Large-Scale Oxidations in the Pharmaceutical Industry†

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† Dedicated to Dr. Frank J. Urban, a source of inspiration to the process research group at Pfizer, on the occasion of his retirement.

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1. Introduction

Oxidation reactions are powerful tools to convert a position that is protected in a lower oxidation state to the desired functionality and for the functionalization of otherwise unfunctionalized positions. Yet despite their power as a synthetic tool and abundant use in academic research, oxidation reactions as a whole comprise as little as 3% of the reactions used on a preparative scale in the pharmaceutical industry.[1] This disparity is likely due to a mixture of factors. To streamline production processes, every effort is made to develop routes that introduce functionality in the correct oxidation state and without protection. While the byproducts of many oxidants are fairly environmentally benign, many of the more selective reagents produce undesirable waste products. Perhaps the greatest factor influencing the hesitation to employ oxidation reactions on a large scale is the safety of these processes. The majority of reactions run in a production facility are in flammable organic solvents, and on a large scale, the potential for static electric discharge in the solvent charge lines or the reactor itself is significant. In the case of reactions other than oxidations, fires and explosions are prevented by starving the solvent and reactants of oxidants. In the case of oxidation reactions, this safety factor is absent and all three elements

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Sally Gut Ruggeri was born in San Francisco, California, in 1960. She received her A.B. from Cornell University in 1982, carrying out research under the direction of Dave Collum. She briefly carried out research at the Scripps Oceanographic Institute with Bill Fenical prior to moving to the Unviersity of Wisconsin—Madison, where she received her Ph.D. in 1987 with Barry Trost. After a National Cancer Institute postdoctoral fellowship at Stanford University with Paul Wender, she joined the Pfizer Process Research Group in 1989.

John Ragan was born in 1962 in Kansas City, Missouri. He received his S.B. degree in chemistry from MIT (1985), where he did undergraduate research with Rick Danheiser. He completed his Ph.D. with Stuart Schreiber at Yale (1985–1988) and Harvard Universities (1988–1990), working on the total synthesis of FK506. Following an American Cancer Society postdoctoral fellowship with Clayton Heathcock at the University of California—Berkeley, he joined Pfizer in 1992, initially in Discovery Chemistry, moving to Chemical Research & Development in 1996, where he is an Associate Research Fellow. He is currently serving on the Board of Editors of *Organic Syntheses*.

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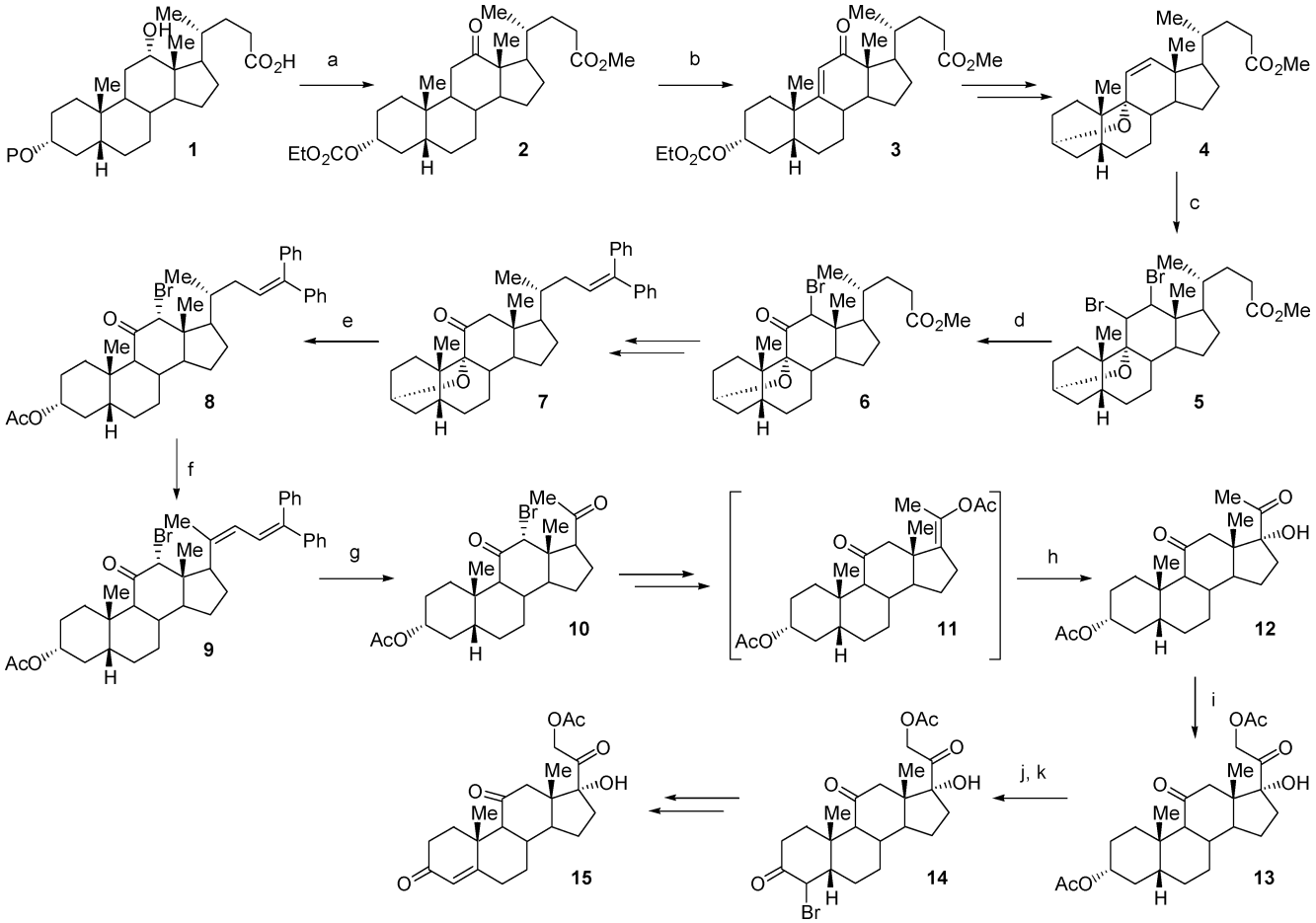
required for combustion (fuel, energy, and oxidant) are present in the reactor. While these issues can be addressed in order to run oxidations routinely and safely on scale, common errors that can occur in a manufacturing environment, such as charging reagents out of order or too rapidly, must be taken into consideration when designing a safe process. These considerations, in addition to the highly reactive nature of many of the oxidants and thermal instability of some products (such as diazo compounds, *N*-oxides, and the like) likely limit the use of oxidative processes in production syntheses.

Caution: Many of the oxidants, oxidation reactions, and products described herein have the potential to release large amounts of energy in an uncontrolled fashion. Investigators considering running a large-scale oxidation reaction should consult the literature, run appropriate safety tests, and take proper precautions when running the reaction.

Despite the challenges, oxidation reactions are routinely run in production facilities to make many of the commercial pharmaceuticals available today. Some classes of drugs require a high number of oxidations to be produced, such as steroids and prostaglandins. A particularly oxidation-rich process depicted in Scheme 1 is the Merck process for converting desoxycholic acid (**1**) to cortisone acetate (**15**). This process was run on a multihundred kilogram scale in the 1950s and 1960s and utilized 11 separate oxidations.[2]

This review covers oxidation reactions run in 1980 or later, on a scale of around 100 g or larger (as demonstrated in the experimental section of the publication), or clearly developed by a process chemistry group to be run on a large scale. Excluded from discussion are biotransformations and oxidative aromatic substitution reactions (such as nitrations and halogenations of aromatic rings). The review is divided into sections based on the functional groups being oxidized, allowing for easy comparison of reagents and substrates used in various transformations.

Scheme 1. Merck Process for Cortisone Acetate (15)[a]



[a] (a) CrO_3; (b) (i) Br_2; (ii) NaOAc; (c) Br_2; (d) $Na_2Cr_2O_7$, CrO_3; (e) (i) HBr; (ii) Ac_2O; (f) (i) NBS, *hν*; (ii) heat; (g) $Na_2Cr_2O_7$, H_2SO_4; (h) monoperphthalic acid, NaOH; (i) Br_2, KOAc; (j) dibromodimethyl hydantoin; (k) Br_2.

2. Oxidation of Carbon–Carbon Bonds

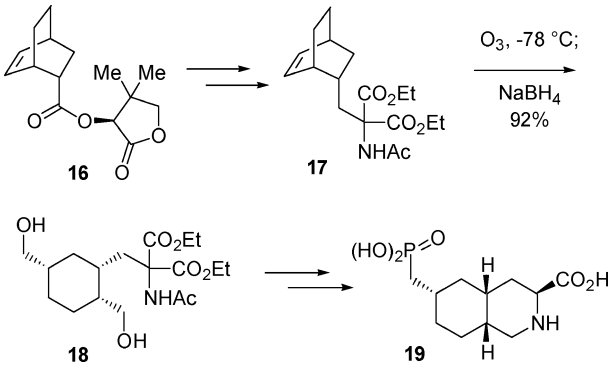
Oxidation of carbon−carbon bonds is frequently utilized in the synthesis of pharmaceutical agents, because the resulting functionalities (e.g., vicinal diols, epoxides, carbonyl compounds) provide valuable synthetic intermediates and are themselves frequently present in the active pharmaceutical ingredient (API). Asymmetric variants of several oxidations (e.g., epoxidations, dihydroxylations) have found numerous applications as exemplified in this section.

2.1. Oxidative Cleavage of Olefins

2.1.1. Ozonolysis

There are several examples of oxidative cleavage of olefins by ozonolysis. Hansen and co-workers utilized a chiral-auxiliary-based Diels−Alder cycloaddition to generate bicyclic olefin **17**, which was cleaved by ozonolysis to generate diol **18** following reductive workup (Scheme 2).[3] The

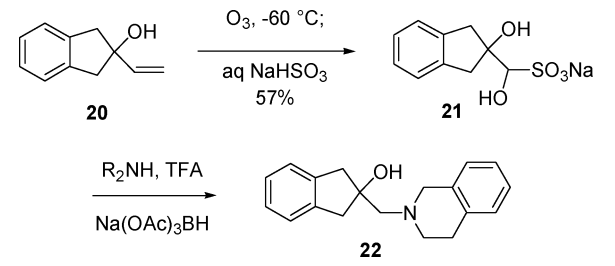
Scheme 2. Olefin Ozonolysis in the Synthesis of LY235959 (19)



suitability of this route for further scale-up was suggested. Further transformations converted this diol to *cis*-perhydroisoquinoline LY235959 (**19**), an *N*-methyl-D-aspartate (NMDA) receptor antagonist.

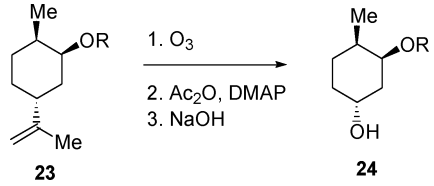
The scale-up of the ozonolysis of olefin **20** (Scheme 3) has been described.[4] The primary ozonide was trapped by methanol to generate the methoxy-hydroperoxide,[5,6] which was treated with aqueous sodium bisulfite ($NaHSO_3$) to effect simultaneous peroxide reduction and bisulfite formation to generate **21** (57% yield on 2.3 kg scale). This bisulfite adduct could be used directly in a reductive amination to generate amines such as **22**.

Scheme 3. Ozonolysis Followed by in-Situ Bisulfite Adduct Formation



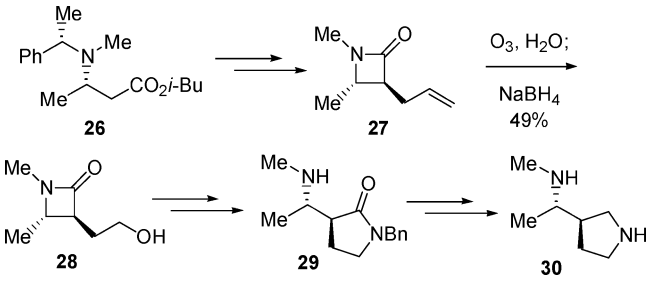
Varie has described the conversion of (*R*)-carvone to protected alcohols **23** (Scheme 4, R = TBS, TBDPS, or CO-*t*-Bu).[7] The propenyl side chain was then cleaved by ozonolysis followed by Criegee rearrangement of the intermediate methoxy-hydroperoxide to generate the acetate of the desired alcohols (**24**).[8]

Scheme 4. Ozonolysis Followed by Criegee Rearrangement



McWhorter described the ozonolysis of olefin **27** to prepare alcohol **28** (Scheme 5), which was converted to

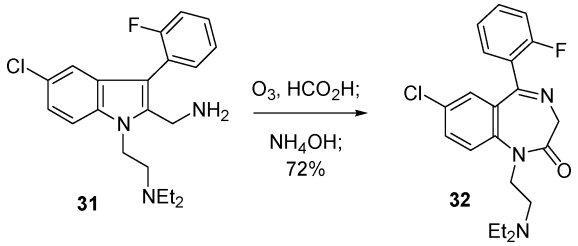
Scheme 5. Synthesis of Premafloxacin (30)



diamine **29**, an intermediate in the synthesis of premafloxacin (**30**).[9] Interestingly, this reaction was executed in water. Several related ozonolyses were also described. The olefin substrates were prepared by asymmetric Michael addition of chiral benzylic amines to esters of crotonic acid.

Workers at Sumitomo reported ozonolytic cleavage of indole **31** and cyclization of the resulting keto-amine to generate benzodiazepine **32** (Scheme 6, 72% yield on 250 g

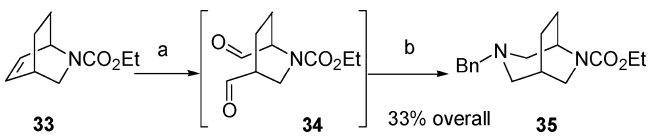
Scheme 6. Ozonolytic Cleavage of an Indole Followed by Cyclization To Generate a Benzodiazepine



scale).[10] Chromium trioxide also effected this oxidative cleavage, but with lower efficiency (28%).

Kleinman utilized ozonolysis of bicyclic carbamate **33** to generate bis-aldehyde **34**, which was treated with benzylamine and sodium cyanoborohydride to generate the bicyclic amine **35** (Scheme 7).[11]

Scheme 7. Conversion of 33 to 35[a]

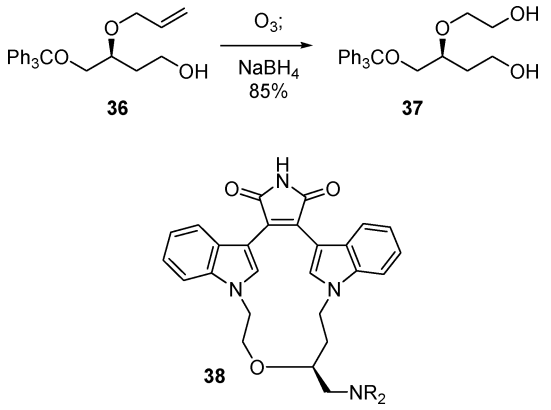


[a] (a) (i) O_3; (ii) Me_2S; (b) $BnNH_2$, sieves, $NaCNBH_3$.

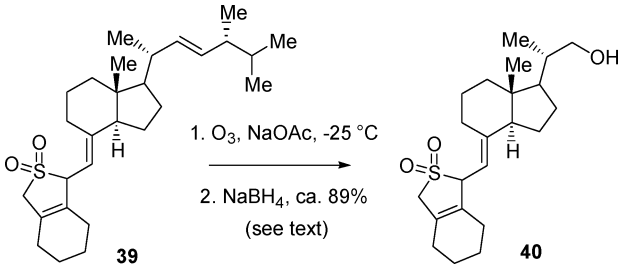
Researchers at Lilly utilized ozonolysis followed by $NaBH_4$ workup to provide diol **37**, an intermediate in the synthesis of protein kinase C (PKC) inhibitors such as **38** (Scheme 8).[12]

Alcohol **40** was prepared from olefin **39** by ozonolysis followed by $NaBH_4$ workup (Scheme 9, ca. 89% yield, 288

Scheme 8. The Synthesis of PKC Inhibitor 38



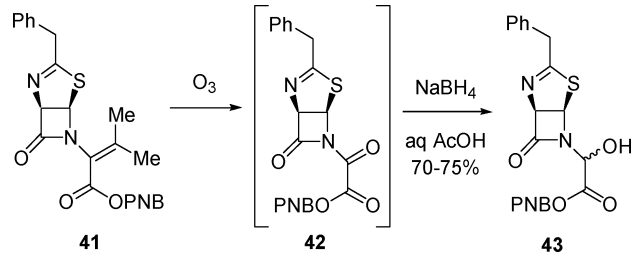
Scheme 9. Ozonolysis in the Preparation of 24(*S*)-Hydroxyvitamin D_2



g scale; yield estimated from a 51% overall yield for a six step sequence).[13] It is noteworthy that the least substituted olefin was selectively oxidized (the proximity of the electron-withdrawing sulfone to the other two olefins may also contribute to this selectivity). Sulfone **40** was a precursor to 24(*S*)-hydroxyvitamin D_2, a metabolite of vitamin D_2.

Ozonolysis of tetrasubstituted enamide **41** has been employed to generate α-hydroxyester **43** (Scheme 10, PNB

Scheme 10. Ozonolysis to Prepare α-Hydroxyester 43



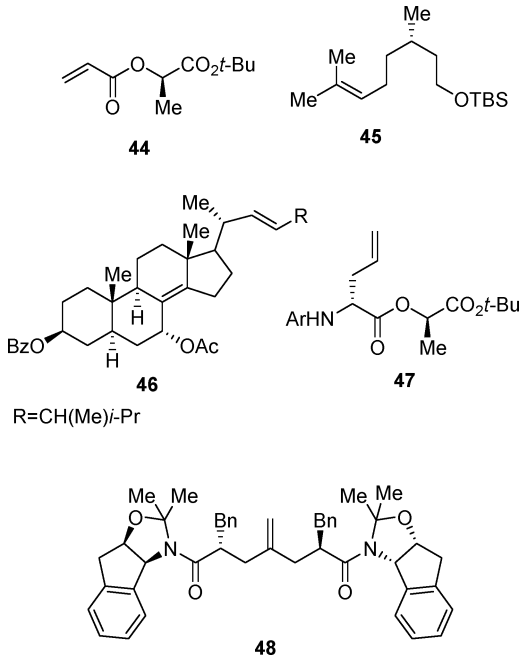
= *p*-nitrobenzyl). This sequence was scaled to 250 kg and proceeded in 70−75% yields. Although the intermediate α-dicarbonyl lactam **42** was not isolated, its direct formation from the ozonolysis (i.e., prior to addition of any reducing agent) indicated that the initial ozonide breaks down to generate this product plus the carbonyl oxide of acetone.[14,15]

Scheme 11 summarizes five further examples (**44**−**48**), all of which were described by process research groups on laboratory scale for the conversion of terminal olefins to aldehydes (**44**, **47**),[16] a 1,2-disubstituted olefin to aldehyde (**46**),[17] a 1,1,2-trisubstituted olefin to an aldehyde (**45**),[18] and a 1,1-disubstituted olefin to a secondary alcohol (**48**).[19] Interestingly, in this last example the product chiral alcohol was C_2-symmetric, such that the secondary carbinol generated in the oxidation was a chirotopic, nonstereogenic center.[20]

2.1.2. Periodate, Peroxide, and Other Reagents

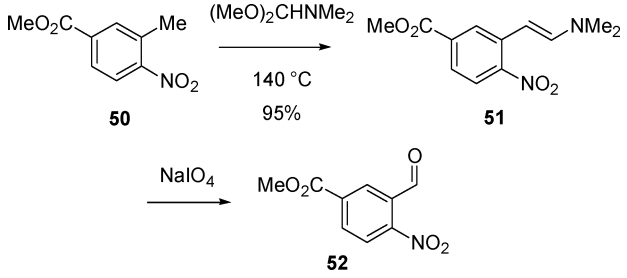
Electron-rich olefins (e.g., enamines) can be oxidatively cleaved by treatment with periodate reagents. A strategy

Scheme 11. Ozonolysis of Olefins to Aldehydes and Ketones



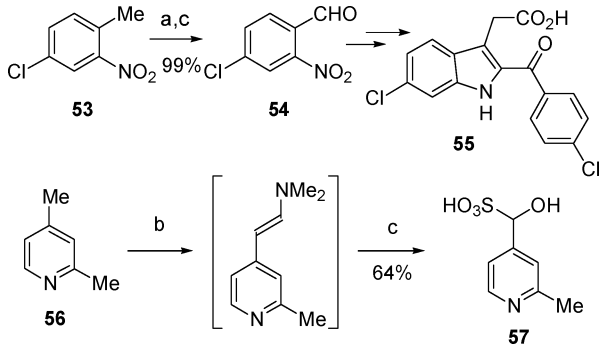
based on this oxidation was developed by Coe and co-workers at Pfizer for oxidation of activated aromatic methyl groups (e.g., *o*-nitrotoluenes).[21] The example shown (Scheme 12, **51** to **52**) proceeds in 95% yield on a 48 g scale.

Scheme 12. Oxidation of Activated Aromatic Methyl Groups



This strategy has been utilized by colleagues in Pfizer's Chemical Research & Development group to prepare aldehyde **54**, a precursor to **55**, a cyclooxygenase (COX)-2 inhibitor, and to prepare bisulfite adduct **57** from 2,4-lutidine (Scheme 13). Nitrobenzaldehyde **54** was prepared in 99%

Scheme 13. Oxidation of Activated Aromatic Methyl Groups[a]



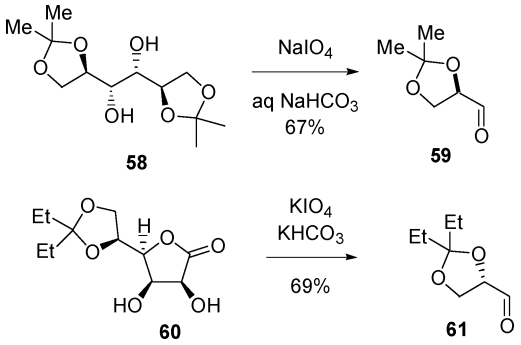
[a] (a) $(MeO)_2CHNMe_2$, DMF, 140 °C; (b) BuLi, Et_2NH, DMF; (c) (i) $NaIO_4$; (ii) H_2SO_3.

yield on a 25 g scale from the corresponding 2-nitrotoluene derivative.[22] Bisulfite adduct **57** was prepared in 64% overall

yield from 2,4-lutidine on a 2.8 kg scale.[23] The regioselective lithiation of 2,4-lutidine had been earlier noted by Evans.[24]

Oxidative cleavage of vicinal diols is frequently utilized in the preparation of aldehydes and ketones. Researchers at Lilly have described extensive optimization and scale-up studies on the preparation of 2,3-*O*-isopropylidene-D-glyceraldehyde (**59**) from D-mannitol, which included the oxidative cleavage of diol **58** (Scheme 14).[25] The periodate

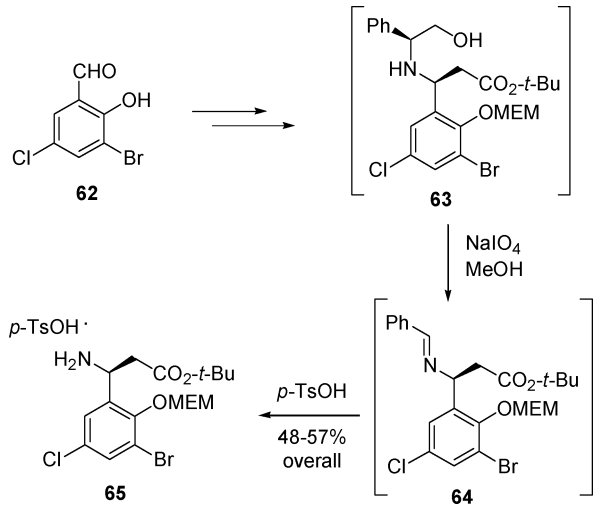
Scheme 14. Preparation of Glyceraldehydes 59 and 61



cleavage proceeded in 67% yield on a 10 g scale and has been successfully scaled to >100 kg quantities. In a subsequent publication,[26] Schmid described an improved preparation of the analogous pentylidene-protected aldehydes from **60** using a buffered potassium periodate system; both enantiomers were prepared.

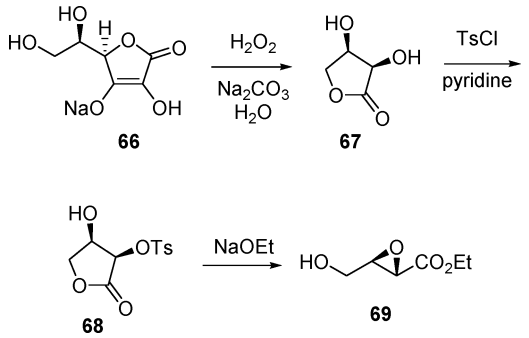
The sequence shown in Scheme 15 was utilized for conversion of salicylaldehyde **62** to β-aminoester **65**,[27] in which oxidative cleavage of amino alcohol **63** to imine **64** was executed on a 150 kg scale. The overall yield for the sequence ranged from 48% to 57%. Sodium periodate was preferred over lead tetraacetate for this oxidation for obvious reasons. Aminoester **65** is a precursor to an $\alpha_v\beta_3$ integrin antagonist.

Scheme 15. Amino Alcohol Cleavage To Prepare an $\alpha_v\beta_3$ Integrin Antagonist



Hydrogen peroxide-mediated oxidation of sodium erythorbate (**66**) was utilized to generate dihydroxylactone **67**, which was converted to epoxide **69** by tosylation and ethanolysis (Scheme 16).[28] This route was preferred for scale-up over other routes examined (e.g., Sharpless AE and derivatization of diethyl tartrate).

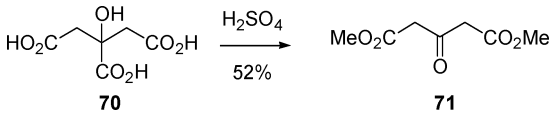
Scheme 16. Preparation of Epoxide 69



Noyori and co-workers have reported the oxidative cleavage of cyclohexene to adipic acid ($HO_2C(CH_2)_4CO_2H$) with 30% hydrogen peroxide, catalytic $Na_2WO_4 \cdot 2H_2O$, and a phase-transfer catalyst ($Me(n\text{-octyl})_3NHSO_4$), both 1 mol %.[29] The crystalline product is isolated by filtration in 90% yield (100 g scale), and the aqueous phase can be recycled into another oxidation by addition of peroxide and phase-transfer catalyst.

Dimethyl-1,3-acetonedicarboxylate (**71**) has been prepared by oxidative decarboxylation of citric acid (**70**); this was executed on a 400 g scale in 52% yield (Scheme 17).[30] This

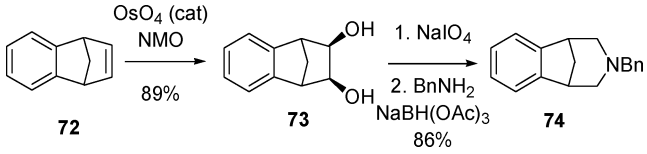
Scheme 17. Preparation of Dimethyl-1,3-acetonedicarboxylate (71) by Oxidative Decarboxylation



procedure is a modification of an *Organic Syntheses* procedure, which utilized fuming H_2SO_4.[31,32]

Several oxidative protocols for the conversion of olefin **72** to bicyclic amine **74** have been described (Scheme 18).[33]

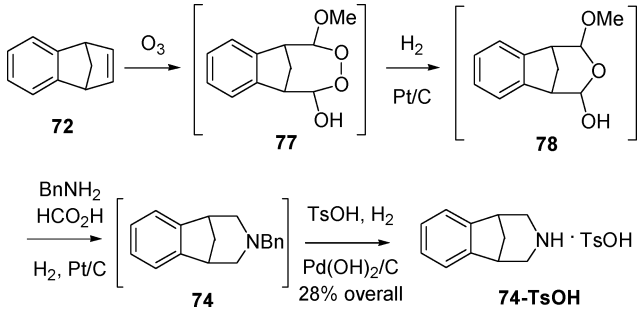
Scheme 18. Conversion of Olefin 72 to Bicyclic Amine 74



Dihydroxylation of **72** can be effected with catalytic OsO_4 (0.126 mol %) and either *N*-methylmorpholine-*N*-oxide or sodium chlorite as stoichiometric oxidants. The former provides an 89% yield of diol **73** on a 400 g scale. Oxidative cleavage with $NaIO_4$ in aqueous dichloroethane (DCE) generates a solution of the bis-aldehyde, which is condensed with benzylamine and reduced with $NaBH(OAc)_3$ directly; the overall yield for this sequence is 86% on a 40 g scale.

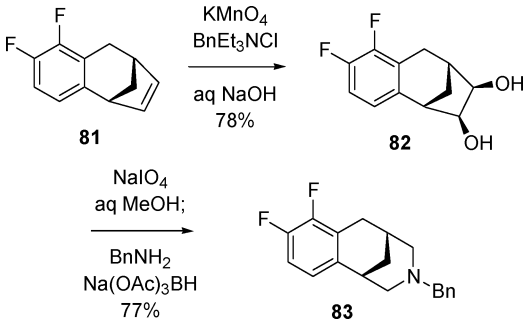
An alternative ozonolysis sequence is also described (Scheme 19), in which the methoxyhydroperoxide is reduced by hydrogenation over Pt/C, and benzylamine and HCO_2H are added to effect reductive amination after further hydrogenation over the same catalyst. Hydrogenolysis over Pearlman's catalyst in the presence of TsOH then effects debenzylation and salt formation. This sequence proceeds without isolation of intermediates to provide a 28% overall yield of the tosylate salt of **74** from olefin **72**; despite its lower yield, the ozonolysis sequence is preferred due to its improved waste stream issues and ease of operation.[33]

Scheme 19. Improved Process for the Conversion of Olefin 72 to Bicyclic Amine 74



Frost has reported a similar dihydroxylation/oxidative cleavage/reductive amination strategy for the conversion of olefin **81** (prepared by an enantioselective Heck cyclization) to benzylamine **83** via diol **82** (Scheme 20).[34] They found

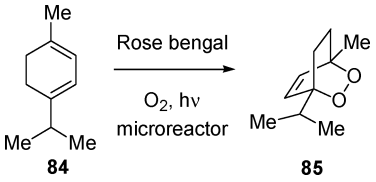
Scheme 20. Conversion of Olefin 81 to Benzylamine 83



that $KMnO_4$ could be used in place of OsO_4 for the dihydroxylation reaction, which simplified handling and waste disposal. This chemistry has been executed on kilogram scale.

Finally, an example is included wherein the authors describe singlet oxygen addition to α-terpinene **84** in a microfabricated nanoreactor (Scheme 21).[35] The experiment

Scheme 21. Addition of Singlet Oxygen to 84 in a Nanoreactor



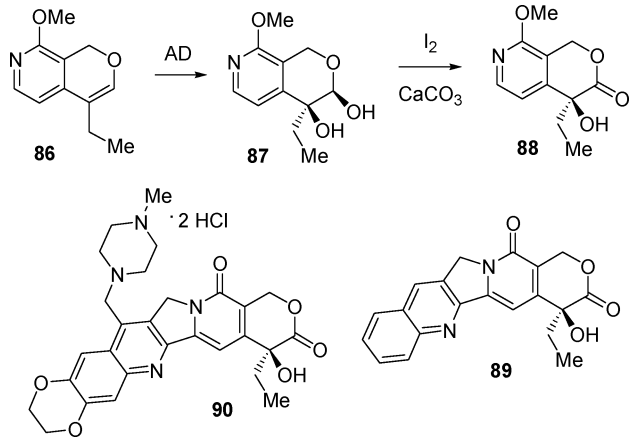
described is on modest scale (ca. 600 mg), but due to the continuous flow nature of the system, it could in principle be effectively scaled to larger throughput. The advantages of flow chemistry relative to batch reactors in this type of photochemical reaction are discussed and represent an important area of research in process chemistry.

2.2. Dihydroxylation of Olefins

2.2.1. Asymmetric Dihydroxylations

There are several examples of the Sharpless asymmetric dihydroxylation (AD) reaction applied to pharmaceutical scale-up efforts. This powerful methodology has found applications for preparation of diols, amino alcohols, epoxides (via cyclization of the product diol), and α-hydroxyketones from dihydroxylation of enol ethers.[36,37] An example of the latter class was reported by Fang and co-workers, who studied the asymmetric dihydroxylation of olefin **86** (Scheme 22).[38] They found that with the DHQD (AD-mix-β)−PHAL

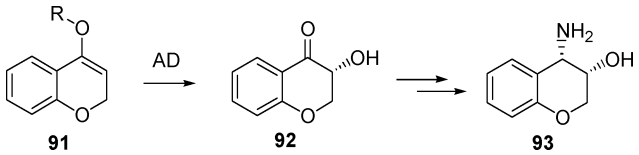
Scheme 22. Dihydroxylation in the Synthesis of Camptothecin (89) and Analog GI147211C (90)



(phthalazine) system, a modest 26% ee was obtained. However, use of the (DHQD)2−PYR (pyrimidine) ligand provided a much improved 94% ee. Oxidation of the hemiacetal product (**87**) provided lactone **88**, which could be converted to camptothecin (**89**) in three steps. This intermediate was also utilized in the synthesis of camptothecin analogue GI147211C (**90**).[39]

The dihydroxylation of enol ethers such as **91** has been studied in the course of preparing aminochromanol **93** (Scheme 23).[40] A variety of enol ethers were examined,

Scheme 23. Dihydroxylation of Enol Ether 91

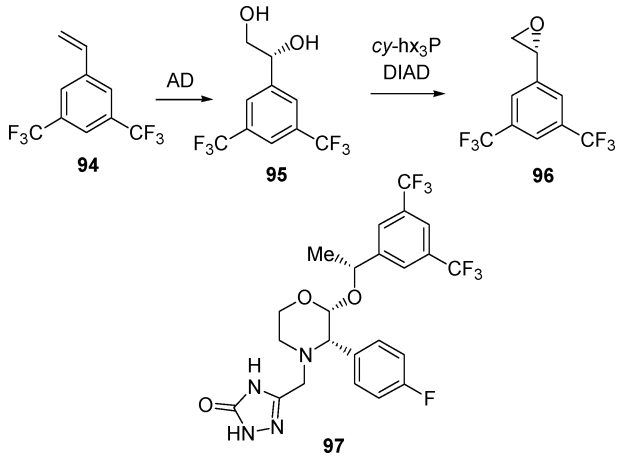


ranging from R = methyl to R = decyl, including branched and heteroatom-substituted side chains. The *n*-pentyl enol ether emerged as an optimal substrate; with the Sharpless AD-mix-β ($K_3Fe(CN)_6$, $Na_2S_2O_8$, K_2CO_3, $K_2OsO_4 \cdot 2(H_2O)$, $MeSO_2NH_2$) and $(DHQD)_2PHAL$ ligand in aqueous acetonitrile, a 99% yield of hydroxy-ketone **92** was realized with 94% ee. The corresponding tetralone and seven-membered ring enol ethers were also studied. Use of freshly prepared AD mix reagent was found to be beneficial, allowing much lower oxidant and solvent levels to be used.

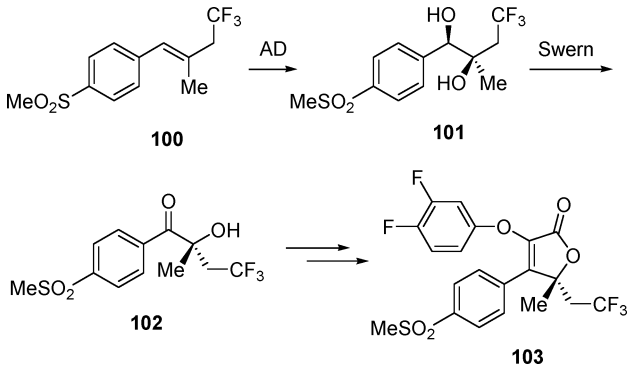
The Sharpless AD system has been applied to the preparation of 3,5-bis-trifluoromethylstyrene oxide (**96**), a precursor to neurokinin-1 (NK-1) antagonist **97** (Scheme 24).[41] The AD-mix-α $(DHQ)_2$−PHAL ligand provided an 80% yield of diol **95** with 92% ee; recrystallization increased the optical purity to 97−99% ee. This diol was then dehydrated under Mitsunobu conditions with *cy*-hx_3P and diisopropylazodicarboxylate to provide epoxide **96**; use of tricyclohexylphosphine in place of Ph_3P was critical for retention of optical purity in the cyclodehydration.

Workers at Merck utilized the Sharpless AD of olefin **100** to prepare tertiary α-hydroxyketone **102** (Scheme 25), a precursor to COX-2 inhibitor L-784,512 (**103**).[42] Several ligands were studied, with $(DHQD)_2PHAL$ providing the highest enantioselectivity (79% ee). The product diol was

Scheme 24. Preparation of NK-1 Antagonist 97



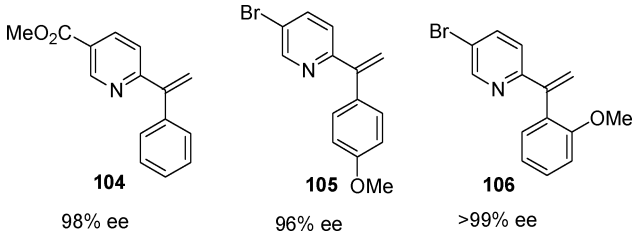
Scheme 25. Dihydroxylation in the Preparation of COX-2 Inhibitor L-784,512 (103)



crystallized to >98% ee. The analogous aryl sulfide substrate was found to provide improved selectivity (82% ee), with generation of a mixture of sulfoxide and sulfone diols; oxidation of this mixture (H_2O_2, cat. Na_2WO_4) provided the sulfone.

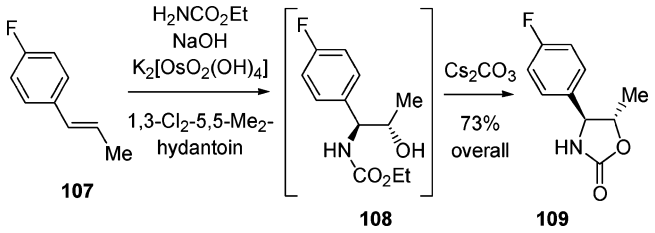
Wang has studied the Sharpless AD of several 1-aryl-1′-pyridylalkenes.[43] While the parent 2-pyridyl olefin gave slow conversion and modest selectivity (20−35% ee), substituted pyridines gave better results. Of 25 substrates examined, 10 gave >75% ee, and 7 were above 94% ee. The best ligand was $(DHQD)_2AQN$. Three of the best substrates are shown in Scheme 26.

Scheme 26. Examples of Olefins That Were Dihydroxylated and Resulting ee of the Products



The Sharpless asymmetric aminohydroxylation has been used to prepare chiral oxazolidin-2-ones (Scheme 27).[44] Optimal results were obtained with the phthalazine ligands (e.g., $(DHQ)_2PHAL$) and 1,3-dichloro-5,5-dimethylhydantoin as stoichiometric oxidant in place of *t*-BuOCl. Enantioselectivity ranged from 88% to 98% ee. Regioselectivity for the benzylamine isomer (vs benzyl alcohol) ranged from 1:1 to 10:1. The undesired isomer could be removed by chromatography or more conveniently by selective base-mediated cyclization to the oxazolidinone (the benzyl alcohol isomer cyclized slugglishly under these conditions). The uncyclized substrate was then hydrolyzed to the amino alcohol, which could be separated by acid extraction. The example shown proceeded in 73% yield and 90−93% ee. The authors indicate that scale-up to kilograms has been performed.

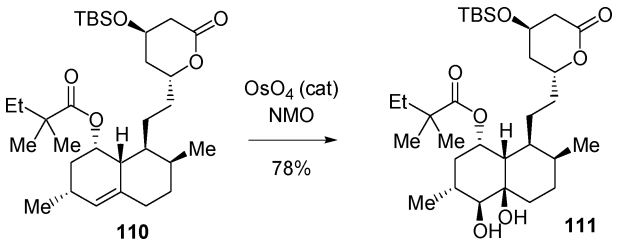
Scheme 27. Sharpless Asymmetric Aminohydroxylation To Prepare Chiral Oxazolidin-2-ones



2.2.2. Non-Asymmetric Dihydroxylations

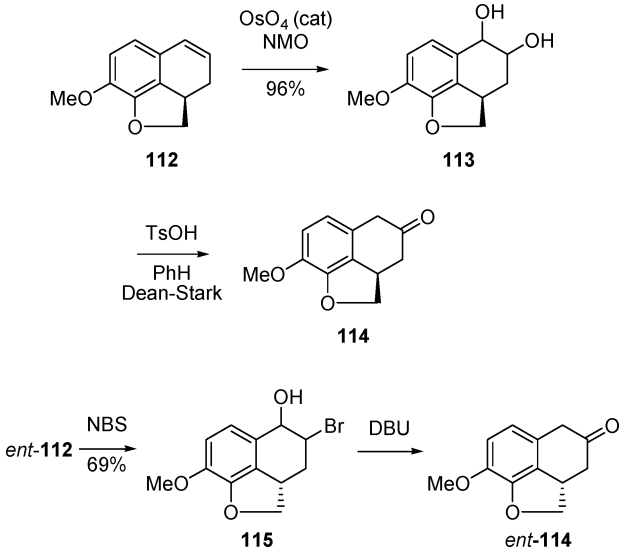
There are several non-asymmetric dihydroxylation scale-ups reported. The diastereoselective dihydroxylation of olefin **110** in the preparation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor L-679,336 has been reported (Scheme 28).[45] Diol **111** was formed in 78% yield on a 500 g scale (39:1 diastereofacial selectivity).

Scheme 28. Diastereoselective Dihydroxylation of Olefin 110



Chemists at Sandoz reported the dihydroxylation of olefin **112** to generate a mixture of cis-diols (**113**), which upon dehydration with TsOH/Dean−Stark conditions generated ketone **114** (Scheme 29).[46] The dihydroxylation proceeded

Scheme 29. Conversion of Olefin 112 to Ketone 114

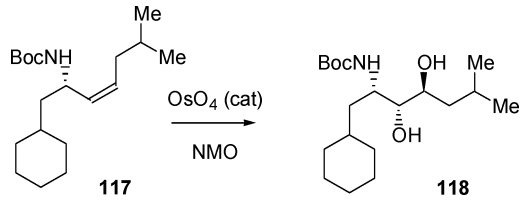


in 96% yield on a 100 g scale. The analogous transformation starting with *ent*-**112** was effected by halohydrin formation

with *N*-bromosuccinimide (NBS), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated dehydrobromination to form *ent*-ketone **114** (presumably via epoxide formation and rearrangement).

The dihydroxylation of allylic amines such as **117** has been studied (Scheme 30).[47] Krysan et al. found a strong solvent

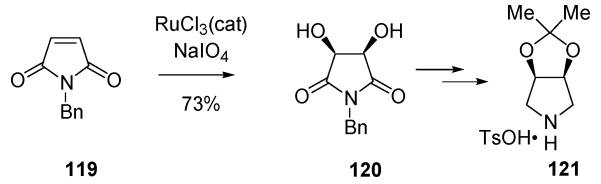
Scheme 30. Dihydroxylation of Allylic Amine 117



dependence for the stereochemical outcome, with 2-propanol preferred over aq THF (82:18 vs 50:50, respectively) for formation of threo isomer **118**. The level of facial selectivity was observed to degrade as the reaction proceeded, which was interpreted as arising from a less selective catalyst generated from oxidation of the intermediate osmium glycolate species. Three other allylic amines were examined, all of which were less facially selective than the 1,2-cis-disubstituted olefin (e.g., the trans isomer was 65:35, and the 1,1-disubstituted olefin was 57:43).

Dihydroxylation of *N*-benzylmaleimide (**119**) to generate diol **120** was reported on a 50 kg scale (73% yield, Scheme 31).[48] This product is a precursor to pyrrolidine−tosylate **121**,

Scheme 31. Preparation of Pyrrolidine−Tosylate 121



which is generated by diol protection, imide reduction with borane−THF, and benzylamine hydrogenolysis. The latter transformation can also be effected by isolation of the borane−amine complex from the imide reduction and treatment with $Pd(OH)_2/C$, which effects simultaneous borane−amine decomplexation and hydrogenolysis.[49]

2.3. Epoxidation of Olefins

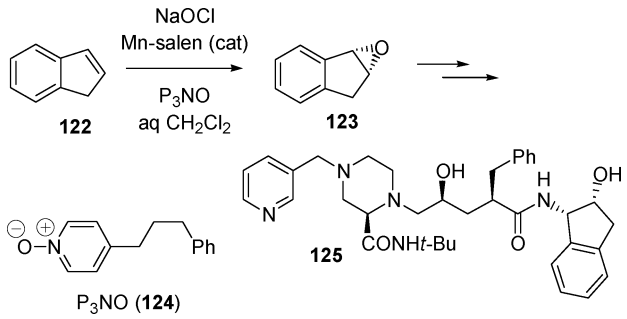
2.3.1. Asymmetric Epoxidations (Including Kinetic Resolutions)

There are several examples of the Jacobsen asymmetric epoxidation[50,51] (AE) applied to pharmaceutical scale-up efforts. Senanayake and co-workers utilized Jacobsen's epoxidation protocol to prepare indene oxide **123**, a precursor to HIV protease inhibitor indinavir (**125**, Scheme 32).[52] A variety of *N*-oxide additives were investigated, from which 4-(3-phenylpropyl)pyridine *N*-oxide (**124**, P_3NO) emerged as an optimal ligand. With this ligand, the catalyst load could be reduced from 1.5 to 0.75 mol % while retaining the yield and enantiomeric excess (88% and 86%, respectively).

A detailed mechanistic study of this epoxidation has been reported by Hughes, Smith, and co-workers,[53] which includes extensive kinetic studies and identifies an unexpected role of the *N*-oxide as a phase-transfer catalyst and metal ligand.

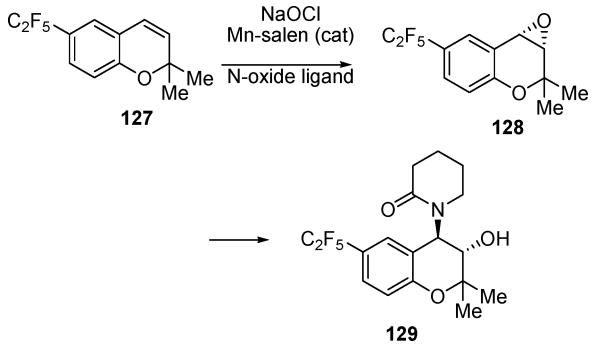
The Mn(III) salen-catalyzed epoxidation of chromene **127** has been utilized to generate epoxide **128**, a precursor to

Scheme 32. Preparation of Indinavir (125)



the selective potassium channel activator BRL 55834 (**129**) (Scheme 33).[54] Optimization efforts identified a 0.1−0.2 mol

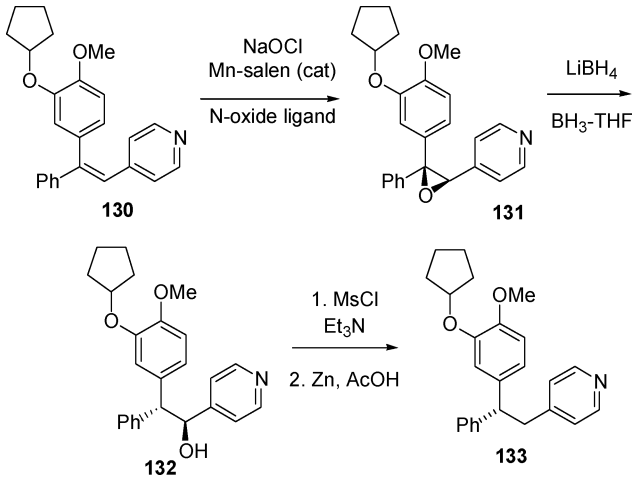
Scheme 33. Synthesis of the Selective Potassium Channel Activator BRL 55834 (129)



% catalyst load and 10 mol % added isoquinoline *N*-oxide to provide 93−95% ee product, which crystallized to enantiomeric homogeneity.

Jacobsen epoxidation of *Z*-olefin **130** to generate epoxide **131** was accomplished in 89% ee (Scheme 34, 1 mol % salen

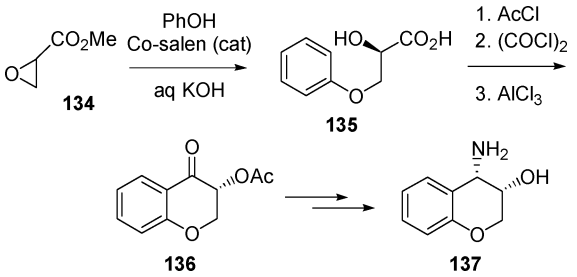
Scheme 34. Synthesis of PDE IV Inhibitor CDP840 (133)



catalyst, 0.5 mol % 4-(3-phenylpropyl)pyridine *N*-oxide ligand).[55] The corresponding *E*-olefin was also studied but found to be a less selective substrate (48% ee). The epoxide was then reductively opened with $LiBH_4/BH_3$−THF, which proceeded with retention of stereochemistry at the doubly benzylic position (intramolecular alkoxide-coordinated hydride delivery to a stabilized carbocation intermediate could rationalize this result). The secondary alcohol was then removed by mesylation and zinc reduction to generate CDP840 (**133**), a phosphodiesterase (PDE) IV inhibitor.

Hansen and co-workers utilized the Jacobsen kinetic resolution (KR) of epoxide **134** to prepare *cis*-aminochromanol **137** (Scheme 35).[56] The KR proceeded in 95% ee.

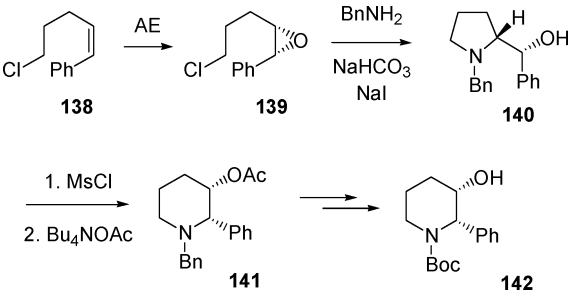
Scheme 35. Preparation of *cis*-Aminochromanol 137 via Jacobsen Kinetic Resolution



Direct epoxidation of chromene was not a viable strategy in this system (cf. indene, Scheme 32) due to competitive C−H oxidation of the chromene.

A Jacobsen epoxidation of *Z*-styrene **138** was utilized in a preparation of 2-phenyl-3-hydroxypiperidine **142** (Scheme 36).[57] The AE proceeded in 75% yield and 94% ee.

Scheme 36. Preparation of *N*-Boc-2-phenyl-3-hydroxypiperidine (142)



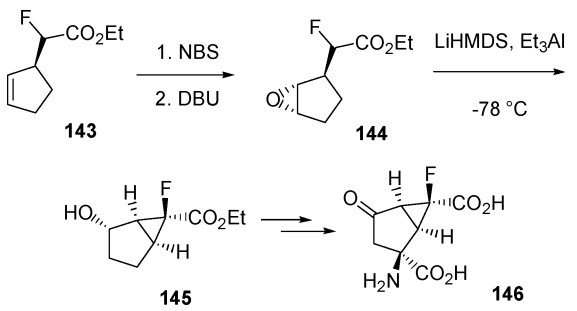
Cyclization of the epoxide with benzylamine provided pyrrolidine **140**, which was ring-expanded to piperidine **141** by mesylation and solvolysis with Bu_4NOAc (via an aziridinium species).

An additional example is the asymmetric epoxidation of styrene **300** to **301** followed by Baeyer−Villiger oxidation in the synthesis of SK&F-104353 (**303**) as depicted in Scheme 70.[58]

2.3.2. Non-Asymmetric Epoxidations

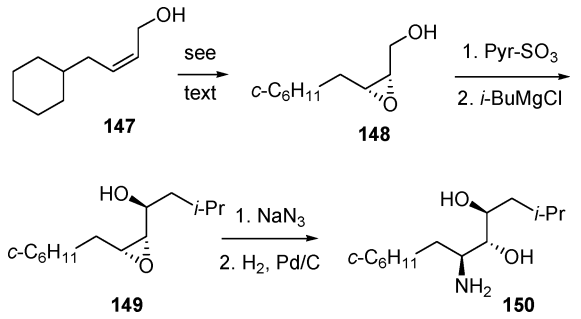
Turning now to nonchiral epoxidations, Zhang and co-workers utilized the trans-selective epoxidation of olefin **143** to generate epoxide **144** (Scheme 37), which upon treatment with base cyclized to generate [3.1.0]-bicyclohexane **145**, a precursor to metabotropic glutamate receptor (mGluR)-2 agonist MGS0028 (**146**).[59] They found that peracid-based epoxidations favored formation of the *cis*-epoxide, whereas bromohydrin formation/cyclization favored the trans isomer (8:1).

Scheme 37. Preparation of mGluR-2 Receptor Agonist MGS0028 (146)



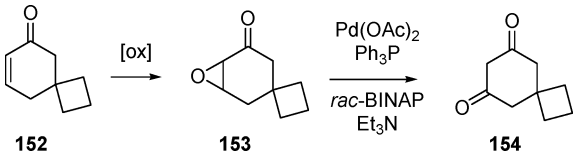
Both achiral (magnesium monoperoxyphthalate, 88%) and chiral (Sharpless AE, 59%, 70% ee) epoxidations of *Z*-olefin **147** have been studied (Scheme 38).[60] Alcohol oxidation and addition of *i*-butylmagnesium chloride provided epoxy alcohol **149**, which upon azide opening and reduction provided aminodiol **150**. Resolution of this amine with tartaric acid provided enantiomerically homogeneous material (>99% ee).

Scheme 38. Preparation of Aminodiol 150



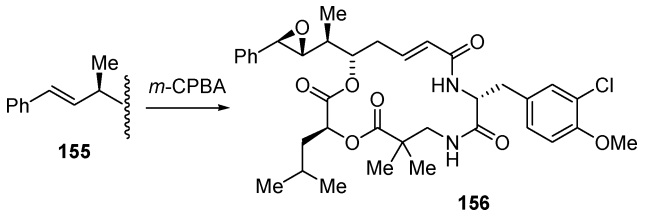
Epoxidation of enone **152** generated epoxyketone **153**,[61] which underwent Noyori's Pd-catalyzed epoxide rearrangement[62] to generate 1,3-diketone **154** (Scheme 39). On lab scale, the epoxidation was effected with basic hydrogen peroxide in methanol. In the pilot plant (26 kg scale), $NaBO_3 \cdot 4(H_2O)$ was utilized as oxidant.

Scheme 39. Epoxidation Followed by Rearrangement To Prepare Diketone 154



Epoxidation of olefin **155** to generate cryptophycin 52 has been reported (**156**, Scheme 40).[63] This epoxidation proceeds with modest (2:1) β/α selectivity.

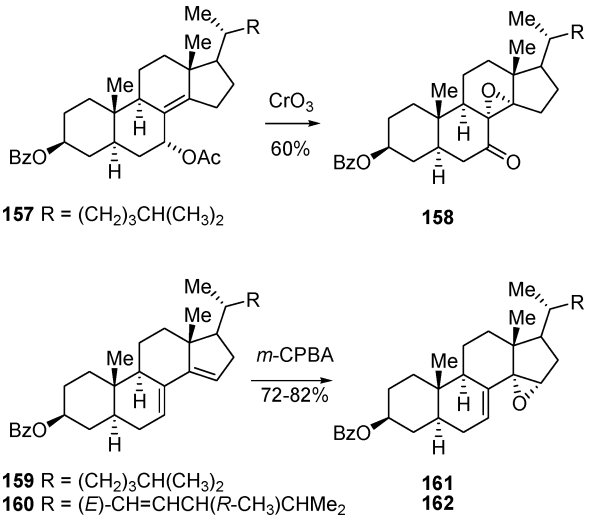
Scheme 40. Preparation of Cryptophycin 52 (156)



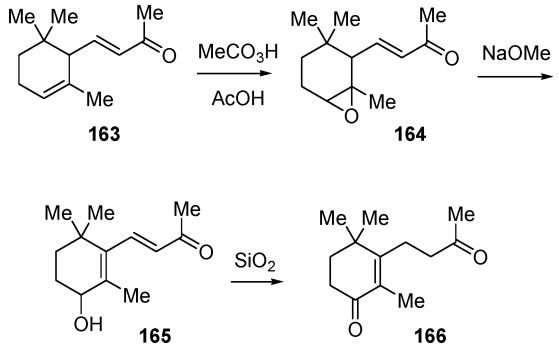
The epoxidation of steroid substrates has been reported as summarized in Scheme 41. Gallagher treated olefin **157** (generated without isolation by SeO_2/AcOH oxidation of 4,4-dimethyl-5α-cholest-7-en-3β-ol benzoate) with CrO_3 to generate epoxyketone **158** on a 100 g scale (ca. 60% yield).[64] Dolle epoxidized olefins **159** and **160** with *m*-chloroperoxybenzoic acid (*m*-CPBA) to provide epoxides **161** and **162** in 72−82% yields on a 300−400 g scale.[17]

α-Ionone **163** was epoxidized on a 200 g scale (Scheme 42, 99% crude yield).[65] The epoxide product **164** was isolated in crude form and treated with NaOMe/MeOH to form allylic

Scheme 41. Steroid Epoxidations



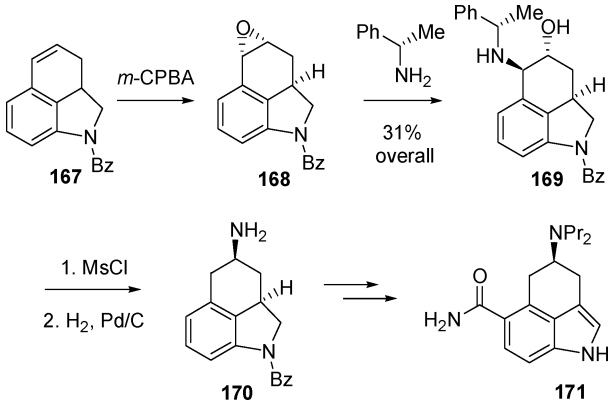
Scheme 42. Epoxidation of α-Ionone 163



alcohol **165**. Treatment with silica gel resulted in isomerization of this material to diketone **166**.

Kress and co-workers reinvestigated the epoxidation of olefin **167**,[66] utilized in the first total synthesis of lysergic acid published by Kornfeld, Woodward, and Lilly colleagues in 1954 (Scheme 43).[67] Unexpectedly, they found this

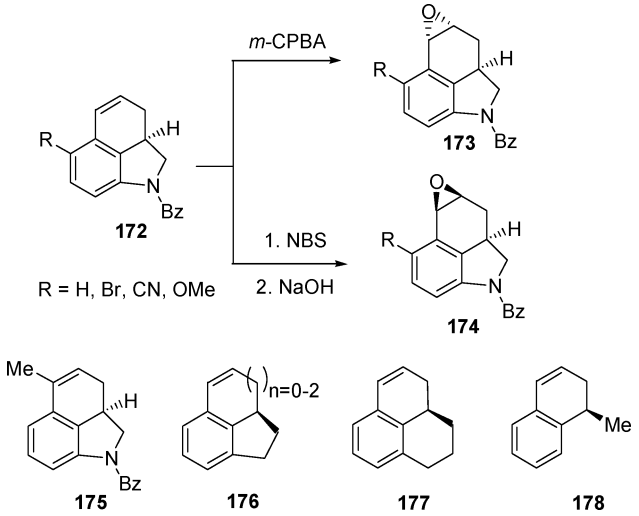
Scheme 43. Synthesis of $5HT_{1A}$ Receptor Agonist LY228729 (171)



epoxidation to be highly diastereoselective (*m*-CPBA or monomagnesiumperoxyphthalate), forming anti-epoxide **168** with >98% diastereoselectivity (455 g scale). The racemic epoxide was then condensed with (*S*)-α-methylbenzylamine; the desired diastereomer **169** condensed from the reaction mixture in 31% overall yield for the epoxidation and amination (62% of theory for racemic epoxide). This amine was then converted to primary amine **170** via an aziridine intermediate. This amine is a precursor to LY228729 (**171**), a potent 5-hydroxytryptamine 1A ($5HT_{1A}$) receptor agonist.

Further studies have been performed on this epoxidation, and it was found that peracid-mediated epoxidation is highly α-selective (86−98% diastereoselectivity), whereas bromohydrin formation and base-mediated closure generates the *β*-epoxides selectively (96−98% diastereoselectivity).[68] The Lilly group has extended these oxidations to several related ergot alkaloids and carbocyclic analogues.[69] They found the same general trends to apply, but with variations in degree of selectivity and product stability depending on substituent patterns and ring size; some representative substrates are shown in Scheme 44. Modeling studies support torsional steering as a key stereocontrol element in these oxidations.

Scheme 44. α and *β* Selective Epoxidations of Ergot Alkaloids and Carbocyclic Analogues



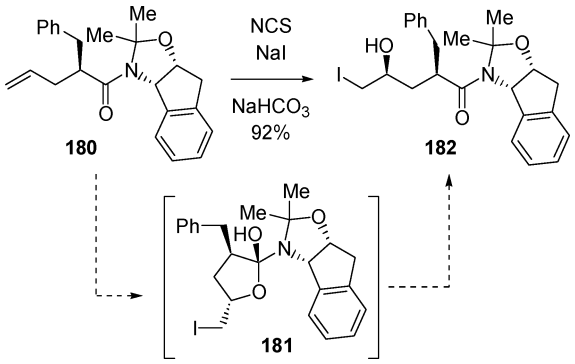
Noyori and co-workers have utilized a peroxide-based oxidation system similar to that reported for cyclohexene cleavage to adipic acid in section 1.1.2 (30% H_2O_2, Na_2WO_4, $Me(n\text{-octyl})_3NHSO_4$, $NH_2CH_2PO_3H_2$) for epoxidation of various olefins in high yields (e.g., 86−99% for terminal olefins).[70,71] This practical, environmentally benign oxidation has been demonstrated on a 100 g scale.

2.4. Halohydrin Formation

Halohydrin formation (addition of "X−OH" across an olefin) is treated as its own category, although the product halohydrins are in several cases converted to the corresponding epoxides by base-mediated cyclization.

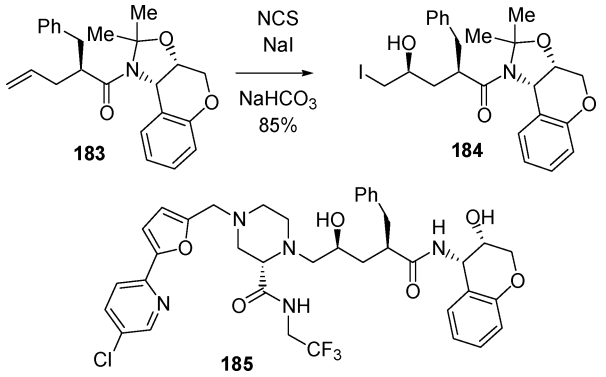
A particularly important application of halohydrin formation is found in the Merck process group's synthesis of indinavir, a marketed HIV-1 protease inhibitor (Scheme 45). Maligres and co-workers reported the selective oxidation of olefin **180** to form iodohydrin **182** in 92% yield (97:3 diastereoselectivity).[72] Interestingly, *N*-chlorosuccinimide/I_2 was as effective for this transformation as *N*-iodosuccinimide. In a subsequent mechanistic study, Rossen and co-workers demonstrated that this reaction proceeds through cyclization of the tetrahedral amide hydrate to generate tetrahydrofuran **181** (and not the originally proposed iminium imidate).[73] Rossen has also reported that the epoxide arising from base treatment of the iodohydrin can be formed directly by electrochemical oxidation of olefin **180** with a NaBr−acetonitrile−water system; the yield (86%) and diastereoselectivity (94:6) are comparable to the iodohydrin method.[74]

Scheme 45. Synthesis of an Intermediate in the Synthesis of Indinavir



The oxidation of terminal olefin **183** to prepare iodohydrin **184**, which was then converted to the epoxide with NaOMe, has been reported (Scheme 46).[75] This intermediate is a

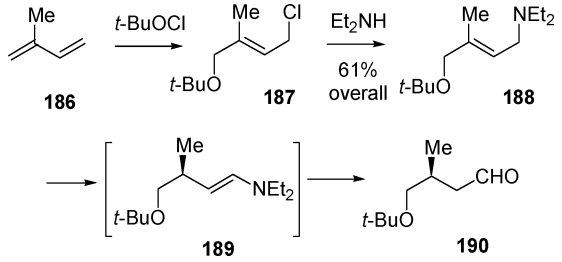
Scheme 46. Synthesis of HIV Protease Inhibitor 185



precursor to second generation HIV protease inhibitor **185**. The reaction proceeded in >85% yield on a 65 g scale.

2-Methyl-1,3-butadiene (**186**) was oxidized with *tert*-butylhypochlorite to provide allylic chloride **187**[76] as a 4:1 mixture of regioisomers (Scheme 47). This mixture was

Scheme 47. Synthesis of Aldehyde 190

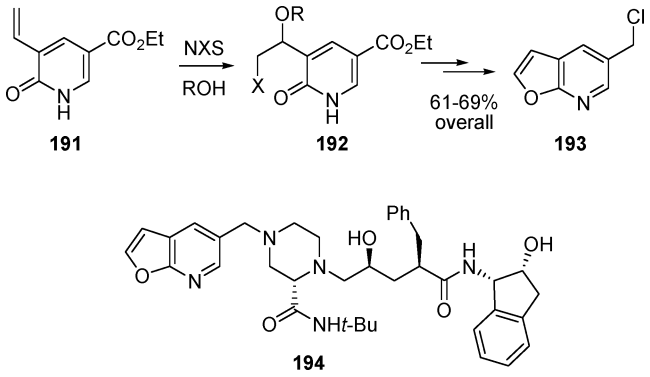


converted to amine **188**, a substrate for Noyori's palladium-catalyzed isomerization to chiral aldehydes.

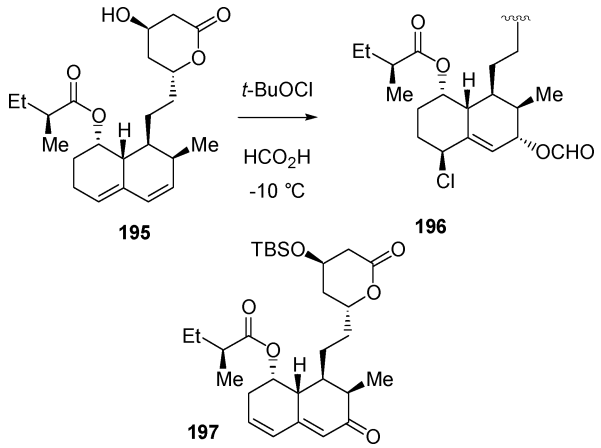
Halohydrins **192** (X = Cl, R = H; *N*-chlorosuccinimide (NCS), aq THF and X = Br, R = Me; NBS, MeOH) were prepared from olefin **191** (Scheme 48).[77] Both intermediates were converted to chloromethyl-furo[2,3-*b*]pyridine **193**, a precursor to HIV protease inhibitor L-754,394 (**194**). The overall yields from olefin **191** to chloride **193** were 61−69% for these sequences.

Chemists at Merck effected oxidation of compactin (**195**) with *t*-BuOCl and HCO_2H to add the elements of "Cl−OCHO" across the diene and generate **196** (Scheme 49).[78] Use of 1 equiv of oxidant was critical to the success of this

Scheme 48. Synthesis of HIV Protease Inhibitor L-754,394 (194)



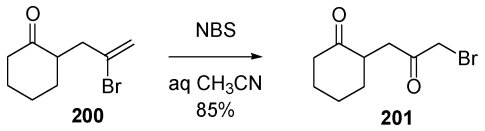
Scheme 49. Derivatization of Compactin (195)



reaction. The product was converted to dienone **197**, a versatile intermediate for preparation of analogues of compactin.

The "oxidative hydrolysis" of vinyl halides (e.g., **200**) to generate α-haloketones (e.g., **201**) has been disclosed.[79] Fifteen examples are included in the report by Morton and Leanna; a representative example that proceeds in 85% yield is shown in Scheme 50.

Scheme 50. "Oxidative Hydrolysis" of a Vinyl Halide



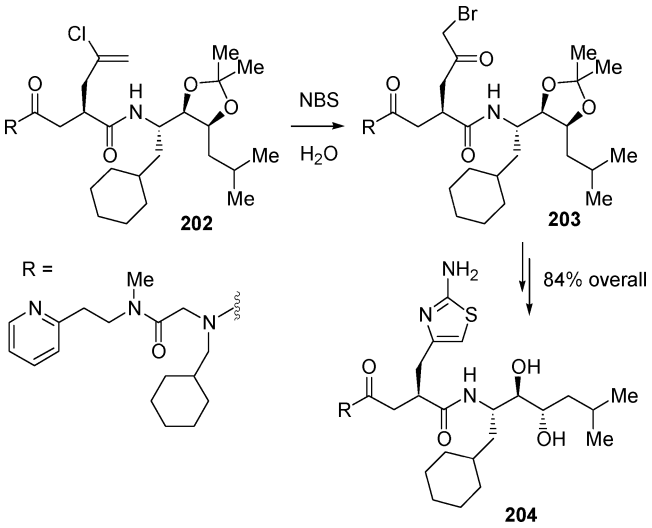
A similar oxidative hydrolysis of vinyl chloride **202** to generate α-bromoketone **203**, a precursor to BILA 2157 BS (**204**, Scheme 51), has also been reported.[80] The hydrolysis−aminothiazole annulation sequence was executed on 340 g in 84% overall yield.

2.5. Furan Oxidations

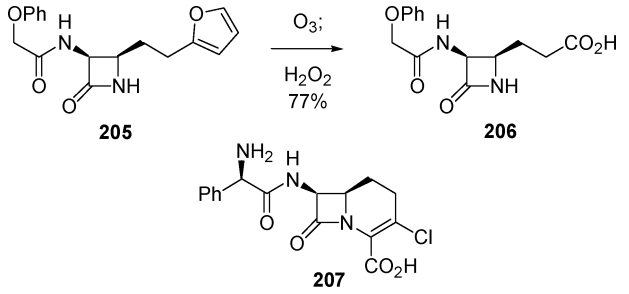
The electron-rich furan ring is readily oxidized and can serve as a masked carbonyl functionality or as a precursor to other heterocycles. Bodurow and co-workers utilized a 2-substituted furan as a masked carboxylic acid in their synthesis of loracarbef (LY163892/KT3777, **207**, Scheme 52).[81] Ozonolysis of furan **205** and oxidative workup provided acid **206** in 77% yield.

Several oxidative functionalizations of the furochromone nucleus of khellin (**208**, Scheme 53) were investigated.[82] For

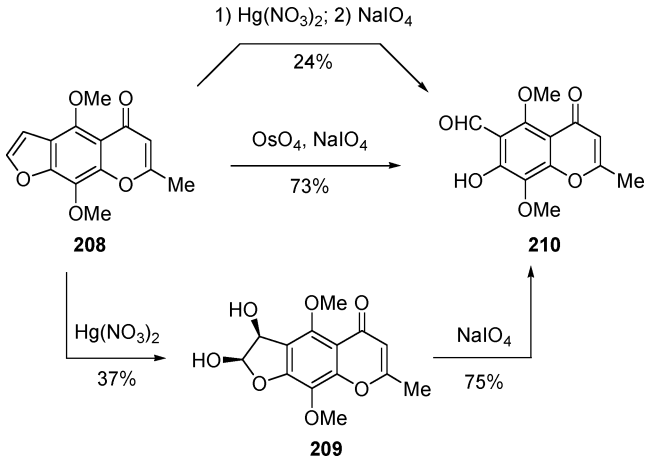
Scheme 51. Synthesis of BILA 2157 BS (204)



Scheme 52. Preparation of Loracarbef (LY163892/KT3777, 207)



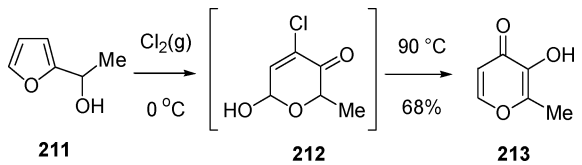
Scheme 53. Oxidation of Khellin (208)



example, several protocols were identified for conversion of khellin to aldehyde **210**; the most efficient was catalytic dihydroxylation with OsO_4 and stoichiometric $NaIO_4$ to effect reoxidation and cleavage of diol **209**.

The oxidation of furfuryl alcohol **211** to γ-pyrone **213** (maltol) has been reported on a 50 g scale (Scheme 54, 68% yield).[83] This sequence proceeds through α-chloroenone **212**, which rearranges to the γ-pyrone upon warming to 90 °C.

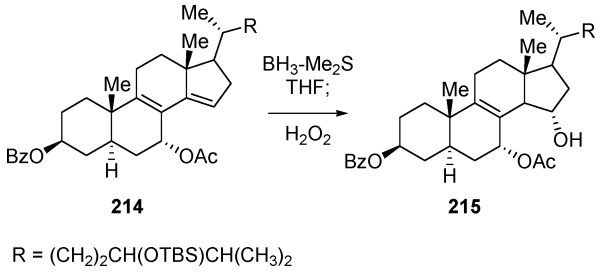
Scheme 54. Synthesis of Maltol (213)



2.6. Hydroboration of Olefins

Hydroborations are included in this section because of the oxidative workup, although the overall transformation does not involve a change in oxidation state. Steroid alcohol **215** was generated from diene **214** by Dolle and co-workers at SmithKline Beecham (Scheme 55, 70% yield based on recovered starting material).[84]

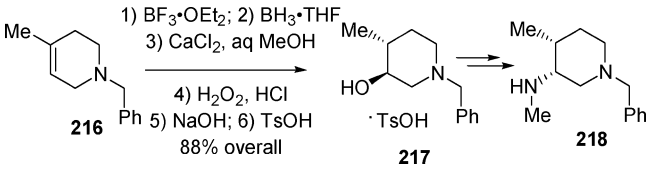
Scheme 55. Synthesis of Steroid 215



R = $(CH_2)_2CH(OTBS)CH(CH_3)_2$

The hydroboration of tetrahydropyridine **216** (Scheme 56) has been reported in the synthesis of **218**.[85] This reaction was executed by precomplexation of the tertiary amine with BF_3-Et_2O (to block borane complexation), addition of BH_3-THF, quench of excess BH-containing intermediates with $CaCl_2-MeOH-H_2O$, and oxidation with hydrogen peroxide under acidic conditions (Oxone can also be utilized for the oxidation).[86] The product was isolated as the tosylate salt by filtration in 88% yield on a 28 kg scale and was converted to *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine (**218**). The retention of the trans stereochemistry from the hydroboration was modest during the oxidative workup (3.5−4.7:1) but of no consequence because oxidation to the ketone was the next operation in anticipation of a reductive amination with methylamine.

Scheme 56. Synthesis of *cis*-*N*-Benzyl-3-methylamino-4-methylpiperidine 218

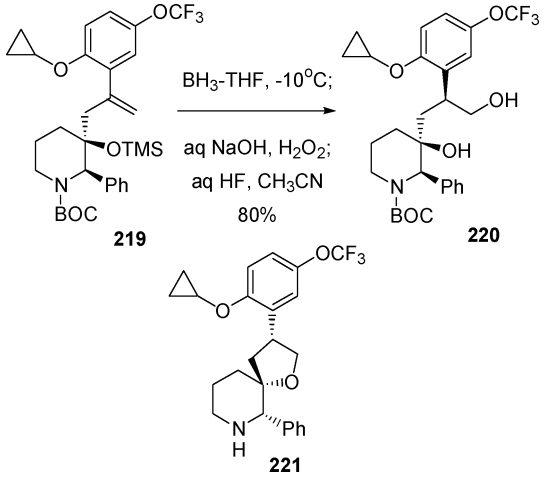


Maligres and co-workers utilized the stereoselective hydroboration of 1,1-disubstituted olefin **219** to generate alcohol **220** with 72−90% selectivity for the desired isomer (Scheme 57).[87] The highest selectivity (90:10) was realized with BH_3-THF at −10 °C. An 80% overall yield of diol **220** was obtained. Blocking the tertiary alcohol as the trimethylsilyl ether led to improved diastereoselectivity; with the free alcohol, 67−78% selectivity was observed. The product alcohol is a precursor to spirobicyclic piperidine **221**, an NK-1 receptor antagonist.

2.7. Oxidative Rearrangements

A number of oxidative rearrangement reactions are used fairly commonly on large scale, including Curtius, Hofmann, and Baeyer−Villiger rearrangements. Some examples of

Scheme 57. Synthesis of NK-1 Receptor Antagonist 221

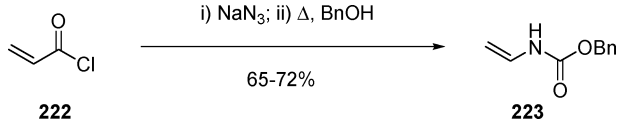


other rearrangements can also be found including Beckmann, Willgerodt, Schmidt, and Lossen rearrangements.

2.7.1. Curtius Rearrangements

A number of examples of Curtius rearrangements are reported in the literature. Researchers at Pfizer and PPG Industries have produced benzyl *N*-vinyl carbamate (**223**) utilizing a Curtius rearrangement from acrolyl chloride (Scheme 58).[88,89] Because the Curtius rearrangement involves

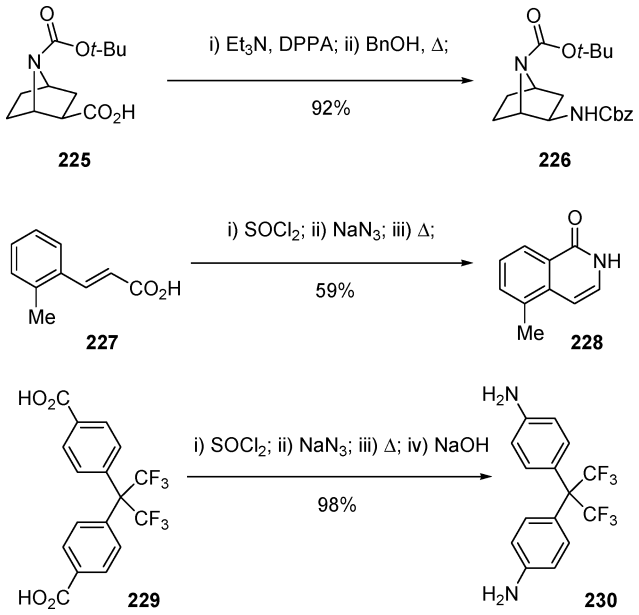
Scheme 58. Synthesis of Benzyl *N*-Vinyl Carbamate



the intermediacy of an acyl azide that must be heated to promote rearrangement, extensive safety testing was undertaken to run this reaction safely. The key to safe operation in this case was the controlled addition of a solution of acyl azide to a heated solution of benzyl alcohol in toluene. The decomposition of azide to isocyanate and reaction with benzyl alcohol to produce product is rapid, and thus the addition rate controls the rate of decomposition of the azide intermediate. Addition of potassium carbonate to the benzyl alcohol solution minimized an acid-catalyzed addition of benzyl alcohol to the product to produce an aminal side product. A modification was made to the procedure in which the acyl azide is added to hot toluene and the resultant isocyanate was distilled into a receiving vessel containing benzyl alcohol at lower (0 °C) temperature. This process also reduced the amount of side product produced and provided the product in high enough purity to crystallize directly from the reaction mixture.

Anjeh reported the Curtius rearrangement on an azabicyclo-[2.2.1]heptane system to produce **226** as depicted in Scheme 59.[90] In this case, the carboxylic acid (**225**) and base were preheated in toluene, and diphenyl phosphoryl azide (DPPA) was added slowly as a solution in toluene to control the rate of azide formation and decomposition. The isocyanate intermediate was then quenched with benzyl alcohol following completion of the Curtius rearrangement. Running the reaction in this manner minimized the amount of acyl azide present in the reaction at any given time and added a degree of safety to the process. A Curtius rearrangement was also utilized to produce 1(*2H*)-isoquinolone **228**.[91] In this

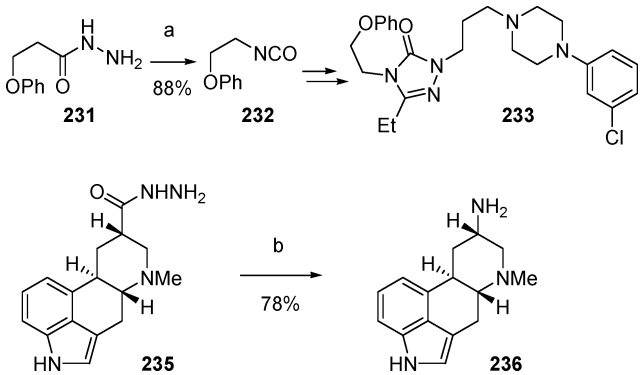
Scheme 59. Examples of Large-Scale Curtius Rearrangements



case, the desired ring system had previously been prepared using a Schmidt rearrangement in lower yield and selectivity. As in the case of am Ende,[88] the acyl azide was generated in solution and added slowly to a hot solvent to promote rearrangement followed by ring closure. The double-Curtius rearrangement of **229** to **230** has also been reported on a 500 g scale.[92]

There are also some examples of Curtius rearrangements wherein the acyl azide was generated by oxidation of an acyl hydrazine. Madding reported a Curtius rearrangement of 3-phenoxypropionyl hydrazide **231** in the synthesis of the antidepressant nefazadone (**233**, Scheme 60). The acyl azide

Scheme 60. Examples of Large-Scale Curtius Rearrangements from Acyl Hydrazine Precursors[a]



[a] (a) (i) $NaNO_2$, HCl; (ii) Δ; (b) (i) $NaNO_2$, H_2SO_4; (ii) Δ.

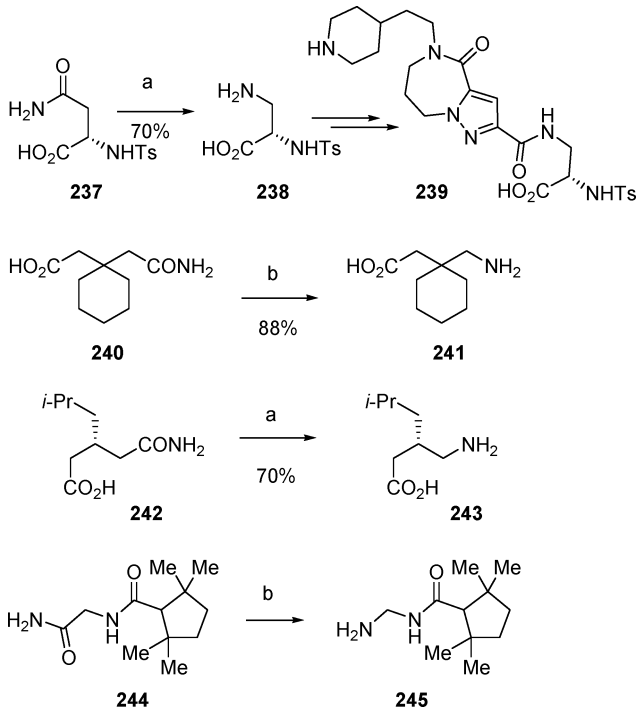
was generated in solution using $NaNO_2$ and HCl, and the solution of acyl azide was slowly added to a hot solvent to effect rearrangement. This procedure was executed on a 700 g scale in 88% yield after trapping of the isocyanate with propionyl hydrazide.[93] Lei utilized this same transformation in the synthesis of nefazadone.[94] Finally, ergoline derivative **236** was synthesized from **235** using a similar procedure.[95]

2.7.2. Hofmann Rearrangements

Hofmann rearrangements are used on a large scale to afford a transformation similar to that of the Curtius. Amato

reported a Hofmann rearrangement in which the bromination, rearrangement, and hydrolysis reactions were separated into distinct stages by careful control of reaction temperature (Scheme 61).[96] This procedure, used in the synthesis of

Scheme 61. Examples of Large-Scale Hofmann Rearrangements[a]



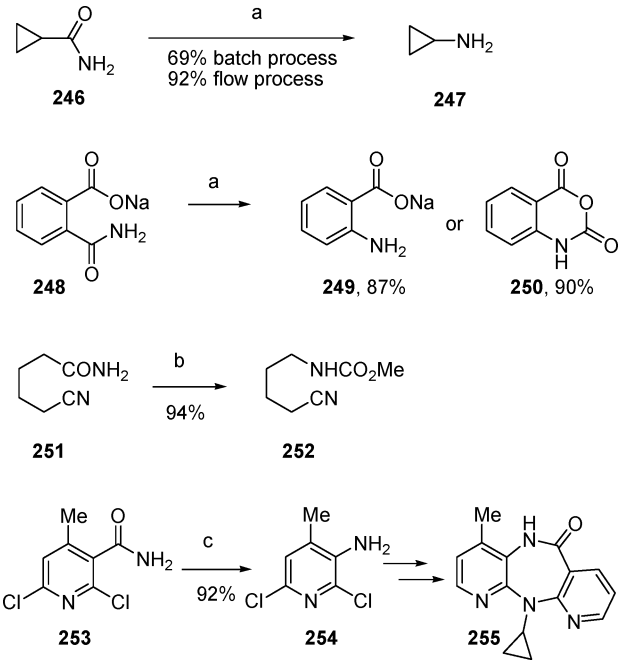
[a] (a) NaOH, NaOBr; (b) NaOH, NaOCl.

fibrinogen receptor agonist **239**, was executed on a 2.9 kg scale. The use of a Hofmann rearrangement as the penultimate step in the synthesis of gabapentin (**241**), an anticonvulsant, has been reported by two research groups.[97,98] A similar strategy was utilized to make the related pregabalin (**243**) on a pilot plant scale.[99] The transformation of **244** into **245** utilizing a Hofmann rearrangement has also been disclosed.[100]

Cyclopropylamine was produced using a Hofmann rearrangement in a batch process;[101] a similar procedure to produce cyclopropylamine was executed in a flow reactor at a rate of 0.66 kg of product per hour (Scheme 62).[102] Also reported was the production of anthranillic acid (**249**) or isatoic anhydride (**250**) from phthalic acid amide sodium salt (**248**) in a flow process. The product formed was dependent on whether sodium hydroxide was added to the reaction mixture. The two could be produced at rates of 2.7 kg/h at 87% yield and 2 kg/h at 90% yield, respectively. Shapiro utilized a Hofmann rearrangement to convert 5-cyanovaleramide (**251**) to methyl *N*-cyanobutylcarbamate (**252**) in the synthesis of azafenidin.[103] In this procedure, the brominated amide intermediate was added to refluxing methanol to effect rearrangement. A Hofmann rearrangement was also utilized in the synthesis of nevirapine (**255**) to make a 3-aminopyridine derivative **254** from the corresponding nicotinic acid derivative **253**.[104,105]

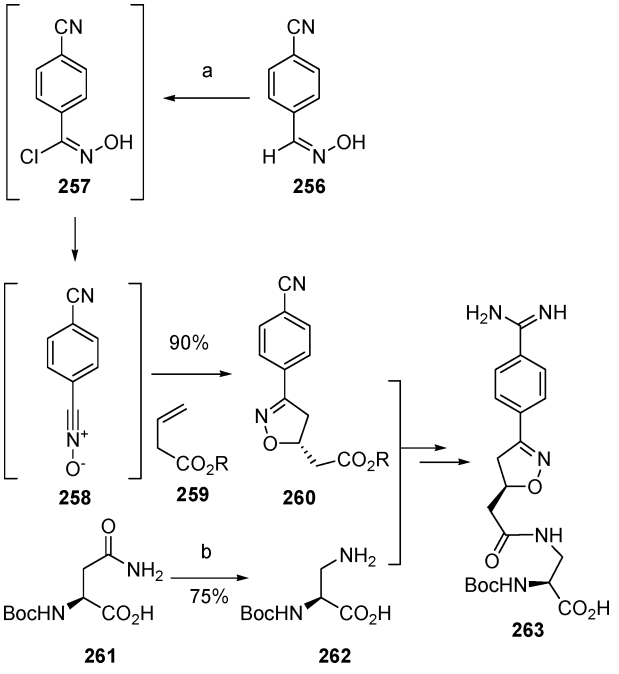
Over 23 kg of **261** was processed through a Hofmann rearrangement in Zhang's preparation of anti-thrombotic agent **263** (Scheme 63).[106] In this case, iodosobenzene was found to provide superior results to hypochlorites and other common oxidants.

Scheme 62. Examples of Large-Scale Hofmann Rearrangements[a]



[a] (a) NaOCl, NaOH; (b) Br_2, NaOMe; (c) NaOBr.

Scheme 63. Synthesis of Anti-Thrombotic Agent 263[a]



[a] (a) (i) NCS; (ii) Et_3N; (b) $PhI(OAc)_2$.

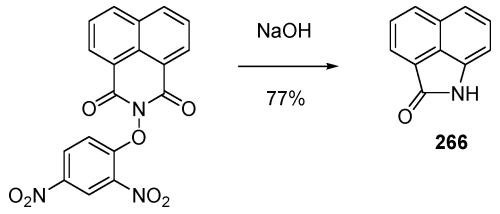
2.7.3. Lossen Rearrangement

A Lossen rearrangement was employed in the synthesis of benz[*cd*]indol-2(1*H*)-one **266** and a derivative thereof (Scheme 64).[107] Safety concerns drove the workers to employ *o*,*p*-dinitrophenol rather than chloride as a leaving group. The transformation was reported on a 1.8 kg scale.

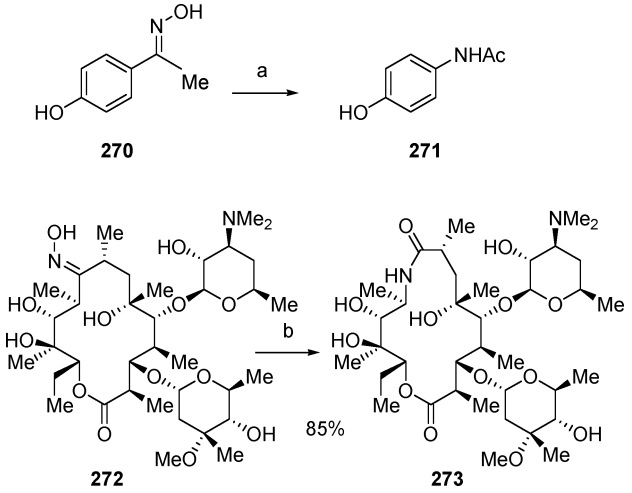
2.7.4. Beckmann Rearrangement

The Beckmann rearrangement has been widely utilized in the synthesis of acetaminophen (**271**); the reports differ primarily in the catalyst that facilitates the rearrangement

Scheme 64. Large-Scale Lossen Rearrangement



Scheme 65. Beckmann Rearrangements[a]



[a] (a) KI, $SOCl_2$, Δ; (b) TsCl, pyridine or $NaHCO_3$.

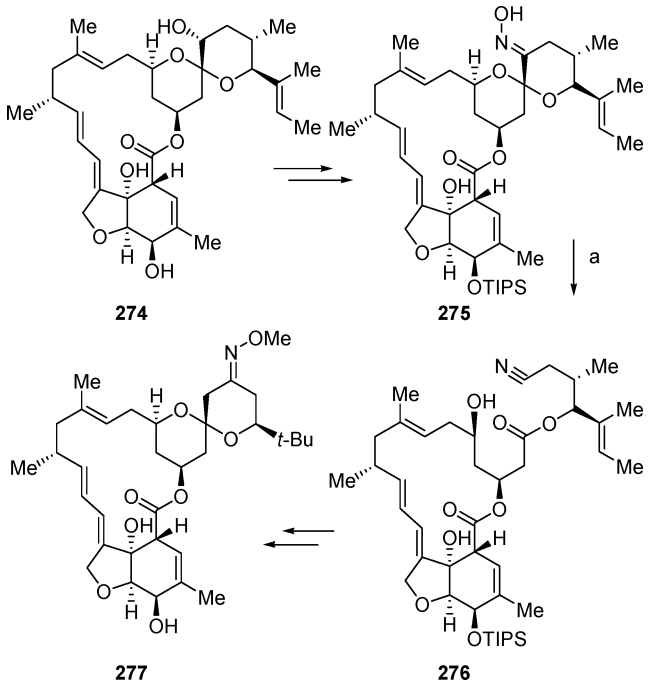
(Scheme 65). Potassium iodide,[108,109] thionyl chloride,[110] Amberlist 15,[111] trifluoroacetic acid, sulfur dioxide, and many others have been reported as catalysts for this transformation on large scale with yields generally 70−90%. A Beckmann rearrangement of **272** to **273** was also utilized in the synthesis of azithromycin.[112−117]

Andrews utilized a Beckmann fragmentation to transform milbemycin VM-44866 (**274**) into SB-201561 (**277**) (Scheme 66).[118] The five step sequence was carried out on a 0.5 kg scale in 30% overall yield.

2.7.5. Baeyer−Villiger Reaction

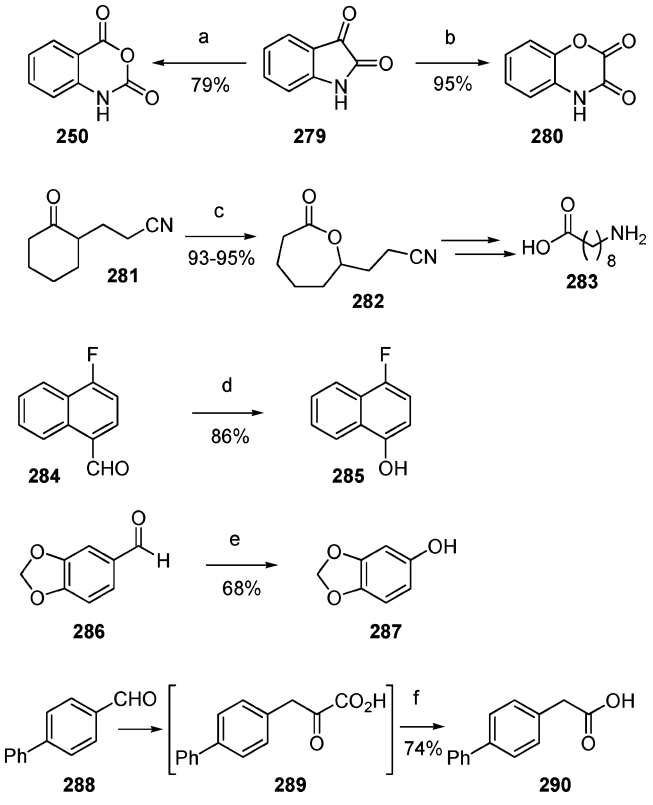
The Baeyer−Villiger oxidation is widely used on an industrial scale to prepare a number of substrates, from fairly simple to more complex ones (Schemes 67−73). Reisenweber has reported the conversion of isatin **279** to isatoic anhydride (**250**) and 2,3-dioxo-1,4-benzoxazine (**280**)[119,120] in methodology that is complementary to the work of Jones[102] in preparing isatoic anhydrides using a Hofmann rearrangement (Scheme 67). The product obtained is dependent on the oxidant used; hydrogen peroxide in acetic acid lead to formation of anhydride **250**, while the use of $K_2S_2O_8$ in sulfuric acid resulted in production of the benzoxazine **280**. The synthesis of azelaic acid (**283**) and other 9-substituted nonanoic acids via oxidation of 2-substituted cyclohexanone **281** in a batch process was described on 270 kg scale;[121,122] more recently, the process was demonstrated using cyclohexane percarboxylic acid in hexane.[123] Kuo reported a synthesis of sesamol (**287**),[124] and Boswell reported the synthesis of 4-fluoro-1-naphthol (**285**);[125] both were synthesized via oxidation of the corresponding aldehyde followed by hydrolysis. A synthesis of *p*-phenylphenylacetic acid (**290**) from benzaldehyde **288** on a 1 kg scale has also been described.[126] The aldehyde (**288**) is converted to a hydantoin

Scheme 66. Beckmann Fragmentation in the Synthesis of a Milbemycin[a]



[a] (a) NosCl, Et_3N.

Scheme 67. Baeyer−Villiger Oxidations on Large Scale[a]

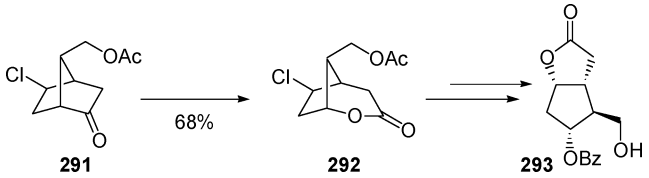


[a] (a) H_2O_2, AcOH, H_2SO_4; (b) $H_2S_2O_8$, H_2SO_4; (c) *c*-hexCO_3H; (d) *m*-CPBA; (e) H_2O_2, Ac_2O; (f) H_2O_2.

that is hydrolyzed to α-ketoacid **289**, then oxidized to the desired product. The entire sequence of reactions proceeds in 74% yield.

Chemistry developed by Corey is still used industrially to synthesize the Corey lactone (**293**) (Scheme 68).[127,128] This synthesis utilizes a Baeyer−Villiger oxidation of functionalized bicyclo[2.2.1]heptane (**291**) to establish the stereo-

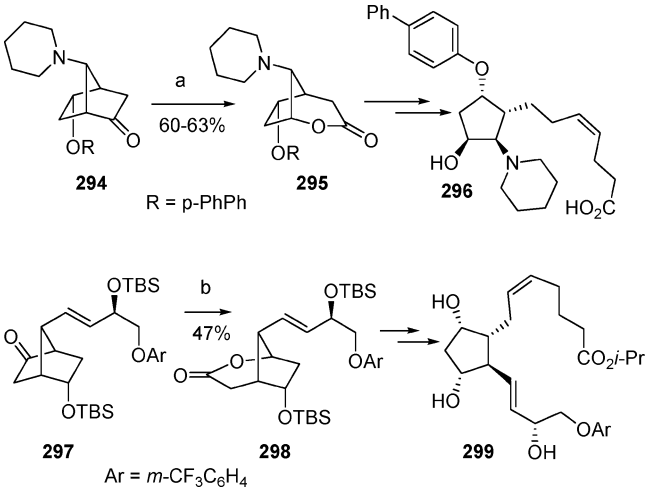
Scheme 68. Baeyer−Villiger Oxidation in the Corey Lactone Synthesis



chemistry of the five-membered ring of the prostaglandins, and its execution on a 2.4 kg scale has been described.[129]

Similar strategies have been used in the synthesis of prostaglandin-like drugs as shown in Scheme 69. Coleman

Scheme 69. Baeyer−Villiger Oxidations in the Synthesis Prostaglandins[a]

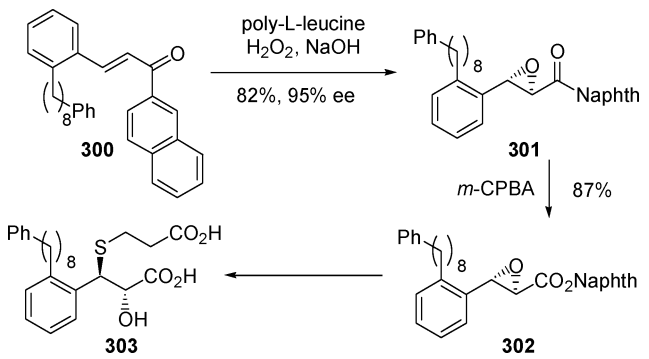


[a] (a) H_2SO_4, $MeCO_3H$; (b) $MeCO_3H$, AcOH, NaOAc.

applied a Baeyer−Villiger oxidation in the synthesis of prostaglandin analogue **296** on a 162 kg scale.[130] The generation of *N*-oxides as intermediates in the reaction appears to improve selectivity for the desired lactone over the undesired one, and careful control of conditions resulted in the hydrolysis of the undesired lactone in the presence of the desired one, thereby facilitating purification. In the synthesis of travaprost (**299**), a Baeyer−Villiger oxidation followed by a selective hydrolysis similar to that of Coleman[130] was utilized to facilitate purification of the 3:1 mixture of regioisomers.[131,132]

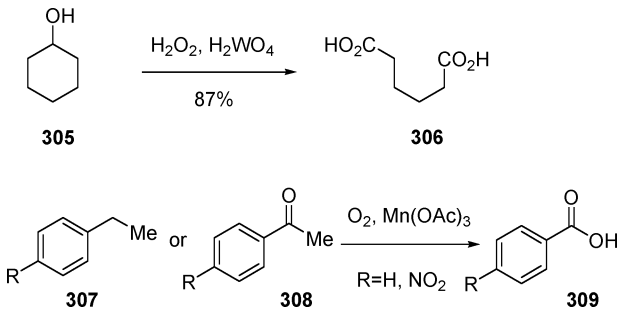
Asymmetric epoxidation was followed by Baeyer−Villiger oxidation in the synthesis of SK&F-104353 (**303**) as depicted in Scheme 70.[58] Following the Baeyer−Villiger run on 1 kg of material, the product was isolated in 87% yield with the optical purity improved to 99.5% ee.

Scheme 70. Synthesis of SK&F-104353 (303)



Processes where a Baeyer−Villiger oxidation occurs during a cascade of other oxidations have also been reported (Scheme 71). The oxidation cascade of either cyclohexanone

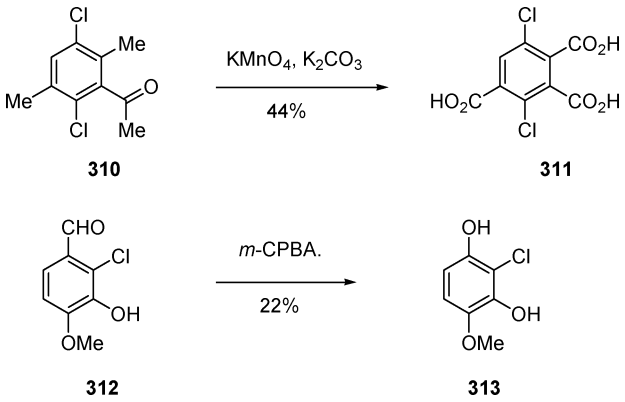
Scheme 71. Baeyer−Villiger Oxidations in Oxidation Cascades



or cyclohexanol to adipic acid (**306**) has been reported.[133] Using hydrogen peroxide and a tungsten catalyst, cyclohexanol is oxidized to cyclohexanone, a Baeyer−Villiger oxidation occurs followed by hydrolysis, and the product hydroxyl acid is oxidized further to the diacid (**306**). The oxidation of ethylbenzene to benzoic acid using oxygen and a manganese catalyst was reported, and the kinetics of this process were studied carefully.[134−136]

Baeyer−Villiger oxidation in concert with benzylic oxidation was utilized to produce **311** from **310** (Scheme 72).[137]

Scheme 72. Baeyer−Villiger Oxidation



In the synthesis of a related compound (**313**), Lyttle also employed a Baeyer−Villiger oxidation of aldehyde **312**.

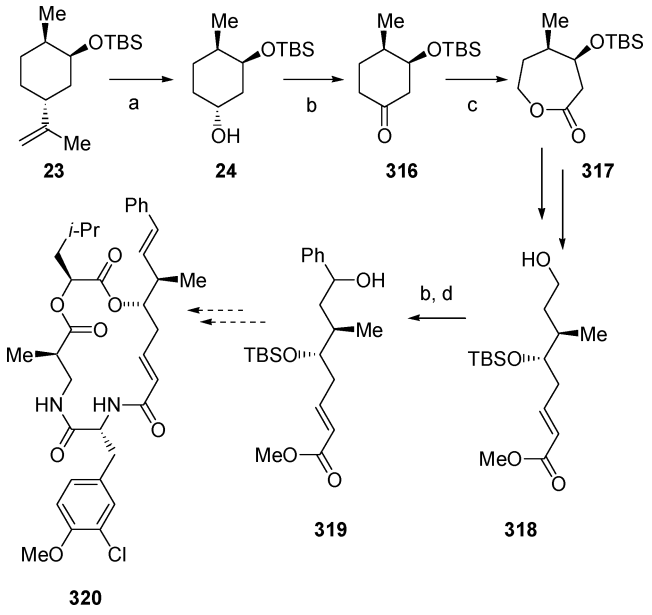
Varie reported the use of a Baeyer−Villiger oxidation on compound **316** using urea−hydrogen peroxide complex (UHP) and trifluoroacetic anhydride (TFAA) as the oxidant (Scheme 73).[7] Using this system, very high (98:2) selectivity for the desired product (**317**) was observed at 80% conversion. Using other oxidant systems, the selectivity was notably lower. This process was carried out in the course of a 0.5 kg campaign to produce cryptophycin A fragment **319**.

2.7.6. Other Oxidative Rearrangements

Other oxidative rearrangements have been utilized on large scale (Schemes 74 and 75). Challenger utilized an oxidative ring contraction to produce **323** from **321** using hydrogen peroxide and sulfuric acid.[138]

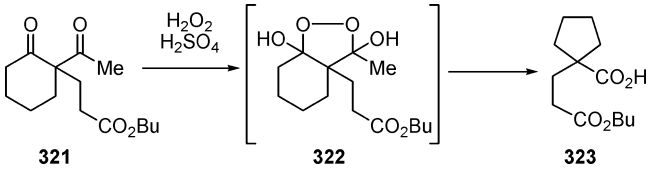
A Willgerodt reaction was utilized early in the development of naproxen (**326**) on a 500 kg scale (Scheme 75).[139,140] Chapman reported an interesting rearrangement reaction for the synthesis of ibuprophen methyl ester (**328**).[141]

Scheme 73. Synthesis of Cryptophycin A[a]

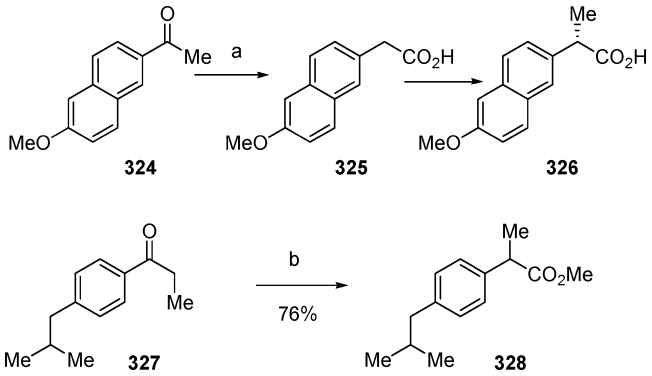


[a] (a) O_3, Ac_2O; (b) TEMPO, NaOCl; (c) TFAA, UHP; (d) PhMgBr.

Scheme 74. Oxidative Ring Contraction



Scheme 75. Other Oxidative Rearrangements[a]



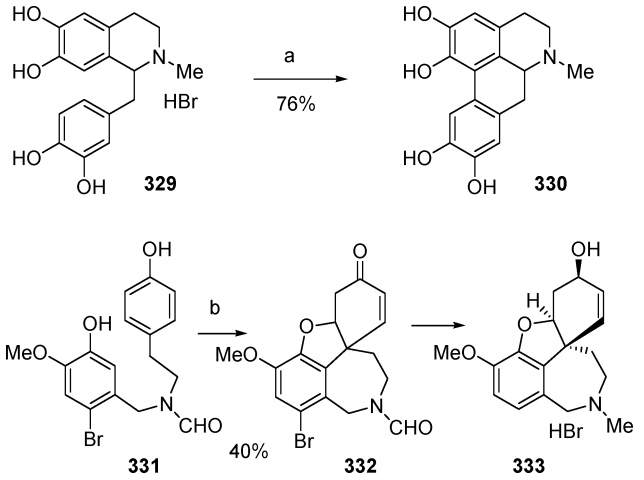
[a] (a) S_8, morpholine; (b) $PhI(OAc)_2$, $(MeO)_3CH$, H_2SO_4.

2.8. Aromatic Ring Oxidation

While oxidative substitution reactions of aromatic rings are outside the scope of this review, there are a few C−C bond oxidations of aromatic systems that are worthy of note. An intramolecular oxidative aromatic coupling reaction was utilized in the synthesis of antitussive agent **330** (Scheme 76).[142] Oxidation of one of the bis-phenols with $FeCl_3$ was followed by intramolecular trapping by the other bis-phenol. This transformation was carried out on a 1 kg scale.[142,143] Galanthamine (**333**) was synthesized from a fairly simple substrate (**331**) via an intramolecular oxidative aromatic coupling reaction on a 12 kg scale.[144] In this case, oxidation is achieved using $K_2[Fe(CN)_6]$.

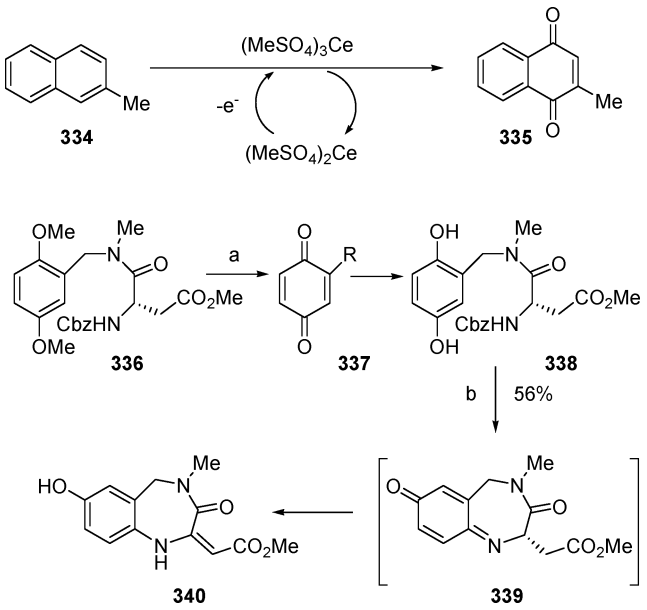
Harrison reported the electrochemical oxidation of naphthalene **334** to naphthoquinone **335** and applied it to the synthesis of vitamin K3 (Scheme 77).[145] Hayes utilized the oxidation of aryl methyl ether **336** followed by reduction to demethylate to phenol **337** in the synthesis of **338**.[146] Following Cbz deprotection, a second phenol−quinone oxidation was effected with Fremy's salt to afford benzodiazepine **340**.

Scheme 76. Oxidative Cyclization of Phenols[a]



[a] (a) $FeCl_3$, NaOAc; (b) $K_3[Fe(CN)_6]$, K_2CO_3.

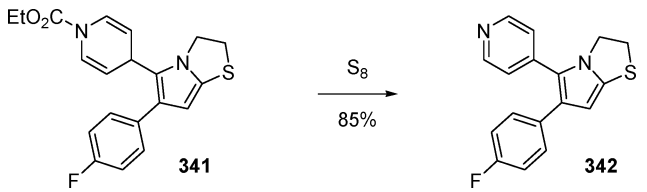
Scheme 77. Oxidation to Produce Quinines[a]



[a] (a) CAN; (b) Fremy's salt.

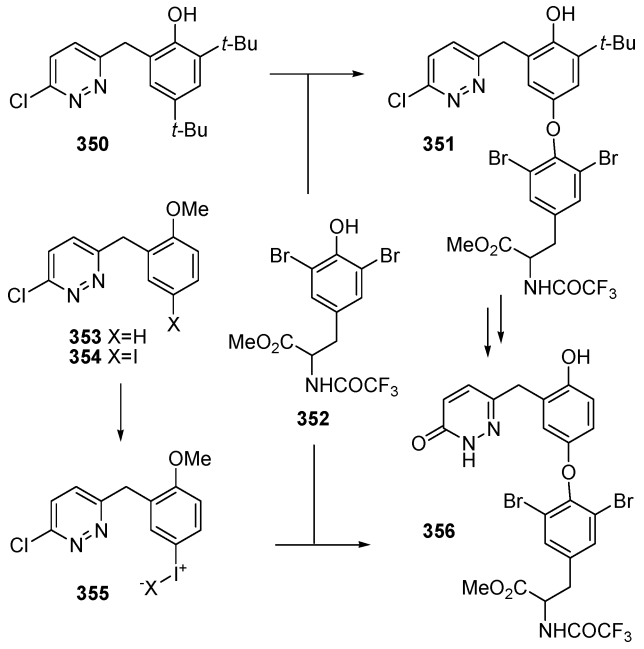
Aromatization of dihydropyridine **341** with sulfur was exploited in a regiospecific synthesis of **342** (Scheme 78).[147]

Scheme 78. Aromatization to Produce Pyridines



Hickey reported complementary syntheses of **356** (Scheme 79), a protected version of SK&F-94901, in a series of papers.[148,149] In the first approach reported, di-*tert*-butylphenol **350** was oxidized using MnO_2, and phenol **352** trapped the intermediate *para* to the phenol. Following loss of the *tert*-butyl group effected with $TiCl_4$, product **356** was

Scheme 79. Oxidative Formation of Aryl Ethers



obtained in 55% yield. As an alternative, a series of iodonium salts (**355**) were prepared from either **353** or **354**, and phenol **352** was coupled to provide intermediate **356**. From anisole **353**, the iodonium triflouroacetate was synthesized on a 600 g scale using iodine, triflouroacetic acid, and fuming nitric acid as the oxidant to provide the salt in 95% yield. The same salt could alternatively be prepared from the iodoanizole **354** using ammonium persulfate as the oxidant; in this case, a 75% yield was reported. Alternatively, the iododichloride could be prepared from the iodide via the addition of chlorine. This complex was generated on a 40 g scale in 92% yield and was used to generate mixed iodonium salts.

3. Oxidation of Carbon–Hydrogen Bonds

The oxidation of activated C−H bonds is often utilized in the pharmaceutical industry. Common examples include enolate halogenation, oxygenation, amination, dehydrogenation, and the oxidation of benzylic and allylic positions.

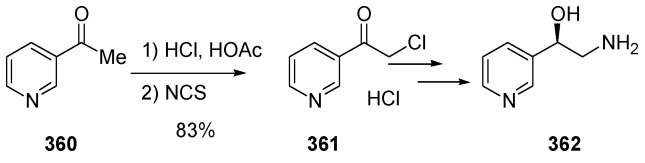
3.1. Oxidation α to a Carbonyl

Probably the most common replacement of a C−H bond by a more electronegative element is the reaction of an enol or enolate with an electrophile. While one might argue that this is really an electrophilic addition to a highly electron-rich olefin and not truly an oxidation, one cannot argue the importance of such reactions to synthetic organic chemistry.

3.1.1. By Halogen

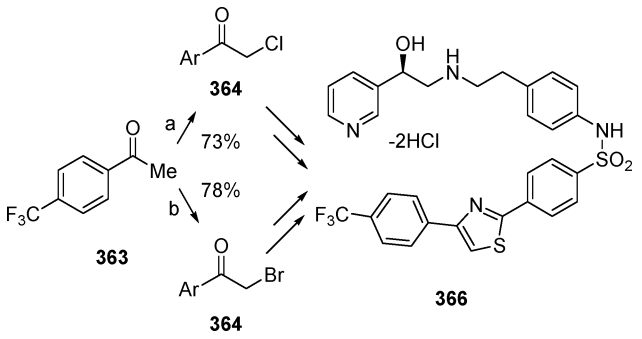
The most common reactions of this oxidation class are halogenations. Examples can be found of everything from simple methyl ketones to complex steroids. The most common halogenating agents are the elemental forms of the halogens (Cl_2, Br_2, I_2). *N*-Halo imides (usually NBS, NCS, or dibromobarbituric acid) are also common. For example, the synthesis of (*R*)-2-amino-1-(3-pyridinyl)ethanol (**362**), a subunit of numerous β_3 adrenergic receptor agonists, such as **366**, has been carried out on large scale by the chlorination of ketone (**360**) with NCS in 83% yield (Scheme 80).[150]

Scheme 80. Chlorination of 3-Acetylpyridine



Chlorination of ketones can also be accomplished with sulfuryl chloride.[151] In another β_3 adrenergic receptor agonist synthesis, the Merck group chlorinated **363** in 73% yield (Scheme 81).[152] The same ketone (**363**) could also be

Scheme 81. Chlorination with SO_2Cl_2[a]

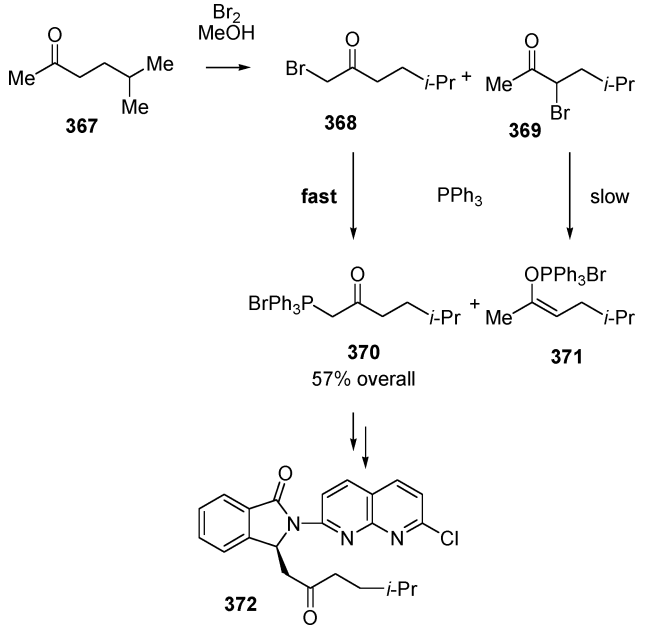


[a] (a) $SOCl_2$; (b) HOAc, Br_2.

brominated with Br_2 in acetic acid in 78% yield. Either haloketone could be carried on to **366**.

Another interesting example of the bromination of a ketone has been reported (Scheme 82). Bromination of ketone **367**

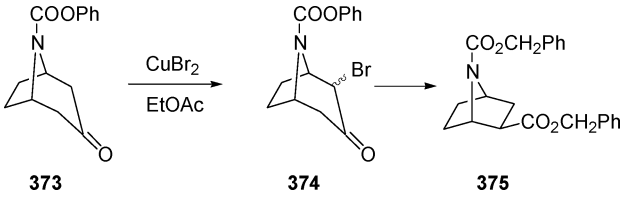
Scheme 82. Synthesis of Pagoclone (372)



with bromine in methanol produced a 63:37 ratio of bromoketones **368** and **369**.[153] The authors took advantage of the large rate difference of the subsequent reaction with PPh_3. The primary bromoketone reacts much faster with PPh_3, allowing isolation of **370** in 57% overall yield (115 kg). Phosphonium salt **370** was carried on to pagoclone (**372**).

Cupric bromide ($CuBr_2$) is known to be a mild brominating agent for ketones.[154] A large scale example is the bromination of ketone **373**.[90] Treatment of **373** with $CuBr_2$ in EtOAc

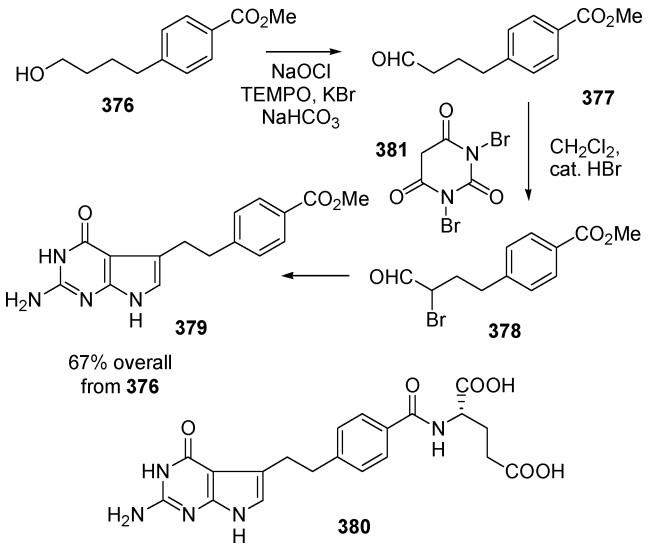
Scheme 83. Bromination with $CuBr_2$



results in 85% conversion to bromoketone **374** (Scheme 83). The crude bromide is then subjected to a Favorskii rearrangement producing ester **375**, which is carried on to amine **226** (Scheme 59), an intermediate in the preparation of α7 nicotinic acetylcholine receptor agonists. Although $CuBr_2$ often demonstrates useful selectivity differences over Br_2 one detriment is that it requires the use of 2 equiv of $CuBr_2$.

Although rare, aldehydes can also be α-brominated. In a Lilly synthesis of antifolate LY231514 (**380**) (Scheme 84),

Scheme 84. Synthesis of Antifolate LY231514 (380)



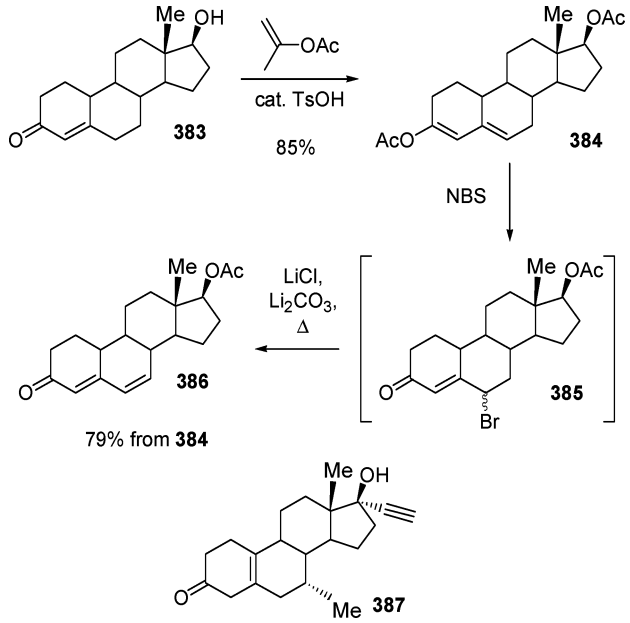
aldehyde **377** was brominated with dibromobarbituric acid (**381**).[155] The bromide was not isolated but carried into the next step as a crude solution. The yield of the bromination must be high, because **379** was isolated in 67% overall yield from **376**.

α,β-Unsaturated ketones can be brominated in the γ -position, usually via dienol esters or ethers. A recent example of this process can be found in the synthesis of the steroid tibolone (**387**, Scheme 85).[156] Dienol acetate **384** was treated with NBS to generate the γ-bromoketone **385**. It was not isolated but eliminated in situ to produce the dienone **386** in excellent overall yield.

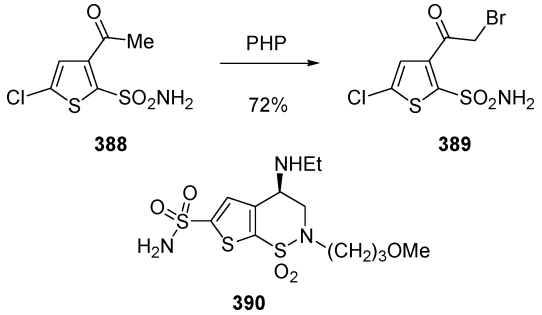
Other reagents that are often used to brominate ketones are pyridinium hydrobromide perbromide (PHP) and phenyltrimethylammonium perbromide (PTAB). Unlike Br_2, PHP and PTAB are stable crystalline solids, which increases the ease of handling. They act like Br_2 and in some cases offer superior results. Two examples of their large scale use are shown herein. In the first example (Scheme 86), workers at Alcon have brominated methyl ketone **388** with PHP in 72% yield.[157] Further conversion yields the carbonic anhydrase inhibitor brinzolamide **390**.

PTAB has been used to brominate methylandrostanalone (**391**) in 76% yield (Scheme 87).[158] Bromination of this substrate with Br_2 resulted in a low yield. Bromoketone **392** can be further converted to oxandrolone (**393**).

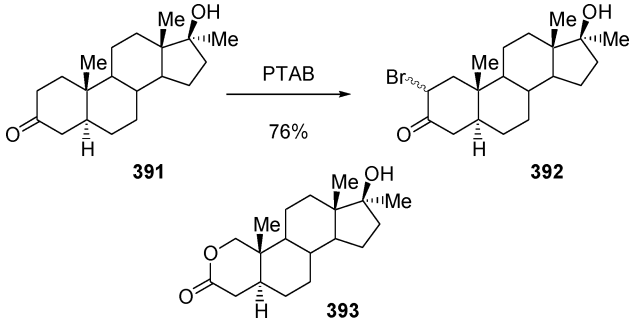
Scheme 85. Synthesis of Tibolone (387)



Scheme 86. Synthesis of Brinzolamide (390)



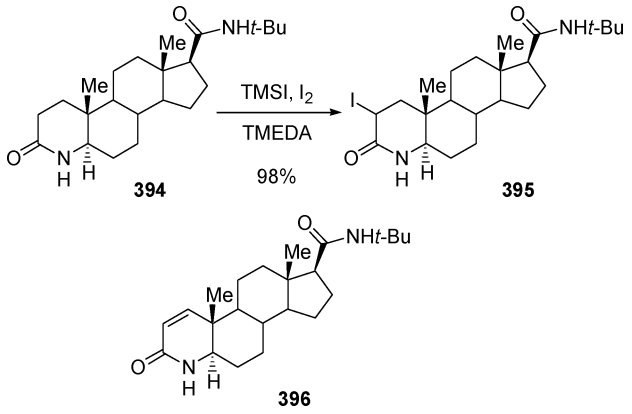
Scheme 87. Synthesis of Oxandrolone (393)



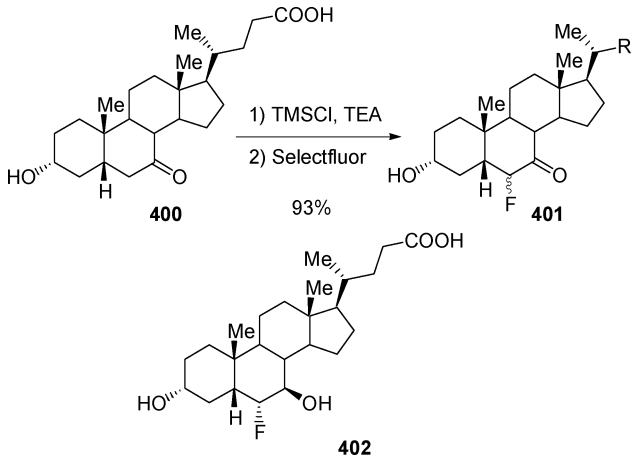
α-Halogenation of amides is not as common as the corresponding reaction of ketones. Workers from Merck have developed a general procedure for α-iodination or α-bromination of secondary amides and applied it to the synthesis of finasteride (**396**, Scheme 88).[159] Treating **394** with trimethylsilyl iodide (TMSI) and I_2 produces α-iodoamide **395** in 98% yield.

Introduction of fluorine can also be accomplished by use of an electrophilic fluorinating agent. Introduction of a fluorine at various positions of steroids often improves their biological activity. For example, treatment of the in-situ generated enol ether of **400** with 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) produces fluoroketone **401** in 93% yield (Scheme 89).[160] Further elaboration of **401** produces 6α-fluoroursodeoxycholic acid (**402**), a potential agent for treatment of

Scheme 88. α-Iodination of Amide 394



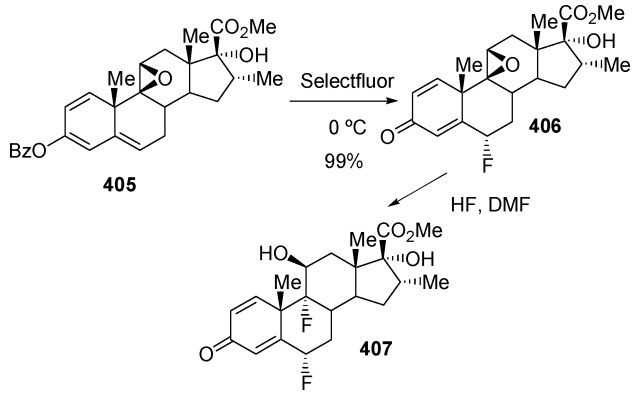
Scheme 89. Fluorination with Selectfluor



colorectal cancer.

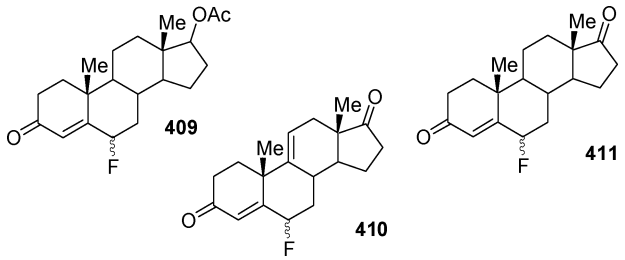
Another example of the use of Selectfluor can be found in the preparation of **406**, an intermediate in the synthesis of several anti-inflammatory agents (Scheme 90). Fluorination of dienol ester **405** produces **406** in excellent yield.[161] Opening of the epoxide with HF produces **407**.

Scheme 90. Fluorination of 405



A comparison of the reaction of several fluorinating agents (*N*-fluorobenzenesulfonimide [NFSI], *N*-fluoropyridinium pyridine heptafluorodiborate[NFPy], and Selectfluor) with three key steroidal 3,5-dienol acetates to produce the fluorinated products (**409**−**411**) has been reported (Scheme 91).[162] In general, Selectfluor had the best combination of reactivity and minimal byproduct formation.

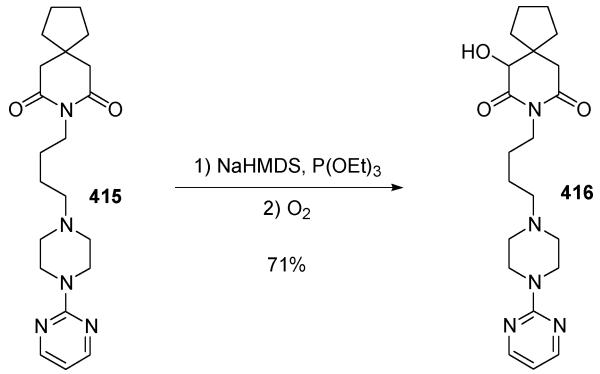
Scheme 91. Comparison of Fluorinating Agents



3.1.2. By Oxygen

Introduction of oxygen α to a carbonyl is much less common on a large scale than halogenation. This may be due to the more hazardous nature of common oxygenating agents (peracids, O_2, etc.). One interesting example of a large scale (10 kg) oxygenation that illustrates some of the safety concerns is the synthesis of 6-hydroxybuspirone (**416**) from buspirone (**415**, Scheme 92).[163] Treatment of **415** with sodium hexamethyldisiloxane (NaHMDS) generates the enolate, which is then oxygenated with oxygen, producing **416** in 71% yield. Triethyl phosphite must be present in the reaction mixture before the introduction of O_2 so that the intermediate peroxide is reduced and does not build up in the reaction mixture. Additionally, the concentration of oxygen in the headspace of the reactor must be carefully controlled so as to not reach levels where it would form a combustible mixture with the solvent vapors.

Scheme 92. Synthesis of 6-Hydroxybuspirone (416)



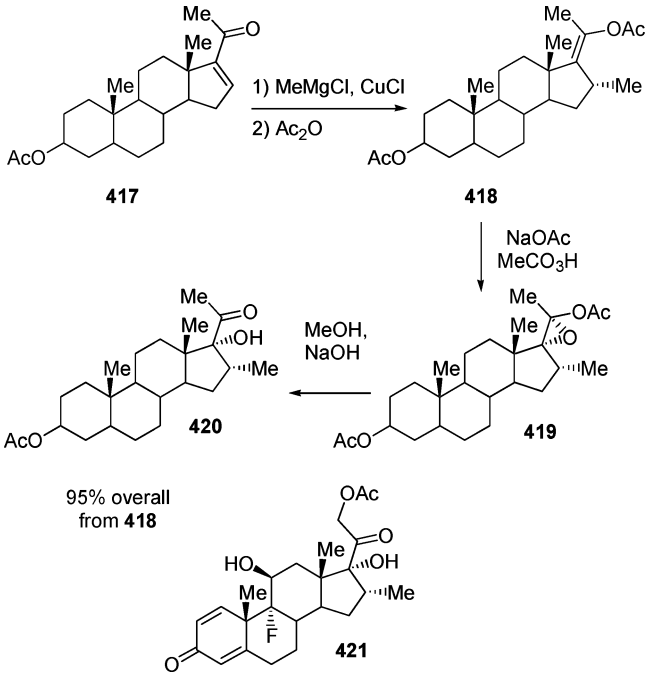
An example of a peracid oxidation can be found in a publication describing a synthesis of dexamethasone (**421**, Scheme 93).[164] A copper-catalyzed 1,4-addition of MeMgCl to enone **417** followed by trapping the intermediate enolate produced **418**. Epoxidation with peracetic acid buffered with sodium acetate produced epoxide **419**. Hydrolysis of the acetate provided the desired α-hydroxyketone **420** in 95% yield.

3.1.3. By Nitrogen

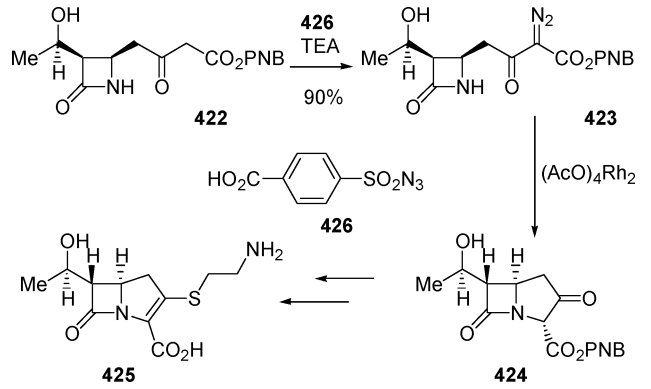
Direct introduction of nitrogen α to a carbonyl is rare. It is usually accomplished by displacement of a leaving group already in place. One classic example of the direct introduction of nitrogen can be found in the synthesis of thienamycin (**425**, Scheme 94).[165] Ketoester **422** is converted to diazo compound **423** in 90% yield. Rhodium-catalyzed carbene insertion efficiently produces the bicyclic nucleus.

Likewise, loracarbef (Scheme 95, **430**) was prepared by a similar strategy.[81] Diazotization of **427** was accomplished in 85% yield with *p*-dodecylbenzenesulfonyl azide, a reagent

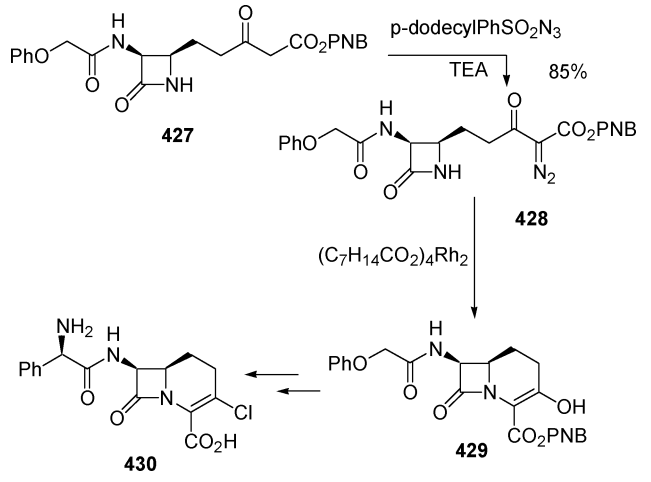
Scheme 93. Synthesis of Dexamethasone (421)



Scheme 94. Synthesis of Thienamycin (425)



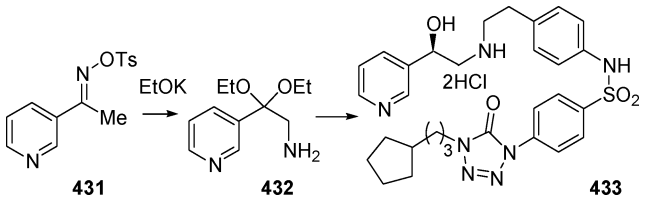
Scheme 95. Synthesis of Loracarbef (430)



that has been shown to have a better safety profile than other sulfonyl azides.[166]

A Neber rearrangement was utilized by Chung to synthesize 3-pyridylaminomethyl ketal **432** in the synthesis of β_3 adrenergic receptor agonist **433** (Scheme 96).[167−169] While this was an effective method for the synthesis of kilogram

Scheme 96. Neber Rearrangement.

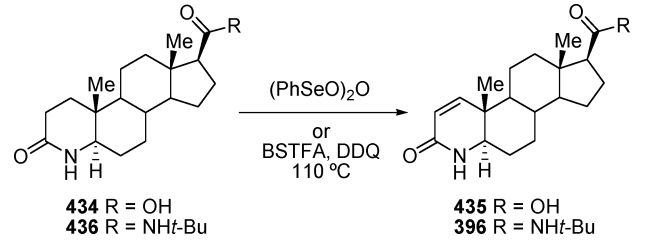


quantities of the candidate, Chung and others have noted that the tosyloxime intermediate in the rearrangement reaction (**431**) is shock sensitive[167] and decomposes at a low temperature via a Beckmann rearrangement.[170]

3.1.4. α,β Unsaturation

A few methods have been developed to directly introduce α,β unsaturation from the corresponding saturated carbonyl. Workers at Merck have published several methods for this transformation. The classical method, benzeneseleninic anhydride, converts lactam **434** to the α,β-unsaturated derivative **435** in 60% yield (Scheme 97).[171] Merck workers also

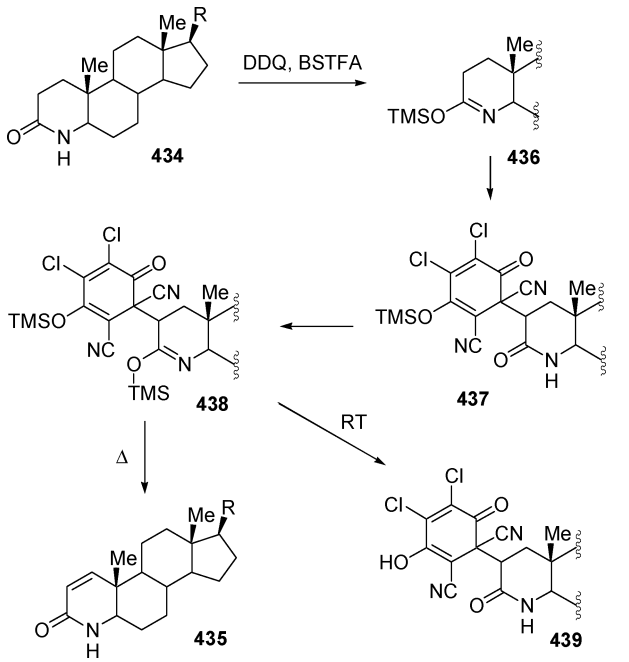
Scheme 97. Dehydrogenation of a Cyclic Lactam



found that using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in conjunction with bis(trimethylsilyl)trifluoroacetamide (BSTFA) would also perform the direct oxidation of **434** to **435** in 85% yield.[172] The same oxidations can be applied to **436** to produce finasteride (**396**) in similar high yield.

The Merck workers provide spectroscopic evidence for the following interesting mechanism (Scheme 98). Amide

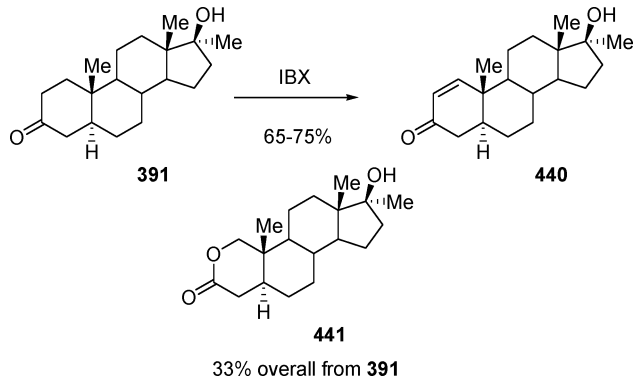
Scheme 98. DDQ Oxidation Mechanism



434 is rapidly converted to the *O*-silylimidate **436**, which reacts slowly with DDQ to produce adduct **437**. BSTFA resilylates **437** forming **438**, which fragments at high temperature producing **435**. If the reaction is run at room temperature, the fragmentation does not occur, and adduct **439** can be isolated.

Another method of introducing Δ-1 unsaturation into a steroid skeleton is *o*-iodoxybenzoic acid (IBX).[173] Treatment of methylandrostanalone (**391**) with IBX produces **440** in 65−75% crude yield (Scheme 99). Carrying this material on to oxandrolone (**441**) gives a 33% overall yield from **391**.

Scheme 99. Oxidation with IBX

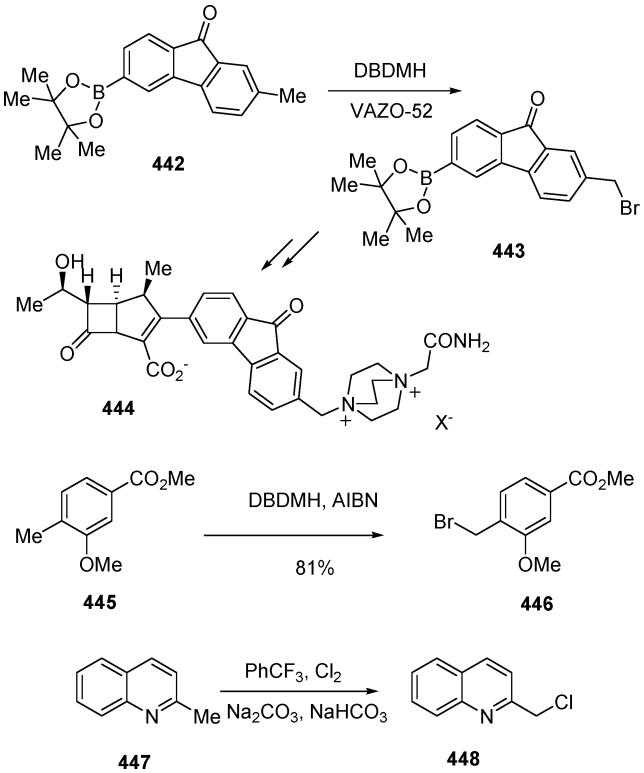


3.2. Benzylic and Allylic Oxidations

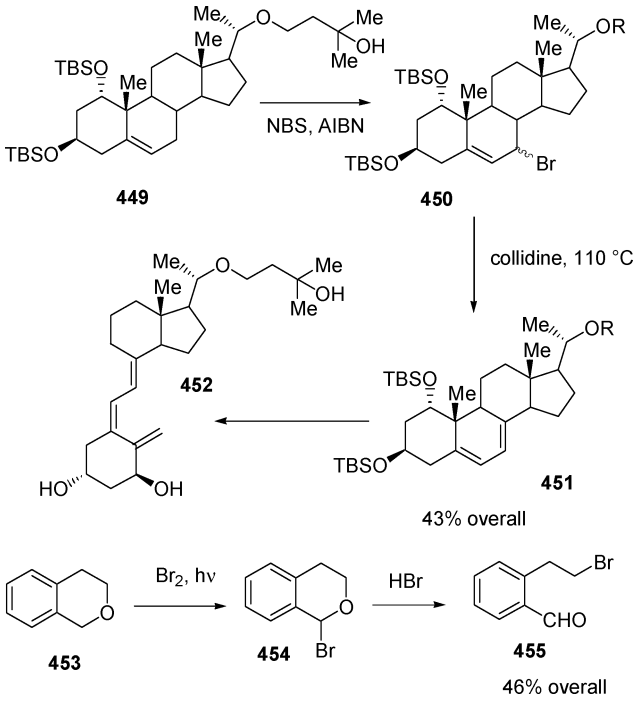
3.2.1. Halogenations

There are few examples of benzylic or allylic halogenation. The scarcity of examples may be because the resulting benzylic or allylic halides are reactive alkylating agents, potential impurities that are greatly frowned upon in the pharmaceutical industry. The few examples that have been reported are for the synthesis of early intermediates (Schemes 100 and 101).[174−179] Different halogen sources can be used.

Scheme 100. Benzylic Halogenation



Scheme 101. Allylic and Benzylic Halogenation



Elemental halogens (Cl_2 or Br_2) can be used or *N*-halo amides or imides (*N*-bromosuccinimide [NBS], 1,3-dibromo-5,5-dimethylhydantoin [DBDMH], etc). Free radical initiation is generally accomplished by azo derivatives. DuPont has developed a number of azo derivatives that offer different stabilities so one can tailor the reaction to different solvent and temperature combinations.[180]

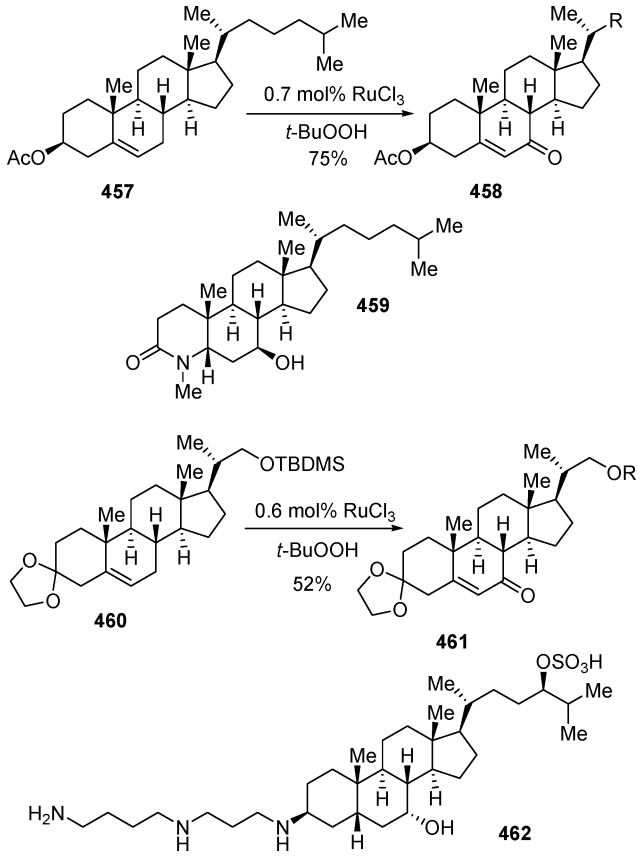
3.2.2. Oxidations

In the course of studying the synthesis of MK-386 (**459**), Merck workers sought a better method for allylic oxidation of cholesteryl acetate (Scheme 102, **457**). Most oxidations in the literature were chromium based and therefore environmentally unfriendly. The Merck workers developed a ruthenium-catalyzed *tert*-butylhydroperoxide oxidation, which could be performed on a kilogram scale, that produced the desired enone **458** in 75% yield.[181] Subsequently, workers at Schering used a similar procedure to oxidize **460**, an intermediate in the synthesis of squalamine **462**.[182] They obtained their desired enone in 52% yield on a 17 kg scale.

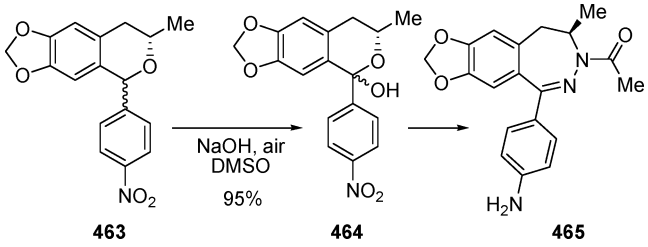
An interesting benzylic oxidation was developed by workers at Lilly in the course of the preparation of **465**, a novel benzodiazepine derivative (Scheme 103).[183] The relatively high acidity of the benzylic proton allows for its easy ionization. Oxidation with O_2 (in air) yields the hemiketal **464**. No peroxide was detected as an intermediate leading the Lilly workers to believe that the intermediate peroxide is quickly reduced by the DMSO.

A classic example of benzylic oxidation is the removal of *p*-methoxybenzyl (PMB) ethers by oxidation, often with DDQ. Two interesting large-scale examples of this reaction can be found in the synthesis of discodermolide (**474**, Scheme 105) by Novartis. DDQ oxidation of **470** (18 kg) is performed under anhydrous conditions, and the adjacent alcohol adds to the intermediate benzylic cation to form acetal **471** in 50% yield (Scheme 104).[184] In a later stage of the synthesis, two PMB protecting groups are removed simultaneously (Scheme 105).[185]

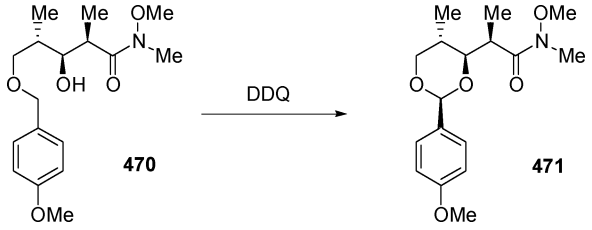
Scheme 102. Synthesis of MK-386 (459) and Squalamine (462)



Scheme 103. Preparation of Benzodiazepine Derivative 465



Scheme 104. Acetal Formation by Oxidation



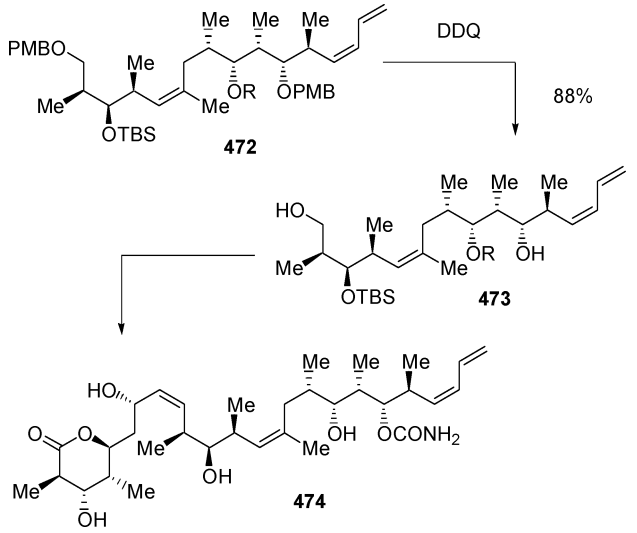
3.3. Oxidation α to a Heteroatom

In the previous section several examples of oxidation of benzylic ethers were presented. Although it is known that simple ethers will oxidize via a radical mechanism to form hazardous peroxides, there are few synthetically useful examples. One such example is the oxidation of acetal **475** (Scheme 106).[186] Interestingly, if the ozonolysis is prolonged, the primary alcohol (**476**) will slowly oxidize to the carboxylic acid.

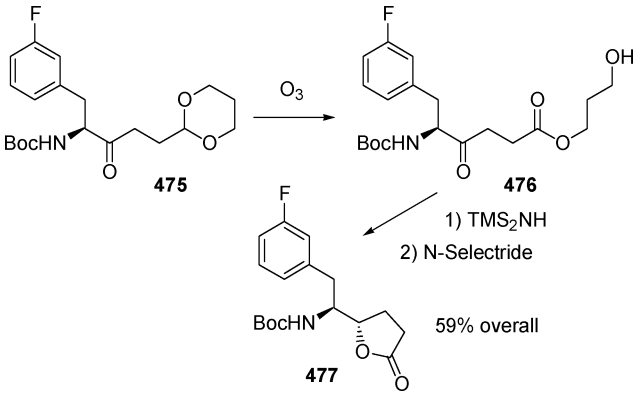
3.4. Aromatization

In the synthesis of the serotonin receptor agonist **479** (Scheme 107), aromatization of **478** was accomplished by

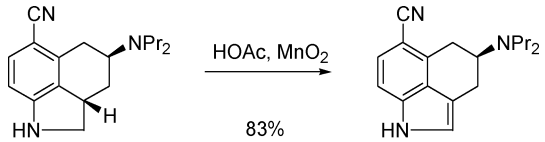
Scheme 105. Double Deprotection by DDQ



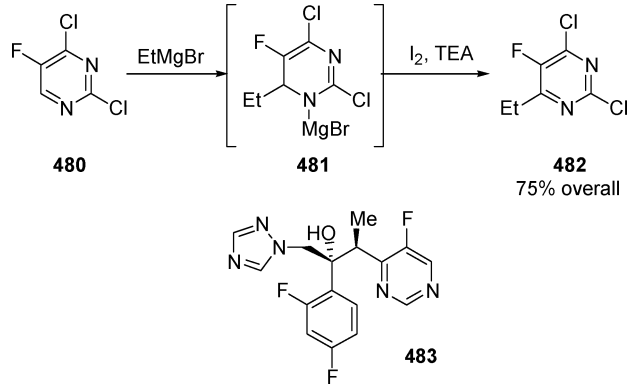
Scheme 106. Ozonolysis of an Acetal



Scheme 107. Aromatization of 478



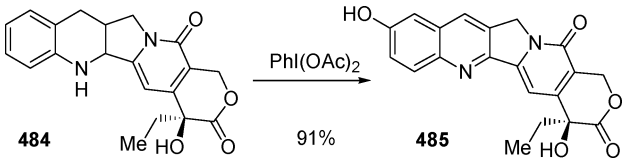
Scheme 108. Synthesis of Voriconazole (483)



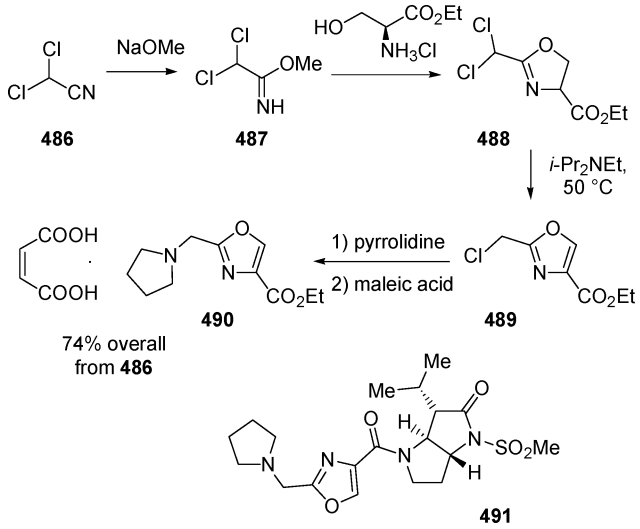
treatment with MnO_2.[187] An interesting solvent effect was noted; HOAc greatly accelerated the reaction such that only 2 equiv of MnO_2 was required.

In the synthesis of voriconazole (Scheme 108), a key ethylpyrimidine (**482**) was prepared by addition of ethyl

Scheme 109. Synthesis of 10-Hydroxycamptothecin (485)



Scheme 110. Synthesis of 491



Grignard to a pyrimidine followed by in-situ oxidation with iodine.[188]

Another interesting aromatization is found in the synthesis of 10-hydroxycamptothecin (**485**, Scheme 109).[189] The reaction actually proceeds by oxidation *para* to the aniline nitrogen followed by a rapid aromatization. The desired product can also be further oxidized, but the authors found that by careful selection of solvent, **485** would precipitate from the reaction mixture as it was formed, protecting it from further oxidation.

The last example (Scheme 110) is actually a 1,4-elimination followed by tautomerization of **488** to the aromatic oxazole **489**, an intermediate on the way to **491**.[190]

4. Oxidation of Nitrogen and Carbon–Nitrogen Bonds

The oxidation of nitrogen atoms encompasses many common reactions such as diazotization, formation of *N*-oxides and *N*-chlorides, and oxidative cyclizations. Oxidation of C−N bonds is much less common and encompasses nitrile−oxide formation (arguably a C−H oxidation followed by elimination), amine to imine transformations, and aromatizations.

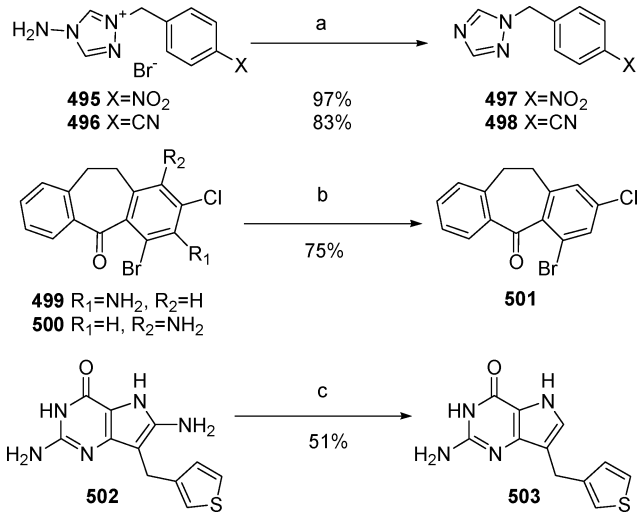
4.1. Diazotization

The most common nitrogen oxidation run on large scale in the literature is diazotization of an aniline. In general, the diazo compound is not isolated as a safety precaution and reacted without isolation, although in a few rare cases, isolations were reported. In almost every case, the diazotization is run using $NaNO_2$ in acid as the oxidant. Several examples are provided herein, categorized by the manner in which the intermediate is trapped.

4.1.1. Diazotization Followed by Reduction to C–H

A number of examples of diazotization followed by reduction have been reported (Scheme 111). The deamination

Scheme 111. Diazotization Followed by Reduction[a]



[a] (a) (i) $NaNO_2$, H_2O, HCl; (ii) NH_4OH; (b) $NaNO_2$, H_3PO_2; (c) (i) $NaNO_2$, HCl; (ii) H_3PO_2, $CuSO_4$ or H_2, Pd/C, HCl.

of 1,2,4-triazol-1-yl compound **495**[191] via the diazo intermediate was reported; the same reaction was reported on a related structure (**496**) as well.[192] Fu reported the diazotization of a mixture of anilines (**499** and **500**) on a 77 kg scale.[193] In this case, it was critical to eliminate the presence of residual halides from the previous step to minimize debromination during the hypophosphorus acid reduction. The reduction of **502** to CI-1000 (**503**) via diazotization followed by reduction of the azide was accomplished in 37% yield using hypophosphorus acid as the reducing agent.[194] Reduction using sponge Ni catalyst and hydrogen was a preferable procedure, with a reported 51% yield on a 23.4 kg scale. Interestingly, in this case the diazonium chloride salt was collected by filtration, but care was taken to keep the solids water-wet.

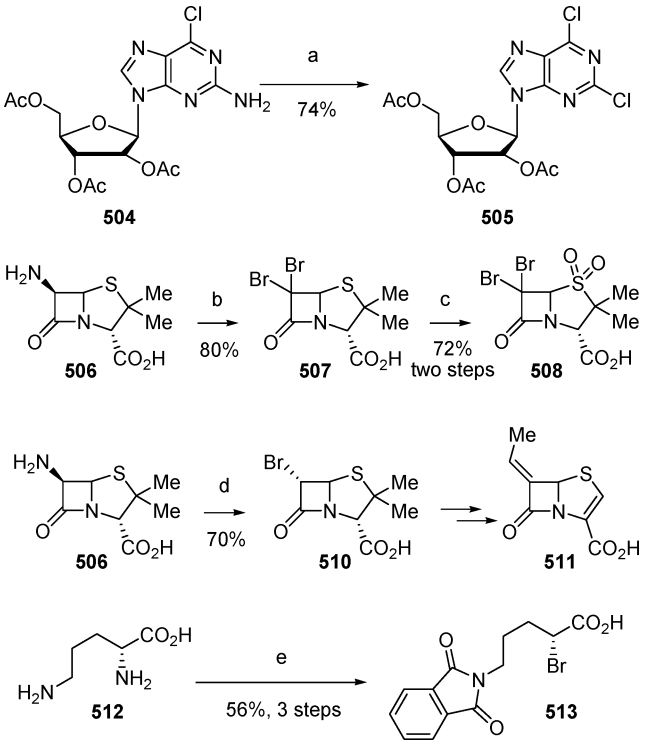
4.1.2. Conversion of Amino Group to Halide via Diazotization

Conversion of an amine to the corresponding halide has also been reported (Scheme 112). In the synthesis of an adenosine derivative, amine **504** was converted into chloride **505** via the azide using *n*-pentylnitrite as the oxidant in the presence of trityl chloride.[195] Barth and Volkmann reported the synthesis of **507** from 6-aminopenicillinic acid (6-APA, **506**) in their synthesis of an intermediate (**508**) for the manufacture of sulbactam,[196,197] in which the dibromide is produced. A similar procedure was utilized to prepare monobromopenicillanic acid (**510**) from 6-APA (**506**) in a synthesis of β-lactamase inhibitor **511.**[198] Ornithine (**512**) was converted to **513** in a three-step process including diazotization followed by trapping with bromide; this transformation was reported on 17.4 kg scale.[199]

4.1.3. Diazotization Followed by Cross-Coupling

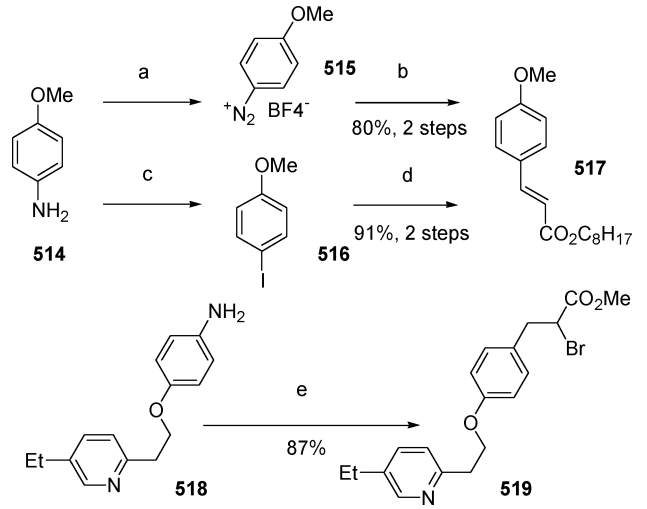
Azides are frequently generated as coupling partners in metal-mediated cross-coupling reactions. A number of examples are shown in Scheme 113. Several instances of the synthesis of 2-ethylhexyl *p*-methoxycinnamate (**517**) from aniline **514** have been reported. In one case, the Heck coupling was run using the azide (**515**) as the coupling partner;[200] in two other cases, the aryl iodide (**516**) was prepared from the azide as the coupling partner.[201,202] The reaction run by Caskey was executed on 56 lb in 91% overall

Scheme 112. Diazotization Followed by Halogenation[a]



[a] (a) *n*-pentONO, Ph_3CCl, K_2CO_3; (b) Br_2, H_2SO_4, $NaNO_2$; (c) $KMnO_4$, H_3PO_4; (d) HBr, $NaNO_2$; (e) (i) $CuSO_4$, KOH; (ii) *N*-carboethoxyphthalimide; (iii) $NaNO_2$, HBr, KBr.

Scheme 113. Diazotization Followed by Heck Coupling[a]



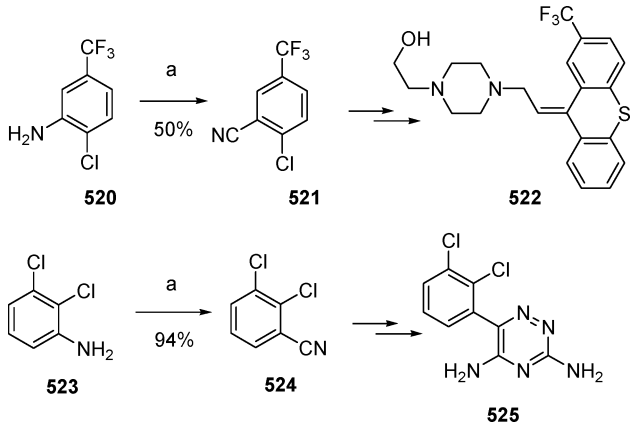
[a] (a) $NaNO_2$, $NaBF_4$, H_2SO_4; (b) Li_2PdCl_4, NaOAc, CuCl, 2-ethylhexyl acrylate; (c) $NaNO_2$, NaI, H_2SO_4; (d) $BuNH_2$, $Pd(dba)_2$, 2-ethylhexyl acrylate; (e) HBr, $NaNO_2$, Cu_2O, methyl acrylate.

yield. Lala Rajendra reported the conversion of **518** to **519** via the azide.[203]

Copper-catalyzed cyanations of azides on a large scale have also been reported. The Sandmeyer reaction of **520** to **521**, an intermediate in the synthesis of Fluanxol (**522**), was reported on a 24 kg scale (Scheme 114).[204] Extensive safety testing and process modification were undertaken to run the process in standard manufacturing equipment. The Sandmeyer reaction of **523** to **524** was utilized in the synthesis of lamotrigine (**525**); the reaction was reported on a 650 g scale.[205]

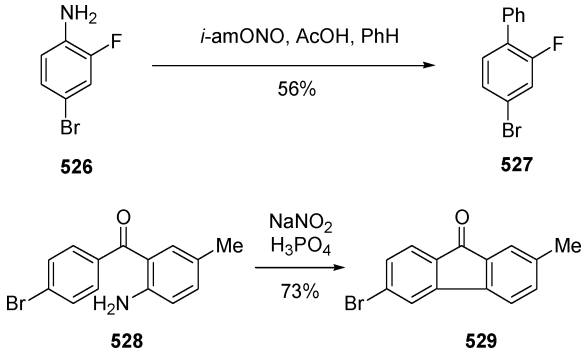
Hylton reported the diazotization of **526** followed by electrophilic substitution of benzene to make biphenyl **527**

Scheme 114. Sandmeyer Reaction[a]



[a] (a) (i) $NaNO_2$, H_2SO_4; (ii) CuCN, NaCN.

Scheme 115. Electrophilic Aromatic Substitution



(Scheme 115).[206] The synthesis of fluorenone **529** from aniline **528** via an intramolecular version of the electrophilic substitution reaction with an azide was described in the synthesis of a carbopenem antibiotic.[174]

4.1.4. Diazotization Followed by Carbonylation or Sulfonylation

Similar metal-mediated processes can be run to carbonylate or sulfonylate the azide intermediates generated from anilines (Scheme 116). A modified Beech reaction was utilized to convert aniline **531** to oxime **532** on a 200 g scale.[207] Siegrist reported the carbonylation of the azide derived from **533** to produce diacid **534**.[208] Aniline **535** was converted to a mixture of sulfonyl chloride and bromide;[152] the bromide is introduced from the hydrobromide salt of the starting material. Maintaining the azide in solution was critical to the safe operation of this process.

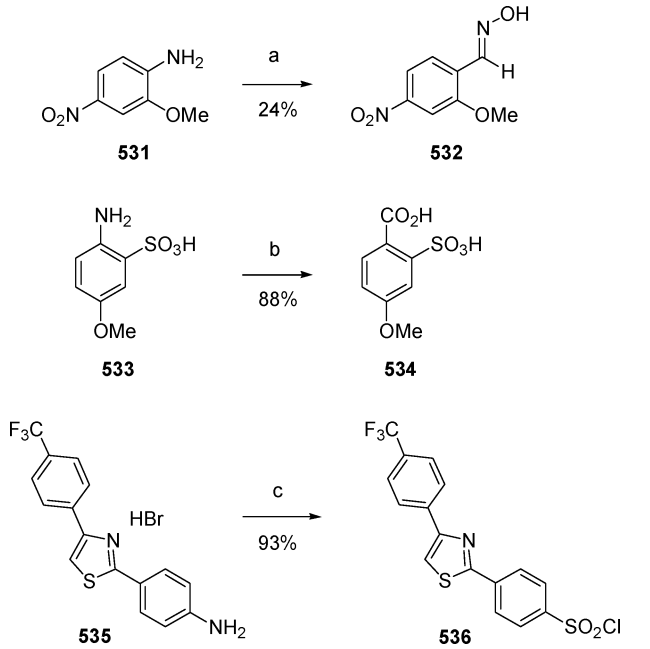
4.1.5. Conversion of an Amine to an Alcohol via Diazotization

Processes for the conversion of an aliphatic amine to the corresponding alcohol have been reported on a large scale (Scheme 117). Coutts reported the conversion of L-valine (**537**) to (*S*)-2-hydroxyisovaleric acid (**538**) on 710 g.[209] Additionally, phenylalanine (**539**) could be converted to phenyllactic acid (**540**) under similar reaction conditions.[13]

4.1.6. Diazotization and Reduction to the Hydrazine

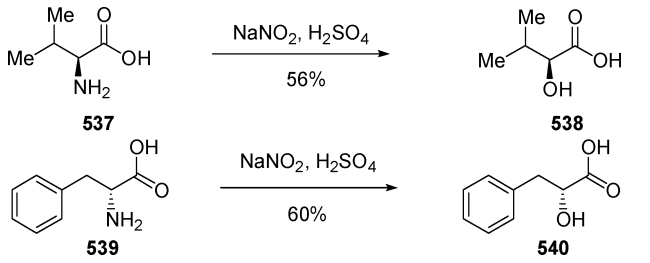
Diazotization of an aniline followed by partial reduction of the azide intermediate produces a net oxidation from amine to hydrazine (Scheme 118). In the synthesis of azafenidin (**545**), Shapiro diazotized anilines **541** and **542** followed by

Scheme 116. Carbonylation and Sulfonylation of Azides[a]

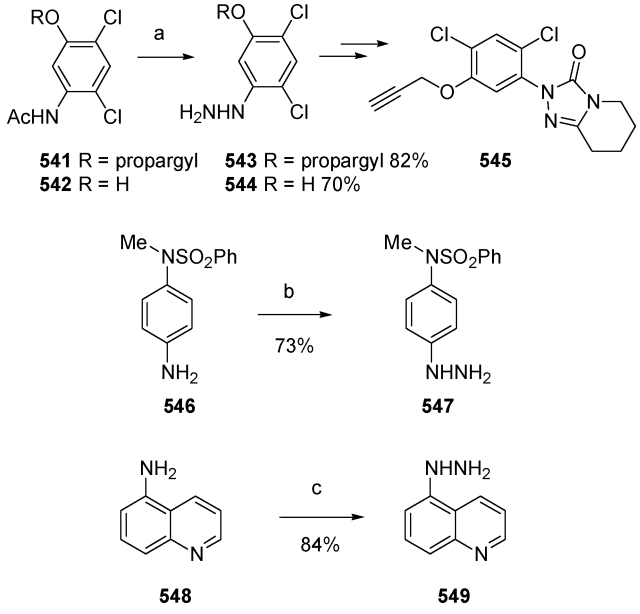


[a] (a) (i) $NaNO_2$, HCl; (ii) $NH_2OH{\cdot}HCl$, $(CH_2O)_n$, $CuSO_4$, Na_2SO_3, NaOAc; (b) (i) $NaNO_2$, HCl; (ii) H_2NSO_3H, $PdCl_2$, CO, H_2O; (c) (i) $NaNO_2$, HCl, HOAc; (ii) SO_2, CuCl.

Scheme 117. Conversion of Aliphatic Amines to Alcohols



Scheme 118. Conversion of Anilines to Hydrazines[a]

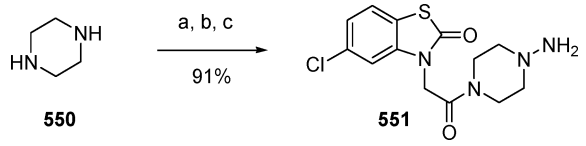


[a] (a) (i) $NaNO_2$, HCl; (ii) Na_2SO_3; (b) (i) $NaNO_2$, HCl; (ii) $Na_2S_2O_4$; (c) (i) $NaNO_2$, HCl; (ii) ascorbic acid.

reduction with sodium sulfite to produce hydrazines **543** and **544**. In the case where R is propargyl, the reaction gave 82% yield of **543**; however, the case where R is OH was preferred and run on a 500 g scale in >70% yield.[103] The preparation of hydrazine **547** from aniline **546** was reported using sodium dithionite as the reducing agent in a preparation of sumatriptan.[210] Ascorbic acid was utilized as the reducing agent in the synthesis of hydrazine **549** from 5-aminoquinoline (**548**) via the corresponding azide.[211]

Diazotization of piperazine (**550**) followed by reduction with zinc metal resulted in the corresponding hydrazine, which was isolated as its benzaldehyde hydrazone prior to amide formation and deprotection to prepare FR062732 (**551**, Scheme 119).[212]

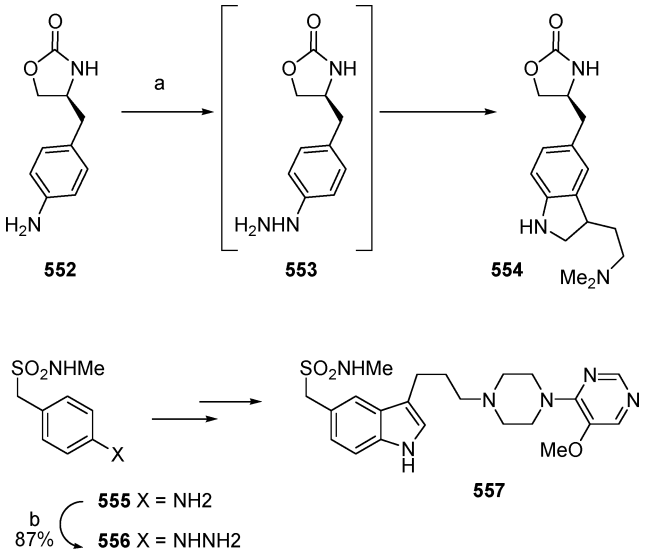
Scheme 119. Conversion of an Aliphatic Amine to the Hydrazine[a]



[a] (a) (i) $NaNO_2$, HOAc; (ii) Zn(0); (iii) PhCHO, 65%; (b) RCOCl, Et_3N, 93%; (c) $H_2NOH{\cdot}HCl$, HCl, 62%.

In a synthesis of indole **554** via the Fischer indole synthesis, the intermediate hydrazine was generated via diazotization of **552** followed by reduction with sodium sulfite (Scheme 120).[213,214] The sequence was executed on a

Scheme 120. Fischer Indole Synthesis[a]



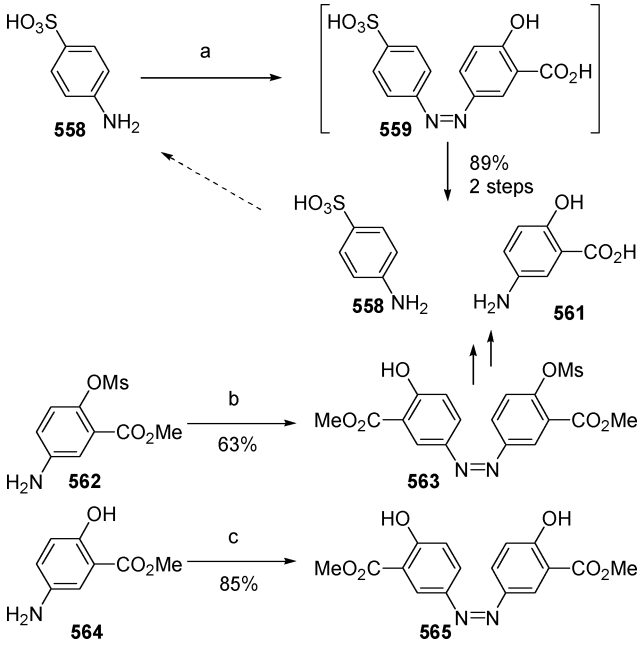
[a] (a) (i) $NaNO_2$, HCl; (ii) Na_2SO_3, HCl, (iii) RCHO; (b) (i) $NaNO_2$, HCl; (ii) $SnCl_2$.

19.2 kg scale with no yield reported. Likewise, a diazotization−reduction−Fischer sequence was used to synthesize the indole component of avitriptan (**557**).[215]

4.1.7. Preparation of Diazo Dyes

Trapping a diazoaryl compound generated from an amine as an azo dye has been demonstrated for several substrates, as shown in Schemes 121−123. This methodology was utilized in two separate preparations of 5-aminosalicylic acid (**561**, Scheme 121). In Sjörstrand's synthesis, *p*-aminobenzenesulfonic acid (**558**) was used as a recyclable reagent for the derivatization of salicylic acid.[216] *p*-Aminobenzenesulfonic acid was diazotized and trapped with salicylic acid to produce azo compound **559**. Hydrogenation returned the aminobenzenesulfonic acid and an equivalent of aminosali-

Scheme 121. Synthesis of 5-Aminosalicyclic Acid via Trapping of Azides as Diazo Dyes[a]



[a] (a) (i) $NaNO_2$, H_2SO_4; (ii) salicylic acid; (iii) Pd/C, H_2; (b) (i) $NaNO_2$, HCl; (ii) methyl salicylate, KOH; (c) H_2O_2, HOAc.

cylic acid. In a similar approach, a derivative of 5-aminosalicylic acid itself (**562**) was used as the precursor to the diazo intermediate, reacting with an equivalent of salicylic acid to provide 2 equiv of aminosalicylic acid after hydrogenation and hydrolysis.[217] Although not a diazotization, the synthesis of a similar azo compound (**565**) was achieved through the oxidative dimerization of methyl 5-aminosalicilate using hydrogen peroxide in acetic acid.[218]

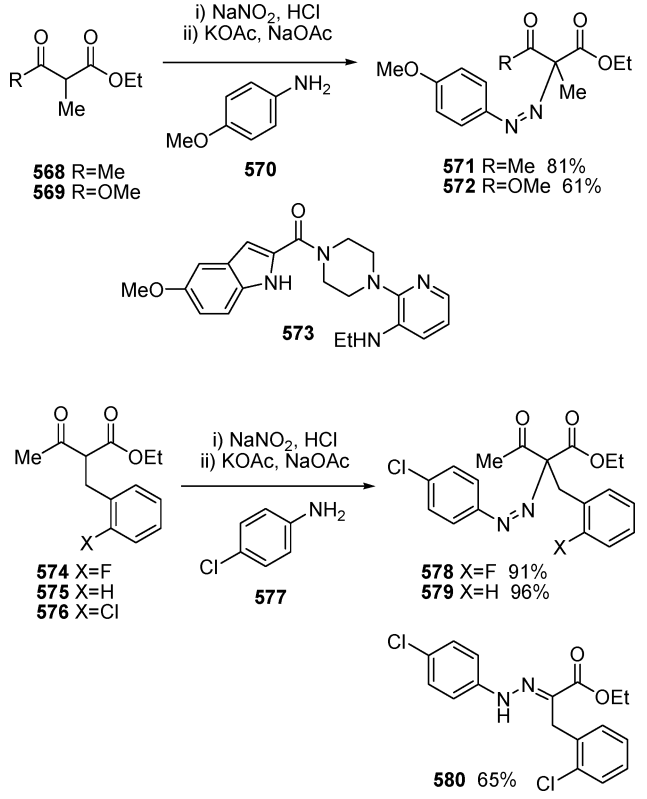
In two similar routes to atevirdine (**573**), the enolates of ethyl 2-methylacetoacetate (**568**) and methyl 2-methylmalonate (**569**) were utilized to trap *p*-methoxyphenyl azide as the diazo intermediates **571** and **572**, which after deacetylation and decarboxylation, respectively, resulted in the α-iminoester (Scheme 122).[219] In a similar process, Inaba reported the trapping of *p*-chlorophenyl azide with a series of *o*-substituted 2-benzylacetoacetates, **574**, **575**, and **576**, to provide the diazo dye intermediates in two cases (unsubstituted (**579**) and *o*-fluorobenzyl (**578**)) and the α-iminoester (**580**) directly in the case of the *o*-chlorobenzyl acetoacetate.[10]

Zalipsky reported the trapping of a *p*-sulfamidoazide derived from **581** with a series of phenols (Scheme 123); yields were not provided.[220] In two complementary routes to R-83842 (**590**), the intramolecular trapping of diazo intermediates generated from **588** and **591** by the *o*-amino group to form benzotriazoles **589** and **592** was reported to give 58% and 62% yield, respectively.[221]

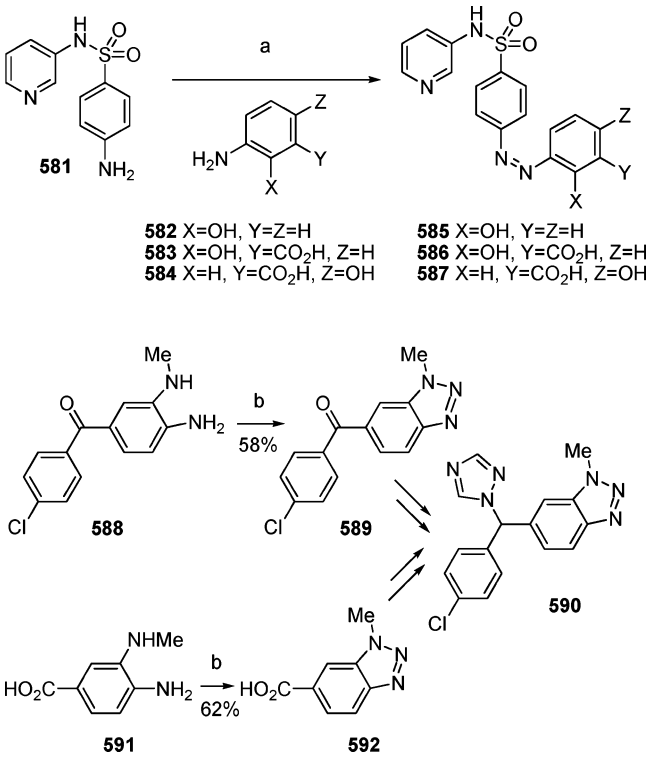
4.2. Oxidative Cyclization of *O*-Nitroanilines

A similar strategy for cyclization was utilized by researchers at Pfizer in the synthesis of benzofurazan **596** from substituted *o*-nitroaniline **595** using sodium hypochlorite as the oxidant (Scheme 124).[222] The benzofurazan was introduced on an advanced intermediate (**595**) to avoid the use of 5-hydroxybenzofurazan, which decomposes at a low temperature (133 °C, 2666 J/g) with a large amount of energy. The three-step sequence of S_NAr reaction, benzofurazan cyclization, and *N*-oxide reduction was reported on a 32 kg scale.

Scheme 122. Trapping of Azides as Diazo Dyes by Acetoacetate and Malonate Enolates



Scheme 123. Trapping of Azides as Diazo Dyes[a]

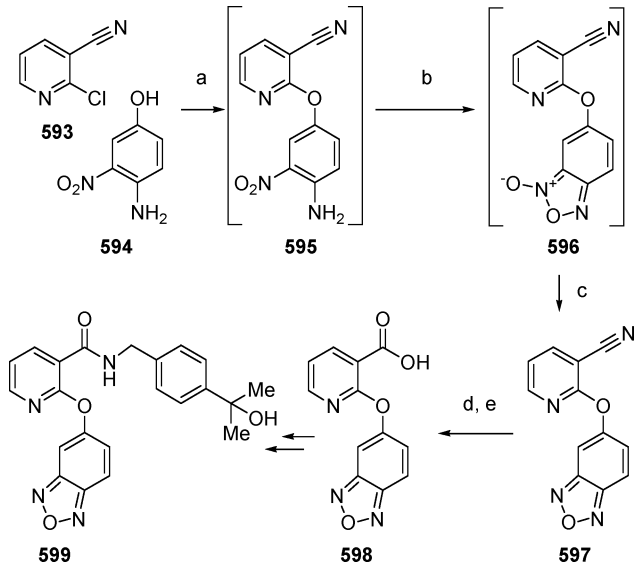


[a] (a) (i) $NaNO_2$, HCl; (ii) **582**, **583**, or **584**, K_2CO_3; (b) $NaNO_2$.

4.3. Pyridine *N*-Oxides

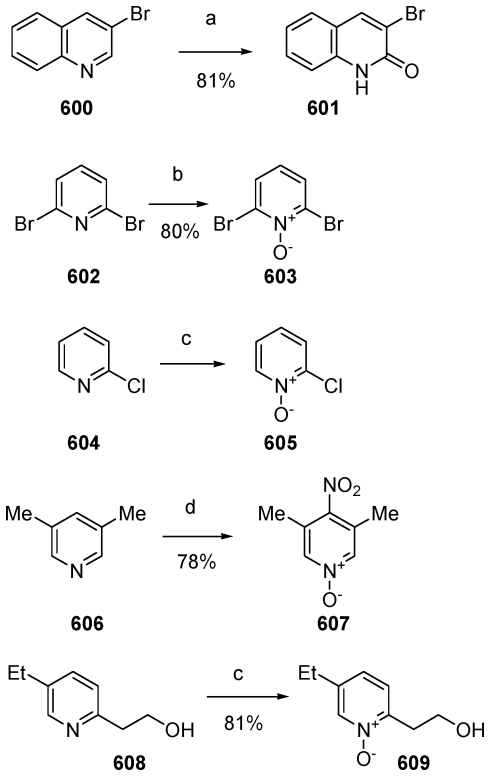
The synthesis of pyridine *N*-oxides has been extensively utilized on a large scale (Scheme 125). Payack utilized a rearrangement of the *N*-oxide of 3-bromoquinoline (**600**) to produce the 2-quinolone (**601**) on a 4.1 kg scale.[223] The

Scheme 124. Oxidation of *o*-Nitroanilines to Benzofurazan Oxides[a]



[a] (a) K_2CO_3, DMSO; (b) NaOCl; (c) $P(OEt)_3$, 75%, 3 steps; (d) DIBAL-H, 47%; (e) $NaClO_2$, NaH_2PO_4, 89%.

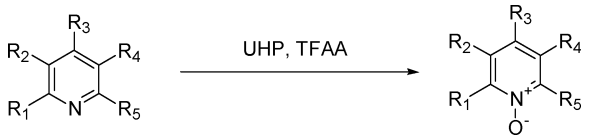
Scheme 125. Oxidation of Pyridines to Pyridine *N*-Oxides[a]



[a] (a) (i) $MeReO_3$, H_2O_2; (ii) TsCl, K_2CO_3; (b) H_2O_2, TFA; (c) H_2O_2, HOAc; (d) (i) H_2O_2, TFA; (ii) $NaNO_2$, H_2SO_4.

oxidant utilized was hydrogen peroxide in the presence of 0.5 mol % $MeReO_3$ catalyst. The oxidation of 2,6-dibromopyridine (**602**) on a 4 kg scale was realized using hydrogen peroxide in TFA.[224] Reagent stoichiometry was carefully studied in the oxidation of 2-chloropyridine (**604**) using hydrogen peroxide in acetic acid with either H_2SO_4 or $NaHSO_4$ as a catalyst.[225] In a preparation of omeprazole, an oxidation of 3,5-dimethylpyridine (**606**) followed by nitration of the *N*-oxide was utilized.[226] Finally, Pandey has oxidized pyridine **608** to its *N*-oxide (**609**) using hydrogen peroxide in acetic acid.[227]

Table 1. Use of H_2O_2/TFAA in the Oxidation of Pyridines to Pyridine *N*-Oxides



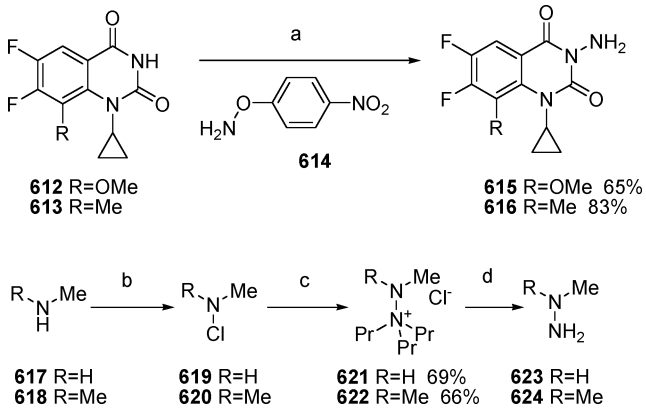
R_1	R_2	R_3	R_4	R_5	yield (%)
H	Br	H	CO_2Et	H	91
H	H	H	CN	Cl	70
H	NO_2	H	H	Br	82
H	NO_2	H	H	OMe	56
H	CF_3	H	H	Cl	82
CO_2Me	H	H	H	CO_2Me	55
H	CO_2Me	H	H	Me	81
H	H	CO_2Et	H	H	83
H	H	CO_2Et	CO_2Et	H	98
H	H	H	CONHEt	H	63
H	H	CO_2Me	H	CO_2Me	98
H	H	H	COMe	H	48
H	H	H	COPh	H	98

Hydrogen peroxide with TFAA has been reported as an effective oxidant for the production of pyridine *N*-oxides, as demonstrated on a number of variously substituted substrates (Table 1).[228]

4.4. Amination of Nitrogen

Although diazotization is the most common method in the literature for conversion of N−H to N−N bonds, electrophilic sources of nitrogen have also been reported (Scheme 126).

Scheme 126. Electrophilic Amination of N−H[a]



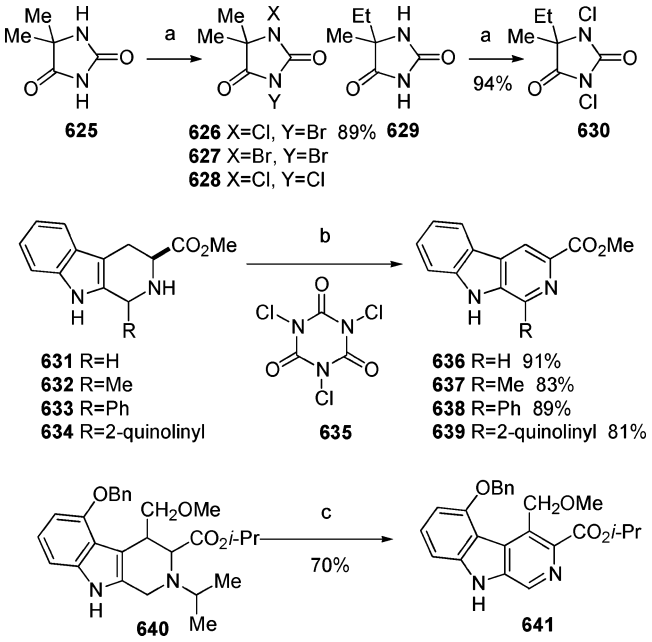
[a] (a) K_2CO_3; (b) NaOCl; (c) Pr_3N; (d) NH_3.

Compounds **612** and **613** were oxidized to the corresponding hydrazides **615** and **616** using hydroxylamine **614** as the oxidant and potassium carbonate as the base.[229] Several related hydroxylamines were evaluated from a perspective of safety and yield for this transformation. Methylchloramine (**619**) and dimethylchloramine (**620**), utilized in the synthesis of hydrazines on a 0.5 mol scale,[230] were generated by oxidation of the amines with NaOCl, kept in solution, then reacted with propylamine to make hydrazinium chlorides **621** and **622**, respectively. These salts could be reacted with ammonia to produce the corresponding hydrazines.

4.5. Halogenation of Amines

Halogenation of nitrogen is a method used to produce disinfectants and to activate the nitrogen to attack by

Scheme 127. Electrophilic Halogenation of N−H[a]



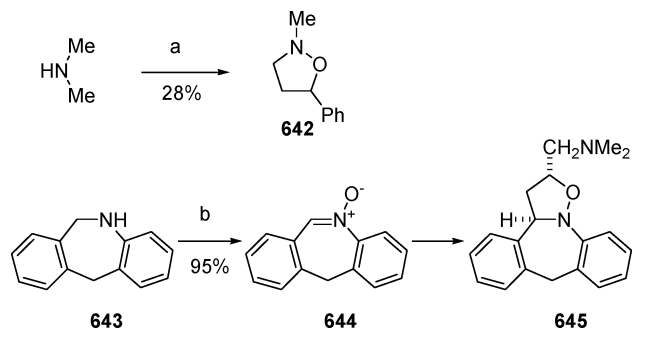
[a] (a) NaOH or $Ca(OH)_2$, Cl_2 or Br_2; (b) **635**; (c) $(CH_2O)_n$, TsOH, **635**, Et_3N.

nucleophiles or to elimination (Scheme 127). A number of large-scale preparations of dihalogenated hydantoins, which are used as disinfectants, have been reported. *N*-Bromo-*N*′-chlorodimethyl hydantoin (**626**) was produced on a 1.2 kg scale using NaOH as the base and bromine followed by chlorine as the halogenating agents.[231] Cole reported the production of the dichloro, dibromo, and chlorobromo hydantoins **628**, **627**, and **626** on a 1700 lb scale using $Ca(OH)_2$ as the base.[232] Yields were not reported because the product was pressed into granules mixed with the residual calcium salts. Analogous chemistry on the methyl, ethyl hydantoin **629** to make the dichloro product **630** has also been disclosed.[233] Aromatization of a number of 3-carboxy-tetetrahydro-β-carbolines (**631**−**634, 640**) using trichloro-cyanuric acid (TCCA)[234] via chlorination of the nitrogen followed by elimination has been reported. Yields ranged from 70% to 91% for derivatives **636**−**639** and **641**.[235,236]

4.6. Nitrone Formation

Conversion of an amine to the corresponding nitrone is another category of reaction for which there are large-scale examples (Scheme 128). Theriot oxidized dimethylamine to the corresponding nitrone and trapped it with styrene to isolate **642** in 28% yield.[237,238] The oxidation of **643** to nitrone

Scheme 128. Synthesis of Nitrones[a]



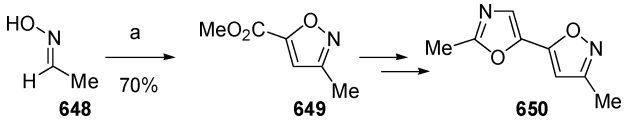
[a] (a) (i) H_2O_2, Na_2WO_4, $NaHCO_3$, (ii) styrene; (b) *m*-CPBA.

644 followed by trapping with *N*,*N*-dimethylallylamine provided product **645** on an 11.7 kg scale.[239] The safety and mechanism of the oxidation were discussed.

4.7. Nitrile Oxides from Aldoximes

Aldoximes can be oxidized to the corresponding nitrile oxide by chlorination followed by elimination with base (Schemes 63 and 129). Although the nitrile oxides are

Scheme 129. Oxidation of Acetaldoxime to the Corresponding Nitrile Oxide[a]



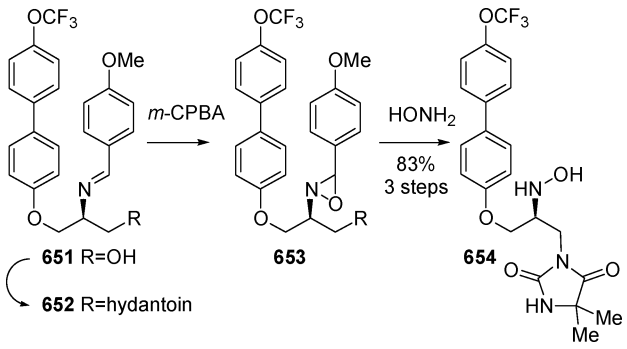
[a] (a) Cl_2, HCl, methyl propiolate.

unstable, they can be trapped with alkenes or alkynes to form isoxazolines and isoxazoles, respectively. To synthesize isoxazole **649**, acetaldoxime was oxidized to the corresponding nitrile oxide, which then reacted with methyl propiolate (Scheme 129).[240] As depicted in an earlier section (section 2.7.2), oxime **256** was oxidized followed by elimination to provide a nitrile oxide, which underwent cycloaddition with **259** in a preparation of anti-thrombotic agent **263** (Scheme 63)[106,241,242] on a 46 kg scale.

4.8. Imine Oxidation

Significantly less common than the oxidation of nitrogen atoms is the oxidation of C−N bonds, though a few large-scale examples are in the literature (Scheme 130). Research-

Scheme 130. Oxidation of an Imine

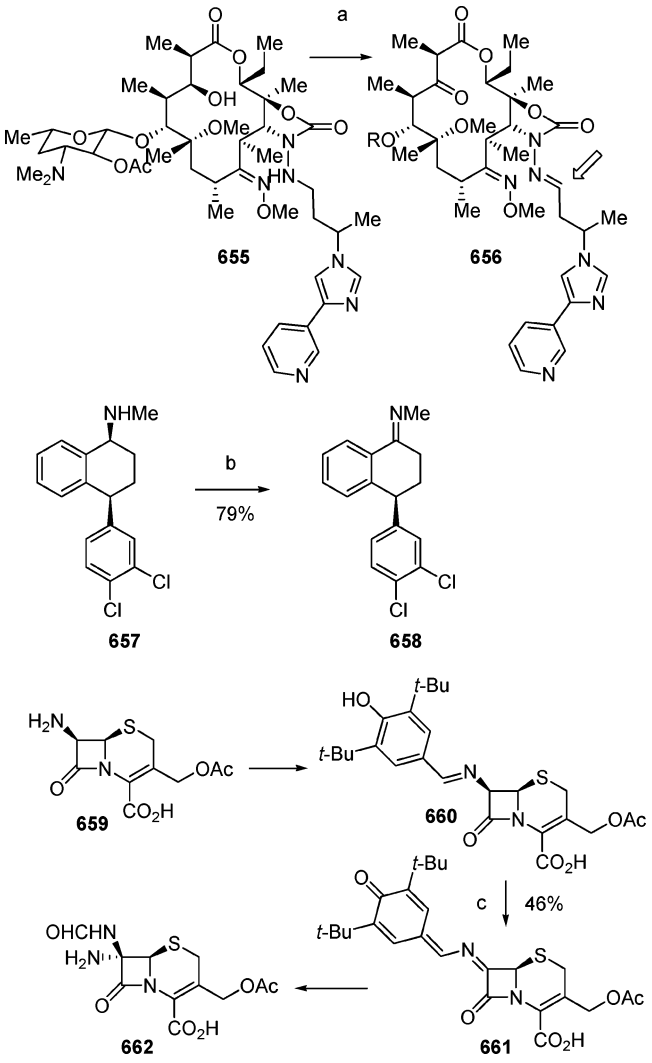


ers at Abbott reported the oxidation of imine **652** with *m*-CPBA to produce oxaziridine **653** as a mixture of isomers.[243] The oxaziridine was opened using hydroxylamine to free the resulting substituted hydroxylamine **654**. The three-step sequence from **651** to **654** was run on a 2.8 kg scale.

4.9. Oxidation of Amines to Imines

The large-scale oxidation of amines to the imines has also been reported (Scheme 131). A 30% impurity, formed in the large-scale oxidation of alcohol **655** to ketone **656**,[244] arose from oxidation of the hydrazide to the corresponding imide under Swern[245] conditions. In a process reported for converting the undesired enantiomer of sertraline (**657**) to the desired enantiomer, the oxidation of **657** to imine **658** was achieved using bromine.[246] Oxidation of cephalosporin

Scheme 131. Oxidation of an Amine to an Imine[a]



[a] (a) (i) DMSO, TFAA; (ii) Et_3N; (b) NaOH, Br_2; (c) DDQ.

659 to 7α-formamido cephalosporin **662** via oxidation of imine **660** to quinone **661**[247] has been carried out on a 1 kg scale.

5. Oxidation of Carbon–Oxygen Bonds

The oxidation of alcohols to the corresponding aldehydes, ketones, or carboxylic acid derivatives remains one of the most utilized chemical transformations in organic synthesis and remains an active research area for the identification of more effective and practical methods.[234,248−250] This is due in part to the development and availability of a plethora of orthogonal protecting groups for alcohols, which often allow for chemoselective deprotection to the desired alcohol prior to its oxidation to the required derivative.[251] Furthermore, the selection of polyoxygenated synthetic targets such as polypropionate and polyketides[252−258] often requires adjustment of the oxidation state of an intermediate prior to further elaboration. While the majority of oxidative methods are acceptable for manufacturing at large scale, one noteworthy exception is the Dess−Martin reagent,[259] which has not been used on a large scale, most likely because of the safety concerns in its preparation and its cost.

In the pharmaceutical industry, synthetic targets are usually simpler than many natural products. These targets lend themselves to synthetic routes designed to carry an oxygenated functionality in the correct oxidation state as part of the starting materials,[1] thus avoiding protecting groups and reducing the number of synthetic operations. One notable exception has been the recent efforts at Novartis for the multikilogram preparation of (+)-discodermolide, an immunosuppressant that is more typical of a synthetic target from an academic laboratory. It is noteworthy that the oxidation of **663** was conducted at a 29 kg scale in one of the early steps of the synthesis (Scheme 132).

Vitamin D analogues, such as calcitriol (**676**), are part of a synthetic class often requiring multiple oxidations. Because of the high potency associated with these compounds, they usually require low volumes of the active pharmaceutical ingredient (API), even after commercialization. As shown in Scheme 133, the preparation of this class of therapeutic agents often necessitates oxidations in the A ring to access the desired coupling partner prior to formation of the exocyclic diene.[260−262]

5.1. Oxidation of Primary Alcohols to Aldehydes

5.1.1. Metal-Mediated Processes

Metal-mediated oxidations were of primary importance before 1980, prior to the introduction of more environmentally friendly methods. Reagents such as chromium trioxide (CrO_3) in pyridine,[263−265] pyridinum chlorochromate (PCC),[266] and pyridinum dichromate (PDC)[267] have been used extensively in academia but sparsely in industry. One example (Scheme 134) of such a process has been demonstrated in the preparation of an α-amino aldehyde using CrO_3 in pyridine without loss of chiral purity.[268]

5.1.2. Moffatt and Modified-Moffatt Processes

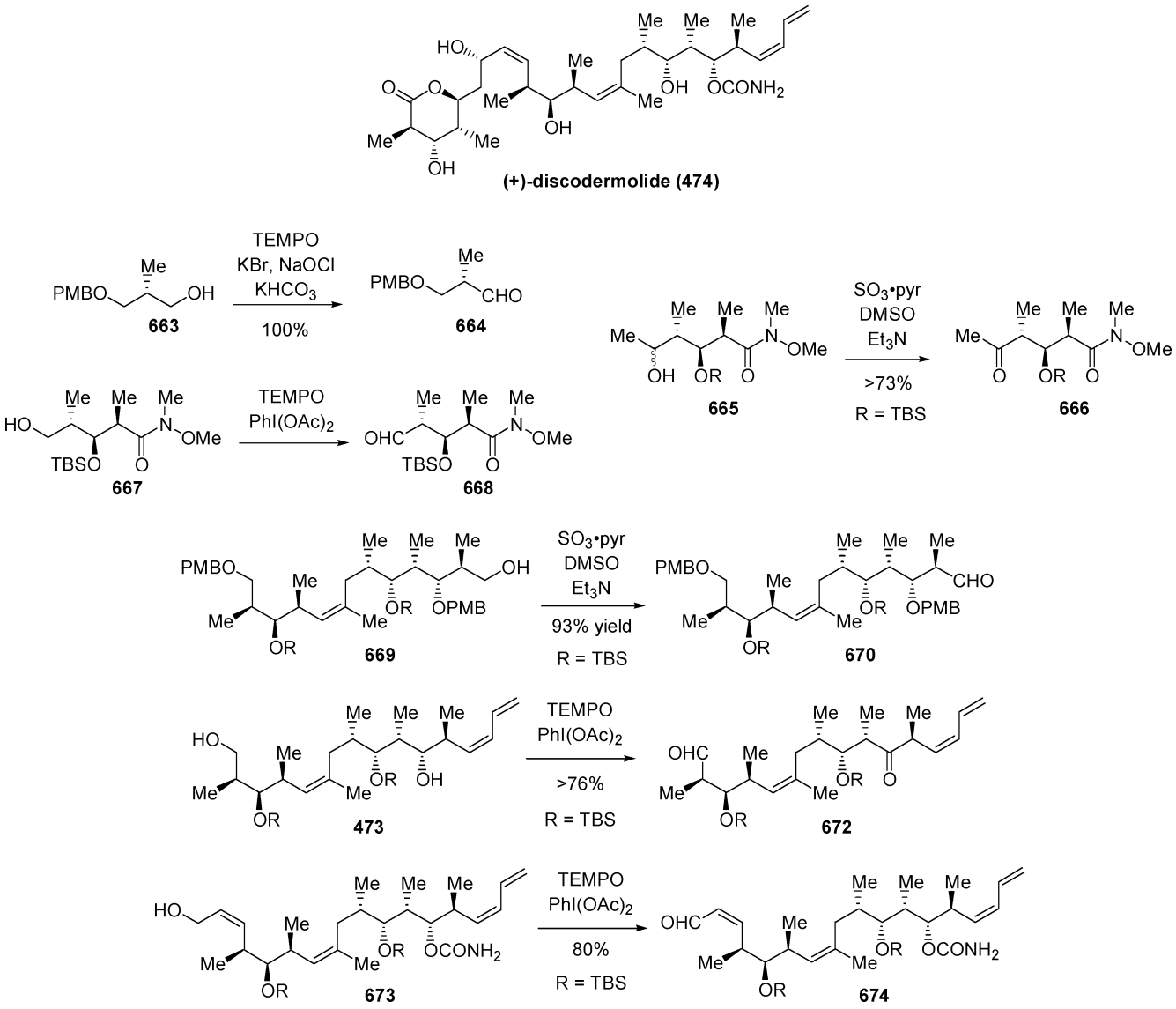
The Moffatt oxidation, originally introduced in 1965,[269] has proven to be one of the methods of choice for the preparation of aldehydes from primary alcohols. This procedure has the advantage of generating an oxosulfenium ion, which is deprotonated under mild conditions. The Swern modification[270] has been used extensively in the pharmaceutical industry as shown in the examples in Scheme 135.[39,271,272]

One major drawback to the Swern oxidation on a large scale is the generation of a large amount of CO_2 and CO during the reaction. One reagent that has gained popularity in industry is the SO_3·pyridine complex.[273] This reagent has the practicality of being a solid and offers the advantage that the reaction can be carried out at or near room temperature, as opposed to the cryogenic conditions usually required when using oxalyl chloride. This also provides the ability to charge additional reagent in the case of an incomplete reaction. For example, phenyl alaninol **695** was oxidized to the corresponding aldehyde on a 190 kg scale without any loss of the chiral purity as part of the synthesis of an HIV protease inhibitor[274] (Scheme 136).

An SO_3·pyridine oxidation was utilized to oxidize alcohol **148** to the aldehyde followed by Grignard addition to generate secondary alcohol **149** (Scheme 38), demonstrating that a sensitive epoxide functionality can tolerate the relatively mild oxidation conditions.[60]

When this class of oxidation is selected, the choice of the reagent activating DMSO, the base forming the ylide, and the reaction temperature are key factors for obtaining a robust process as illustrated in Table 2.[275] The desired transformation of **697** to **698** was successful using either a combination

Scheme 132. (+)-Discodermolide and Representative C−O Oxidations Conducted on Scale



of $(COCl)_2$/Hünig's base, which allowed higher temperatures for processing, or the SO_3·pyridine complex/Et_3N, although the latter required a change in the order of addition. Either protocol provided an acceptable yield and enantiomeric purity.

5.1.3. TEMPO-Mediated Processes

Also discovered in the early 1960s, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)[276,277] has become the catalyst of choice in the industry for the oxidation of primary alcohols. This mild hydroxyl radical catalyst is successful under mild conditions, generally at room temperature, using inexpensive co-oxidants, such as bleach (NaOCl). It can be chemoselective for primary alcohols[278] and is not prone to over-oxidation under the appropriate conditions. As shown in Scheme 137, oxidations of primary alcohols are straightforward using less than 1 mol % of TEMPO and aqueous sodium hypochlorite as the co-oxidant with sodium bicarbonate as a mild base.[60,63,155] The reaction is usually conducted under biphasic conditions using dichloromethane as the solvent and is suitable for sensitive substrates such as a prostaglandin analogue (**293**).[279] An additive, such as NaBr or KBr, may be used to accelerate the rate of the reaction in some cases. The oxidation of **701**, an intermediate in the synthesis of antifolate LY231514, was conducted at Eli Lilly on a 29 kg scale.

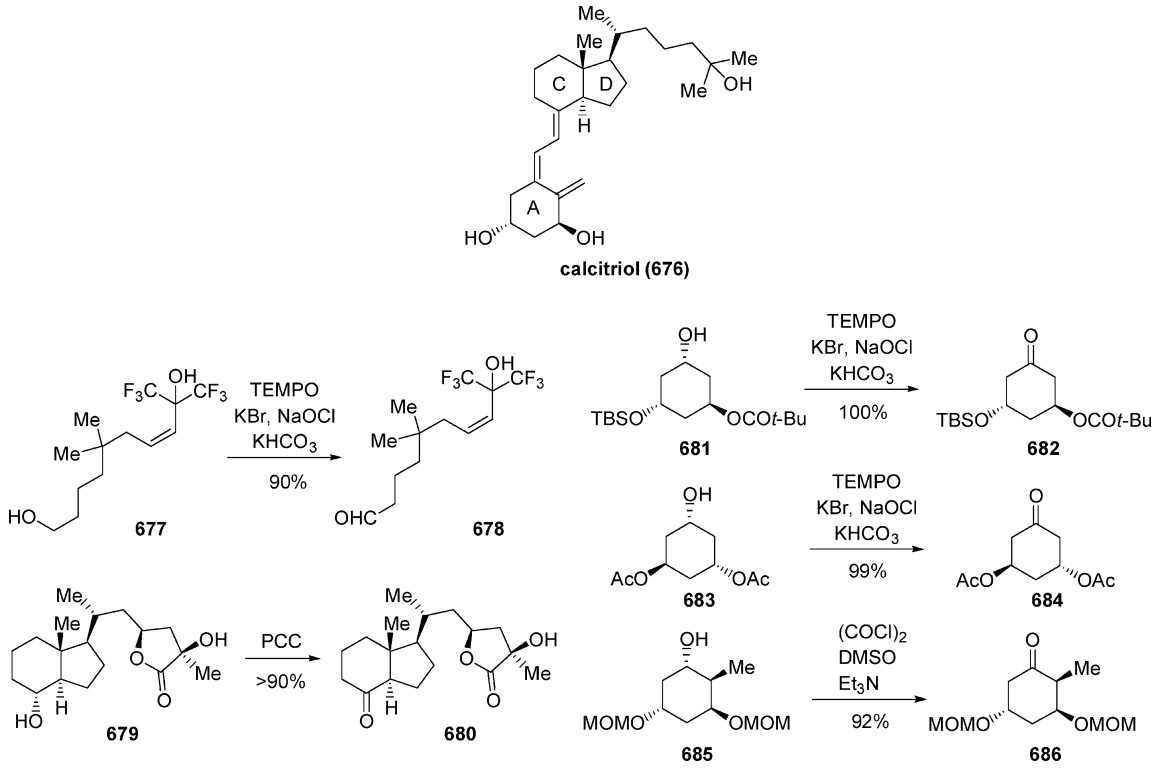
Varie reported the oxidation of alcohol **318** using TEMPO followed by Grignard reagent addition to the aldehyde to produce secondary alcohol **319** in the synthesis of a cryptophycin A fragment (Scheme 73).[7] TEMPO was utilized in the same synthesis to oxidize secondary alcohol **24** to ketone **316**; both oxidations were performed in a 0.5 kg synthesis of fragment **319**. In the synthesis of antifolate LY231514 (**380**) (Scheme 84), aldehyde **377** was generated from alcohol **376** in the first of a three-step process.[155]

TEMPO is also particularly effective for the preparation of chiral α-amino and α-alkoxy aldehydes.[280] A variety of substrates were successfully oxidized using 1 mol % of TEMPO, yielding >95% ee of the desired aldehydes in all cases. (Scheme 138).

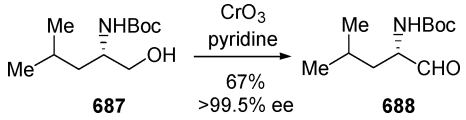
While NaOCl has been the most utilized co-oxidant in the industry, other alternatives such as CuCl in the presence of oxygen[281] and iodine[282] have also been employed as shown in Scheme 139.

In the last example, an interesting study was conducted on the impact of the co-oxidant to avoid an undesired side

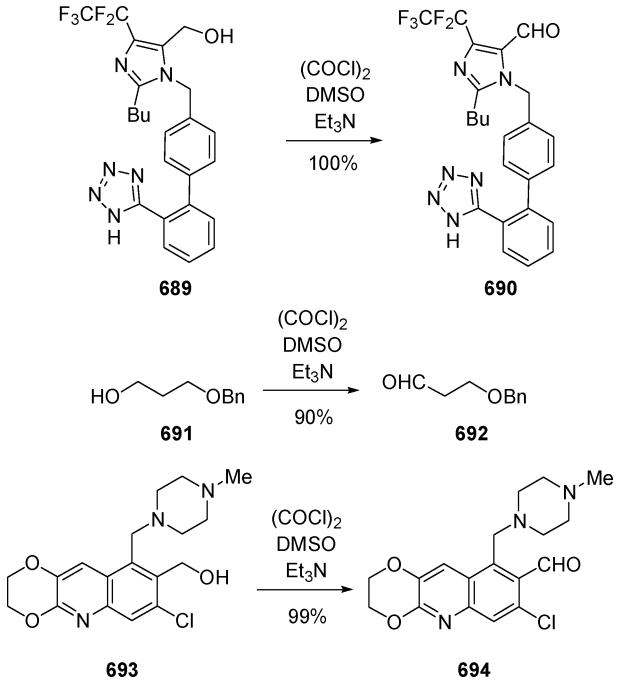
Scheme 133. Representative Oxidations in the Preparation of Vitamin D Analogues



Scheme 134. Preparation of α-Amino Aldehyde Using CrO_3 in Pyridine



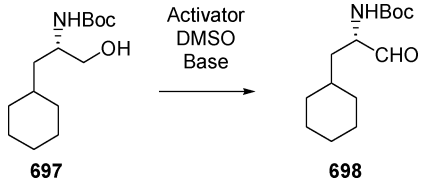
Scheme 135. Oxidation of Primary Alcohols to Aldehydes Using the Swern Protocol



product when conducting the oxidation in toluene. As shown in Table 3, it was found that the use of iodine led to a reaction that proceeded smoothly without generation of the halogenated impurity.

Scheme 136. Preparation of an α-Aminoaldehyde Using SO_3·Pyridine Complex

Table 2. Effect of the Activator in the Oxidation of Amino Alcohol 697



activator	base	temp (°C)	ee (%)	yield (%)
$(COCl)_2$	Et_3N	<−40	66	
$(COCl)_2$	Et_3N	<−70	94	90
$(COCl)_2$	iPr_2NEt	<−15	>95	90
SO_3·pyr	Et_3N	30	33[a]	
SO_3·pyr	Et_3N	30	>95[b]	80

[a] SO_3·pyr added to Et_3N and **697** in DMSO. [b] Et_3N and SO_3·pyr in CH_2Cl_2 added to **697** and DMSO in CH_2Cl_2.

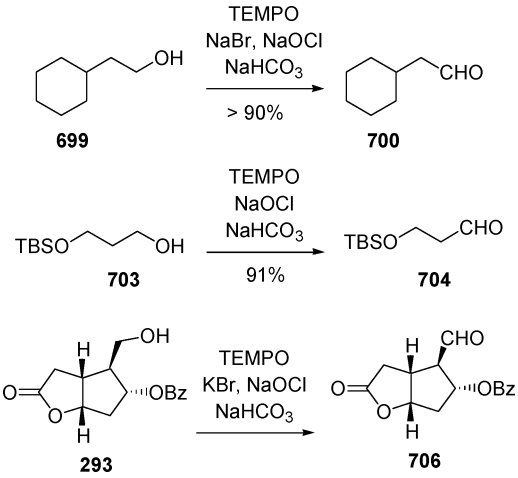
5.2. Oxidation of Secondary Alcohols to Ketones

5.2.1. Metal-Mediated Processes

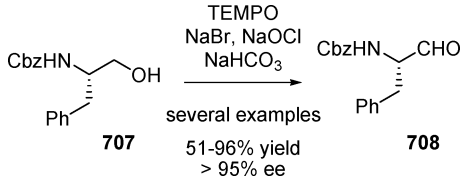
There are still a few stoichiometric metal-mediated oxidations of secondary alcohols reported from process groups since 1980. A classic example is the oxidation of **1** using CrO_3 in the Merck synthesis of cortisone to access the 12-keto derivative **2** (Scheme 1).[2]

In recent years, the use of catalytic quantities of a metal catalyst to promote oxidation has gained in popularity,

Scheme 137. Representative Examples of the Preparation of Aldehydes Using TEMPO



Scheme 138. Preparation of Chiral α-Amino and α-Alkoxy Aldehydes Using TEMPO and NaOCl



Scheme 139. Alternative Co-oxidants

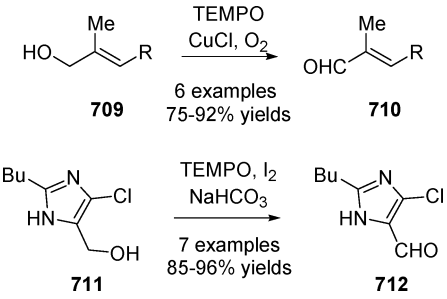
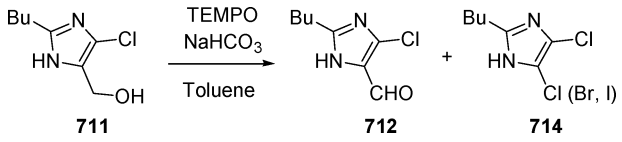


Table 3. Use of Iodine as a Co-oxidant for a TEMPO Oxidation in Toluene

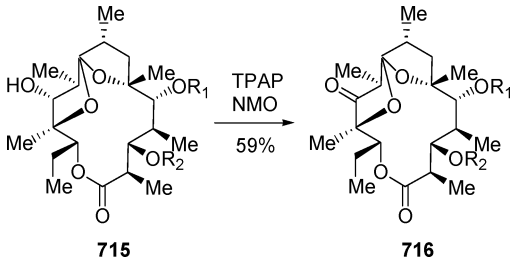


oxidant	yield **712**	yield **713**
2 equiv Br_2	trace	<50%
1 equiv Br_2	trace	80%
1.1 equiv NBS	trace	85%
1 equiv NCS	trace	85%
2 equiv I_2	93%	ND

especially in the case of secondary alcohols, which cannot over-oxidize. One such example (Scheme 140) is tetra-*n*-propylammonium perruthenate (TPAP),[283] which is capable of selective oxidation of a very sensitive macrolide using *N*-methylmorpholine *N*-oxide (NMO) as the co-oxidant.[284]

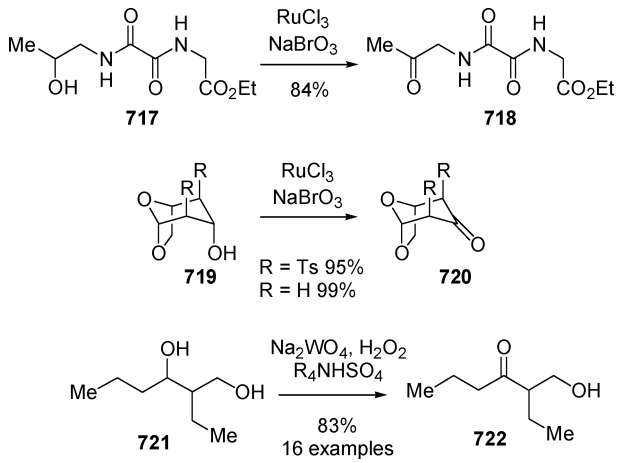
Another efficient catalytic reagent is RuO_4, usually generated from $RuCl_3$ and a co-oxidant. It is only suitable for oxidation of secondary alcohols, since primary alcohols produce a carboxylic acid. Approximately 1 mol % of ruthenium is employed, usually in aqueous acetonitrile, and

Scheme 140. TPAP Oxidation of a Macrolide



the preferred co-oxidant is sodium bromate ($NaBrO_3$) because of its reactivity, cost, and innocuous side products.[285] An acidic buffer such as acetic acid can be employed if the substrate or product is sensitive to the high pH resulting from the co-oxidant. In the oxidation of **719**, use of NaOCl yielded only 15% of desired product **720**, while epimerization was observed if a large excess of NaOCl or $NaIO_4$ were used. However, a 95% yield of the desired, stereochemically intact product was obtained when $NaBrO_3$ was used.[286] This was in contrast with previous experience on a related compound where NaOCl was an acceptable co-oxidant as shown in Scheme 141.[287] In another metal-mediated oxidation, catalytic

Scheme 141. Use of $RuCl_3$ or Na_2WO_4 for the Preparation of Ketones



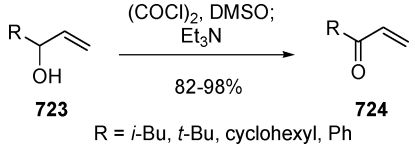
amounts of Na_2WO_4 in the presence of H_2O_2 have been demonstrated as an effective oxidant of secondary alcohols in the presence of a phase transfer catalyst. It also proved to be chemoselective for secondary over primary alcohols as demonstrated in the oxidation of **721** to ketone **722**.[288,289]

5.2.2. Moffatt and Modified-Moffatt Processes

The oxidation of secondary alcohols through activation of DMSO has been used extensively in the pharmaceutical industry for the preparation of ketones. One interesting observation noted from publications originating from the pharmaceutical industry is the wide range of activating agents used on large scale, compared to the default use of oxalyl chloride in many academic laboratories. While the Swern protocol[270] has been reported for the efficient oxidation of allylic alcohols (**723**) to vinyl ketones (**724**,[290] Scheme 142), it is usually not preferred because of the hazards associated with oxalyl chloride, the off-gassing resulting from its use, and the fact that alternative reagents are available.

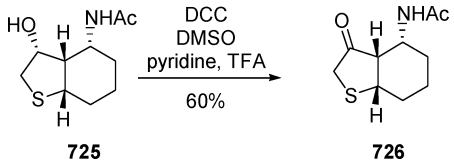
The original Moffatt procedure using 1,3-dicyclohexylcarbodiimide (DCC)[269] has received minimal attention because of the urea produced as a side product but has been

Scheme 142. Use of Oxalyl Chloride in the Oxidation of Vinyl Alcohols



utilized in the preparation of a perhydrobenzo[*b*]thiophene such as **726** as shown in Scheme 143.[291] It is noteworthy to

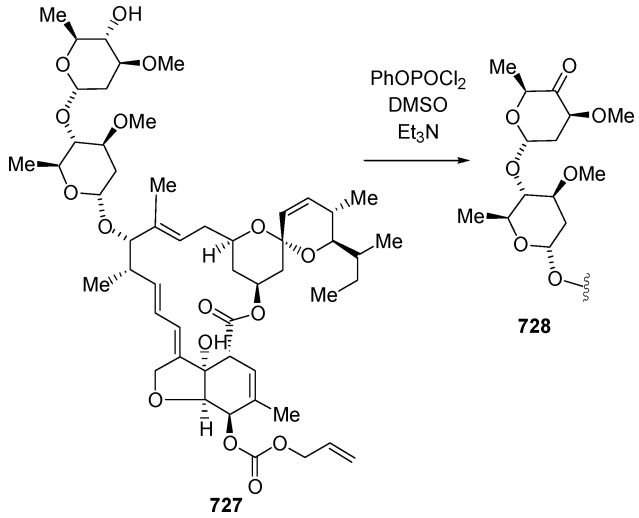
Scheme 143. DCC-Mediated Oxidation



mention that this protocol allows for the chemoselective oxidation of an alcohol in the presence of a thioether.

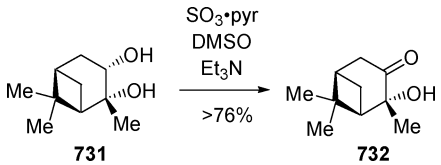
One example where the choice of activating agent was critical to success was reported by researchers at Merck for the preparation of an avermectin derivative.[292,293] It was found that phenyl dichlorophosphate[294] could be employed in a solvent such as isopropyl acetate to effectively accomplish the desired oxidation of a very sensitive substrate (**727**) shown in Scheme 144.

Scheme 144. Oxidation of 727 Using $PhOPOCl_2$



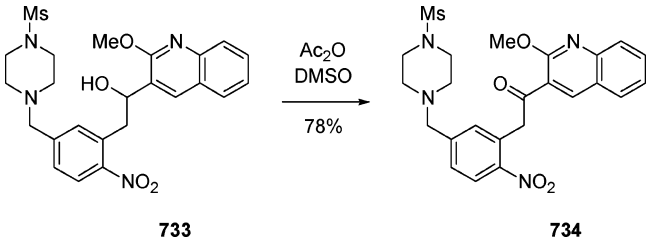
As previously discussed, use of the SO_3·pyridine complex is practical since it is a safe, crystalline, and noncorrosive oxidant. Its use has been documented by Boehringer Ingelheim as a convenient procedure for the preparation of 2-hydroxy-3-pinanone (**732**) in two steps from α-pinene (Scheme 145).[295]

Scheme 145. Synthesis of 2-Hydroxy-3-pinanone



Another example where the choice of activating reagent was important was in the oxidation of benzylic alcohol **733** where α-chloroketone was isolated as the sole product in 47% yield when oxalyl chloride was used. However, the desired ketone (**734**) was isolated in 78% yield when acetic anhydride was used (Scheme 146). Two major impurities

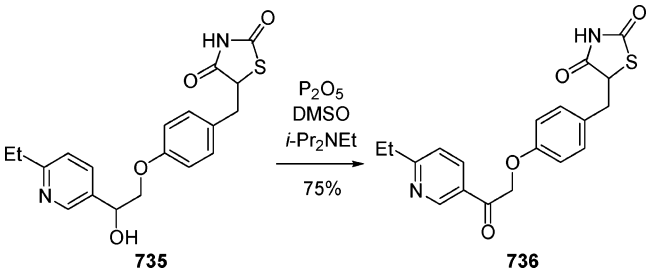
Scheme 146. Use of Acetic Anhydride in the Oxidation of a Benzylic Alcohol



were observed: the thioether resulting from reaction of the alcohol with the sulfur ylide generated from the oxosulfenium ion (10%) and the benzylic acetate (3%).[296]

Another reagent that has proven to be practical for the large scale activation of DMSO is P_2O_5.[297,298] While it might not be the preferred method on laboratory scale because of the handling difficulties associated with small quantities of a hygroscopic solid, it is a remarkably inexpensive and mild reagent, and since phosphoric acid is the side product generated, the reaction does not require the use of cryogenic conditions. As shown in Scheme 147, P_2O_5 was found to be

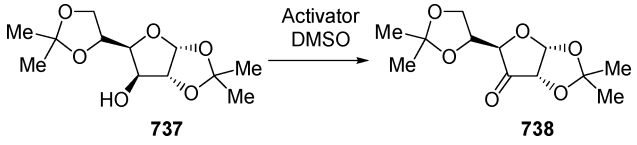
Scheme 147. Oxidation Using P_2O_5/DMSO



the method of choice for the preparation of ketone **736**.[299] In this case, the stoichiometry of the DMSO and P_2O_5 as well as the choice of base proved to be very important factors to minimize generation of the methylthioether resulting from alkylation of the imide.

Generation of the methylthioether as an impurity is often a problem encountered with the modified-Moffatt oxidations.[300] As shown in Table 4, a glucofuranose (**737**) prone

Table 4. Effect of Activator on Thioether Formation



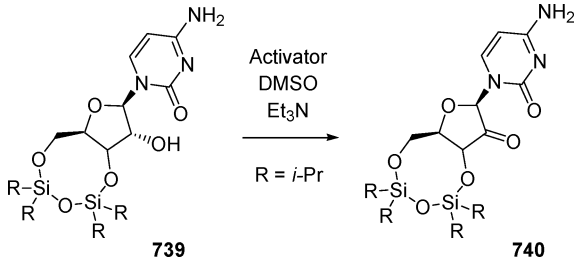
activator	yield (%)	observation
Ac_2O	>58	thioether observed
P_2O_5	73	minimal thioether observed

to alcohol alkylation could be efficiently oxidized when P_2O_5 was used rather then Ac_2O, which might be the result of a more facile displacement versus elimination of the oxosulfenium species.[301]

Another efficient reagent for the activation of DMSO is trifluoroacetic anhydride, which has the disadvantage of being a corrosive and low-boiling liquid. However, in the

case of the preparation of ketonucleoside **740**, TFAA proved to be the only efficient reagent to effect the oxidation of **739**. As shown in Table 5, other reagents, including TPAP,

Table 5. Reagent Evaluation for the Preparation of Ketonucleoside 740



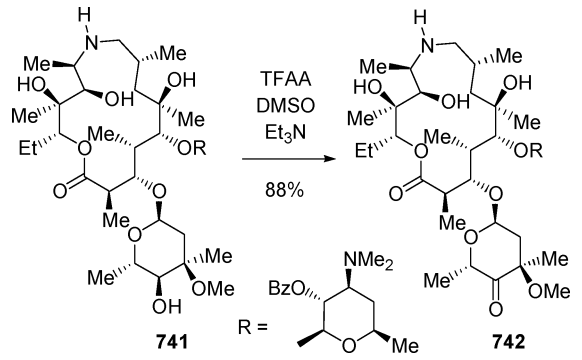
739 **740**

activator	solvent	temp (°C)	% conv
$(COCl)_2$	CH_2Cl_2	−50	0
Ac_2O	DMSO	19	0
P_2O_5	CH_2Cl_2	22	0
TFAA	pyridine	−20	25
TFAA	THF	−15	96

NaOCl, or an Oppenauer oxidation (not shown), failed to produce the desired ketone.[302]

The use of TFAA has also been incorporated in the commercial process for tulathromycin, a semi-synthetic macrolide antibacterial approved in veterinary medicine for the treatment of bacterial respiratory disease (Scheme 148).

Scheme 148. Oxidation in the Tulathromycin Process



741 **742**

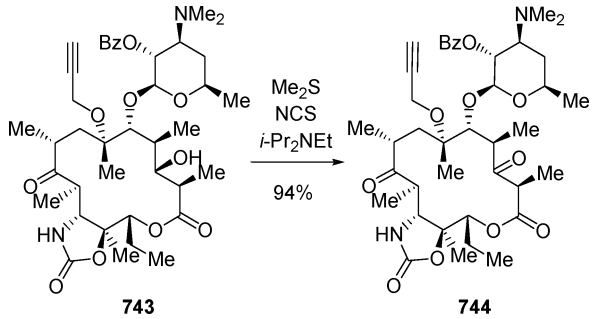
This process has been exemplified at about a 60 kg scale.[303] The use of TFAA was also demonstrated on another macrolide substrate, **655**, in the synthesis of a 3-keto macrolide (Scheme 131).[244]

Another modification of the Moffatt oxidation is the Corey−Kim protocol[304] where the chlorosulfenium ion is generated by oxidation of dimethyl sulfide by either chlorine or *N*-chlorosuccinimide. This procedure has been reported for the oxidation of erythromycin A derivative **743** where *i*-Pr_2NEt proved to be the preferred base for minimizing formation of the methylthio methyl ether.[115] (Scheme 149).

5.2.3. TEMPO-Mediated Processes

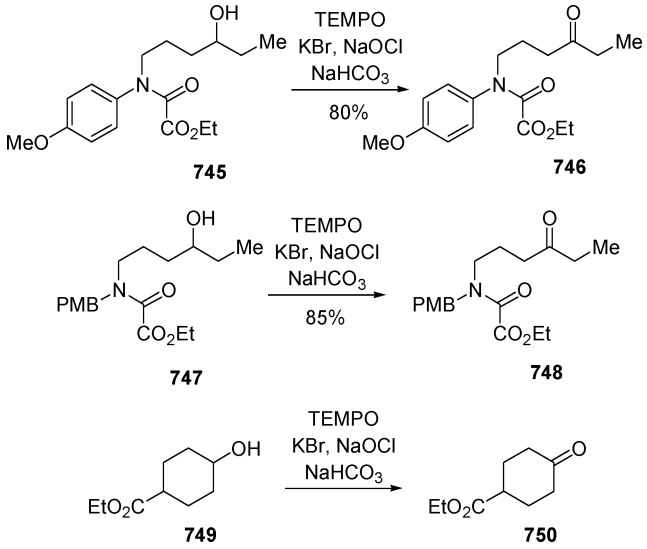
TEMPO-mediated oxidations do not have the same frequency of use for large-scale preparation of ketones from secondary alcohol as the Moffatt-type oxidations do. As shown in Scheme 150, a few substrates have been efficiently oxidized using TEMPO as a catalyst and NaOCl, either as bleach or freshly prepared from calcium hypochlorite and sodium carbonate in water in the presence of KBr.[305,306]

Scheme 149. Oxidation of an Erythromycin A Derivative



743 **744**

Scheme 150. Preparation of Ketones Using TEMPO



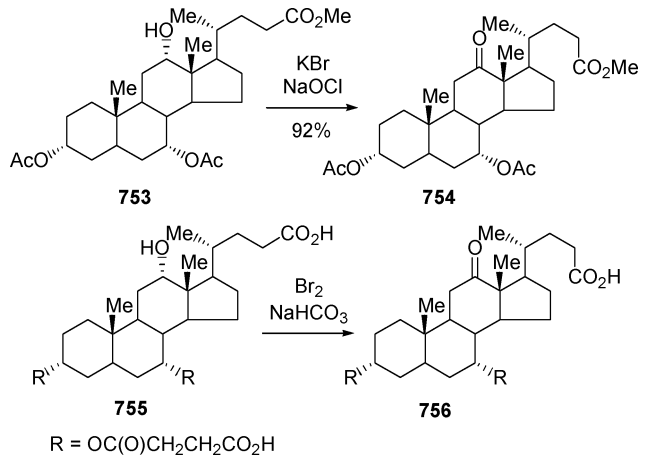
745 **746** **747** **748** **749** **750**

5.2.4. Alternative Processes

An interesting oxidation of cholic acid derivative **753** was accomplished on a 17 kg scale by simply using aqueous NaOCl[307] in the presence of KBr in a mixture of EtOAc and water. This procedure afforded a 92% yield of the desired ketone **754** as shown in Scheme 151.[308] A similar substrate (**755**) was also oxidized, this time using bromine, to provide ketone **756**.[309]

Another oxidation that appears to be seldom used on a large scale is the Oppenauer oxidation. In general, this procedure suffers from the fact that a large excess of a sacrificial ketone must be employed to drive the equilibrium toward the substrate oxidation and that it is difficult to drive

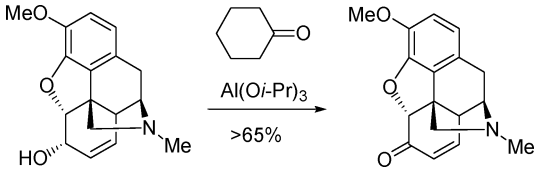
Scheme 151. Oxidation of a Steroid Using NaOCl/KBr



753 **754** **755** **756**

the reaction to completion despite long reaction time. The preparation of codeinone (**758**) from codeine has been reported using this protocol (Scheme 152).[310]

Scheme 152. Oppenauer Oxidation of Codeine

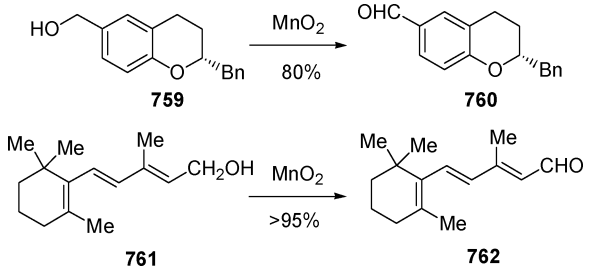


5.3. Oxidation of Benzylic and Allylic Alcohols

5.3.1. MnO_2 Oxidation

Reports of the chemoselective oxidation of benzylic or allylic alcohols in the pharmaceutical industry are scarce, probably because in most cases it could be accomplished through a more conventional oxidation. As shown in Scheme 153, manganese dioxide has been used for the preparation

Scheme 153. MnO_2 Oxidation

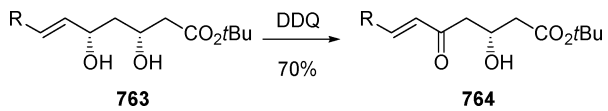


of a dihydrobenzopyrane derivative (**760**) in 80% yield[311] and also for the preparation of key intermediate **762** in the synthesis of isotretinoin at a 1 kg scale in >95% yield.[312] MnO_2 oxidations are usually avoided on a large scale because of the sensitivity of the substrates to the grade/activation of the reagent and the large amount of waste generated from the use of a minimum of 1 equiv of the oxidant.

5.3.2. DDQ Oxidation

Oxidations using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone for the preparation of aldehydes and ketones are also rare. One reported example is the preparation of a HMG-CoA reductase inhibitor side chain (**764**) through the chemoselective oxidation of an allylic alcohol in the presence of a secondary alcohol in a very sensitive product (Scheme 154).[313]

Scheme 154. DDQ Oxidation of an Allylic Alcohol

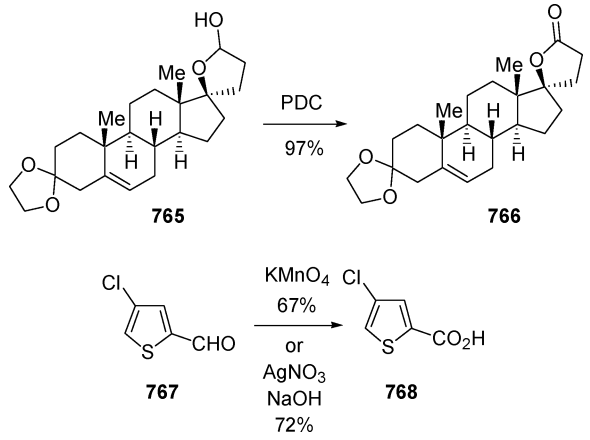


5.4. Oxidation to Carboxylic Acids and Derivatives

5.4.1. Metal-Mediated Oxidations of Aldehydes to Carboxylic Acids and Derivatives

For reasons discussed previously, noncatalytic metal-mediated processes are now used infrequently in oxidations performed on a large scale. As shown in the examples in Scheme 155, conversion of lactol **765** to the desired

Scheme 155. Metal-Mediated Oxidation to Carboxylic Acid Derivatives

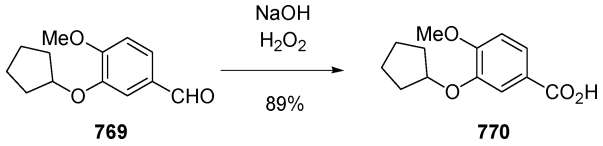


spironolactone **766** was efficiently achieved using PDC.[314] In the second example, Ag_2O (prepared from $AgNO_3$ and NaOH) or $KMnO_4$ both proved to be effective for the oxidation of thiophenecarboxaldehyde **767** to the corresponding carboxylic acid **768**.[315]

5.4.2. Hydrogen Peroxide Oxidation of Aldehydes to Carboxylic Acids and Derivatives

Hydrogen peroxide has been reported as a safe and effective reagent for the preparation of a key benzoic acid intermediate in the synthesis of a PDE IV inhibitor. Benzaldehyde **769** could be oxidized under a variety of conditions, and $NaClO_2$ proved to be acceptable in the presence of sulfamic acid (NH_2SO_3H) at a 5 kg scale (Scheme 156).

Scheme 156. H_2O_2 Oxidation of a Benzaldehyde Derivative



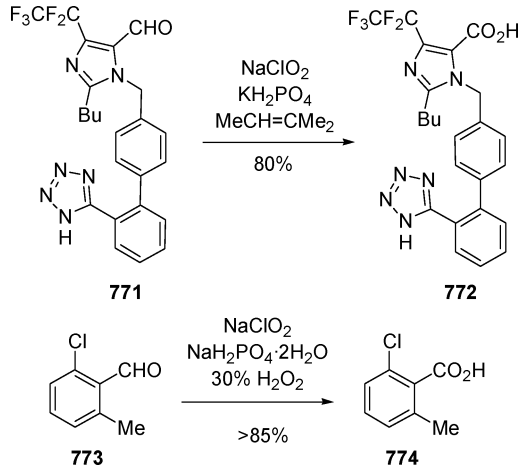
However, chlorination of the aromatic ring was observed and could not be eliminated. To circumvent this problem, H_2O_2 under basic conditions was identified as an inexpensive alternative for the preparation of **770**, providing an 89% yield on a 15 kg scale under conditions optimized for process safety.[316]

5.4.3. Sodium Chlorite Oxidation of Aldehydes to Carboxylic Acids and Derivatives

Probably the most practical method for the oxidation of an aldehyde to the carboxylic acid is sodium chlorite in the presence of a hypochlorite scavenger such as sulfamic acid or an electron-rich olefin or arene.[317] As shown in Scheme 157, the method is generally high yielding, and the pH of the reaction is controlled by a phosphate buffer.[271] In the second example, H_2O_2 is used as the hypochlorite scavenger.[318] While it is counterintuitive to use an oxidant to eliminate hypochlorite, H_2O_2 reacts with HOCl to produce HCl, H_2O, and O_2, which are innocuous side products.

An additional example is in Gut Ruggeri's synthesis of PDE IV inhibitor **597**, where nitrile **599** is hydrolyzed to acid **598** via diisobutylaluminum hydride (DIBAL-H) half reduction of the nitrile to the aldehyde, followed by sodium chlorite oxidation of the aldehyde to acid **598** (Scheme 124). Because the substrate was not prone to chlorination, no

Scheme 157. Oxidation of Aldehydes by $NaClO_2$

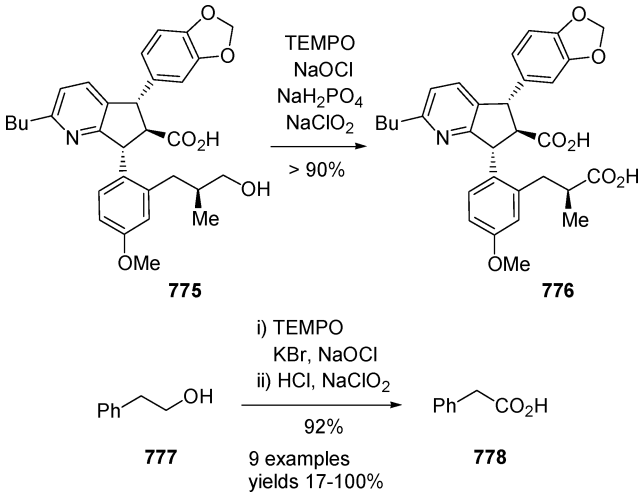


chloride scavenger was used in this reaction, rather the chlorine gas was scrubbed as it was generated.[222]

5.4.4 TEMPO/Sodium Chlorite Oxidation of Alcohols to Carboxylic Acids and Derivatives

Primary alcohols can be directly oxidized to carboxylic acids in a single operation by tandem oxidation to the aldehyde with TEMPO followed by a second oxidation with $NaClO_2$ to provide the carboxylic acid. As shown in Scheme 158, this procedure was applied to an elaborate endothelin

Scheme 158. Direct Conversion of Alcohols to Carboxylic Acids Using TEMPO/$NaClO_2$

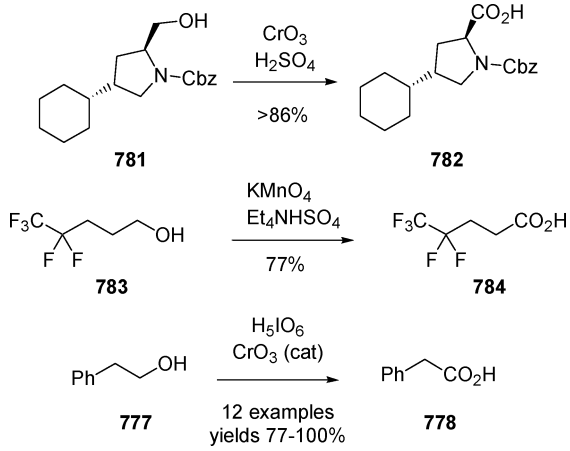


receptor antagonist[319] in greater than 90% yield. Researchers at Fujisawa Pharmaceuticals showed that this approach could be used on several substrates (e.g., **777**) and generally worked well unless a methoxybenzyl moiety, which is prone to chlorination, is present.[320]

5.4.5. Metal-Mediated Oxidation of Alcohols to Carboxylic Acids and Derivatives

As stated in previous sections, noncatalytic metal-mediated oxidations have the disadvantage of generating a large waste effluent and often lead to difficult workups, which are cumbersome at scale. As shown in Scheme 159, the typical Jones oxidation protocol has been used for the oxidation of a proline derivative (**781**),[321] and $KMnO_4$ in the presence of a phase catalyst proved to be efficient in the preparation of pentafluoropentanoic acid (**784**).[322] In 1998, Merck published

Scheme 159. Metal-Mediated Oxidations of Alcohols to Carboxylic Acids and Derivatives



a procedure for the oxidation of primary and secondary alcohols using a catalytic amount of chromium trioxide and 2.5 equiv of periodic acid.[323]

6. Oxidation of Sulfur

Historically, sulfur-containing compounds have comprised an important niche in the pharmaceutical industry, beginning with the rise of antibacterial agents in the early part of the 20th century,[324] and in many of these medicinally active agents, the sulfur is at an elevated oxidation state. While the desired oxidized state of sulfur may be purchased in some cases, such as sulfonates or aryl sulfones, in more complex targets, oxidation of a sulfide is often required.

6.1. Oxidation of a Sulfide to a Sulfoxide

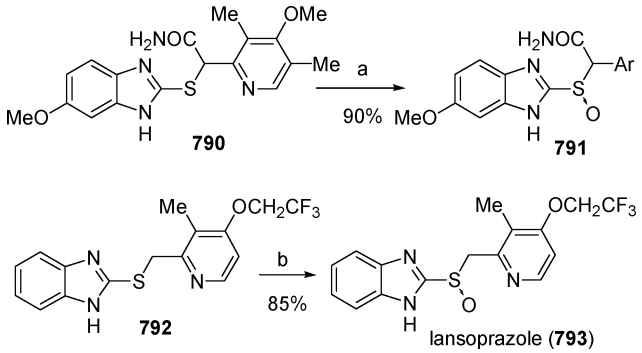
6.1.1. Peroxide-Based Reagents

One of the most common sulfur oxidations found in pharmaceutical research and production is the oxidation of a sulfide to a sulfoxide. The oxidation occurs with a very wide variety of reagents, with the main issue for the reaction being limiting the amount of over-oxidation to the sulfone, usually controlled by the stoichiometry of the oxidant. Historically, hydrogen peroxide has been the most commonly used stoichiometric oxidant to achieve the desired transformation. More recent examples have demonstrated its use with vanadium catalysts, such as in the synthesis of proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole), where the benefits claimed include faster reaction times and the avoidance of low pH conditions, which tend to degrade the product (Scheme 160). Omeprazole (**804**) was synthesized via intermediate **791**, which was generated by oxidation of **790** (92 g).[325] The presence of the primary amide increased the crystallinity of **791** relative to the compound lacking it, making it easier to purge the sulfone impurity. Saponification and decarboxylation then gave the desired product. Lansoprazole (**793**) was synthesized by the oxidation of **792** (200 g) with *tert*-butyl hydroperoxide (TBHP), and the authors claimed superior selectivity in suppression of the sulfone.[326] The chief benefits of peroxides are their availability, low cost, and benign byproducts. The main detraction is the safety issue in handling them.

6.1.2. Peracid Oxidations

Another common class of reagents for the oxidation of sulfide to sulfoxide is organic peracids, such as peracetic

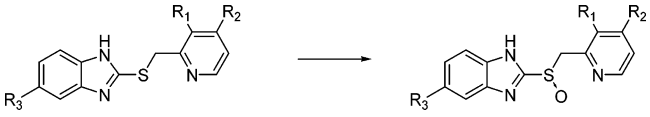
Scheme 160. Peroxide Oxidations in the Synthesis of Proton-Pump Inhibitors[a]



[a] (a) 30% H_2O_2, $VO(acac)_2$; (b) *tert*-butyl hydroperoxide, $VO(acac)_2$ (acac = acetylacetone).

acid or *m*-CPBA. These peracids have been used extensively in the synthesis of the proton pump inhibitors, some examples of which are shown in Table 6, although this reaction has

Table 6. Peracid Oxidation

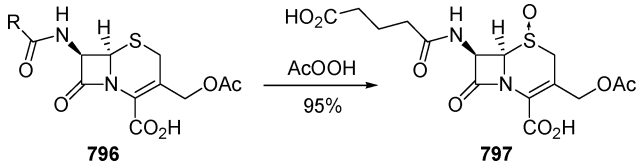


target	R_1	R_2	R_3	oxidant	yield
lansoprazole (**793**)	CH_3	OCH_2CF_3	H	*m*-CPBA	57%[a]
pantoprazole (**794**)	OCH_3	OCH_3	$OCHF_2$	CH_3CO_3H	86%[b]
(**795**)	OCH_3	Cl	$OCHF_2$	ϵ-phthalimido-hexanoic peracid	89%

[a] After recrystallization. [b] Yield over two steps (alkylation of the sulfide and oxidation); 70% charge of peracid based on quantitative yield in coupling step.

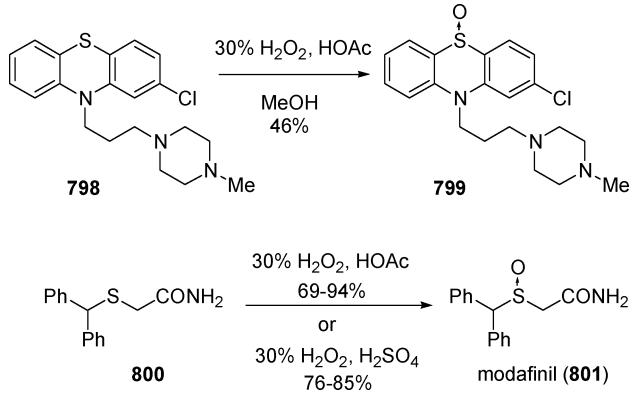
been effected by many other groups.[327−329] Lansoprazole (**793**) was synthesized (40 kg) using slow addition of a solution of *m*-CPBA in chloroform to suppress the formation of impurities.[330] Pantoprazole (**794**) was synthesized (50 kg) by oxidation with peracetic acid in a mixture of dichloromethane, water, and methanol to allow the reaction temperature to be lowered, minimizing the production of sulfone.[331] One somewhat unusual variation is the use of ϵ-phthalimidohexanoic peracid, a reagent claimed to be inexpensive and whose byproduct acid is easily removed by aqueous washing, as demonstrated in the synthesis of an intermediate (**795**) to pantoprazole (50 g).[332] The use of peracids has also been demonstrated for other structural classes, such as cephalosporins, as shown in the synthesis of **797** (37 kg) in Scheme 161.[333] The peracid reagents are usually inexpensive and readily available. The major detraction from their use, aside from the usual safety issues, is the need to purge the resulting organic acid, which can be a much more difficult task than with inorganic reagents.

Scheme 161. Peracid Oxidation of a Cephalosporin



In some cases, it is not clear what the exact nature of the oxidizing species is, especially when hydrogen peroxide is used as the oxidant in acidic media.[334] For example, the conversion of acetic acid to peracetic acid with hydrogen peroxide is reported to be slow in the absence of a stronger acid catalyst,[335] but some of the oxidations carried out in such a system occur at elevated temperatures for prolonged reaction times. In these instances, the reaction rate may be dependent on the conversion of the acid to the peracid, but this issue is not usually discussed in the publications reviewed. For example, the conversion of **798** (102 g) to **799** required refluxing temperatures for 17 h (Scheme 162),[336] while the oxidation to form modafinil (**801**) has been

Scheme 162. Hydrogen Peroxide Oxidations in Acidic Media

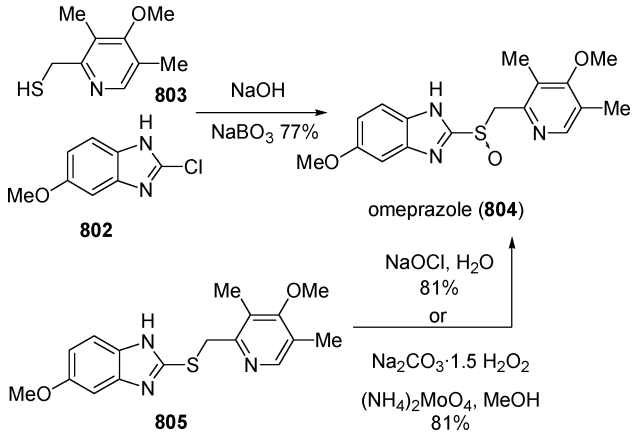


reported at a range of temperatures with organic (45−250 g)[337−340] or inorganic acids (50 g).[341]

6.1.3. Inorganic Oxidants

Inorganic oxidants have also been used to oxidize sulfides to sulfoxides. These reagents are relatively inexpensive and generate byproducts that are often more readily purged from the product than organic-based oxidants; some are also nonhazardous, environmentally benign, or both. Omeprazole (**804**) has been synthesized by a last-step oxidation using sodium perborate,[342] sodium hypochlorite,[343] or sodium percarbonate as the stoichiometric oxidant to a molybdenum catalyst[344] (Scheme 163).

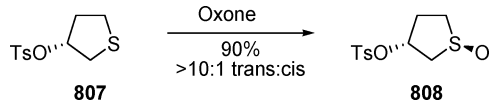
Scheme 163. Synthesis of Omeprazole (804)



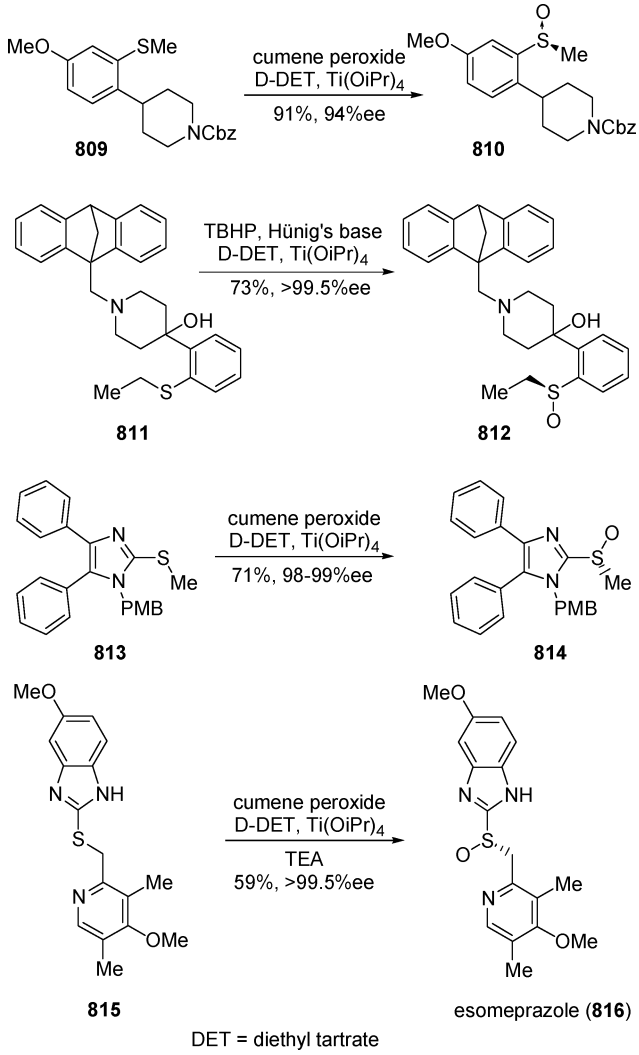
6.1.4. Stereoselective Oxidations

In systems where the oxidation of a sulfide to a sulfoxide can lead to the formation of a new chiral center, stereoselective oxidation of the sulfur may be achieved by either

Scheme 164. Asymmetric Oxidation via Substrate Control



Scheme 165. Asymmetric Oxidation via Reagent Control



substrate or reagent control, as demonstrated by the examples in Schemes 164 and 165. Oxone has been successfully utilized to control the relative stereochemistry of a sulfide oxidation, presumably due to the steric bulk of the inorganic complex, in the synthesis of penem side chain **808** (Scheme 164).[345]

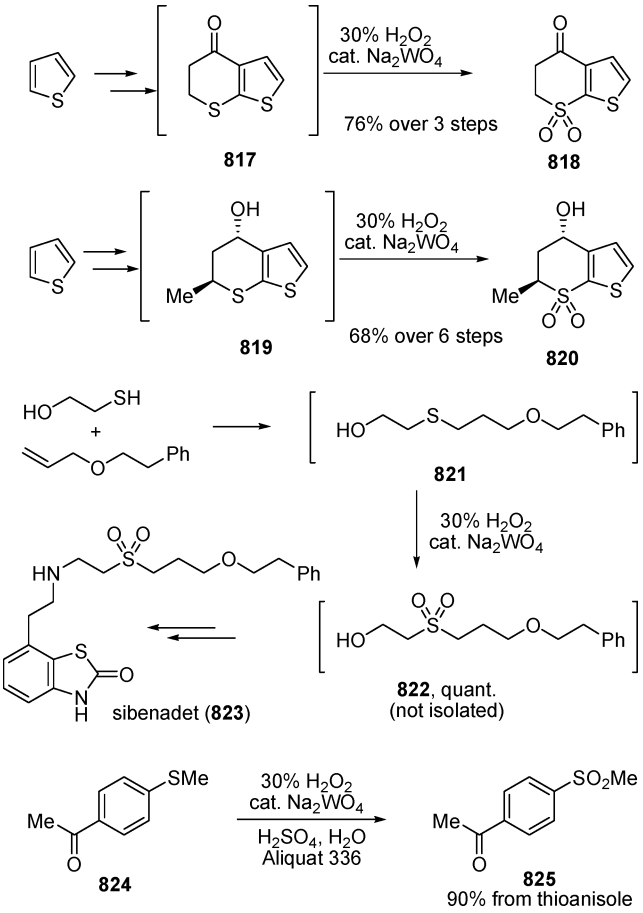
The Kagan modification[346] of the Sharpless reagent has been successfully scaled up for a number of substrates (Scheme 165). In these cases, alkyl peroxides give the best stereoselectivity. Conveniently, they can be purchased in anhydrous form or with low water content, since the water level is often critical to the success of the asymmetric induction. The enantioselectivity is highest for rigid substrates or those in which there is a large disparity in size between the two substituents on sulfur, such as substrates **809**,[347] **811**,[348] and **813**.[349] Esomeprazole (**816**), the single enantiomer of omeprazole (**804**), was also synthesized (6 kg) using this procedure.[350] In an interesting application of this method, omeprazole was synthesized by the same group using the standard conditions but with the racemic tartrate ligand.[351] These conditions were claimed to be advantageous because the product precipitated from the reaction mixture, avoiding over-oxidation to the sulfone and the tedious pH adjustments usually required to remove impurities.

6.2. Oxidation of a Sulfide to a Sulfone

6.2.1. Peroxide-Based Reagents

Sulfones are another form of oxidized sulfur commonly found in pharmaceuticals. As mentioned previously, in many cases the sulfone can be installed at the correct oxidation state by direct sulfonylation, but in some cases, it has been formed by oxidation of the corresponding sulfide. Once again, hydrogen peroxide is the most commonly utilized stoichiometric oxidant and has been demonstrated for a wide range of substrates. In the past 15 years, its use with catalytic sodium tungstate has been particularly exploited, since the reaction is usually carried out under phase transfer conditions, and the byproducts are water-soluble (Scheme 166). These

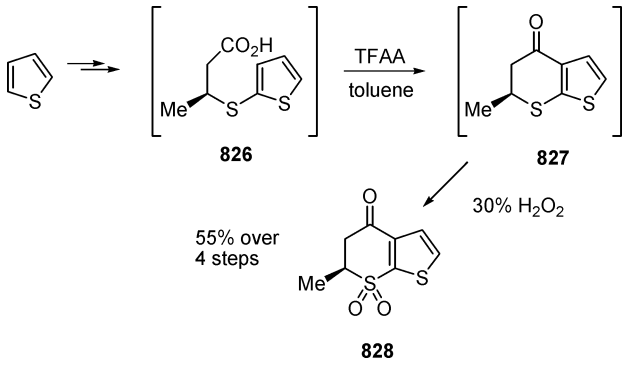
Scheme 166. Metal-Catalyzed Oxidation of Sulfides to Sulfones with Hydrogen Peroxide



conditions have been used in the synthesis of carbonic anhydrase inhibitor intermediates **818**[352] and **820**,[353] sibenadet (**823**),[354] and COX-2 inhibitor intermediates such as **825**.[355]

As with the sulfoxides, there are some cases where the actual oxidizing species is ambiguous, since hydrogen peroxide in an organic acid is a commonly used system. For example, in the conversion of **827** to **828** (Scheme 167), hydrogen peroxide is reported to be the oxidant, but residual TFA/TFAA from the previous step is not removed prior to addition of the peroxide, making it unclear whether peroxide or trifluoroperacetic acid is the oxidant.[356]

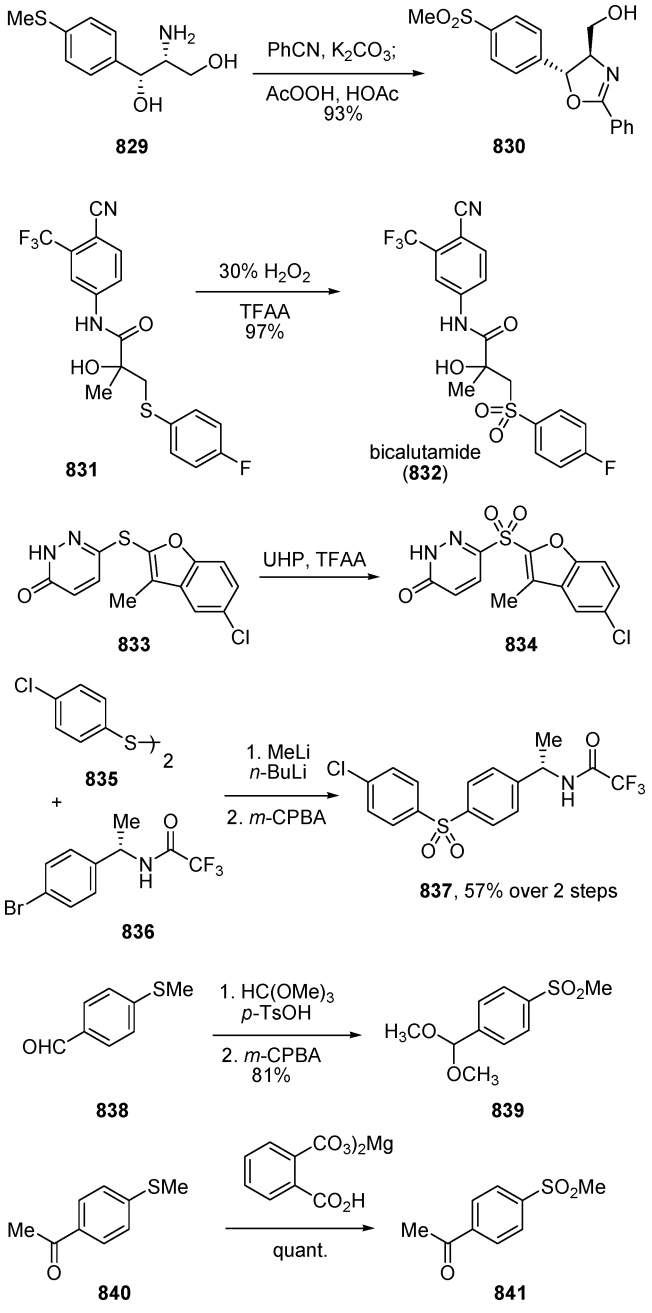
Scheme 167. Peroxide Oxidation of a Sulfide to Sulfone



6.2.2. Peracid Oxidations

Peracids have also been employed to achieve the oxidation to sulfones, as shown in Scheme 168. Compound **830**, a precursor to florfenicol, was synthesized on a 100 kg scale by peracetic acid oxidation of the protected amino alcohol.[357] Bicalutamide (**832**) and compound **834** were prepared by oxidation using trifluoroperacetic acid, generated in situ from trifluoroacetic anhydride and hydrogen peroxide, the latter added either as an aqueous solution or as the solid complex with urea.[358,359] Compound **837**, an intermediate to a cannabinoid receptor ligand, was synthesized from **835** and **836** using *m*-CPBA without the isolation of the intermediate sulfide.[360] Other simple sulfone building blocks have been synthesized by oxidation using both *m*-CPBA (**839**, 65 g)[361] and magnesium monoperoxyphthalate (MMPP, **841**, 197 g).[362]

Scheme 168. Peracid Oxidation of Sulfides to Sulfones

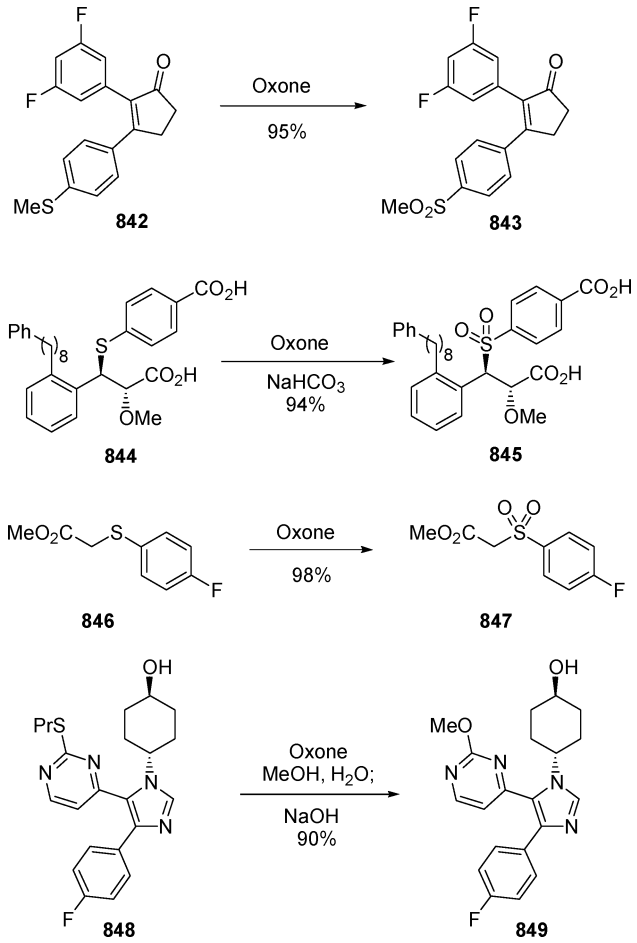


6.2.3. Inorganic Oxidants

Inorganic oxidants have been used to effect large-scale oxidations to sulfones, as shown in the synthesis of **508**, a precursor to sulbactam (Scheme 112).[196,363]

One special inorganic oxidant that is more commonly used in this situation than in other sulfide oxidations is Oxone, since it readily gives the sulfone oxidation state with little contamination from the corresponding sulfoxide and tolerates a wide variety of functional groups (Scheme 169). In the synthesis of COX-2 inhibitor **843**, researchers at Merck found that the sulfone was cleanly formed from precursor **842** in high yield, and that residual palladium from a previous step was also purged during the oxidation.[364] The oxidation of sulfide **844** required a carbonate buffer to give a good yield

Scheme 169. Oxidation of Sulfides to Sulfoxides Using Oxone



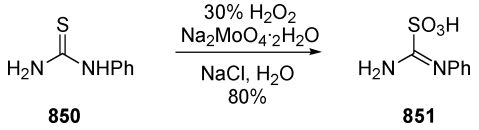
of sulfone **845**.[365] *p*-Fluorothiophenol was alkylated, and the resulting sulfide (**846**, 72 g) was oxidized in situ to produce **847**.[366] In some cases, the sulfone itself is a transiently generated intermediate, as in the conversion of **848** to **849**, in which the sulfide was oxidized in the presence of an alcohol that displaced the resulting sulfone once the pH was elevated. Oxone is inexpensive, and the resulting salts are easily separated from most products; however, its greatest drawback is its high molecular weight relative to the amount of oxygen it delivers, which requires large mass charges relative to most substrates.

6.3. Oxidation of a Sulfide to a Sulfonic Acid or Sulfonamide

6.3.1. Peroxide-Based Oxidations

The oxidation of a sulfide to a sulfonic acid is not common but has been carried out on a large scale. *N*-Phenylthiourea (**850**, 1.5 kg) was oxidized to its corresponding amidine sulfonic acid **851** using hydrogen peroxide as the stoichiometric oxidant with a molybdenum catalyst (Scheme 170).[367]

Scheme 170. Oxidation of Sulfide to Sulfonic Acid

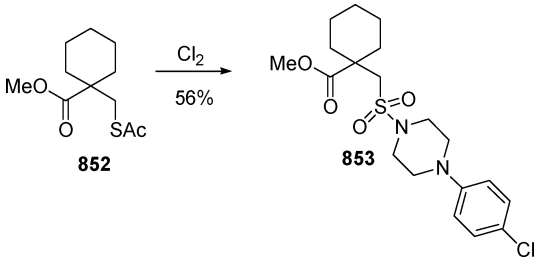


850 **851**

6.3.2. Chlorine Oxidations

Oxidation to a sulfonic acid has also been achieved using chlorine as the oxidant. In many cases, the intermediate sulfonyl chloride is trapped with an amine to form the sulfonamide derivative, as shown in the conversion of **852** (3.8 kg) to **853** (Scheme 171).[368]

Scheme 171. Oxidation of a Thioacetate to Sulfonic Acid with Chlorine



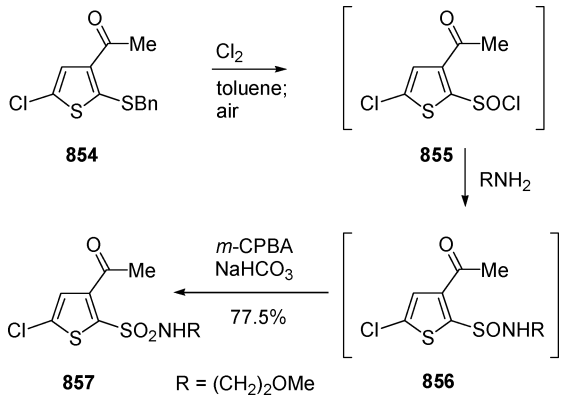
852 **853**

One unusual case of a sulfide oxidation to a sulfonic acid equivalent was demonstrated by workers at Alcon.[157] Direct chlorine oxidation of thioether **854** (Scheme 172) to its corresponding sulfonyl chloride was successful on small scale but erratic during scale-up. Therefore, the two-step procedure to the desired sulfonamide was further broken down into three steps to better control the chemistry: oxidation to sulfenyl chloride **855** (1.2 kg**)**, amination to provide **856**, and oxidation to sulfonamide **857**.

6.4. Oxidation To Form a Sulfur-Containing Heterocycle

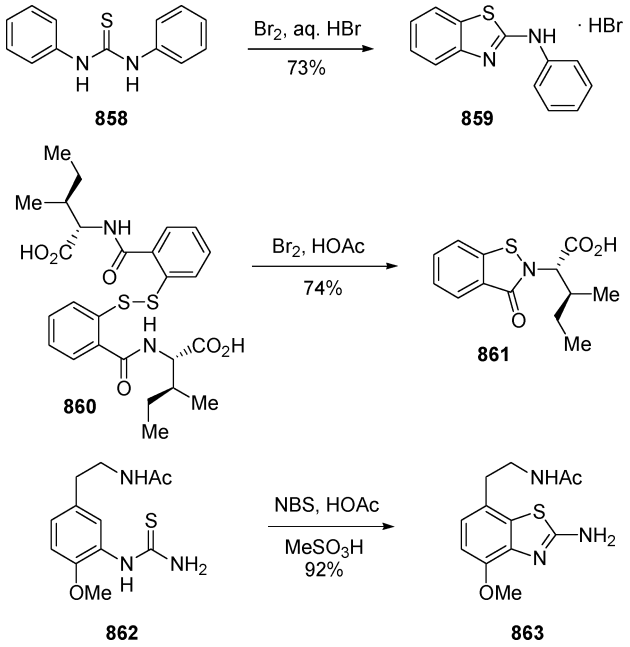
Sulfur-containing heterocycles are also prevalent in the pharmaceutical industry. For the most part, the heterocycles are purchased as commodity chemicals and functionalized, but some examples exist of formation of the ring through an oxidative cyclization, as shown in Scheme 173. The

Scheme 172. Three-Step Oxidation of a Thioether to the Sulfonamide



854 **855** **857** **856**

Scheme 173. Formation of Sulfur-Containing Heterocycles



858 **859** **860** **861** **862** **863**

conditions for the transformation of thiourea **858** (36.5 kg) to benzothiazolamine **859**[369] and disulfide **860** (50 kg) to **861**[370] are typical for the cyclization, employing bromine as the oxidizing agent. Other brominating agents, such as *N*-bromosuccinimide (NBS) have also been used, as in the synthesis of **863**, the nucleus of sibenadet (**823**).[354] The disulfide precursors that are common precursors to these heterocycles are often formed through an oxidative process themselves (vide infra).

6.5. Oxidation of a Sulfide to a Disulfide

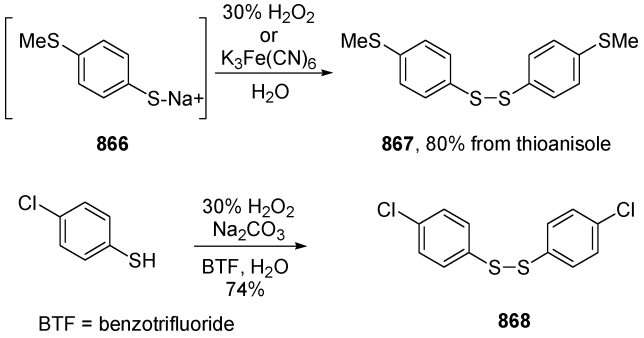
6.5.1. Peroxide-Based Oxidations

Disulfide-containing compounds are also found in pharmaceuticals, either as drug candidates or as intermediates. Hydrogen peroxide has been used to achieve their preparation. For example, disulfides **867**[371] and **868**[372] were conveniently formed from their corresponding thiol precursors (Scheme 174).

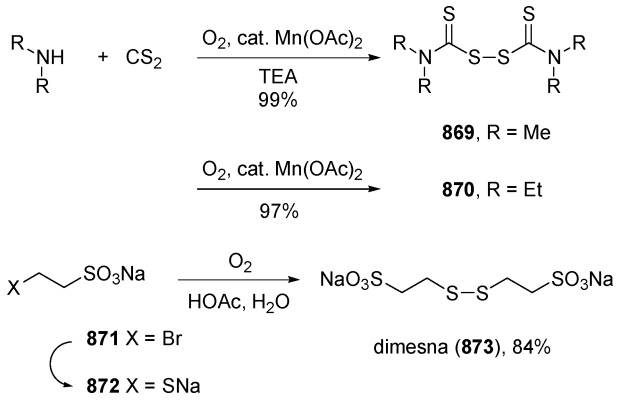
6.5.2. Oxidations with Oxygen

Metal-catalyzed processes with oxygen gas as the co-oxidant have also been scaled up, with the metal used either stoichiometrically or catalytically (Scheme 175). Thiurams

Scheme 174. Disulfide Formation



Scheme 175. Oxidation with Oxygen



such as **869** and **870** have been synthesized via a manganese-catalyzed process, either under standard solvent conditions[373] or as a neat reaction mixture.[374] Dimesna (**873**) is also usually synthesized by a final oxidation, as shown in the oxidation of **872** by workers at BioNumerik.[375] Oxygen gas has the advantage of being the least expensive and most readily available oxidant, but the safety issues surrounding its use make it one of the least frequently used reagents.

7. References

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