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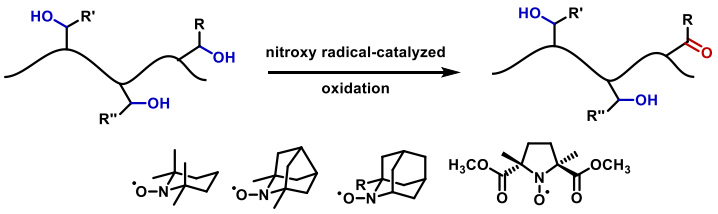
Masatoshi Shibuya



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Nitroxyl radical-catalyzed chemoselective alcohol oxidation for the synthesis of polyfunctional molecules

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ABSTRACT

Alcohol oxidation is one of the most principal transformations used in organic synthesis. During the development of these oxidation methods, chemoselective oxidation of a specific alcohol in a polyol has enabled the discrimination of multiple hydroxy groups, which can increase the synthetic efficiency by reducing the use of protecting groups. This digest highlights recent topics of the catalytic systems using nitroxyl radicals for the chemoselective alcohol oxidation and the representative examples during the synthesis or derivatization of natural products.

Contents

1. Introduction

Chemoselectivity in alcohol oxidation is important for the efficient synthesis of polyfunctional molecules. In particular, chemoselective oxidation of a specific alcohol in a polyol enables the discrimination of multiple hydroxy groups. Such discrimination is conventionally achieved using protecting group chemistry. However, the use of protecting groups requires protection and deprotection steps, which leads to decrease an efficiency of the synthesis. On the other hand, because the chemoselective alcohol oxidation does not require any extra step for the discrimination, it enables a step-economical synthesis of polyfunctional molecules.

2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) is a stable nitroxyl radical, which has unique redox properties. The oxidation of TEMPO generates oxoammonium salts ($TEMPO^+X^-$) and their reduction generates the hydroxylamine (TEMPOH) (Figure 1). [1] After Cella and coworkers reported the TEMPO-catalyzed oxidation of alcohols using *m*-chloroperbenzoic acid as a cooxidant, a variety of catalytic oxidation methods using TEMPO have been developed.[2-8] The preference of TEMPO-mediated oxidation for primary aliphatic alcohols over secondary aliphatic alcohols was demonstrated for the first time in a report on electrooxidation by Semmelhack and coworkers.[3] Anelli

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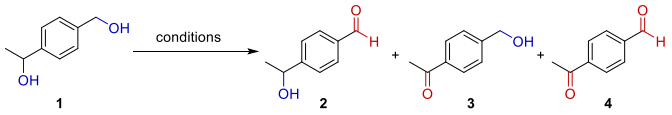
and coworkers reported the chemoselective oxidation of primary aliphatic alcohols using NaOCl as a cooxidant as well as the oxidative lactonization of diols utilizing on this chemoselectivity.[4b] Subsequently, Skarżewski reported the generality of TEMPO-catalyzed chemoselective oxidation using several examples, and Flitsch and Davis reported its usefulness for chemoselective oxidation in carbohydrates. [9,10] This unique chemoselectivity is typically attributed to the steric hindrance around the active site of the TEMPO catalyst. [11] From these reports, TEMPO-catalyzed oxidation has been recognized as a useful method for the chemoselective oxidation of primary alcohols. Many successful applications in the total synthesis of natural products have been reported. This digest focuses on the recent progress of nitroxyl radical-catalyzed chemoselective oxidations with selected applications toward the synthesis of natural products.

Figure 1. The structures of TEMPO, TEMPOH, and TEMPO$^+$X$^-$

2. Chemoselective oxidation of primary benzylic/allylic alcohols over secondary benzylic/allylic alcohols

Benzylic and allylic alcohols are generally more susceptible to oxidation than aliphatic alcohols. Chemoselective oxidation of a primary benzylic alcohol over a secondary benzylic alcohol using TEMPO and *N*-chlorosuccinimide (NCS) in the addition to the chemoselective oxidation of a primary aliphatic alcohol has been reported by Einhorn and coworkers using diol **1** as a model substrate. (Figure 2) [7a] The oxidation of **1** by TEMPO (10 mol%) and NCS (1.1 equiv) selectively affords hydroxyaldehyde **2** in 65% yield together with ketoaldehyde **4** (12% yield). Giacomelli and coworkers also reported the chemoselective oxidation of **1** to produce **2** with 98% conversion using TEMPO (1 mol%) and trichlorocyanuric acid (TCCA) (1.05 equiv) [7c]. In addition to these reports, successful applications of Margarita and Piancatelli's TEMPO/PhI(OAc)$_2$ method [5] to the synthesis of natural products have been reported. In Danishefsky's synthesis of guanacastepene A, the final step involved the chemoselective oxidation of the primary allylic alcohol in diol **5** (Figure 3).[12] The two-step yield combining the hydrolysis of the corresponding acetonide to give **5** was 59–68%. Baran and coworkers also reported the chemoselective oxidation of a primary allylic alcohol over a secondary allylic alcohol to give the corresponding hydroxyaldehyde during the synthesis of antroquinonol A metabolite **7** (Figure 4) [13]. The subsequent Kraus–Pinnick oxidation afforded hydroxy acid **7** in 57% yield.[14]



conditions	2	3	4
10 mol% TEMPO, NCS (1.1 equiv), *n*Bu$_4$NCl, CH$_2$Cl$_2$-H$_2$O, rt, 2.15 h	65%	<0.1%	12%
1 mol% TEMPO, TCCA (1.05 equiv), CH$_2$Cl$_2$, rt, 15 min	98%	—	—
1.5 mol% RuCl$_2$(PPh$_3$)$_3$, 4.5 mol% TEMPO, chlorobenzene, O$_2$/N$_2$ (8/92; v/v), 10 bar, 100 °C, 18 h	64%	<1%	5%
5 mol% CuBr$_2$, 5 mol% bpy, 5 mol% TEMPO, 10 mol% NMI, CH$_3$CN, rt, air (open), 1 h, rt	94%	<1%	6%

Figure 2. Chemoselective oxidation of the benzylic primary alcohol in diol **1**

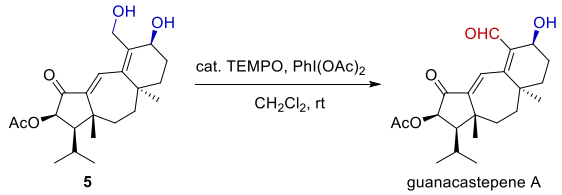


Figure 3. Chemoselective oxidation of a primary allylic alcohol during the total synthesis of guanacastepene A.

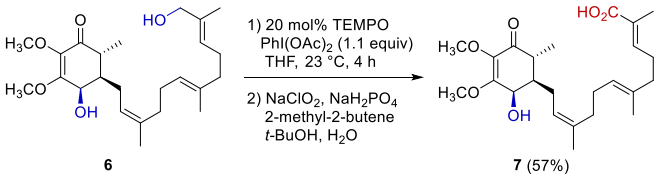


Figure 4. Chemoselective oxidation of a primary allylic alcohol during the synthesis of antroquinonol A metabolite **7**.

In terms of this type of chemoselective oxidation, the efficiency of several oxidation methods using molecular oxygen or air as a terminal oxidant has also been reported (Figure 2). Sheldon and coworkers reported that aerobic oxidation using TEMPO and RuCl$_2$(PPh$_3$)$_3$ also promoted the chemoselective oxidation of **1**. [15] In 2011, Stahl and Hoover developed a highly efficient catalytic aerobic oxidation of alcohols using Cu(I) salt/2,2'-bipyridine (bpy) ligand, TEMPO, and *N*-methylimidazole (NMI). [16] Although [Cu(MeCN)$_4$]X (X = OTf$^-$, BF$_4^-$, and PF$_6^-$) showed high performance for the oxidation of alcohols, the oxidation using less active CuBr$_2$ afforded better results for the chemoselective oxidation of **1**. In addition to these reports, the efficiency of Semmelhack's TEMPO/CuCl method using molecular oxygen was been demonstrated in the total synthesis of natural products. [6] In the synthesis of epoxyquinol A by Porco Jr and coworkers, diol **8** was chemoselectively oxidized to hydroxyaldehyde **9** and 2*H*-pyrans **10** (Figure 5).[17] After treating the mixture of **9** and **10** with aqueous MeOH, epoxyquinol A was obtained in 55% yield. Mehta's group also reported several total syntheses of natural products employing this type of chemoselective oxidation reaction.[18] The chemoselective oxidation of triol **11** gave dihydroxyaldehyde **12** in the synthesis of **13**, which was the originally-assigned structure of the polyketide antibiotic eupenoxide (Figure 6).[18b]

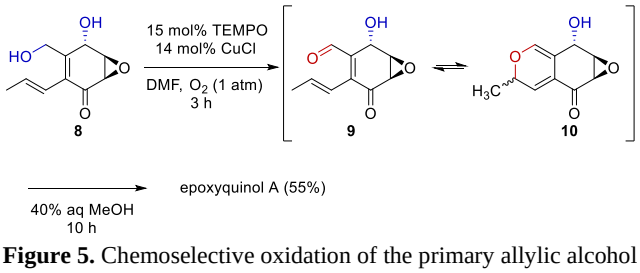


Figure 5. Chemoselective oxidation of the primary allylic alcohol during the synthesis of epoxyquinol A.

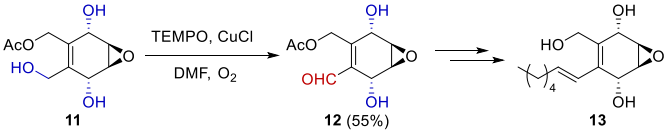


Figure 6 Chemoselective oxidation of triol **11** to give dihydroxyaldehyde **12**

3. Chemoselective oxidation of benzylic or allylic alcohols over aliphatic alcohols

Although MnO_2 oxidation has been widely applied in the chemoselective oxidation of benzylic and allylic alcohols in the presence of aliphatic alcohols,[19] several successful applications of TEMPO-catalyzed oxidation reaction toward this chemoselective oxidation have also been reported. Essigmann and Kobertz reported the chemoselective oxidation of the primary benzylic alcohol in **14** during the synthesis of a *cis*-syn furan-side photoproduct formed from a psoralen derivative and thymidine (Figure 7).[20] The chemoselective oxidation proceeded in the presence of primary aliphatic alcohol and phenol using oxygen, TEMPO, and CuCl to afford aldehyde **15** in 70% yield. Ghosh and Li achieved the chemoselective oxidation of the allylic primary alcohol within diol **16** using TEMPO and $PhI(OAc)_2$, which was the final step in the total synthesis of brevisamide (Figure 8).[21] Zhao and coworkers reported the chemoselective oxidation of the allylic alcohol in diol **17** to give hydroxyenone **18** during their study of derivatization of *ent*-kaurene diterpenoid, which exhibit selective inhibitory activity on 11β-hydroxysteroid dehydrogenase (11β-HSD) (Figure 9). [22] Zhabinskii and coworkers reported the chemoselective oxidation of lactol **19** to give lactone **20** maintaining the secondary alcohol (Figure 10) [23]. Removal of the TMS group and acetonide moiety lead to the synthesis of brassinolide, which is a plant hormone.

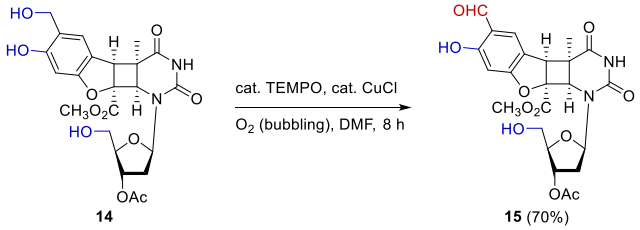


Figure 7. Chemoselective oxidation of a benzylic alcohol during the synthesis of a benzofuran-thymidine photoproduct.

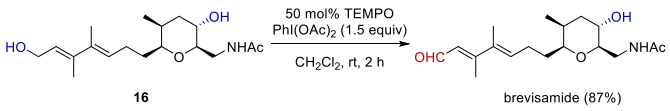


Figure 8. Chemoselective oxidation of an allylic alcohol during the total synthesis of brevisamide.

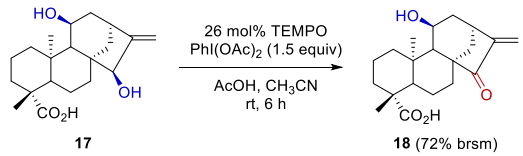


Figure 9. The chemoselective oxidation of the allylic alcohol in the derivatization of *ent*-kaurene diterpenoid.

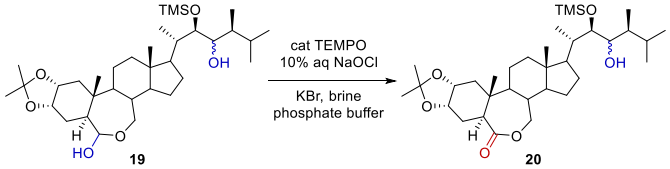


Figure 10. Chemoselective oxidation of lactol **19** to give lactone **20** during the total synthesis of brassinolide.

In addition to these successful transformations used in the total synthesis or derivatization of natural products, Kawabata and coworkers developed electronically-tuned nitroxyl radical catalyst **21**, which catalyzes the chemoselective oxidation of benzylic and allylic alcohols over aliphatic alcohols (Figures 11 and 12).[24] Chemoselective oxidation of propargylic alcohols has also been reported, although the yield and chemoselectivity are moderate. Because of the high oxidation potential of **21**, a strong oxidant, $PhI(OCOCF_3)_2$, is required as the cooxidant when compared to TEMPO-catalyzed oxidation.

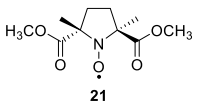


Figure 11. The structure of nitroxyl radical catalyst **21**.

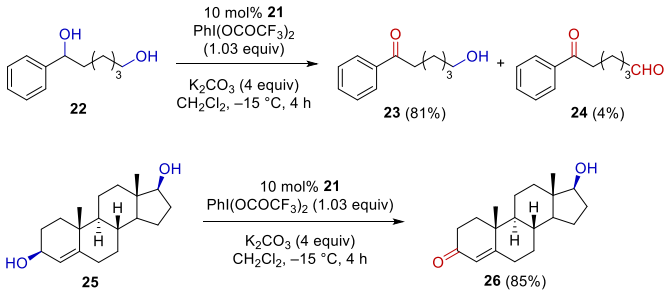


Figure 12. The chemoselective oxidation by **21**/$PhI(OCOCF_3)_2$.

4. Chemoselective oxidation of primary neopentyl alcohols over secondary aliphatic alcohols

Because of the steric hindrance, the efficiency of the oxidation of primary neopentyl alcohols using TEMPO is often low and a relatively large amount of TEMPO is required. Nicolaou and coworkers reported the TEMPO-mediated chemoselective oxidation of diol **27** to give hydroxyaldehyde **28** during the synthesis of the originally assigned structure of vannusal B (Figure 13).[25] Although 1.0 equivalent of TEMPO was required for the oxidation, **28** was obtained in high yield (88%). In the following synthesis of the revised structure of vannusal B by the same group, a similar chemoselective oxidation of the primary neopentyl alcohol was achieved by 1-Me-AZADO as the catalyst,[26] which was developed by Iwabuchi *et al.* as a highly efficient oxidation catalyst.[27] 20 mol% of 1-Me-AZADO efficiently catalyzed the chemoselective oxidation of diol **29** to give hydroxyaldehyde **30**. After acetylation of **30**, the corresponding acetate was isolated in 87% yield over two steps.

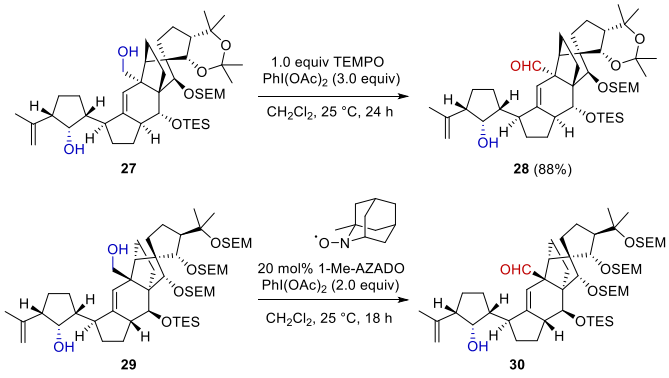


Figure 13. Chemoselective oxidation of diols **27** and **29** to give hydroxyaldehydes **28** and **30**, respectively during the synthesis of the original and revised structures of vannusal B.

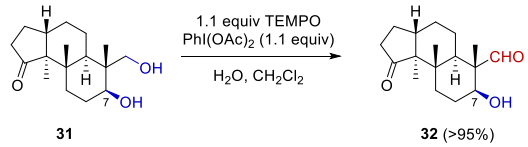
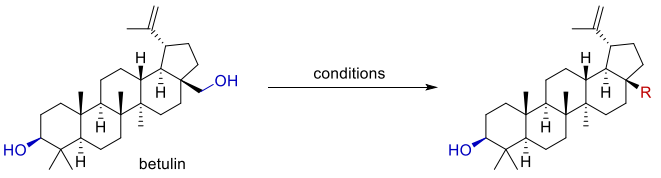


Figure 14. Chemoselective oxidation of diol **31** to give hydroxyaldehyde **32** during the synthesis of (–)-nodulisporic acid D.

Smith and coworkers have reported the TEMPO-mediated chemoselective oxidation of diol **31** to give hydroxyaldehyde **32** during the synthesis of (–)-nodulisporic acid D (Figure 14).[28] They showed that biphasic conditions (CH_2Cl_2/H_2O = 1:1) are necessary to suppress any undesired epimerization at the C7 position via a retro-aldol/aldol reaction pathway.

The chemoselective oxidation reaction of betulin bearing primary neopentyl and secondary aliphatic hydroxy groups has been reported by several groups (Figure 15). The chemoselective oxidation of betulin to betulinic acid was achieved via electrochemical oxidation in the presence of an excess amount of TEMPO for the first time.[29] Interestingly, Csuk and coworkers reported the chemoselective oxidation of betulin to betulinal using a modified Zhao's oxidation method (TEMPO/NaOCl/$NaClO_2$), which was originally reported as an oxidation method to convert primary alcohols into carboxylic acids. [8b,30] In this case, $Bu_4NBr{\cdot}H_2O$ was added to the reaction mixture. They also reported 4-AcNH-TEMPO-catalyzed chemoselective oxidation of betulin to give betulinic acid. AcO^{n}Bu and phosphate buffer (0.67 M, pH 6.7) were used as the optimal solvent system and $Bu_4NBr{\cdot}H_2O$ was also added. Bica and coworkers reported a two-step oxidation of betulin to give betulinic acid as a manufacturing process.[31] The oxidation of betulin by TEMPO and $PhI(OAc)_2$ to give betulinal was used in the first step, followed by Kraus–Pinnich oxidation. [14] This oxidation was applicable to the crude extract containing betulin obtained from birch bark.



conditions	product (yield)
22 equiv TEMPO, AcOH, NH_4OH, +1.0 V vs. SCE, 50 °C; $NaClO_2$, ^{t}BuOH	betulinic acid (60%) (R = CO_2H)
7 mol% TEMPO, $NaClO_2$ (2 equiv), NaOCl (2 mol%), ^{n}Bu_4NBr, CH_2Cl_2, phosphate buffer, 35 °C; NaOCl (3 equiv), ^{n}Bu_4NBr	betulinal (92%) (R = CHO)
7 mol% 4-AcNH-TEMPO, $NaClO_2$ (2 equiv), NaOCl (2 mol%), ^{n}Bu_4NBr, AcO^{n}Bu, phosphate buffer, 50 °C; NaOCl (1.7 equiv)	betulinic acid (86%) (R = CO_2H)
20 mol% TEMPO, $PhI(OAc)_2$ (3 equiv), AcO^{n}Bu, H_2O, ^{t}BuOH; $NaClO_2$ (2.6 equiv), NaH_2PO_4, 2-methyl-2-butene, H_2O	betulinic acid (89%) (R = CO_2H)

Figure 15. Chemoselective oxidation of betulin

Shibuya, Iwabuchi, and coworkers developed 1,5-dimethyl-9-azanoradamantane *N*-oxyl (DMN-AZADO) (Figure 16). [32] DMN-AZADO has a compact nucleus and two tetrasubstituted α-carbons, one on each side of the nitroxyl radical moiety, which enable the efficient chemoselective oxidation of primary alcohols over secondary alcohols. The superiority of this catalyst to TEMPO for the chemoselective oxidation of primary neopentyl alcohols has been demonstrated (Figures 17 and 18). They reported that 2 mol% of DMN-AZADO can efficiently catalyze the chemoselective oxidation of betulin into betulinal. Eight examples of the chemoselective oxidation of diols bearing a primary neopentyl and secondary hydroxy groups into their corresponding hydroxyaldehydes were demonstrated. Several examples of the chemoselective oxidation of the diols to their corresponding hydroxy acids using NaOCl(cat) and $NaClO_2$ were also demonstrated.

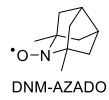


Figure 16. Structure of DMN-AZADO

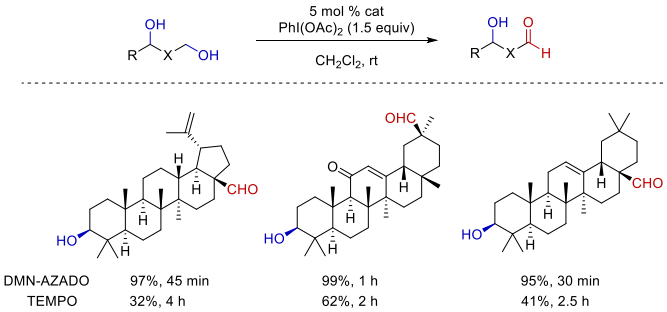


Figure 17. DMN-AZADO-catalyzed chemoselective oxidation of primary neopentyl alcohols into their corresponding aldehydes.

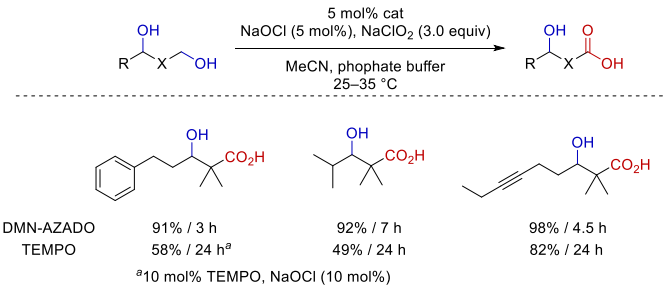


Figure 18. DMN-AZADO-catalyzed chemoselective oxidation of primary neopentyl alcohols into their corresponding carboxylic acids.

5. Chemoselective oxidation of less hindered secondary aliphatic alcohols.

Several successful chemoselective oxidations of less hindered secondary aliphatic alcohols in polyols in the presence of secondary aliphatic alcohols have also been reported. Carreira and Kleinbeck reported the chemoselective oxidation of triol **33** to give dihydroxyketone **34** during the synthesis of bafilomycin A_1 (Figure 19). [33] The less hindered secondary hydroxy at C19 was selectively oxidized by TEMPO and $PhI(OAc)_2$ leaving the C7 and C12 hydroxy groups intact. Baran and coworkers reported the chemoselective oxidation of triol **35** to give dihydroxyketone **36** using TEMPO and NaOCl during the synthesis of vinigrol (Figure 20). [34] Modification of the resultant ketone moiety completed the total synthesis.

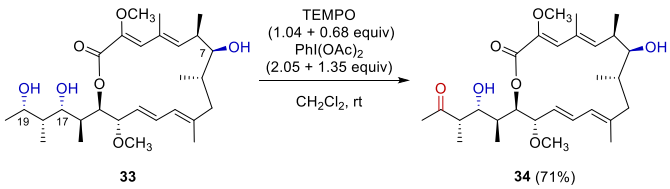


Figure 19. Chemoselective oxidation of the less hindered secondary aliphatic alcohol during the synthesis of bafilomycin A_1.

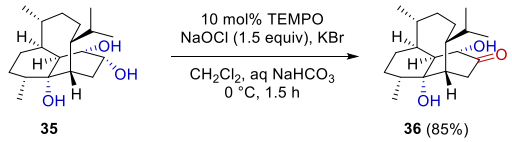


Figure 20. Chemoselective oxidation of the less hindered secondary aliphatic alcohol during the synthesis of vinigrol.

6. Chemoselective oxidation of 1,2-diols to α-hydroxy acids.

Although there are several reports on the chemoselective oxidation of 1,2-diols to prepare α-hydroxy acids using conventional TEMPO oxidation methods (TEMPO/NaOCl or TEMPO/NaOCl/$NaClO_2$) (Figure 21),[35] It is pointed that oxidative cleavage easily proceeds during the one-pot oxidation of 1,2-diols to α-hydroxy acids. [35-37] Shibuya and coworkers also reported that the nitroxyl radical-catalyzed oxidative cleavage of 1,2-diols gives their corresponding one-carbon-shorter carboxylic acids (Figure 22).[37] The oxidative cleavage reaction proceeds faster in the presence of 1-Me-AZADO than in the presence of TEMPO. The control experiments described in this report suggest that the C-C bond cleavage step occurs after over-oxidation of the α-hydroxy acid to form the corresponding α-keto acid.

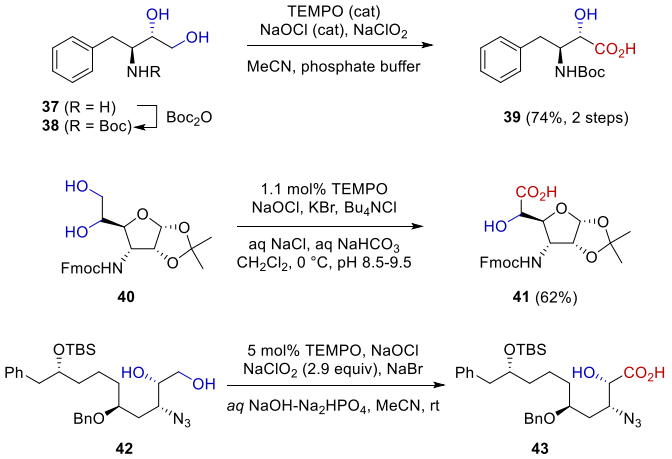


Figure 21. Precedents for the chemoselective oxidation of 1,2-diols to give α-hydroxy acids.

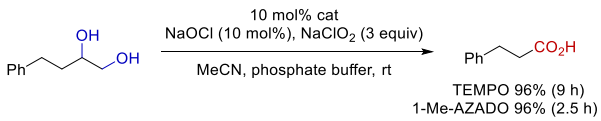


Figure 22. Nitroxyl radical-catalyzed oxidative cleavage.

Baskaran and Chinthapally have reported the TEMPO-mediated chemoselective oxidation of 1,2-diols into their corresponding α-hydroxy acids (Figure 23).[38] Although a stoichiometric amount of TEMPO is required, tuning of the reaction solvent (acetone and 5% aq $NaHCO_3$) and temperature (0 °C) allowed the chemoselective oxidation to occur using TEMPO and NaOCl. Optically active α-hydroxy acids were also prepared from their corresponding optically active 1,2-diols using this method without any unwanted epimerization at the C2 position.

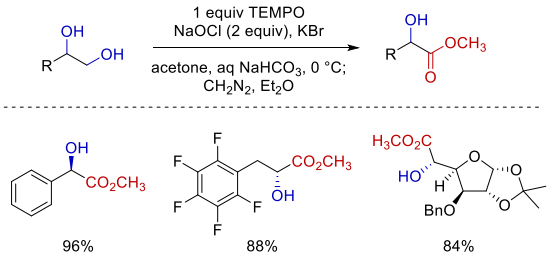


Figure 23. Chemoselective oxidation of 1,2-diols to α-hydroxy acids by the TEMPO-NaOCl system.

Shibuya and coworkers have reported the chemoselective TEMPO-catalyzed oxidation of 1,2-diols to give α-hydroxy acids (Figure 24). [39] In this catalytic system, control through phase separation under biphasic conditions involving hydrophobic toluene and phosphate buffer enabled the chemoselective oxidation reaction to occur. They found that the catalytically active species, $TEMPO^{+}Cl^{-}$, immediately reacts with $NaClO_2$ to generate a hydrophobic charge-transfer (CT) complex (TEMPO–ClO_2) under the reaction conditions, which plays an important role in the chemoselectivity.

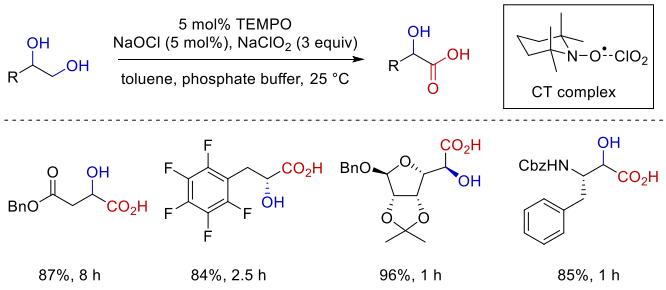


Figure 24. TEMPO-catalyzed chemoselective oxidation of 1,2-diols to give α-hydroxy acids.

7. Oxidative lactonization.

The oxidation of 1,4- and 1,5-diols typically afford their corresponding γ- or δ-lactones through the formation of lactol intermediates under conventional TEMPO-catalyzed oxidation conditions.[4b] If the diol bears primary and secondary hydroxy groups, oxidation of the primary alcohol proceeds prior to that of the secondary alcohol to selectively generate the corresponding lactol, which is oxidized to the corresponding lactone [40]. Van der Marel and coworkers reported the preparation of 1-thio uronic acid lactones via oxidative lactonization using TEMPO and $PhI(OAc)_2$ from their corresponding dihydroxy 1-thio glycopyranosides (Figure 25).[41] They reported that a biphasic system involving CH_2Cl_2 and H_2O is effective for the oxidative lactonization reaction. In addition, TEMPO-mediated oxidative lactonization has been applied in a variety of total synthesis. Three recent examples are shown in Figure 26.[42-44] Interestingly, Iwabuchi and coworkers reported the formation of β-lactone using AZADO-catalyzed oxidative lactonization during the synthesis of salinosporamide A (Figure 27).[45]

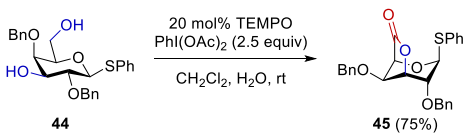


Figure 25. Oxidative lactonization used to prepare 1-thio-uronic acid lactone.

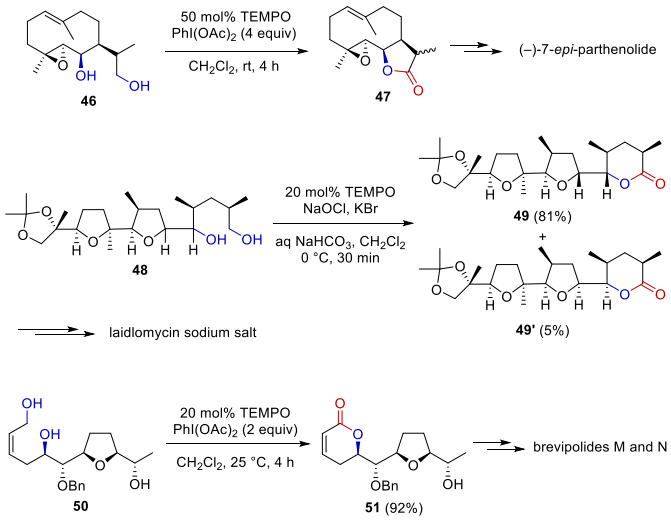


Figure 26. Recent examples of TEMPO-mediated oxidative lactonization during the total synthesis of natural products.

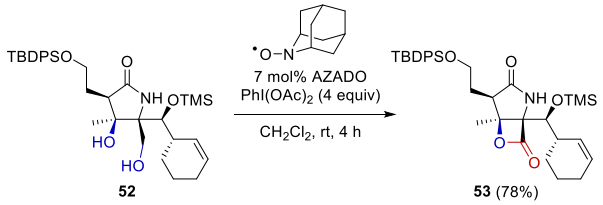


Figure 27. β-Lactone formation by the AZADO-catalyzed oxidative lactonization.

Sasaki and coworkers found that seven-membered lactone **55** can be constructed from 1,6-diol **54** via oxidative lactonization using TEMPO-PhI(OAc)$_2$ (Figure 28).[46] The oxidative lactonization reaction was used to construct the D ring of (–)-brevenal. They also reported that a variety of seven-membered lactones and an eight-membered lactone containing a *cis*-olefin can be formed using the TEMPO-PhI(OAc)$_2$ method (Figure 29).[47]

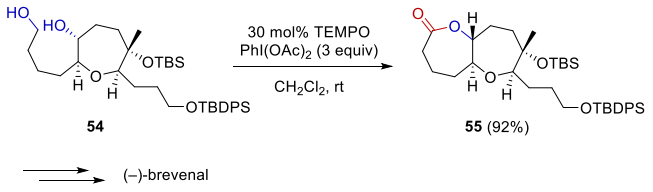


Figure 28. Oxidative lactonization used during the total synthesis of (–)-brevenal.

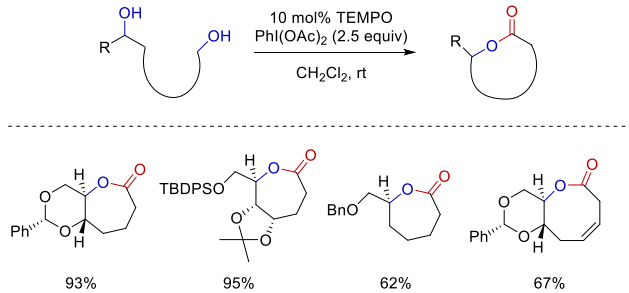


Figure 29. The formation of medium-sized lactones via oxidative lactonization.

Stahl and Xie reported the oxidative lactonization by the aerobic oxidation system using (bpy)Cu(I)/nitroxyl radical. (Figure 30).[48] (bpy)Cu(I) and 9-azabicyclo[3.3.1]nonan-*N*-oxyl(ABNO) efficiently promoted the oxidative lactonization of symmetrical diols,[49] whereas (bpy)Cu(I) and TEMPO catalytic system exhibit superior reactivity for the chemoselective oxidative lactonization of primary-secondary diols. The Cu(I)-TEMPO catalytic system also promoted the oxidative lactonization through the selective oxidation of less hindered primary alcohols of asymmetrical primary-primary diols.

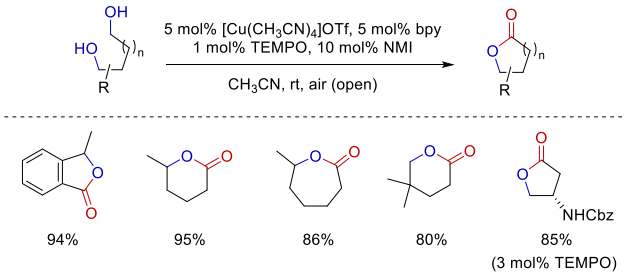


Figure 30. Oxidative lactonization by Cu(I)-TEMPO aerobic oxidation.

8. Chemoselective oxidation of primary aliphatic alcohols over secondary aliphatic alcohols.

Since the early studies suggested the preference of TEMPO-catalyzed oxidation for primary aliphatic alcohols over secondary aliphatic alcohols as-mentioned in the introduction,[3,4,9,10] this type of chemoselective oxidation has been used in various aspects of organic synthesis. The successful chemoselective oxidation of not only simple substrates, but also complex polyfunctional substrates has been reported. Selected examples of chemoselective oxidation during the late-stages of the total synthesis of natural products are shown in Figure 31. Carreira and coworkers reported the preparation of erythronolide A seco acid **57** via the chemoselective oxidation of triol **56**. Macrolactonization of **57** and a further 3 steps lead to the total synthesis of erythronolide A (Figure 31a).[50] Smith and Simov reported the chemoselective oxidation of diol **58** to give hydroxy acid **59** during the total synthesis of the marine natural product (–)-clavosolide A, which has a dimeric dilactone structure. After dimerization of **59**, debenzylation and bis-glycosidation of the resultant macrocyclic dilactone completed the total synthesis (Figure 31b).[51] Similar chemoselective oxidations have also been employed during the total synthesis of (–)-clavosolide and its related natural product by other groups.[52] Chamberlin and Vaswani reported the chemoselective oxidation of diol **60** to give hydroxy acid **61** during the total synthesis of kaitocephalin (Figure 31c).[53] Removal of the methyl and Boc groups in **61** completed the total synthesis. Scheidt and coworkers reported the total synthesis and structural revision of the marine macrolide neopeltolide in 2008 (Figure 31d).[54] In this report, precursor **63**, which was used for the key Lewis acid-mediated macrocyclization involving a Prins-type reaction, was prepared via the chemoselective oxidation of diol **62**. Paterson and coworkers reported the two-step chemoselective conversion of diol **64** into hydroxy acid **65** during the total synthesis of spirastrellolide A methyl ester (Figure 31e).[55] Selective removal of C37 TES group of **65** afforded the corresponding seco acid, which was a precursor to the macrolactonization step. Reisman and coworkers reported the total synthesis of (–)-trichorabdal A employing the chemoselective oxidation of diol **66** as the final step (Figure 31f).[56] Sasaki and coworkers reported the chemoselective oxidation of the primary aliphatic alcohol in tetraol **67** during the total synthesis of gambieric acid A (Figure 31g).[57] A subsequent Kraus–Pinnick oxidation followed by treatment with TMSCH$_2$N$_2$ afforded trihydroxy ester **68** over three-steps in 66% yield from **67**.[14] The total synthesis was completed after deprotection and hydrolysis. Kadota, Takamura, and coworkers reported the chemoselective oxidation of diol **69** to give hydroxyaldehyde **70** during the synthesis of 6-chlorotetrahydrofuran acetogenin **71** (Figure 31h).[58] The subsequent construction of the (*Z*)-enyne via a Julia olefination reaction and an additional four-step transformation lead to **71**.

Kang and coworkers have reported the total synthesis of inostamycin A employing the chemoselective oxidation of polyol **72** as the final step (Figure 31i).[59] Inostamycin A was isolated as its sodium salt (**73**).

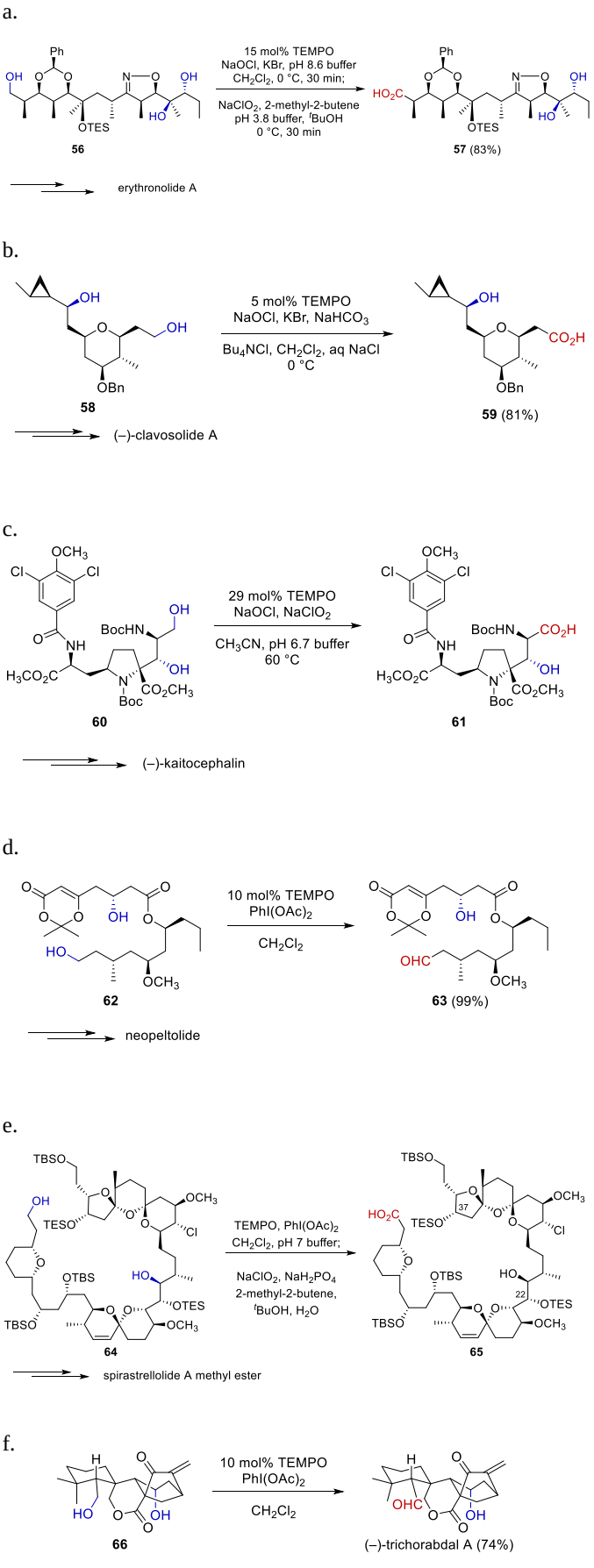


Figure 31. Examples of the TEMPO-catalyzed chemoselective oxidation of primary aliphatic alcohols over secondary aliphatic alcohols during the total synthesis of natural products.

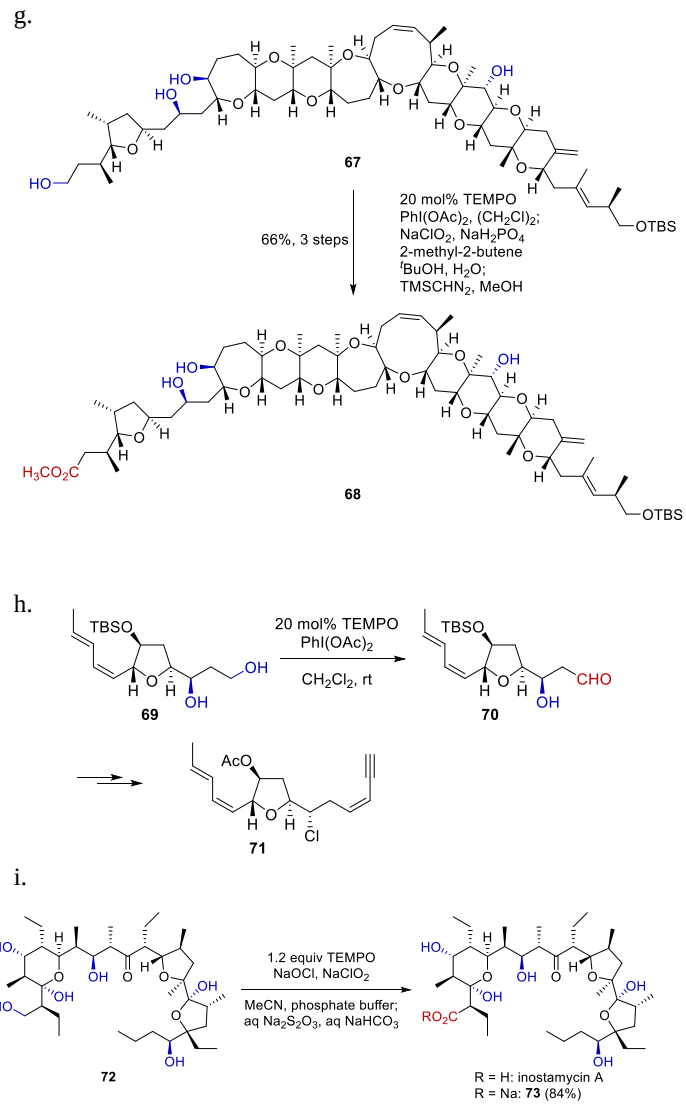


Figure 31. Examples of the TEMPO-catalyzed chemoselective oxidation of primary aliphatic al cohols over secondary aliphatic alcohols during the total synthesis of natural products. (continued).

Mori and coworkers reported the DMN-AZADO-catalyzed chemoselective oxidation of tetraol **74** to give trihydroxyaldehyde **75** in the last stage of the total synthesis of the cytotoxic marine natural polycyclic ether, gymnocin-A (Figure 32). [60] The total synthesis of gymnocin-A was completed via the Wittig olefination of **75** with **76**.

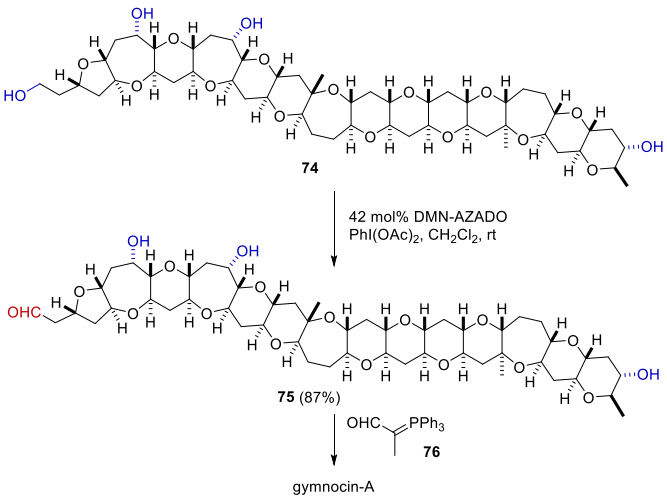


Figure 32 DMN-AZADO-catalyzed chemoselective oxidation during the total synthesis of gymnocin A.

Stahl and Hoover reported an aerobic oxidation reaction using the (bpy)Cu(I)/TEMPO system to carry out the chemoselective oxidation of primary aliphatic alcohols over secondary aliphatic alcohols (Figure 33).[16].

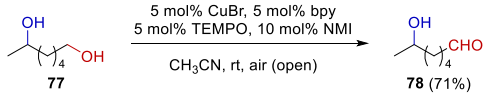


Figure 33. Chemoselective oxidation of primary aliphatic alcohols over secondary aliphatic alcohols via aerobic oxidation.

9. Miscellaneous

As described in the section describing the chemoselective oxidation of 1,2-diols, α-keto acids readily undergo oxidative cleavage with the release of CO_2 under conventional oxidation conditions. [36,37] Shibuya and coworkers reported that aerobic oxidation using AZADO and $NaNO_2$ enables the chemoselective oxidation of α-hydroxy acids to give α-keto acids without promoting the undesired oxidative cleavage reaction (Figure 34).[61]

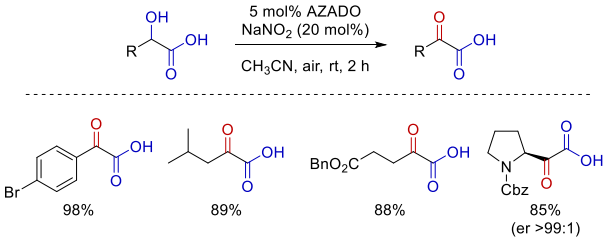


Figure 34. Chemoselective oxidation of α-hydroxy acids to give α-keto acids.

Iwabuchi and coworkers have reported the chemoselective oxidation of amino alcohols into amino carbonyl compounds using the bpyCu(I)/AZADO aerobic oxidation system.[62] Chemoselective alcohol oxidation proceeds in the presence of not only tertiary benzylic and allylic amines but also alkyl-substituted tertiary, secondary, and primary amines. They also demonstrated the chemoselective oxidation of mesembranol to give (–)-mesembrine using the AZADO-Cu(I) oxidation system.

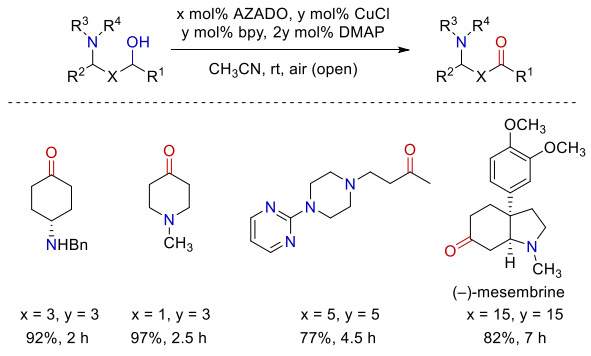


Figure 35. Chemoselective oxidation of amino alcohols to give amino carbonyl compounds.

Although divalent sulfur compounds are labile under oxidation conditions, Iwabuchi and coworkers reported that the bpyCu(I)-AZADO aerobic oxidation system can enable the chemoselective oxidation of alcohols in the presence of 1,3-dithianes and sulfides (Figure 36). [63] A 1:2:1:2 ratio of AZADO/CuCl/bpy/DMAP was found to be optimal for this chemoselective oxidation reaction.

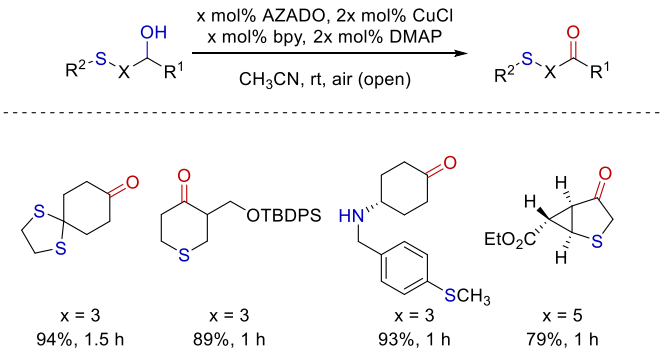


Figure 36. Chemoselective oxidation of alcohols in the presence of divalent sulfur.

10. Conclusions and perspectives

As disclosed in this paper, various types of chemoselective oxidation reactions of polyols have been reported since the chemoselectivity observed for primary aliphatic alcohols over secondary aliphatic alcohols in TEMPO-catalyzed oxidations was reported in the 1980s. In addition to TEMPO, nitroxyl radical **21**, which has a preference for the oxidation of benzylic and allylic alcohols over aliphatic alcohols, and DMN-AZADO, which enables the chemoselective oxidation of sterically hindered primary alcohols such as a neopentyl alcohol over secondary aliphatic alcohols have been developed. Although the conventional nitroxyl radical-catalyzed oxidation reactions using NaOCl, $PhI(OAc)_2$, or $NaOCl/NaClO_2$ as a cooxidant have been widely used, it is notable that nitroxyl radical-Cu(I) and nitroxyl radical-NO_x catalytic systems used for the aerobic oxidation are effective in the several chemoselective oxidation reactions.[64] This digest represents the scope of the nitroxyl radical-catalyzed chemoselective oxidation for the synthesis of polyfunctional molecules reported to date. Further advances in this field will lead to an increase in the efficiency of organic synthesis.

Acknowledgments

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