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Selective oxidation of secondary alcohols

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1. Introduction

The oxidation of alcohols to carbonyl compounds is a fundamental synthetic transformation, and a wide variety of reagents have been developed for this important reaction.[1–3] Favorable attributes of an alcohol oxidation procedure include high conversions, the absence of side products, the use of available, inexpensive, non-toxic reagents, mild conditions, high chemoselectivity, and compatibility with other functional groups. Some recent methods that have been used extensively in synthesis include the Dess–Martin periodinane,[4] activated dimethyl sulfoxide,[5] tetra-*n*-propylammonium perruthenate (TPAP),[6] and 2,2,6,6,-tetramethylpiperidin-1-oxyl (TEMPO).[7] The synthesis of natural products frequently involves the manipulation of compounds with multiple oxygen-containing functional groups at different oxidation states, and it is often necessary to selectively oxidize a single secondary or primary alcohol group within the same molecule. This problem has historically challenged synthetic chemists in the areas of carbohydrate and steroid synthesis, and many of the early developments in selective oxidation originated from these fields. Individual alcohol groups can be exposed to or obscured from reactivity with oxidants through selective protection and deprotection, although this increases the total number of steps in the synthesis and decreases the overall yield. Selective oxidizing agents that are able to directly distinguish secondary from primary alcohols offer a desirable alternative to the use of protecting groups in synthesis.

Many commonly used reagents oxidize secondary alcohols at rates slightly faster than primary alcohols, but these have not been practical for selective oxidations because of the small magnitudes of rate differences. The purpose of this report is to survey those reagents that have proven to be highly selective for the oxidation of secondary aliphatic alcohols in the presence of primary alcohols. Reagents that oxidize activated allylic and benzylic alcohols in the presence of aliphatic alcohols are not covered in this report. The evidence for secondary>primary selectivity has been

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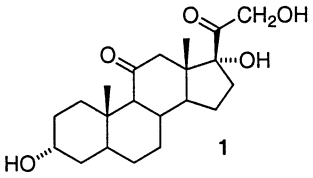
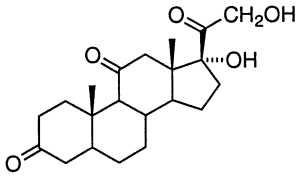
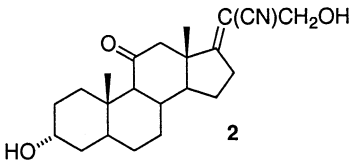
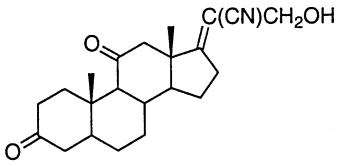
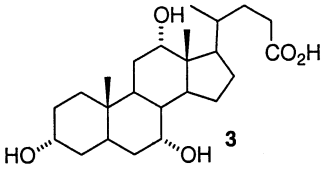
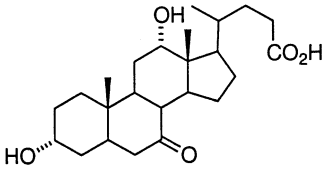
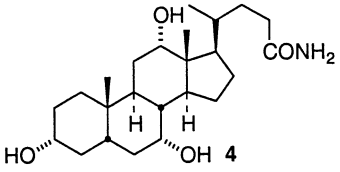
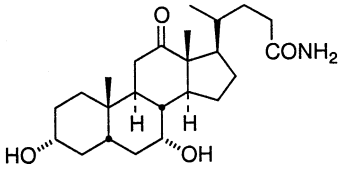
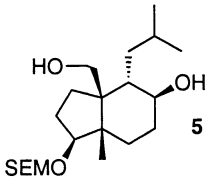
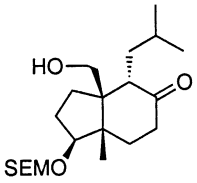
Table 1. Secondary-selective alcohol oxidation using *N*-bromoamide reagents

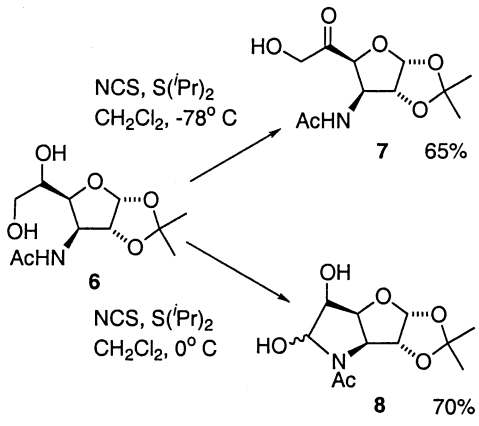
Substrate	Reagent	Product(s)	Yield (%)	Ref.
	2 equiv. NBA, ^{t}BuOH, H_2O 10°C, 5 h		71	12
	4 equiv. NBA, CH_3OH, H_2O pyridine rt, 5 h		90–96	13
	NBS, acetone, H_2O		70	9
	Br_2, Na_2Co_3, MeOH, 0–4°C		78	10
	NBS, DME, H_2O		36	11

gleaned from examples of intermolecular competition experiments and regioselective oxidations of diols and polyhydroxylated compounds. Oxidations that discriminate between two or more different secondary alcohols on the basis of their local steric environment are also included. The oxidative kinetic resolution of racemic secondary alcohols, and the asymmetrization of *meso*-secondary diols by oxidation are also discussed as methods for obtaining optically active secondary alcohols. Representative examples have been organized according to the general classes of reagent to emphasize the variety of substrates that are compatible with the reaction conditions.

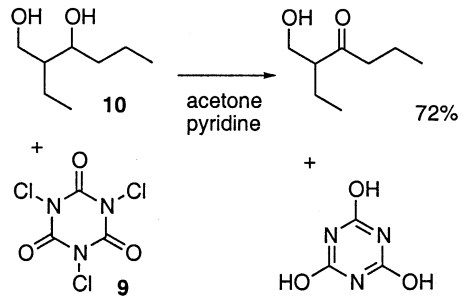
2. Chemical oxidants

2.1. Halogen-based oxidants

A variety of N-halogenated reagents have been used for the selective oxidation of secondary alcohols, including *N*-bromoacetamide (NBA), *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS) as shown in Table 1. Selective oxidation of the 3-α-hydroxyl in the trihydroxypregnane derivative **1** was achieved with NBA in aqueous *tert*-butanol.[12] This reagent also oxidized the secondary alcohol of **2** in preference to the substituted primary allylic alcohol group.[13] *N*-Bromosuccinimide exhibits a general preference for the oxidation of secondary alcohols, and is sensitive to the immediate steric environment such that axial alcohols are typically oxidized faster than equatorial.[8] NBS is a much stronger oxidant and less selective in solvents consisting of aqueous ^{t}BuOH or ^{t}BuOH/pyridine. The regioselective oxidation of the C_7 alcohol of cholic acid **3** by NBS in aqueous acetone was an early demonstration of the selective oxidation of a polyhydroxy compound.[9] Regioselective oxidation at C_{12} of the cholic acid derivative **4**



Scheme 1.



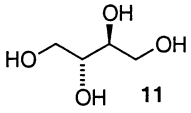
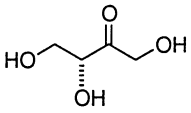
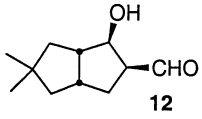
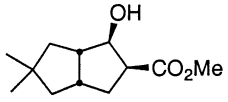
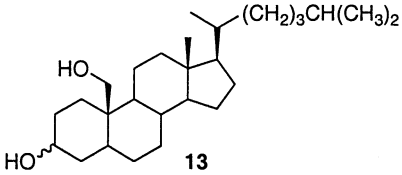
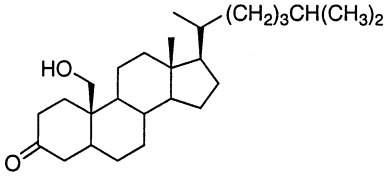
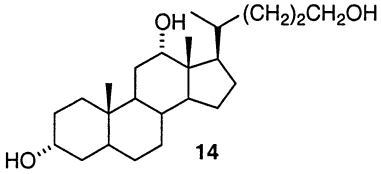
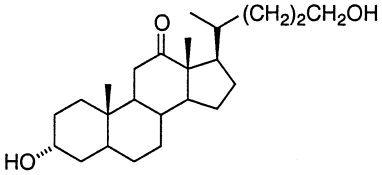
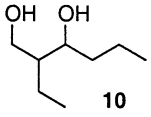
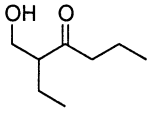
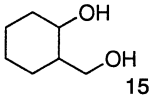
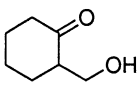
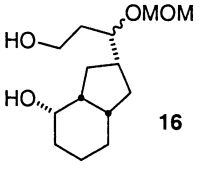
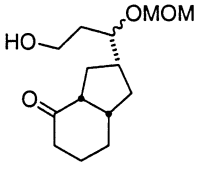
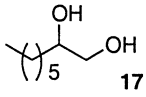
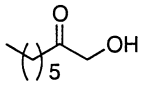
Scheme 2.

was accomplished by in situ formation of the *N*-bromoamide, followed by intramolecular oxidation.[10] The diol **5** was oxidized to the ketone using NBS in aqueous dimethoxyethane.[11]

The combination of *N*-chlorosuccinimide and diisopropyl sulfide provides a system which exhibits temperature-controlled selectivity (Scheme 1).[14] When the oxidation of diol **6** was conducted at −78°C, the ketone **7** was obtained, while maintaining the oxidation at 0°C produced the lactol **8** by selective oxidation of the primary alcohol. With this method a mixture of decan-1-ol and heptan-3-ol was oxidized at 0°C in an intermolecular competition, producing decanal in 90% yield, while the secondary alcohol was recovered in 90% yield. The selectivity of the reaction was also affected by sterics, such that oxidations using the less hindered *n*-butyl sulfide were non-selective.

Trichloroisocyanuric acid (ICC, **9**) rapidly oxidizes secondary alcohols in acetone solvent buffered with pyridine. The competitive oxidation of 3-heptanol and 1-nonanol produced 98% 3-heptanone and 88% unreacted 1-nonanol.[15]

Table 2. Selective oxidation of secondary alcohols with halogens

Substrate	Reagent	Product(s)	Yield (%)	Ref.
 11	Br_2, $CaCO_3$ H_2O, 25°C, 20 h		21[a]	17
 12	3 equiv. Br_2 (9:1) MeOH, H_2O, $NaHCO_3$		94	18
 13	1.1 equiv., Cl_2, 5 equiv., pyridine, $CHCl_3$		α: 62 β: 100	23
 14	1.1 equiv., Cl_2, 7 equiv., pyridine, $CHCl_3$		59[b]	23
 10	Br_2, HMPT, $NaHCO_3$, H_2O, CH_2Cl_2		91	19
 15	Br_2, HMPT, $NaHCO_3$, H_2O, CH_2Cl_2		93	19
 16	Br_2, HMPT, $NaHCO_3$, CH_2Cl_2		84	20
 17	Et_4NCl_3, pyridine, DABCO, CH_3CN, rt		100	21

[a] Isolated as the acetonide.
[b] Diketone=22% yield.

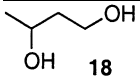
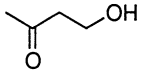
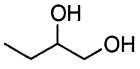
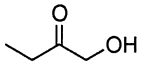
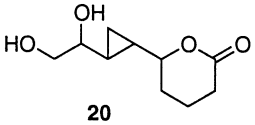
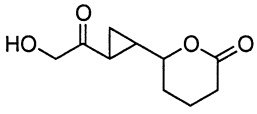
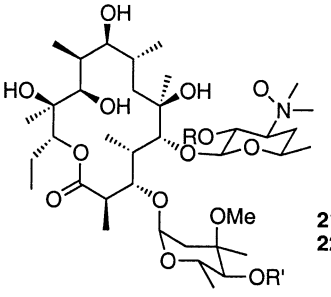
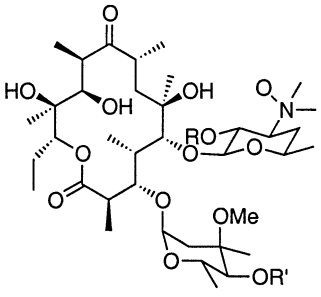
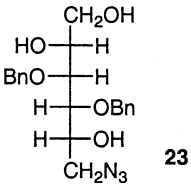
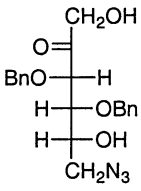
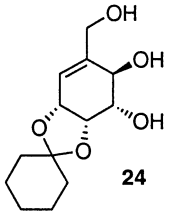
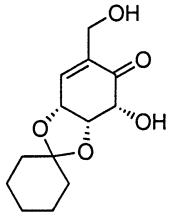
This reagent selectively oxidized the secondary alcohol of 2-ethyl-1,3-hexanediol **10** to give the hydroxy ketone in high yield (Scheme 2). The formation of chlorinated ketone byproducts was minimized by including pyridine as a buffer and using acetone as solvent.

The halogens Br_2 and Cl_2 are effective for selective alcohol oxidations under a variety of conditions as shown by the examples in Table 2. Primary and secondary alcohols are oxidized by aqueous Br_2 to acids and ketones, respectively,[16] This method has some preparative value for the oxidation of polyhydroxy compounds because these products can be separated easily.[17] Aldehydes such as **12** were preferentially oxidized to esters in the presence of a secondary alcohol with Br_2 in aqueous methanol.[18] The secondary alcohol of steroid **13** was oxidized to the ketone in the presence of the primary C_{19} alcohol with Cl_2-pyridine. The hindered alcohol of triol **14** was oxidized preferentially at the 12-position.[23] The addition of hexamethylphosphoric triamide (HMPT) to Cl_2 or Br_2 in CH_2Cl_2 at $-40°C$ results in a reagent that is selective for the oxidation of secondary alcohols in competition experiments with primary alcohols. The 1,3-diol **10** was oxidized with Br_2/HMPT to give the hydroxy ketone in 91% yield. Cyclohexanol **15** was similarly oxidized to the hydroxy ketone in excellent yield.[19] This method was used to synthesize the hydroxyketone from diol **16** in a synthesis of the aphidicolane B/C/D-ring system.[20]

Tetraethylammonium trichloride provides a practical source of chlorine, and oxidizes secondary alcohols to ketones in the presence of pyridine, and diazabicyclo[2.2.2] octane (DABCO) in acetonitrile.[21] The 1,2-diol **17** was oxidized to the hydroxy ketone in quantitative yield. Chlorination of propargylic and allylic alcohols was observed in preference to oxidation with this system. Resin-bound thiazolium hydrotribromide (HBr_3) in a two phase mixture of CH_2Cl_2 and aqueous NaOH was used to oxidize the secondary alcohol of 1,3-butanediol to give the hydroxyketone in 93% yield.[22]

The rapid oxidation of secondary tributyltin alkoxides with Br_2 has proven to be a synthetically useful method as shown in Table 3. The addition of bis(tri-*n*-butyltin) oxide

Table 3. Selective oxidation of diols with bis(tri-*n*-butyltin) oxide/Br_2

Substrate	Reagent	product(s)	Yield (%)	Ref
 **18**	$(Bu_3Sn)_2O$, Br_2, CH_2Cl_2, rt		66	25
 **19**	$(Bu_3Sn)_2O$, Br_2, CH_2Cl_2, rt		68	25
 **20**	$(Bu_3Sn)_2O$, Br_2, CH_2Cl_2, rt		64	26
 **21** : R, R' = H **22** : R = Ac, R' = CO_2Bn	$(Bu_3Sn)_2O$, Br_2, CH_2Cl_2, rt		58 57	27 28
 **23**	$(Bu_3Sn)_2O$, Br_2, CH_2Cl_2, rt		75	29
 **24**	$(Bu_3Sn)_2O$, Br_2, CH_2Cl_2, rt		51	30

$(Bu_3Sn)_2O$ to secondary, benzylic, and allylic alcohols forms the corresponding tributyltin alkoxides, which were rapidly oxidized to carbonyls by Br_2.[24] Primary alcohols were found to be unreactive with $(Bu_3Sn)_2O+Br_2$ in CH_2Cl_2, while secondary alcohols were converted to the ketones in high yield.[25] Using this method 1,2- and 1,3-primary–secondary diols were converted to the hydroxy ketones in high yield. This method was used to oxidize a cyclopropyl-substituted 1,2-diol **20** to the corresponding ketone in good yield.[26] Regioselective oxidations at C9 of the erythromycin derivatives **21** and **22** were observed using this method.[27,28] The 1,2-diol group of the azide **23** was oxidized to the hydroxyketone in the presence of a free secondary hydroxyl.[29] The triol **24** underwent selective oxidation of the secondary allylic alcohol to produce the dihydroxyketone.[30]

Diols react with dibutyltin oxide to produce cyclic dibutylstannylenes, which are preferentially oxidized with Br_2 at secondary positions to give the corresponding keto alcohols as shown in Table 4. The benzylated glucose derivative **25** was selectively oxidized at the secondary C_4 hydroxyl.[31] The axial secondary alcohol in the tetraol **26** was oxidized selectively by the dibutylstannylene/Br_2 procedure.[32] Different regioselectivity was observed for the dibutylstannylene-mediated oxidation of the α- and β-anomer of glycosides **27** and **28**, producing the 2-keto and 3-keto products, respectively.[33] Regioselective oxidation of the acyclic secondary alcohol in triol **29** gave access to the ketone used in a synthesis of 2-acetamido-1,2-dideoxynojirimycin.[34] The addition of Br_2 to the stannylene intermediate at temperatures below rt leads to competitive oxidation of the primary alcohol. A modified procedure using catalytic amount of dibutyltin oxide and bromide ion with electrochemical generation of 'Br^+' effectively oxidized the dibutylstannylene intermediate and was used for the oxidation of 1,2-diols.[35] A competition experiment demonstrated highly selective oxidation of *cis*-1,2-cyclohexanediol **30** in the presence of a five-fold excess of cyclohexanol. *cis*-1,2-Cyclohexanediol was oxidized at a rate approximately three times faster than the *trans*-isomer with this system.

A variety of oxohalide reagents are suitable for

Table 4. Selective oxidation of secondary diols with dibutyltin oxide/Br_2

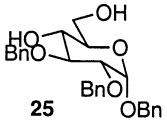
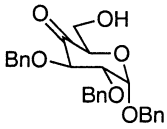
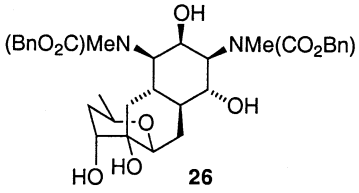
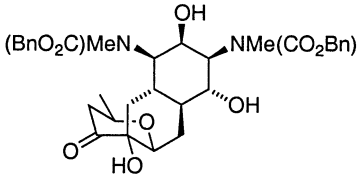
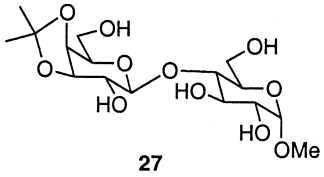
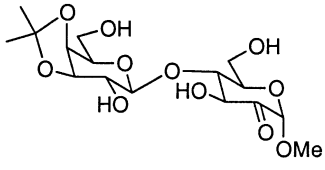
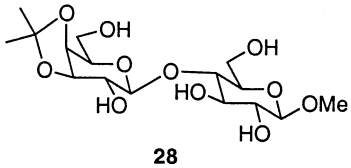
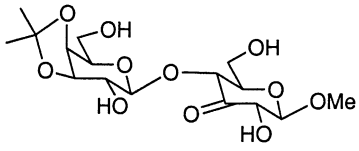
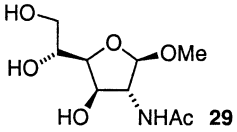
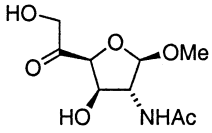
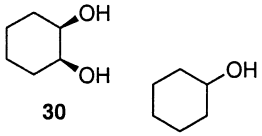
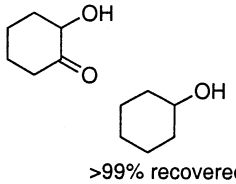
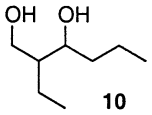
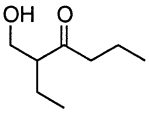
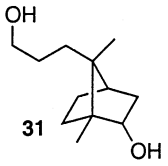
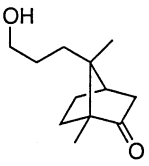
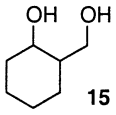
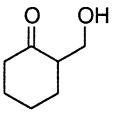
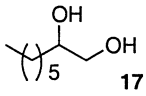
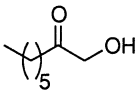
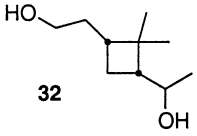
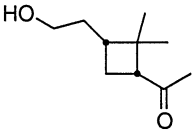
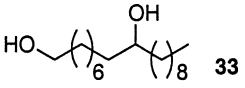
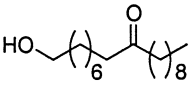
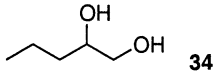
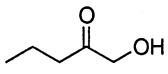
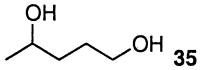
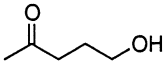
Substrate	Reagent	product(s)	Yield (%)	Ref
 **25**	(1) Bu_2SnO, MeOH, Δ (2) Br_2, CH_2Cl_2, Bu_3SnOCH_3		87	31
 **26**	(1) Bu_2SnO, MeOH, Δ (2) Br_2, Bu_3SnOCH_3, CH_2Cl_2, −10°C		92	32
 **27**	(1) Bu_2SnO, CH_3CN, 90°C, 16 h (2) Br_2, CH_2Cl_2, Bu_3SnOCH_3		34	33
 **28**	(1) Bu_2SnO, CH_3CN, 90°C, 16 h (2) Br_2, CH_2Cl_2 Bu_3SnOCH_3		50	33
 **29**	(1) Bu_2SnO MeOH, Δ (2) Br_2, CH_2Cl_2, Bu_3SnOCH_3		52	34
 **30** 5 equiv.	Electrolysis 2F mol^{-1}, Bu_2SnO, Et_4NBr, MeOH, 0°C	 >99% recovered	84	35

Table 5. Selective oxidation of secondary alcohols with hypohalite reagents

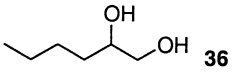
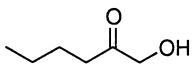
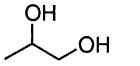
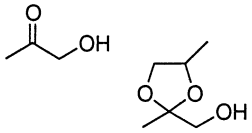
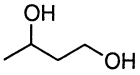
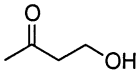
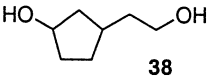
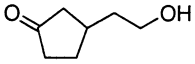
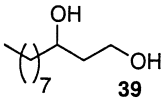
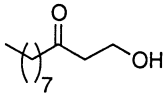
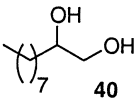
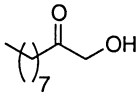
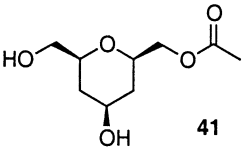
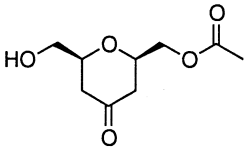
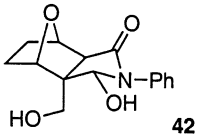
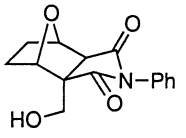
Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **10**	NaOCl, CH_3CO_2H		85	36
 **31**	NaOCl, CH_3CO_2H		91	37
 **15**	NaOCl, CH_3CO_2H		90	37
 **17**	NaOCl, CH_3CO_2H		73	37
 **32**	NaOCl, CH_3CO_2H		83	37
 **33**	Cl_2, MeOH, $NaHCO_3$, Cl_3CCO_2H		95	40
 **34**	HOF–CH_3CN		N.R.	41
 **35**	HOF–CH_3CN		N.R.	41

secondary-selective alcohol oxidations as shown in Table 5. Sodium hypochlorite in acetic acid efficiently oxidizes secondary alcohols to ketones.[36] This procedure is convenient and inexpensive, and selectively oxidizes the secondary alcohol of a variety of diols such as **10**, **15**, **17**, **31**, **32**.[37] Primary aliphatic alcohols were slowly converted to esters under these conditions. Calcium hypochlorite is an inexpensive, commercially available solid that is easy to store and use.[38] Secondary alcohols were selectively oxidized by calcium hypochlorite with a catalytic amount of a hypochlorite ion exchange resin in an organic solvent.[39] A competition between cycloheptanol and 1-heptanol gave 85% cycloheptanone and 98% recovered unreacted *n*-heptanol. Methyl hypochlorite, generated from the reaction of Cl_2 with methanol in a buffered medium, selectively oxidized the secondary alcohol of primary–secondary diol **33** in 95% yield.[40] In comparison, the selectivity for the hydroxyketone was 7:1 at 99.6% conversion using ICC in acetone/pyridine as the oxidant with this substrate. The secondary alcohols of 1,2-diol **34** and 1,4-diol **35** were preferentially oxidized by hypofluorous acid.[41] The reagent was generated directly from F_2 and water, and displays interesting chemoselectivity. Isolated alkenes were oxidized to epoxides, and alkyl amines were oxidized to nitro compounds in preference to alcohol oxidation. The reagent also slowly oxidizes ketones to esters, converts secondary ethers to ketones,[42] and oxidizes enols to α-hydroxyketones.[43]

Sodium bromate ($NaBrO_3$) has been used as a selective alcohol oxidant under a variety of conditions shown in Table 6. Primary–secondary 1,2- and 1,3-diols **36**, **37**, and **18** were oxidized by $NaBrO_3$ selectively to hydroxyketones in the presence of sodium bisulfite ($NaHSO_3$) in aqueous acetonitrile.[44] Hypobromous acid (HOBr) was reportedly generated as an active species under these conditions. Alkyl ethers were oxidized to esters, and bromohydroxylation of alkenes also occurred under these conditions. Primary alcohols were oxidized to esters by $NaBrO_3$/$NaHSO_3$.[45] The addition of ammonium chloride (NH_4Cl) to $NaBrO_3$ in aqueous acetonitrile oxidizes secondary and benzylic alcohols, but does not oxidize saturated primary alcohols. This method was used to oxidize 2-ethyl-1,3-hexanediol **10**, and the hydroxy ketone was isolated in 50% yield.[46] The reaction was pH dependant and requires chloride ion, generating Br_2 and Cl_2 under these conditions.

Cerium(IV) catalyzed the oxidation of secondary alcohols to ketones, and diols **38**–**40** to the hydroxyketones with $NaBrO_3$ in aqueous acetonitrile.[47,48] Cerium(IV) ammonium nitrate $(NH_4)_2Ce(NO_3)_6$ and cerium(IV) sulfate $Ce(SO_4)_2$

Table 6. Selective alcohol oxidation with sodium bromate

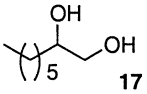
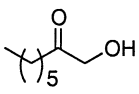
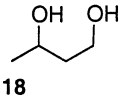
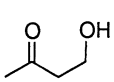
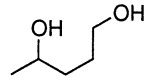
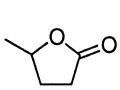
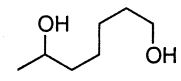
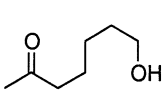
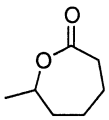
Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **36**	$NaBrO_3$, $NaHSO_3$, CH_3CN, H_2O		89	44
 **37**	$NaBrO_3$, $NaHSO_3$, CH_3CN, H_2O		1 93	44
 **18**	$NaBrO_3$, $NaHSO_3$, CH_3CN, H_2O		90	44
 **38**	$(NH_4)_2Ce(NO_3)_6$, $NaBrO_3$, CH_3CN, 80°C		89	47,48
 **39**	$Ce(SO_4)_2$, $NaBrO_3$, CHO_3CN, 80°C		88	47,48
 **40**	$Ce(SO_4)_2$, $NaBrO_3$, CH_3CN, 80°C		50	47,48
 **41**	$Ce(SO_4)_2$, $NaBrO_3$, CH_3CN/ H_2O		28	49
 **42**	$Ce(SO_4)_2{\cdot}2H_2SO_4$, $KBrO_3$, CH_3CN, H_2O		48	50

were found to be equally effective. Competitive oxidation of a mixture of 1-dodecanol and 4-dodecanol produced only 3% of the aldehyde and 98% ketone. The presence of alkene groups was reported to inhibit the oxidation. The secondary alcohol of diol **41** was oxidized using this procedure to give the ketone in 28% yield.[49] The cerium(IV) catalyzed oxidation of the secondary aminal **42** with bromate proceeded in the presence of the primary alcohol.[50] The attempted oxidation of this substrate using other methods such as NaOCl/HOAc,[37] NBS in aqueous ethylene glycol dimethyl ether,[11] DDQ in acetonitrile,[51] Fetizon's reagent (Ag_2CO_3/celite),[52] and $VO(OAc)_2$/^{t}BuOOH[53] all failed to give the desired imide product.

Diols undergo oxidation with sodium bromite trihydrate in acetonitrile in the presence of alumina, but the selectivity depends on the distance between the hydroxyl groups as shown in Table 7.[54] Secondary selectivity was observed with 1,2- and 1,3-diols. Oxidation of the primary alcohol to produce the lactone occurred with 1,4- and 1,5-diols, and the oxidation of 1,6-diols proceeded with essentially no selectivity.

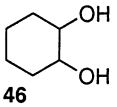
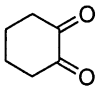
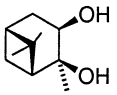
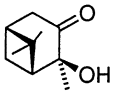
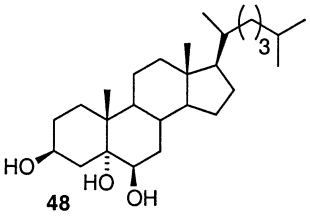
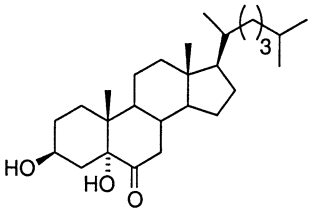
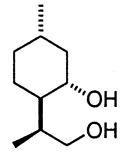
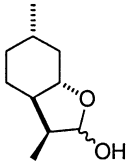
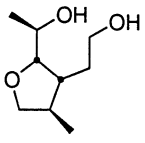
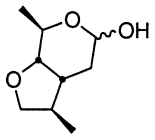
Hypervalent iodine(V) derivatives such as the Dess–Martin periodinane **44** (DMP) and *o*-iodoxybenzoic acid **45** (IBX) have found wide use in organic synthesis as mild reagents

Table 7. Oxidation with sodium bromite/alumina

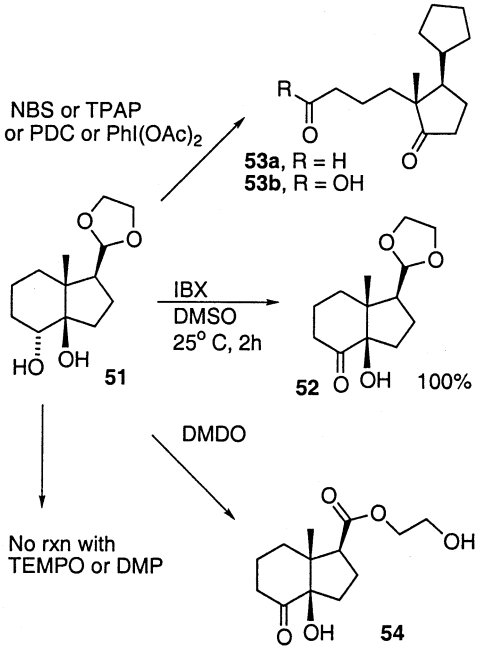
Alcohol	Product	Yield (%)
 **17**		76
 **18**		65
 **43**		72
 **44**		44
		56

$NaBrO_2$, Al_2O_3, CH_3CN.

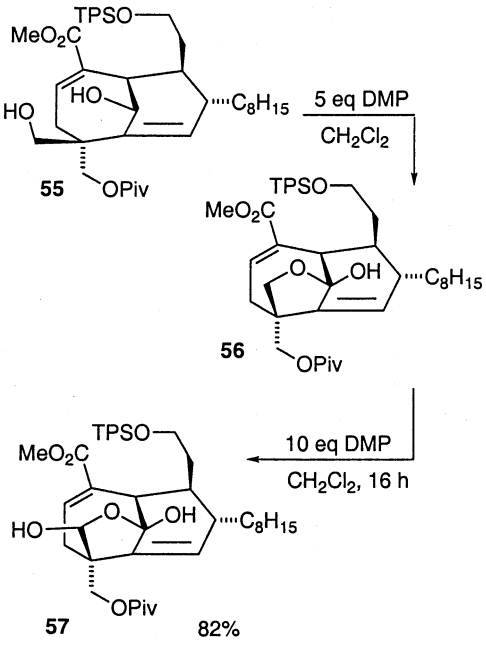
Table 8. Selective alcohol oxidation with iodoxybenzoic acid in DMSO

Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **46**	2.5 equiv. IBX, DMSO		81	55
 **47**	1.5 equiv. IBX, DMSO/THF		86	55
 **48**	1.5 equiv. IBX, DMSO		85	55
 **49**	1.2 equiv. IBX, DMSO, rt		81	57
 **50**	IBX, DMSO, rt		56	58

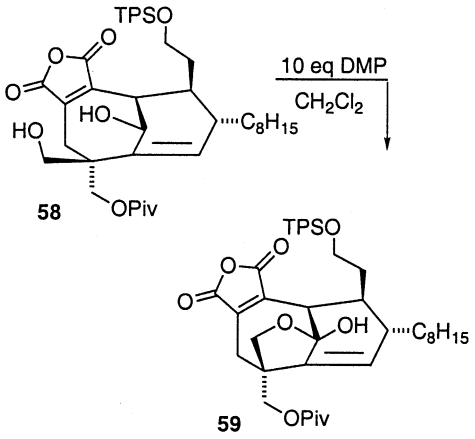
for the oxidation of both primary and secondary alcohols.[4] The Dess–Martin periodinane is soluble in a variety of organic solvents and requires anhydrous conditions. The related reagent IBX is generally insoluble in most organic solvents, but dimethylsulfoxide solutions of IBX are conveniently prepared and are not affected by moisture. The glycol C–C bond of 1,2-diols typically undergoes cleavage during attempted oxidation with DMP.[4] The oxidation of



Scheme 3.

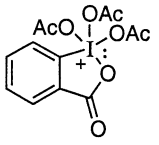


Scheme 4.

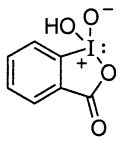


Scheme 5.

1,2-diols with IBX can be controlled to produce α-hydroxyketones as shown in Table 8.[55] Further oxidation leads to α-diketones. Mechanistic studies have provided insight into the different product distributions from 1,2-diols using IBX and DMP.[56] Statistical mixtures of isomeric monoesterified alkoxyperiodinane intermediates are produced in a fast pre-equilibrium with IBX and asymmetrically substituted 1,2-diols in DMSO-d_6. This observation demonstrates the low sensitivity of the complexation step to steric hindrance. The related DMP reagent reacts with chelating diols to produce spirobicyclic iododioxolane intermediates, which then preferentially break down to yield C–C cleavage products instead of alcohol oxidation. The oxidation of *cis*- or *trans*-1,2-cyclohexanediol with 2.5 equiv. IBX in DMSO proceeds to the α-diketone. The secondary–tertiary 1,2-diol **47** was oxidized to the hydroxyketone in high yield. Triol **48** was oxidized selectively at the secondary alcohol of the 1,2-diol in the presence of the isolated secondary alcohol, although 12% of the diketone was also obtained. The selective oxidation of the primary alcohol occurs using IBX in DMSO for the oxidation of primary–secondary 1,4-diol **49**,[57] and 1,5-diol **50**.[58] The further oxidation of alcohols or aldehydes and ketones to α,β-unsaturated carbonyls with IBX has recently been reported.[59]

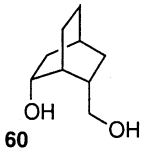
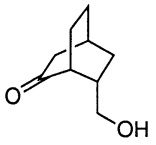
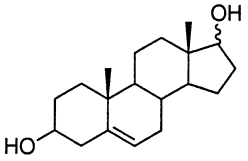
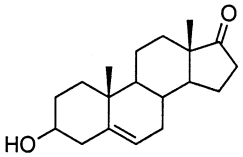
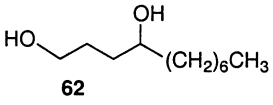
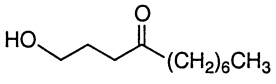
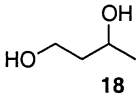
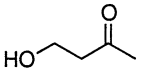
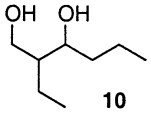
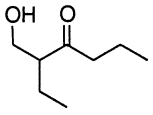
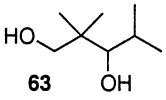
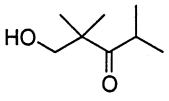
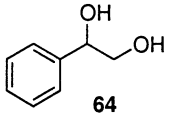
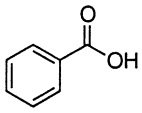


DMP **44**



IBX **45**

Table 9. Molybdenum-catalyzed oxidation of secondary alcohols with peroxides

Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **60**	$(NH_4)_6Mo_7O_{24}$, K_2CO_3, H_2O_2, Bu_4NCl, THF rt, 24 h		88	62
 **61**	$(NH_4)_6Mo_7O_{24}$, K_2CO_3, H_2O_2, Bu_4NCl, THF rt, 6 days		90	62
 **62**	$[PhCH_2NMe_3][Mo(O)Br_4]$, ^tBuOOH, C_6H_6, 60°C		60	63
 **18**	$[C_5H_5N^+(CH_2)_{15}CH_3]_3[PMo_{12}O_{40}]^{3-}$, ^tBuOOH, benzene, 75°C		97	64
 **10**	$[C_5H_5N^+(CH_2)_{15}CH_3]_3[PMo_{12}O_{40}]^{3-}$, ^tBuOOH, benzene, 75°C		100	64
 **63**	$[C_5H_5N^+(CH_2)_{15}CH_3]_3[PMo_{12}O_{40}]^{3-}$, ^tBuOOH, benzene, 75°C		100	64
 **64**	$[C_5H_5N^+(CH_2)_{15}CH_3]_3[PMo_{12}O_{40}]^{3-}$, ^tBuOOH, benzene, 75°C		77	64

The 1,2-diol **51** was found to be highly sensitive to the oxidation conditions during attempts to prepare the ketone **52** (Scheme 3).[60] A variety of reagents were investigated, but only IBX was found to produce the desired α-hydroxyketone. Oxidative cleavage of the glycol C–C bond occurred with NBS, TPAP, pyridinium dichromate (PDC), and iodosobenzene diacetate to give keto-aldehyde **53a** and keto-acid **53b** products. Dimethyldioxirane preferentially oxidized the acetal protecting group to produce ester **54**. No reaction was observed using TEMPO or DMP.

In another synthetic application, the sterically hindered secondary alcohol **55** was rapidly oxidized with DMP in the presence of the primary alcohol to produce the isolable hemiketal **56** (Scheme 4).[61] Further oxidation with 10 equiv. DMP, 16 h resulted in oxidation of the primary alcohol group via the open chain tautomer to produce the stable hemiacetal **57**. The oxidation reaction of a related molecule **58** possessing the maleic anhydride functional group proceeded similarly to produce the hemiketal **59**, that was conformationally locked under the reaction conditions and resistant to further oxidation with DMP (Scheme 5).

2.2. Peroxides

Peroxides are readily available, inexpensive, and generally considered to be 'clean' oxidants for metal catalyzed oxidations. A variety of molybdenum-catalyzed secondary-selective alcohol oxidations have been reported as shown in Table 9. The secondary alcohol of diol **60** was selectively oxidized with 30% aqueous H_2O_2 in the presence of tetrabutylammonium chloride as a phase transfer agent using catalytic ammonium molybdate in THF at room temperature.[62] The sterically hindered secondary alcohol **61** was oxidized preferentially to the less hindered alcohol. Alkene epoxidation was suppressed by controlling the pH using potassium carbonate. Benzyltrimethylammonium tetrabromooxomolybdate $[PhCH_2NMe_3][Mo(O)Br_4]$ was an effective catalyst for the oxidation of secondary alcohols with ^{t}BuOOH. With this system 2-octanol was oxidized competitively with 1-octanol to give the ketone in 87% yield, while the primary alcohol was recovered in 87%.[63] The secondary alcohol of 1,4-diol **62** was selectively oxidized to the hydroxy ketone under these conditions. The cetylpyridinium-molybdophosphate catalyst $[PMo_{12}O_{40}][C_5H_5N(CH_2)_{15}CH_3]_3$ oxidizes secondary alcohols with ^{t}BuOOH in benzene at 75°C, but does not oxidize primary alcohols under these conditions.[64] 1,3-Diols **18**, **10**, and **63** were oxidized to the hydroxyketones in quantitative yields, but the 1,2-diol **64** underwent oxidative cleavage under these conditions. Substituted cyclohexanols were also poor substrates for this system. Molybdenum hexacarbonyl was also found to be an effective catalyst, exhibiting similar selectivity under these conditions.[65]

A variety of tungsten-catalyzed selective alcohol oxidations have been reported as detailed in Table 10. Tricetylpyridinium-12-tungstophosphate $[PW_{12}O_{40}][C_5H_5N(CH_2)_{15}CH_3]_3$ (CWP) catalyzes the oxidation of secondary alcohols and diols with H_2O_2 in ^{t}BuOH,[66,67] exhibiting selectivity analogous to the molybdenum/^{t}BuOOH system.[64] While oxidative cleavage of 1,2-diol **36** to the carboxylic acids

Table 10. Tungsten-catalyzed oxidation of secondary alcohols with peroxides

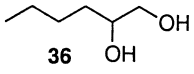
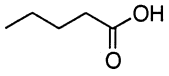
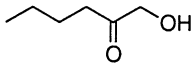
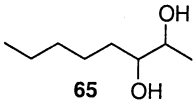
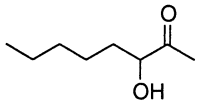
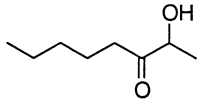
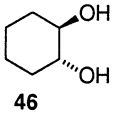
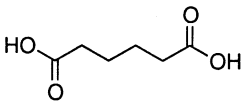
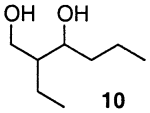
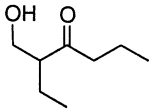
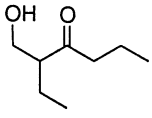
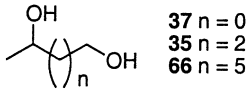
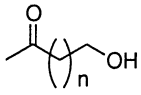
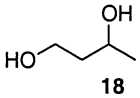
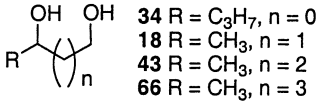
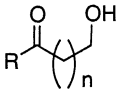
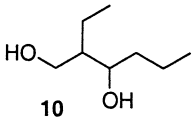
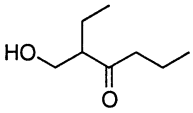
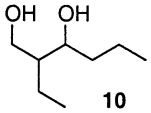
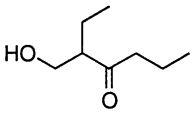
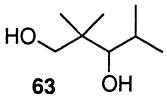
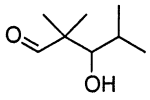
Substrate	Reagent	Product(s)	Yield (%)	Ref
 **36**	CWP (1.6 mol%), H_2O_2, H_2O, ^{t}BuOH		68	68
36	CWP (1.6 mol%), H_2O_2, H_2O, $CHCl_3$, rt, 16 h		93	68
 **65**	CWP (1.6 mol%), H_2O_2, H_2O, $CHCl_3$, rt, 16 h		57	68
			28	
 **46**	CWP (1.6 mol%), H_2O_2, H_2O, $CHCl_3$, rt		54	68
 **10**	Na_2WO_4, $CH_3(n\text{-}C_8H_{17})_3NHSO_4$, 1.1 equiv. H_2O_2		83	71
10	Microwave 10 min Na_2WO_4, H_2O_2, TBAHS		97	74

Table 11. Selective catalytic oxidation of secondary alcohols with peroxides

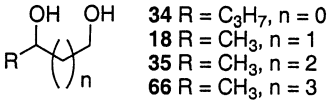
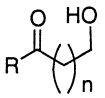
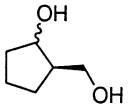
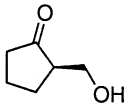
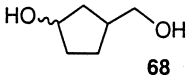
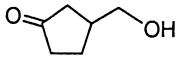
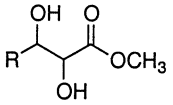
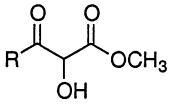
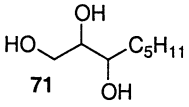
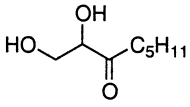
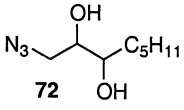
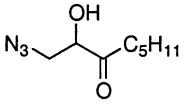
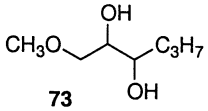
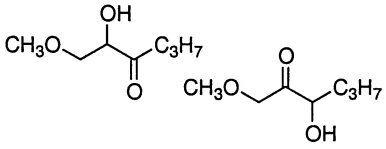
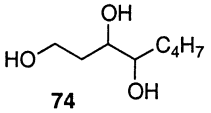
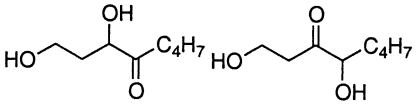
Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **37** n = 0 **35** n = 2 **66** n = 5	cr-PILC/TBHP CH_2Cl_2, rt, N_2 atm		89 100 94	76
 **18**	TBHP, 3A MS MW		36	77
 **34** R = C_3H_7, n = 0 **18** R = CH_3, n = 1 **43** R = CH_3, n = 2 **66** R = CH_3, n = 3	H_2O_2, TS-1		100 84 100[a] 93[a]	78
 **10**	VO(acac), ^{t}BuOOH C_6H_6, Δ		92	53
 **10**	Zr(O-*n*-Pr)$_4$, ^{t}BuOOH CH_2Cl_2, 3 MS 20°C, 5 days		85	79
 **63**	Zr(O-*n*-Pr)$_4$, ^{t}BuOOH CH_2Cl_2, 3 MS 20°C, 2 days		40	79

[a] Isolated as the hemiketol.

was observed in ^{t}BuOH at 60°C, in a biphasic $CHCl_3/H_2O$ system the α-hydroxy ketone was obtained in excellent yield.[68] The yield was lower for 1,2-butanediol under these conditions (43%), presumably due to further oxidation occurring in the water layer with this more hydrophilic substrate. A mixture of α-hydroxyketones was obtained from the oxidation of the unsymmetrical *sec*-*sec*-diol **65**. Cyclic diols were susceptible to oxidative cleavage, and adipic acid was the only product isolated from the oxidation of *trans*-1,2-cyclohexanediol **46**. A variety of other tungsten catalysts have been developed for alcohol oxidations with aqueous H_2O_2 under biphasic conditions, and primary alcohols typically react slower than secondary alcohols.[69,70] Recently, a solvent- and halide-free procedure has been developed using $[Na_2WO_4][CH-(n\text{-}C_8H_{17})_3N]HSO_4]$,[71] and competition experiments using dilute H_2O_2 solutions gave the relative rate of oxidation of 2-octanol/1-octanol=2.7.[72] Other functional groups such as ester, trityl ether, TBDMS ether, THP-ether, and amides were tolerated, and 2-octanol was oxidized preferentially to 1-octene by a factor of 28. Cyclic 1,2-diols undergo extensive oxidation, and this system has been used to synthesize adipic acid from cyclohexene.[73] The 1,3-diol **10** was oxidized to the hydroxyketone in good yield. A microwave-assisted procedure has been developed using tetra-*n*-butyl ammonium hydrogen sulfate, which oxidized **10** in 97% yield.[74] The oxidation of secondary alcohols with H_2O_2 has also been catalyzed by the manganese containing tungsten polyoxometalate anion $[WZnMn_2(ZnW_9O_{34})_2]_{12}$.[75] Primary alcohols were not reactive under these conditions, but alkenes were epoxidized efficiently.

A variety of other secondary-selective catalytic alcohol oxidations using peroxides are shown in Table 11. The oxidations of 1,2-, 1,4-, and 1,7-diols **37**, **35**, and **66**, respectively, using ^{t}BuOOH with catalytic amounts of chromia-pillared montmorillonite (Cr-PILC) were selective for the secondary alcohols.[76] Primary alcohols were oxidized slowly with this system. Secondary alcohols were oxidized in moderate yields by ^{t}BuOOH in the presence of 3 Å molecular sieves under microwave irradiation, and 1,3-butanediol **18** was oxidized to the hydroxyketone.[77] Primary alcohols were reportedly unaffected under these conditions. Titanium doped zeolites (TS-1) catalyze the oxidation of alcohols with H_2O_2, and selectively oxidized the saturated linear 1,2-, 1,3-, 1,4-, and 1,5-diols **34**, **18**, **43**, and **66**, respectively, at the secondary position.[78] Hemiketal products were isolated from the TS-1 catalyzed oxidation of 1,4- and 1,5-diols. A limitation of this methodology is that cyclic diols such as cyclopentanol derivatives were not oxidized. The vanadium complex $VO(acac)_2$,[53] and the zirconium alkoxide complexes $Zr(OR)_4$ were both effective catalysts for the oxidation of 1,3-diol **10** with ^{t}BuOOH.[79] The competitive oxidation of 4-dodecanol/1-dodecanol with $VO(acac)_2$/ BuOOH gave a product ration of ketone to aldehyde greater than 100. 1,2-Diols were oxidatively cleaved under these conditions. Sterically unhindered secondary alcohols react 2–10 times faster than primary alcohols with the catalytic $Zr(OR)_4$/^{t}BuOOH/molecular sieves systems. This reagent oxidizes equatorial cyclohexanols faster than axial, enabling a kinetic resolution.[79] The mechanism is proposed to involve hydride transfer to the coordinated peroxide via a cyclic transition state. It was

Table 12. Selective oxidation of secondary alcohols with dimethyldioxirane

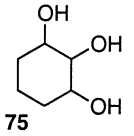
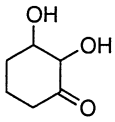
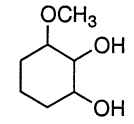
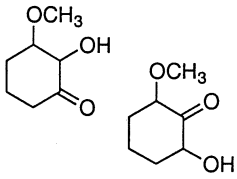
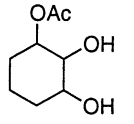
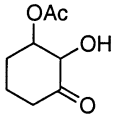
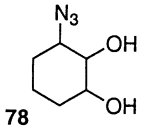
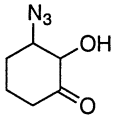
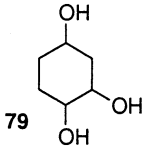
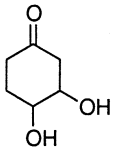
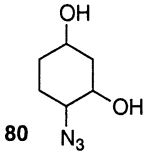
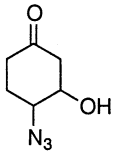
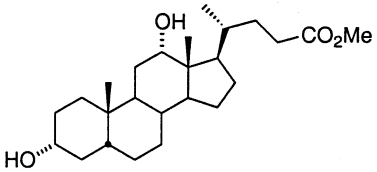
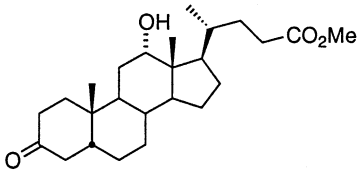
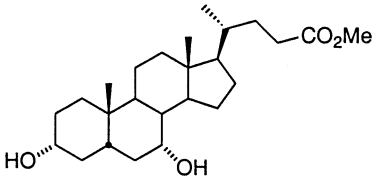
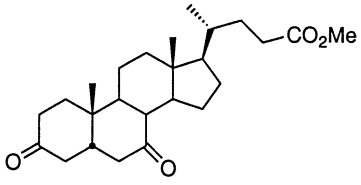
Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **34** R = C_3H_7, n = 0 **18** R = CH_3, n = 1 **35** R = CH_3, n = 2 **66** R = CH_3, n = 3	DMDO, acetone		100 90 60 60	78
 **67** - *cis* **67** - *trans*	DMDO, acetone		85	78
	DMDO, acetone		Complex mixture	
 **68**	DMDO, acetone		82	78
 **69** R = Me **70** R = C_9H_{19}:	DMDO, acetone		77	83
	DMDO, acetone		10	83
 **71**	DMDO, acetone		59	84
 **72**	DMDO, acetone		>90	84
 **73**	DMDO, acetone		76, 14	84
 **74**	DMDO, acetone		75 50/50	84

necessary to remove the water formed during the reaction by adding molecular sieves or activated alumina to avoid hydrolysis of the metal alkoxide. The diols **10** and **63** were oxidized at rates slower than less hindered alcohols, and the selectivity was reversed for the highly hindered secondary alcohol **63**, resulting in a primary-selective oxidation to give the hydroxy aldehyde. Secondary alcohols were oxidized by ^{t}BuOOH with a ruthenium complex of *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane (Cn^*)[$Cn^*Ru(O_2CCF_3)_3$], but the oxidation of primary alkyl alcohols was ineffective and the starting alcohols were recovered.[80]

2.3. Dioxiranes

Dimethyldioxirane (DMDO) is a versatile electrophilic oxidizing reagent that generally oxidizes secondary faster than primary alcohols, although alkenes are typically oxidized in preference to alcohols. The alcohol oxidation reaction involves insertion into the C–H bond, a transition state that is sensitive to stereoelectronic effects. This feature was shown to be advantageous for the selective oxidation of the highly functionalized alcohol substrates shown in Table 12. *endo*-2-Norbornanol was oxidized at a rate 40 times faster than the *exo*-isomer, consistent with a mechanism involving O-atom insertion into the alcohol α-C–H bond.[81] Dimethyldioxirane preferentially oxidizes the secondary alcohol of 1,2-, 1,3-, 1,4-, and 1,5-diols **34**, **18**, **35**, **66**, respectively, without further oxidation to α-diketones.[78] Monooxidation is favored because the strong dipole of the ketone carbonyl destabilizes the transition state for subsequent oxygen insertion.[82] The selectivity for monooxidation of saturated linear diols decreases for 1,4- and 1,5-diols, as the deactivating effect of the carbonyl is reduced. Higher selectivity with these substrates was observed using the H_2O_2/TS-1 system discussed previously.[78] The *cis*-cyclopentanol derivative **67** was oxidized to the ketone in very good yield. A complex mixture of oxidation products was obtained from the *trans*-stereoisomer, in which the preferred approach to the secondary C–H bond is blocked by the hydoxymethylene substituent. Both stereoisomers of the 1,3-disubstituted cyclopentanol **68** were oxidized with DMDO. The non-symmetrical diols **69** and **70** were selectively oxidized at the β-hydroxy, remote from the ester group, although the rate of oxidation of **70** was reduced

Table 13. Oxidation of cyclohexanol derivatives with dimethyldioxirane

Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **75**	DMDO, acetone		>90	84
 **76**	DMDO, acetone		74 16	84
 **77**	DMDO, acetone		>90	84
 **78**	DMDO, acetone		>90	84
 **79**	DMDO, acetone		>48	84
 **80**	DMDO, acetone		>95	84
 **81**	2 equiv. DMDO, acetone, 0–5°C		75	85
 **82**	2 equiv. DMDO, acetone, 0–5°C		91	85

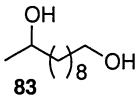
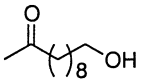
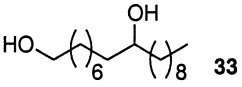
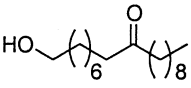
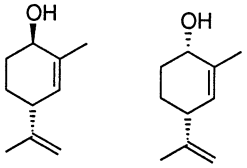
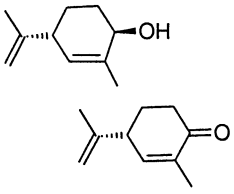
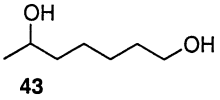
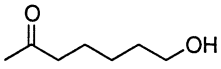
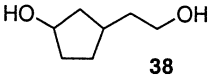
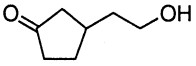
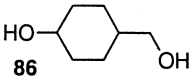
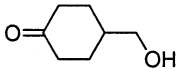
by hindrance from the long alkyl chain.[83] The oxidation of the 1,2,3-triol **71** and azide diol **72** proceeded selectively at C_3.[84] A mixture of 3-keto and 4-keto diols was produced from the 1,3,4 triol **74**.

A variety of cyclohexyl polyol derivatives **75**–**80** in Table 13 were regioselectively oxidized with DMDO.[84] Selective oxidation of the secondary polyhydroxy steroid alcohol **81** with dimethyldioxirane has been reported.[85] The secondary alcohol group at position 3 was readily oxidized by DMDO, but the 12-position was unreactive due to steric interactions between the side chain methyl in a transition state in which there is intramolecular H-bonding to the second oxygen of DMDO. Both the 3- and the 7-hydroxyl groups in diol **82** were efficiently oxidized by DMDO. Dioxiranes generated in situ from oxone and chiral cyclic ketones have been used to oxidize secondary alcohols, and were reported to be unreactive with primary alkyl alcohols.[86]

2.4. Oppenauer oxidation variations

The selective oxidation of secondary alcohols can be achieved using the Oppenauer oxidation and other processes that involve hydride transfer to an acceptor as shown in

Table 14. Oppenhauer oxidation and hydride transfer

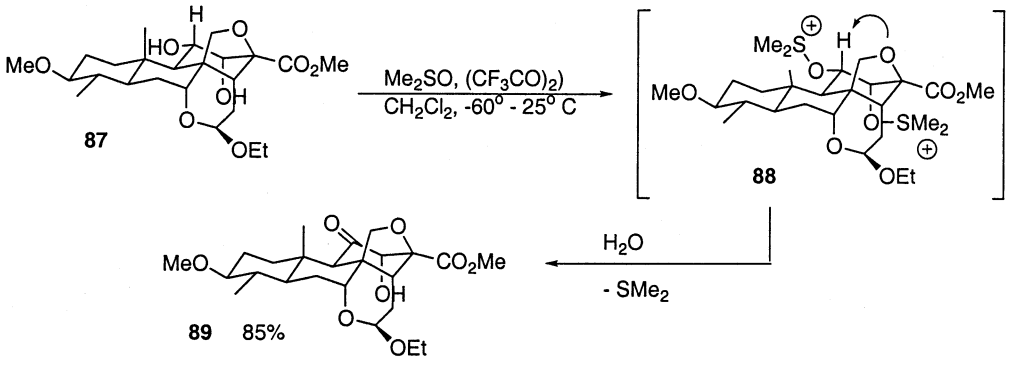
Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **83**	Al_2O_3, 2 equiv. PhCHO, 25° C, 24 h		65	88
 **84**	Cp_2ZrH_2, PhCHO, 130°C, 6 h		81	89
 **33**	$Al(O^tBu)_3$, benzoquinone, 55°C, 16 h		87	40
 **85** anti/syn = 58:42	$HOB(C_6F_5)_2$, 3 equiv. ^{t}-BuCHO, 1 equiv. $MgSO_4$, toluene		52 48	92
 **43**	2.1 equiv. Ph_3CBF_4, CH_2Cl_2		80 (91)[a]	93
 **38**	2.1 equiv. Ph_3CBF_4, CH_2Cl_2		59 (85)[a]	93
 **86**	2.1 equiv., Ph_3CBF_4, CH_2Cl_2		53 (79)[a]	93

[a] Isolated yield (%) from bistrityl ether.

Table 14. Secondary reactions such as ether formation, dehydration, and aldol condensation can be competitive under standard Oppenauer reaction conditions.[87] Secondary alcohols were readily oxidized using a modified reagent consisting of alumina-supported trichloroacetaldehyde or benzaldehyde, under mild conditions that tolerate many functional groups.[88] With this system primary alcohols react slowly, and diol **83** was selectively oxidized at the secondary position. Bis(cyclopentadienyl)zirconium dihydride Cp_2ZrH_2 was an effective catalyst for Oppenauer type oxidation, and secondary alkyl alcohols such as **84** were oxidized efficiently using equimolar amounts of benzaldehyde as an acceptor with heating at 130°C.[89] This system exhibits reversed primary-selectivity with 1,2-, and 1,3-diols, producing the hydroxyaldehydes preferentially.[90] The zirconium alkoxide complex $Zr(O^tBu)_4$ was also found to be an excellent catalyst for the Oppenauer type oxidation with chloral as the hydride acceptor, but the selectivity for aliphatic alcohols has not been reported.[91] Oppenauer oxidation of the diol **33** with $Al(O^tBu)_3$ and benzoquinone as the acceptor gave the hydroxyketone with a selectivity for the secondary alcohol of 7:1.[40] Bis(pentafluorophenyl)borinic acid $(C_6F_5)_2BOH$ was found to be an effective Oppenauer oxidation catalyst using excess pivaldehyde as the hydride acceptor in toluene with $MgSO_4$.[92] Allylic and benzylic alcohols react rapidly, while moderate yields of ketones from secondary alcohols and low yields of aldehydes from primary alcohols were reported. The reagent is sensitive to steric effects, so that the *syn* diastereomer of carveol was oxidized faster than the *anti*. The selective oxidation of secondary alcohols **43**, **38**, and **86** with trityl tetrafluoroborate has been reported.[93] The reaction proceeds via carbenium ion induced hydride abstraction from the trityl ethers formed in situ. Hydride abstraction from secondary trityl ethers was highly favored over primary. The isolated yields of hydroxyketone products was higher starting from the bistrityl ethers.[94] Substrates such as 1,2-diols, and sterically hindered diols such as 2-ethyl-1,3-hexanediol, and 2,2-dimetyl-1,3-butanediol were not oxidized with this procedure.

2.5. Miscellaneous reagents

The Swern oxidation and related methods based on the electrophilic activation of dimethylsulfoxide (Me_2SO) are widely used in synthesis, although few examples of primary–secondary selectivity have been reported.[5] Aliphatic primary and secondary alcohols can be oxidized in the presence of allylic or benzylic alcohols using Me_2SO/$CF_3CO)_2O$, due to the formation of trifluoroacetates from the activated alcohols.[95] Studies on the competitive oxidation of alcohols with $Me_2SO/(COCl)_2$ at −60°C have demonstrated

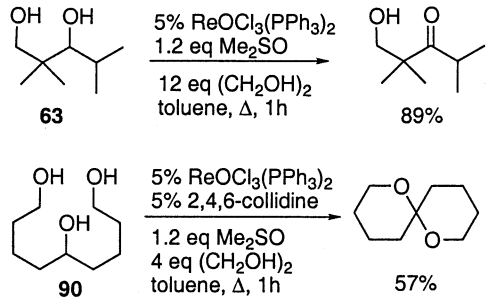


Scheme 6.

that electron-deficient alcohols were generally less reactive, and that secondary alcohols were oxidized at rates slightly faster than primary.[96] Under these conditions chlorodimethylsulfonium chloride reacts with a mixture of alcohols under kinetic control to produce an initial mixture of alkoxysulfonium ions, however, equilibration with remaining alcohol proceeds. The addition of triethylamine base rapidly completes the reaction, and the product distribution reflects the composition of the alkoxysulfonium ions. The selective oxidation of the equatorial alcohol in diol **87** was accomplished using a modified base-free procedure with excess $Me_2SO/CF_3CO)_2O$, followed by rapid warming of the mixture (Scheme 6).[97] The tetrahydrofuran oxygen acts intramolecularly as a base to remove the axial C-11 hydrogen, while the remote alkoxysulfonium ion is unaffected and undergoes hydrolysis to the alcohol during the work up.

A rhenium-catalyzed oxidation of alcohols with Me_2SO in the presence of ethylene glycol was recently shown to convert secondary alcohols to the corresponding ketals.[98] Primary alcohols reacted at slower rates to produce the acetals. The hindered diol **63** was oxidized selectively at the secondary alcohol to give the hydroxyketone in high yield as shown in Scheme 7. Triol **90** was also selectively oxidized at the secondary position followed by intramolecular cyclization to give the spiro ketal in good yield. The faster oxidation of secondary alcohols is consistent with a mechanism where the rate-determining step involves decomposition of a metalloester intermediate.

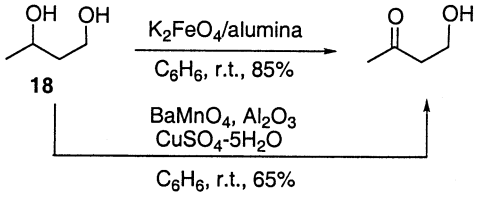
Potassium ferrate (K_2FeO_4) is insoluble in most organic solvents, but was effective as a heterogenous reagent in the presence of basic $Al_2O_3/CuSO_4$.[99] Secondary alcohols were oxidized to ketones but primary alcohols react very slowly under these conditions (Scheme 8). This reagent effectively oxidized the secondary alcohol in 1,3-butanediol **18** to give the hydroxy ketone in high yield. Allylic alcohols were also rapidly oxidized, but the presence of alkenes inhibits the oxidation of saturated secondary alcohols. Manganate has been shown to be a selective heterogenous oxidizing agent using a solid mixture of $BaMnO_4$, Al_2O_3, and $CuSO_4{\cdot}5H_2O$ in benzene.[100] Primary alcohols react very slowly, and **18** was selectively oxidized to give the hydroxyketone in 65% yield.



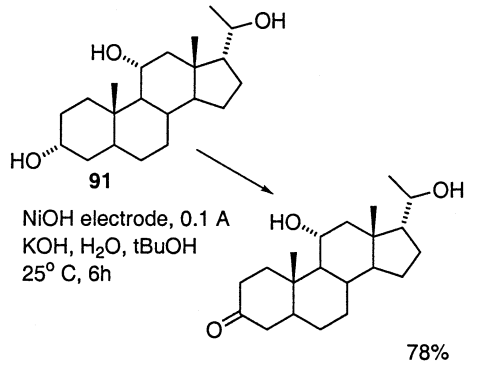
Scheme 7.

The heterogenous oxidation of primary and secondary alcohols occurred on a nickel oxide hydroxide surface that was electrochemically regenerated at a nickel hydroxide electrode (Scheme 9). Sterically hindered secondary alcohols were oxidized more slowly, enabling the C_3-selective oxidation of pregnanetriol **91**.[139]

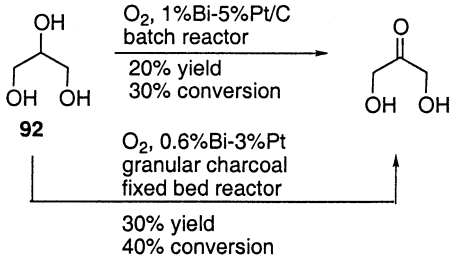
The selective aerobic oxidation of the secondary alcohol of glycerol **92** was accomplished using a Bi–Pt catalyst in acidic media (Scheme 10).[101] Glyceric acid was produced as a byproduct, and was the major product in the absence of



Scheme 8.



Scheme 9.



Scheme 10.

bismuth. Higher conversions to dihydroxyacetone were possible using a fixed bed reactor.[102]

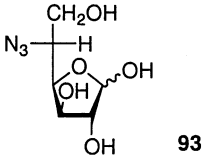
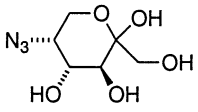
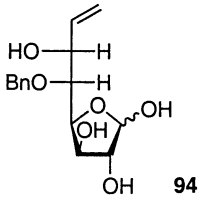
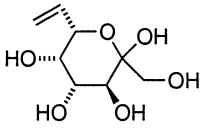
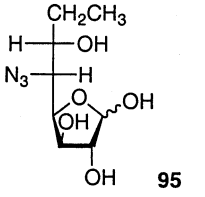
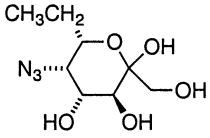
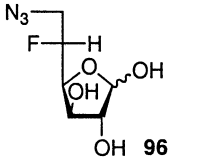
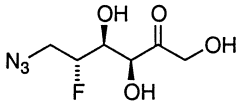
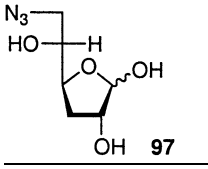
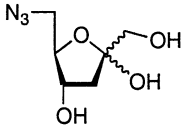
2.6. Reagent chemoselectivity

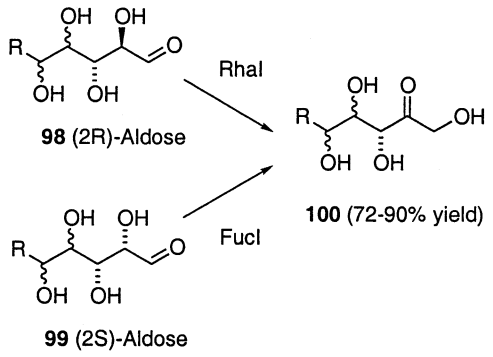
Chemoselectivity is an important consideration when choosing an oxidizing reagent for a particular synthetic application. Side reactions with other functional groups, loss of protecting groups, oxidative bond fragmentations, rearrangements, and epimerization are examples of possible problems. The oxidizing agents discussed in this review are generally considered to be mild, but some incompatibilities of halogen-based oxidants, peroxides, and Oppenauer-type oxidations with various functional groups are highlighted in this section.

Bromine and Cl_2 are powerful oxidizing agents that react readily with unsaturated groups. Other common side reactions include the α-halogenation of carbonyls, and the oxidation of aldehydes to acids or esters. Hydrogen bromide is produced by the oxidation of alcohols with NBS, and initiates the formation of Br_2 through further reaction with NBS. Hypobromous acid is generated from NBS in aqueous media, such that alkenes are converted to bromohydrins under these conditions. Similar side reactions can accompany alcohol oxidations using chlorine-based oxidants such as NCS, and ICC. Aliphatic α-hydroxy acids can undergo oxidative cleavage with NBS. The reaction of amines with positive halogen species can result in N-halogenated compounds and C–N bond cleavage products. The hypervalent iodine reagents DMP and IBX are compatible with many functional groups, and preferentially oxidize alcohols in the presence of amines and sulfides.

Alkene epoxidation occurs preferentially to alcohol oxidation in many systems that use peroxides. Other alkene oxidation products such as diols, α-hydroxy carbonyl compounds, and oxidative cleavage may also be observed when using peroxides. This order of reactivity can

Table 15. Isomerase-mediated synthesis of 2-keto derivatives

Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **93**	Glucose isomerase immobilized $MgSO_4$ 60°C, 24 h		81	105
 **94**	Glucose isomerase immobilized $MgSO_4$ 60°C, 24 h		48	105
 **95**	Glucose isomerase immobilized $MgSO_4$ 60°C, 24 h		61	105
 **96**	Glucose isomerase immobilized $MgSO_4$ 60°C, 8 h		54	106
 **97**	Glucose isomerase immobilized $MgSO_4$, Na_2CO_3 pH 8.5, 40°C, 3 days		70	107



Scheme 11.

sometimes be affected through pH control, or by using biphasic systems with phase transfer catalysis. Oxidation at sulfur and nitrogen are common with peroxides. Peroxy acids can be produced in situ from aldehydes under aerobic conditions and lead to the formation of other oxidized products. Dioxiranes generally prefer the oxidation of sulfur and nitrogen heteroatoms>alkenes>alcohols.

Oppenauer-type oxidations are generally compatible with a variety of acid-insensitive functional groups. Alcohols can be oxidized preferentially in the presence of otherwise easily oxidized functionalities such as alkene, sulfide, and selenide groups using alumina-supported chloral. These reaction conditions are also compatible with strained carbocyclic ring systems and isolated alkenes. Some common side reactions in Oppenauer oxidations include aldol condensation, ester formation, and alkene migration to form conjugated products.

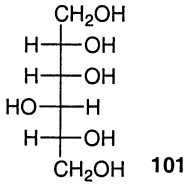
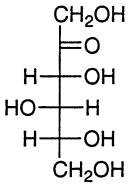
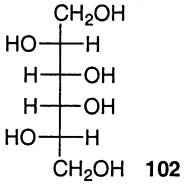
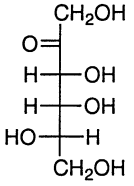
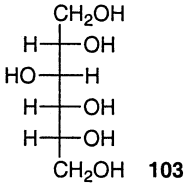
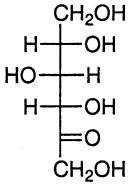
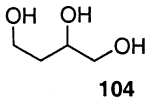
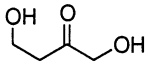
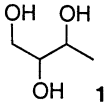
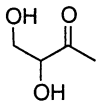
3. Enzymatic oxidations

3.1. Isomerases

Carbohydrates are a valuable resource of polyhydroxy compounds, and are excellent substrates for selective enzymatic oxidations.[103] Glucose isomerase catalyzes the interconversion of D-glucose and D-fructose and is used industrially to generate high fructose corn syrups.[104] This enzyme has been shown to exhibit wide substrate specificity, and is a useful tool for the conversion of aldoses to ketoses. Although the oxidation state of the substrate does not change with isomerization, this reaction provides a highly selective entry to ketone products as shown in Table 15. The isomerization of deoxy-azido compounds **93**, **95**, and the unsaturated furanose **94** gave the corresponding ketopyranose derivatives.[105] Azido-fluoro analogues of D-fructose were synthesized using glucose isomerase catalyzed isomerization of **96** and **97** as a key step.[106,107]

The two ketol isomerases isolated from overexpression clones, L-rhamnose isomerase (RhaI) and the L-fucose isomerase (FucI), catalyze the isomerization of L-rhamnose and L-fucose, respectively (Scheme 11). These enzymes

Table 16. Microbial and enzymatic oxidation of secondary alcohols

Substrate	Reagent	Product(s)	Yield (%)	Ref.
 **101**	*Pseudomonas* sp. Ac, L-glucitol dehydrogenase 35 h		97	109
 **102**	Galacticol dehydrogenase, $NAD^+/NADH+H^+$ lactate dehydrogenase lactate/pyruvate		78	110
 **103**	*Gluconobacter oxydans*, D-Sorbital dehydrogenase, 28 h		100	111
 **104**	*Candida boidinii*, CH_3OH, pH 7 30°C, 2 days		78	112
 **105**	*C. boidinii*, CH_3OH, pH 7 30°C, 2 days		N.R.	112

accept a variety of stereochemically related aldoses for conversion, RhaI isomerizes (2*R*)-aldoses, while FucI isomerizes (2*S*)-aldoses to the ketoses in high yields.[108]

3.2. Dehydrogenases

Regiospecific oxidation of polyols can be accomplished enzymatically using alcohol dehydrogenases as shown in Table 16. Regioselective bacterial oxidation of L-glucitol (**101**) by the bacterial dehydrogenase enzyme provides access to the rare sugar D-sorbose in excellent yield.[109] The enzymatic C_5-selective oxidation of galactitiol (**102**) with partially purified galacticol dehydrogenase provides access to the rare sugar tagatose in 78% yield.[110] The cofactor NAD was used catalytically and regenerating in situ with lactate dehydrogenase. The C_5-position of D-sorbitol **103** was selectively oxidized by the D-sorbitol dehydrogenase of bacterial strains of gluconobacter oxydans to give L-sorbose, a key intermediate in the industrial synthesis of vitamin C.[111] The maximum L-sorbose productivity of 200 g L^{-1} was achieved after 28 h from starting concentrations of 200 g L^{-1} D-sorbitol. Oxidation of the secondary hydroxyl group of triol **104** with methanol yeast *C. boidinii* KK912 gave the hydroxyketone.[112] No other oxidation products were detected in the reaction mixture. The selective oxidation of the secondary alcohol in 1,2,3-butanetriol (**105**) was also observed using this system although the yield was not reported.

4. Kinetic resolution/desymmetrization

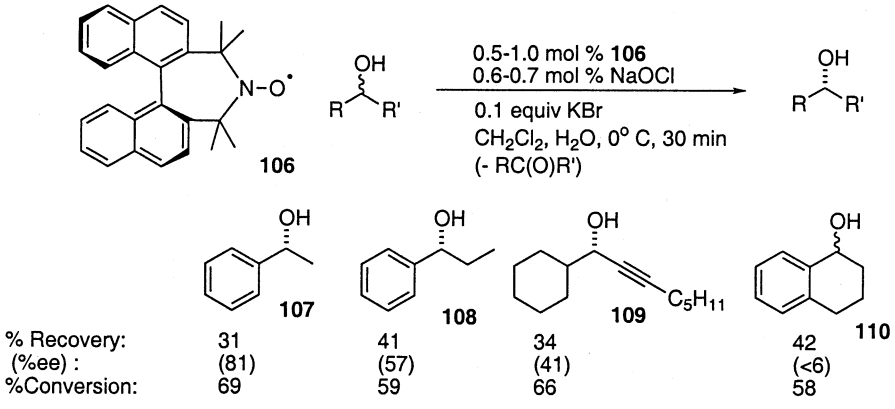
Chiral non-racemic secondary alcohols are important substrates for asymmetric synthesis, and non-naturally occurring optically active alcohols are valuable synthetic targets.[113] Racemic mixtures of secondary alcohols can be easily generated to provide starting materials for oxidative kinetic resolution. The selective oxidation of one enantiomer of a racemate has the potential to recover the unreacted alcohol enantiomer with yields approaching a maximum of 50 at 50% conversion. The oxidative desymmetrization of *meso*-diols provides another route to optically active hydroxyketones, with the potential to be highly efficient with maximum yields of up to 100%. The results of recent efforts to develop reagents and catalysts for the enantioselective oxidation of racemic secondary alcohols and *meso*-diols are discussed in this section.

4.1. Nitroxyl radicals/*N*-oxo ammonium salts

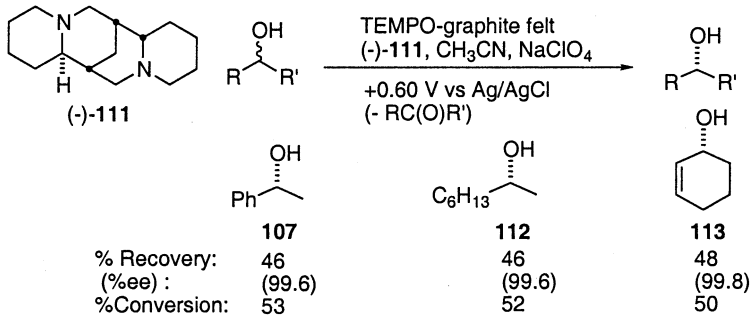
Nitroxyl radicals such as 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) are effective catalysts for the oxidation of alcohols under a variety of conditions which produce *N*-oxo ammonium salts.[7] High primary-selectivity has been observed for alcohol oxidations using nitroxyl radicals/*N*-oxo ammonium salts, however, these reagents are effective for the oxidation of secondary alcohols. Several synthetic routes are available for the preparation of chiral non-racemic nitroxides.[114] Acyl nitroxides derived from (−)-3-pinanecarboxylic acid were used for the kinetic resolution of benzoin and *meso*-hydrobenzoin to produce benzoin of 7–15% ee, respectively.[115] Similar studies using chiral acyl nitroxides derived from (−)-fenchone also gave poor selectivity in the oxidation of racemic 2-methyl-1-phenylpropanol.[116] Chiral piperidine nitroxides were used for the asymmetric oxidation of the *meso* compound *cis*-1,2-cyclohexanedimethanol, providing the α-hydroxyketone in up to 38% ee.[117] The attempted kinetic resolution of racemic 1-phenylethanol was unsuccessful with this reagent.

The chiral nitroxide catalyst (−)-(*S*)-3,5-dihydro-3,3,5,5-tetramethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine-*N*-oxyl **106** was prepared in >97% ee and used for the enantioselective oxidation of a variety of secondary alcohols (Scheme 12).[118] A variety of substituted benzylic alcohols were oxidized using 0.5–1.0 mol% **106**, 0.6–0.7 equiv. of NaOCl and 0.1 equiv. KBr in CH_2Cl_2/H_2O for 30 min at 0°C. The oxidation of (*R*)-1,2,3,4-tetrahydro-1-naphthol (**110**) was unselective under these conditions.

The electro-oxidative kinetic resolution with chiral nitroxide catalyst **106** under constant current conditions in a simple undivided cell with two Pt plate electrodes and mixed CH_2Cl_2/H_2O solvent has been reported.[119] The selectivity was improved by conducting the reaction at low temperature (−15°C), such that (*R*)-1-phenylethanol was recovered in 43% yield with 91% ee at 57% conversion. The chiral *N*-oxyl catalyst **106** was recovered and used repeatedly up to three times without an appreciable change in efficiency or selectivity. The necessity for an organic solvent can be avoided by conducting the electrooxidation in an aqueous silica gel disperse system.[120] The electrocatalytic oxidation of racemic sec-aryl alkyl alcohols using a chiral azaspiro[5.5]undecane-*N*-oxyl radical



Scheme 12.



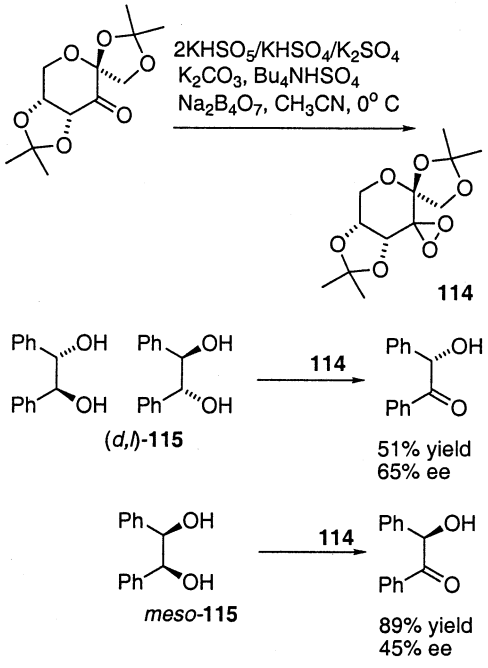
Scheme 13.

prepared from acetonin and (+)-dihydrocarvone left the alcohols with 50–70% ee.[121,118]

Enantioselective oxidation of a variety of secondary alcohols by preparative controlled potential electrolysis with TEMPO-modified graphite-felt electrode in the presence of (−)-sparteine (**111**) as a chiral base left the alcohols with very high enantiopurity (Scheme 13).[122]

4.2. Dioxiranes

The oxidation of a variety of optically active *sec*,*sec*-1,2-diols with the achiral reagent dimethyldioxirane DMDO produced α-hydroxy ketones in high yield and optical purity.[123] The asymmetric oxidation of hydrobenzoin diols using a chiral fructose-derived dioxirane **114** has been described (Scheme 14).[124] The dioxirane **114** was generated in situ from the ketone and potassium peroxymonosulfate in CH_3CN, K_2CO_3, Bu_4NHSO_4, $Na_2B_4O_7$ at 0°C. The oxidation of the *meso*-diol **115** produced (*R*)-benzoin in 89% yield with 45% ee. The oxidative kinetic resolution of racemic (*d*,*l*)-hydrobenzoin produced the (*S*)-hydroxy ketone with 65% ee at 51% conversion.

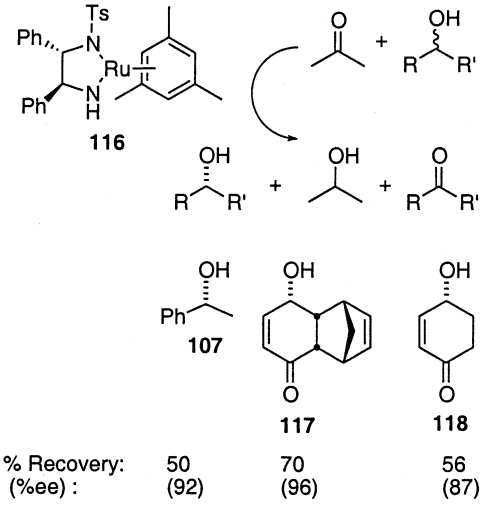


Scheme 14.

4.3. Transition metal catalysis

Catalytic asymmetric transfer hydrogenation using chiral diamine-based Ru(II) arene complexes such as **116** has been used for the kinetic resolution of racemic secondary alcohols **107**, and for the desymmetrization of *meso*-1,4-diols to produce hydroxyketones **117**, **118** in good yields and high enantiopurity (Scheme 15).[125] The reaction occurs in acetone at room temperature, transferring a hydride from the alcohol substrate to acetone. The mechanism proceeds via an intermediate Ru-hydride species. This Ru(II)-catalyzed asymmetric hydrogen transfer has been used as a key step in the synthesis of (−)-chokol G,[126] (+)-tanikolide,[127] (+)-frontalin, and (−)-malyngolide.[128] Ruthenium catalysts prepared from $RuCl_2(PPh_3)_3$ and chiral oxazolinylferrocenylphosphine ligands have also been shown to be effective for the oxidative kinetic resolution of racemic aryl–alkyl alcohols in acetone.[129]

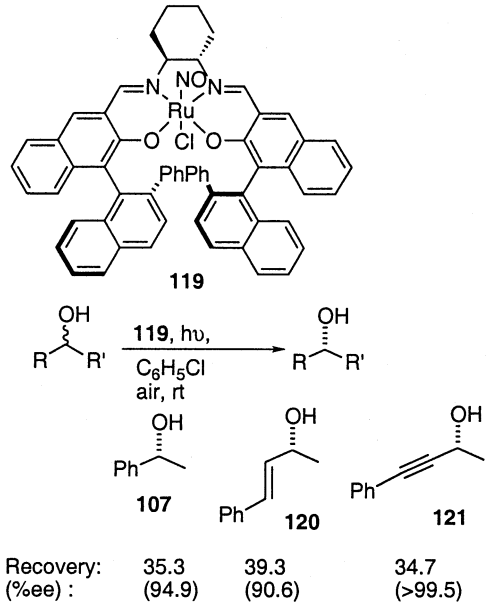
The availability of transition metal catalysts for asymmetric oxidations makes these systems of interest for kinetic resolutions. Catalytic oxidative kinetic resolutions of racemic secondary alcohols using chiral Ru-porphyrin/2,6-dichloropyridine-*N*-oxide,[130] and (salen)Mn(III)/PhIO provided alcohols of low enantiopurity.[131] Recently, highly effective Ru- and Pd-catalyzed aerobic oxidative kinetic resolutions of secondary alcohols have been reported.[132–134] The use of O_2 as the co-oxidant is a par-



Scheme 15.

ticularly desirable feature from economic and environmental perspectives.

The chiral (nitroso)(salen)ruthenium(II) chloride catalyst **119** was used for kinetic resolution of racemic secondary alcohols in air with fluorescent lamp irradiation (Scheme 16).[132] Benzylic **107**, allylic **120**, and propargylic alcohol substrates **121** were resolved in >90% ee.



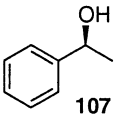
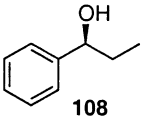
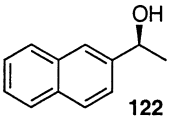
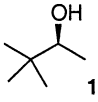
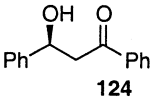
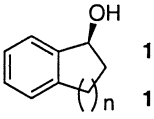
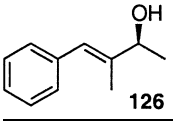
Scheme 16.

The Pd-catalyzed aerobic oxidation of racemic secondary alcohols using $Pd(OAc)_2$ and (−)-sparteine **111** as a chiral ligand afforded resolved benzylic alcohols with high enantiopurity as shown in Table 17.[133] The reaction was also suitable for the kinetic resolution of an aliphatic alcohol **123**, and the oxidative desymmetrization of the *meso*-1,3-diol to give β-hydroxyketone **124**. Similar results were obtained using the palladium norbornadiene (nbd) complex $Pd(nbd)Cl_2$ with (−)-sparteine as a chiral ligand.[134] The reaction was also found to be suitable for cyclic substrates **110**, **125**, and for the allylic alcohol **126**. The simplicity of the reaction conditions makes it feasible to obtain the resolved alcohol products in >50% yield by reducing the isolated ketone to racemic alcohol, and repeating the kinetic resolution cycle.

4.4. Enzymatic methods

Enantiomerically pure secondary alcohols are available from microbial and enzymatic reduction of ketones, and through kinetic resolutions using lipase-catalyzed esterification or ester hydrolysis. Oxidative kinetic resolution with microbial or isolated enzyme systems provides an additional route to these valuable compounds that has not been widely used for secondary alcohols. Baker's yeast was effective for the kinetic resolution of 1-aryl- and 1-heteroaryl ethanols to afford alcohols with >95% ee.[135] Cyclic and acyclic secondary alcohols can be resolved using *Yarrowia lipolytica* yeast strains.[136] Enzyme-catalyzed alcohol oxidations are sometimes hindered by unfavorable thermodynamics and strong product inhibition. Continuous product extraction in a differential circulation reactor was used to overcome the inhibition of glycerol dehydrogenase, resulting in the isolation of (*S*)-1-phenyl-1,2-ethanediol >99% ee at 50% conversion.[137] The enantioselective oxidation of racemic α-hydroxy acids with glycolate dehydrogenase provided (*R*)-hydroxy acids with very high enantiopurity.[138] Substrates with large steric demands adjacent to the hydroxy were not accepted as substrates by the enzyme.

Table 17. Pd/O_2 oxidative kinetic resolution

Alcohol	Method[a,b]	Recovery (%ee)
 **107**	A B	34.1% (98.2) 37% (98.7)
 **108**	A B	40.6% (82.0) 40% (93.1)
 **122**	A B	34.3% (95.9) 44% (99.0)
 **123**	A	41.5% (77.8)
 **124**	A	69% (82)
 **125** n = 1, B **110** n = 2, B	**125** *n*=1, B **110** *n*=2, B	30% (93.4) 31% (99.8)
 **126**	B	29% (91.8)

[a] A: $Pd(OAc)_2$, **111**, DCE, O_2, 60°C. [133]
[b] B: $Pd(nbd)Cl_2$, **111**, MS3A, O_2, $PhCH_3$, 80°C.[134]

5. Conclusions

The synthetic chemist currently has a variety of reagents available to choose from when attempting to selectively oxidize a secondary alcohol. High selectivity is possible with inter- and intramolecular competitions of secondary–primary alcohols when the substrate structure is compatible with the reaction mechanism of the reagent. Halogen derivatives and peroxide/catalyst systems have been widely used, and can be expected to maintain an important role in synthesis. New developments in dioxiranes, homogenous and heterogenous catalysis, and enzymatic oxidations have

extended the scope of suitable substrates greatly. Efficient routes to optically active secondary alcohols through the oxidative kinetic resolution of racemic mixtures, and the desymmetrization of *meso*-diols can provide these valuable products with high levels of enantiomeric purity. Continuing mechanistic investigations and efforts to develop new reagents and catalysts are anticipated to lead to even higher levels of selectivity, and an increasing number of potential applications in synthesis.

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Biographical sketch

Jeffrey B. Arterburn, a native of Denver, received a B.A. degree in chemistry summa cum laude from the University of Colorado, Denver and a Ph.D. degree from the University of Arizona. He conducted post-doctoral research at the Swiss Federal Institute of Technology and the University of Washington. He joined New Mexico State University in 1992 where he is an Associate Professor of Chemistry and Biochemistry. His research interests include the development of selective metal-catalyzed oxidation and amination reactions, and the synthesis of radiopharmaceuticals. He is the director of an NIH-funded New Mexico Biomedical Research Infrastructure Network. He enjoys outdoor sports with his wife and two daughters, and is an avid flyfisher.