-Hydroxy-ketones with aryl or heteroaryl (e.g., 2-furanyl, -thiophenyl, and -pyrrolyl) groups have shown a reasonable range of biological functions.[1] They are also important precursors of 1,2-diols and 1,2-amino alcohols.[2] Several advanced asymmetric and enzymatic techniques have recently been reported to access scalemic α-hydroxy-ketones.[3] The chiral benzoin type α-hydroxy-ketones made by chiral thiazolium or triazolium mediated catalysis[4] are important structural subunits in many biologically active compounds,[5] despite there being some restrictions on their syntheses by crossed benzoin condensations. Additionally, optically active α-hydroxy-α-alkyl-ketones are also important structural subunits in various protein farnesyltransferase inhibitors (e.g., Kurasoin A and Kurasoin B).[6] To our knowledge, there are only a couple of existing systems for resolving a given class

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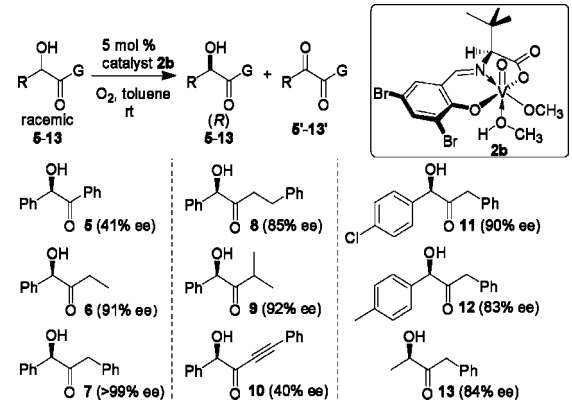
of benzoin. These are asymmetric aerobic oxidation catalyzed by Co(II) or Cu(II) bearing BINAM type ligands (k_{rel} = 8−23) in the presence of TEMPO.[7,8] Notably, the consistency of the optical purity of the benzoins was hampered by easy tautomerization and racemization, even under mild basic conditions. Substrate classes possessing alkyl and heteroaryl α-hydroxy-ketones with a diverse array of α-substituents were also relatively unexplored.

As part of our ongoing programs of using chiral oxidovanadium(V) methoxide complexes in catalyzing asymmetric oxidative couplings of 2-naphthols,[9] site-selective DNA photocleavage,[10] asymmetric aerobic oxidation of α-hydroxycarboxylic acid and phosphonic acid derivatives,[11] and synergistic metal-specific ion transport,[12] we sought to extend their scope[13] to the asymmetric oxidation of α-hydroxyketones bearing alkyl, aryl, and heteroaryl groups, particularly those bearing 2-pyrrolyl appendages. Herein we describe the results of this highly enantioselective, kinetic resolution process.

Benzoin **5** was first used as a test asymmetric aerobic oxidation substrate with oxidovanadium(V) methoxide **2b** derived from 3,5-dibromo-*N*-salicylidene-L-*tert*-butylglycine, which was the best catalyst identified by us for the asymmetric aerobic oxidation of α-hydroxy-phosphonates.[11b] The extent of oxidation for benzoin reached 51% conversion after 8 h in toluene at ambient temperature, but the enantiomeric purity of the recovered (*R*)-benzoin **5** was only 41% ee (k_{rel} = 3, Table 1).[14] We then turned our attention to different types of ketone. Replacing the phenyl group attached to the ketone part of benzoin **5** by alkyl groups, as in substrates **6**−**9**, led to significant increases in the enantiomeric excess of the kinetic resolutions, presumably due to the enhanced

Table 1. Effects of Substituents on the Asymmetric Aerobic Oxidations of Racemic α-Phenyl-α-hydroxyl-ketones **5**−**10** and α-Hydroxy-benzyl-ketones **11**−**13** Catalyzed by **2b**



substrate	t (h)	conv (%)[a]	% ee[b] (yield,[c] %)	k_{rel}[d]
5	8	51	41 (47)	3
6	2.5	55	91 (40)	21
7	3	51	>99 (43)	>211
8	2.2	54	85 (40)	17
9	2	50	92 (48)	79
10	13	49	40 (45)	4
11	3.5	51	90 (46)	42
12	1.5	54	83 (44)	15[e]
13	1	47	84 (42)	98

[a] Determined by ^{1}H NMR analysis of the reaction mixture. [b] Determined by HPLC analysis on Chiralcel OD, OD-H, AD, or 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 = conversion and ee = enantiomeric excess. [e] The selectivity factor was 41 (98% ee) when the reaction was performed at 15 °C after 3.5 h.

ketone coordination strength of these substrates to the catalyst. The order of selectivity factors followed the order of sterics of G:[15] **7** (G = $CH_2C_6H_5$; k_{rel} > 211) > **9** (G = $CH(CH_3)_2$; k_{rel} = 79) > **6** (G = CH_2CH_3; k_{rel} = 21) and **8** (G = $CH_2CH_2C_6H_5$; k_{rel} = 17). In marked contrast, the enantiomeric selectivity dropped to 40% ee (k_{rel} = 4) in the case of alkynyl ketone **10** (G = C≡CC_6H_5) presumably due to reduced steric encumbrance of the alkynyl unit.

Based on the excellent kinetic resolution of benzyl ketone **7**, we screened through two more substrates derived from **7** that possessed *para*- substituents in the α-phenyl moiety (i.e., R = 4-ClC_6H_4 and 4-MeC_6H_4). In these two cases, substrate **12** (k_{rel} = 15) bearing an electron-donating, *para*-methyl group was less enantioselective than substrate **11** (k_{rel} = 42), which bore an electron-withdrawing, *para*-chloro group, despite the higher solubility of **12** in toluene. This electronic effect is consistent with our previous findings.[11] Nevertheless, the selectivity factor in the case of **12** could be improved to 41 (98% ee) when the kinetic resolution was performed at 15 °C (reaction time 3.5 h). Furthermore, the most difficult substrate, **13**, which bears the least sterically demanding α-methyl group, also proceeded smoothly in 1 h with excellent enantiocontrol (k_{rel} = 98) under the same reaction

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(15) G stands for the substituent attached directly to the ketone moiety.

conditions. Conversely, our previous systems and those of Toste only led to about 33% ee on lactate derivatives (i.e., R = CH_3, G = OR).

In line with our previous experience, the enantiocontrol observed for the kinetic resolution of mandelates appears to depend on the steric bulk of the C-3 substituent in the salicylidene template of a given oxidovanadium(V) complex (Figure 1). After screening a couple of sterically demanding

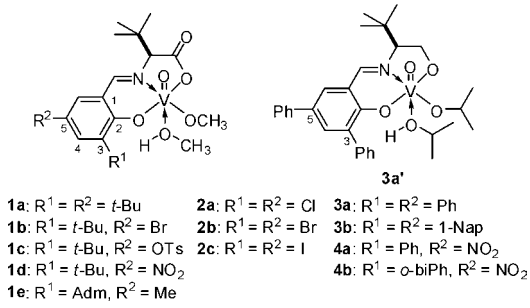


Figure 1. Chiral oxidovanadium(V) methoxides **1**−**4** and complex **3a′** derived from L-*tert*-leucinol.

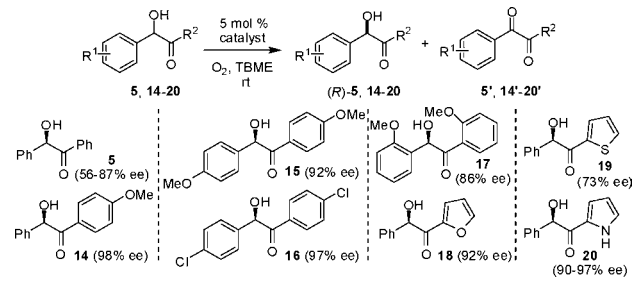
C-3 groups (i.e., *t*-Bu and adamantyl) in the oxidovanadium(V) complexes of *N*-salicylidene-L-*tert*-butylglycines, we found that the steric effect at the C-3 position was not the only dominating factor in the kinetic resolution of a given α-hydroxyketone like **7**. The selectivity factors increased with increasing electron-withdrawing power at the C-5 position of the complexes with the order as follows: **1d** > **1c** > **1b** > **1a** > **1e**.[14d] On the other hand, we studied kinetic resolutions of **7** catalyzed by 3,5-dihalo and -diaryl substituted complexes **2a**−**c** and **3a**−**b**. The selectivity factors followed the order **2b** > **2c** > **2a** in the former series and followed the order **3a** > **3b** in the latter series.[14d] Therefore, the best catalyst classes include 3-*tert*-butyl-5-nitro, 3,5-dibromo, and 3,5-diphenyl based systems **1d**, **2b**, and **3a**.

Next, we switched our attention back to benzoin substrate **5** by using these three optimal catalysts **1d**, **2b**, and **3a** with different solvents. It was found that *tert*-butyl methyl ether (TBME) was the best solvent among toluene, ethyl acetate, CH_2Cl_2, CCl_4, acetone, CH_3CN, DME, diphenyl ether, and several cosolvent systems examined.[16] The selectivity factors (k_{rel}) were improved from 3 by catalyst **2b** in toluene to 6, 8, and 16 by catalysts **1d**, **2b**, and **3a** in TBME (Table 2), respectively. Therefore, subsequent studies on the enantioselective oxidation of other benzoin derivatives **14**−**20** were carried out in TBME with 5 mol % of the best catalyst **3a**.

Benzoin analogues **14**−**20** bearing an electron-donating and/or electron-withdrawing *para*- group in the phenyl ring(s), and three different heteroaryl groups (i.e., 2-furanyl, 2-thiophenyl, and 2-pyrrolyl) in R^2, were further examined. To our expectation, all the aerobic oxidations proceeded

(16) The selectivity factors were not further improved by changing the solvent from toluene to TBME in the aerobic oxidations of benzyl ketones **7** and **11**−**13** by using the optimal catalysts **1d**, **2b**, and **3a**.

Table 2. Effects of Catalysts on the Asymmetric Aerobic Oxidation of Racemic Benzoin **5** and Its Derivatives **14**−**20**



substrate	catalyst	t (h)	conv (%)	% ee (yield, %)	k_{rel}
5	**1d**	14	50	56 (48)	6
5	**2b**	5.5	51	63 (47)	8
5	**3a**	5.5	55	87 (45)	16
14	**3a**	5.5	55	98 (41)	41
15	**3a**	9	51	92 (48)	53
16	**3a**	3	54	97 (45)	44
17	**3a**	19	52	86 (45)	24
18	**3a**	7	55	92 (42)	23
19	**3a**	4	51	73 (46)	12
20	**3a**	30	55	90 (43)	20
20	**3a′**	26	51	50 (46)	5[a]
20	**4a**	59	55	96 (44)	32
20	**4b**	57	50	97 (46)	278

[a] The reaction was performed in acetone.

smoothly at ambient temperature within 4−30 h at 50−55% conversion. The resulting, resolved (*R*)-alcohols were isolated in 41−48% yields and in high to excellent enantioselectivities (86−98% ee; k_{rel} = 20 to 53) except in the case of **19** (k_{rel} = 12). Notably, the selectivity factor (k_{rel}) was improved from 16 to 41 and 53 by installing a methoxy group at the *para*- position of the phenyl ring (R^2) attached to the ketone moiety as in **14** and **15**, respectively, presumably due to the increased steric demand of R^2 and/or increased carbonyl coordination strength to the catalyst. Excellent kinetic resolution (97% ee; k_{rel} = 44) was also achieved (as in benzoin **16**) where an electron-withdrawing chloro group was installed to both *para*- positions of the phenyl rings. In addition, satisfactory resolution results (86−92% ee; k_{rel} = 20 to 24) were also observed by appending either *ortho*-methoxy groups to both phenyl rings (i.e., **17**) or 2-heteroaryl units (i.e., 2-furanyl and 2-pyrrolyl in **18** and **20**) to the ketone moiety despite their possible interference with coordination to the catalyst.

In marked contrast, the asymmetric aerobic oxidation of **20** catalyzed by **3a′** similar to Toste's in-situ-generated oxidovanadium(V) catalyst[17] derived from 3,5-diphenylsalicyaldehyde, L-*tert*-leucinol, and V(O)(O-*i*-Pr)$_3$ proceeded at 51% conversion after 26 h. The reaction led to the resolved alcohol (*R*)-**20** in only 50% ee (k_{rel} = 5) presumably due to the easy racemization of the resolved (*R*)-**20** in view of the more basic nature of the catalyst-**3a′**. On the other hand, the same catalytic reaction that utilized Sekar's catalytic

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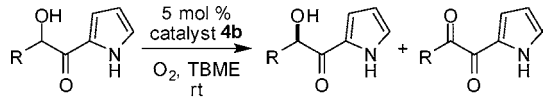
systems[7a,b] only led to (*R*)-**20** in 9% ee (k_{rel} = 1.3). To our delight, introducing an electron-withdrawing nitro group at the C-5 position of the salicylidene template as in catalyst **4a** (R^1 = Ph, R^2 = NO_2) and **4b** (R^1 = *o*-biPh, R^2 = NO_2)[18] (Figure 1) led to even higher enantiocontrol in the resolution of compound **20**, where the selectivity factors were improved to 32 and 278, respectively.

To gain further insight into the substrate scope of the benzoin derivatives bearing a 2-pyrrolyl group at the ketone moiety, we further examined kinetic resolutions of various 2-aryl-[2-hydroxy-1-(1*H*-pyrrol-2-yl)-ethanones] **21**−**28** catalyzed by the best catalyst **4b** (Table 3).

Table 3. Effects of α-Substituent Groups on the Asymmetric Aerobic Oxidation of Racemic 2-Pyrrolyl-ketone Derivates **21**−**30**



21-30 (*R*)-**21-30** **21'-30'**

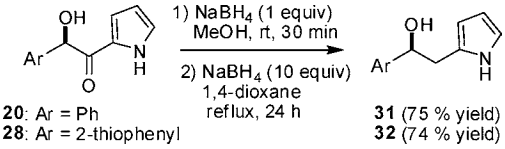
R/substrate	*t* (h)	conv (%)	% ee, (yield, %)	k_{rel}
C_6H_5/**20**	57	50	97 (46)	278
4-ClC_6H_4/**21**	107	50	98 (43)	458
4-MeC_6H_4/**22**	108	51	88 (47)	35[a]
4-$MeOC_6H_4$/**23**	84	51	93 (46)	60[a]
2-ClC_6H_4/**24**	240	53	84 (47)	18
2-MeC_6H_4/**25**	232	57	90 (42)	16[a]
2-$MeOC_6H_4$/**26**	166	51	86 (42)	29
2-Np/**27**	168	50	90 (47)	58[a]
2-thiophenyl/**28**	102	51	96 (47)	97
$(CH_3)_2CH$/**29**	72	50	99 (48)	1057
$PhCH_2CH_2$/**30**	87	50	>99 (44)	>1057

[a] Reactions were performed at 0.01 M substrate concentrations.

Three different α-aryl-substituted substrates **21**−**23**, bearing different *para*- substituents of varying electronic demands, were tested. Substrate **21** which bears an electron-withdrawing chloro group (k_{rel} = 458) is more enantioselective than those (i.e., **22** and **23**; k_{rel} = 35 and 60) possessing electron-donating methyl and methoxy groups. Substrates **24**−**26** bearing α-*ortho*-substituted aryl groups were at least two times less enantioselective (k_{rel} = 16 to 29) than the corresponding *para*-substituted counterparts presumably due to the increased steric repulsion between the *ortho*-substituent and the *o*-biPh group at C-3 of the catalyst template. Nevertheless, the kinetic resolution of α-2-naphthyl and α-(2-thiophenyl) derivatives by asymmetric aerobic oxidation led to excellent enantioselectivities (k_{rel} = 58 and 97) of the recovered (*R*)-alcohols **27** and **28**.[14c] Finally, the enantiocontrol for the asymmetric aerobic oxidations of α-alkyl-substitued substrates, catalyzed by complex **4b**, highly hinged on their sterics. To our delight, substrates **29** and **30** that bear α-isopropyl and 2-phenylethyl groups led to essentially perfect enantioselection (k_{rel} > 1000) in the kinetic resolution events.

As possible applications of **20** and **28** as antidepressant analog precursors, their reductive methylenations were readily achieved by using $NaBH_4$ for their ketone reduction and subsequent reductive displacement of the resulting alcohol intermediates. Both the doubly reduced products **31** and **32** were obtained in 74−75% yields in two steps (Scheme 1). Product **32** may serve as a precursor to a potential antidepressant analog of (*S*)-duloxetine which is a potent dual inhibitor of serotonin and norepinephrine reuptake.[19]

Scheme 1. Direct Reductive Methylenation of **20** and **28** by $NaBH_4$



20: Ar = Ph
28: Ar = 2-thiophenyl

31 (75 % yield)
32 (74 % yield)

We have documented a new kinetic resolution process that exploits the asymmetric aerobic oxidation of α-hydroxyketones catalyzed by oxidovanadium(V) methoxides derived from chiral 3,5-dibromo-, 3,5-diphenyl-, and 3-*o*-biPh-5-NO_2-*N*-salicylidene-L-*tert*-butylglycine templates. Their highly enantioselective aerobic oxidations can be effected at ambient temperature which prevents undesired racemization and/or tautomerization of the substrates. The newly developed catalytic protocol works well with excellent selectivity factors for kinetic resolution of benzoins, α-hydroxy-benzylketones, and α-hydroxy-1-(1*H*-pyrrol-2-yl)-ethanones, auguring well for their potential applications in biomedicinal chemistry.

Acknowledgment. We thank the National Science Council of Taiwan for financial support of this research. Dedicated to the memory of Miss Tomomi Katayama who initiated this study.

Supporting Information Available: Characterization data for complexes **1**−**4**, kinetic resolution of **5**−**30**, oxidized product **5′**−**30′**, calalyst optimizations with **7**, the reductive methylenation products **31** and **32**, and the origin of enantiocontrols. This material is available free of charge via the Internet at http://pubs.acs.org.

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