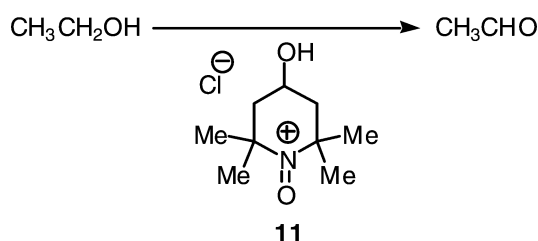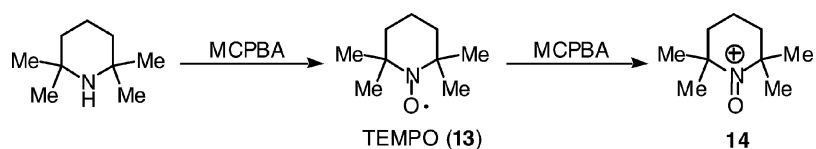# 6

TEMPO-Mediated Oxidations

6.1. Introduction

In 1965, Golubev, Rozantsev, and Neiman reported[1] that treatment of oxoammonium salt **11** with excess of ethanol led to the formation of acetaldehyde.

In 1975, Cella *et al.* demonstrated[2] that alcohols can be oxidized to carboxylic acids by treatment with *m*-chloroperbenzoic acid in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidine (**12**).
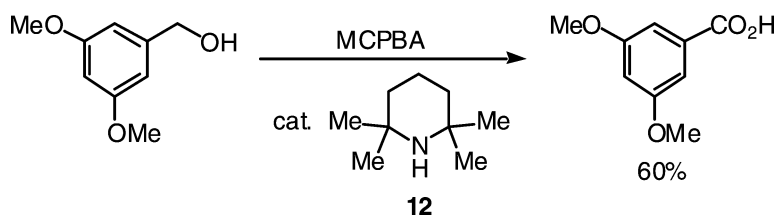

Apparently, MCPBA oxidizes the amine **12**, resulting in a catalytic quantity of the stable radical 2,2,6,6-tetramethylpiperidine-1-oxyl (**13**), normally called TEMPO, that is further oxidized to the oxoammonium cation **14** that operates as the primary oxidant.

Me—⟨ ⟩—Me   →MCPBA→   Me—⟨ ⟩—Me   →MCPBA→   Me—⟨ ⟩—Me
Me N Me   Me N Me   Me N Me
    H   O•   O
                      TEMPO (13)   **14**

Cella made a very important seminal contribution to the TEMPO-mediated obtention of carboxylic acids by showing that oxoammonium salts can be employed catalytically in the transformation of primary alcohols into carboxylic acids. On the other hand, Cella's procedure involves the use of a peracid as secondary oxidant, which is a strong oxidant that interferes with many functional groups.
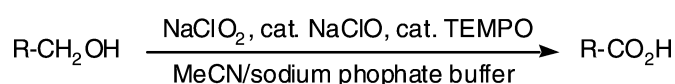
In 1987, Anelli *et al.* published[3] a landmark paper in which they showed that primary alcohols can be oxidized either to aldehydes or to carboxylic acids in a highly efficient and convenient manner, by treating the alcohol in a CH_2Cl_2–water biphasic mixture with chlorine bleach (sodium hypochlorite) in the presence of sodium bicarbonate, potassium bromide, and a catalytic amount of the TEMPO derivative 4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**15**) (4-MeO-TEMPO). The oxidation can be stopped at the aldehyde stage by running it for a short time. Alternatively, it can be brought to the carboxylic acid stage by adding a phase-transfer catalyst that causes a great acceleration of the oxidation.

Anelli`s oxidation of primary alcohols to carboxylic acids

$R\text{-}CH_2OH$ ⟶ $R\text{-}CO_2H$

NaClO, cat.

15

CH_2Cl_2/water, $NaHCO_3$, KBr
phase transfer catalyst
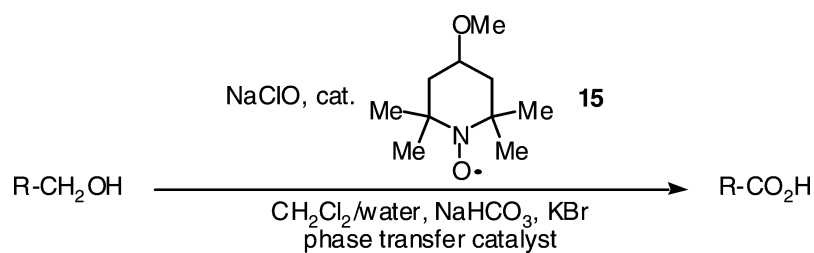
One important limitation of Anelli's procedure is the need to utilize sodium hypochlorite as stoichiometric oxidant, a compound that has a great tendency to produce chlorinations in some sensitive substrates. This tendency to chlorination can be mitigated by employing Zhao's modification of Anelli's procedure, which was published[4] in 1999. In this modification, the secondary oxidant—sodium hypochlorite—is used in catalytic amounts rather than in excess, the reagent being regenerated by addition of stoichiometric sodium chlorite, a compound that lacks the strong chlorinating tendency of sodium hypochlorite.

Zhao`s modification of Anelli`s oxidation

$$R\text{-}CH_2OH \xrightarrow[\text{MeCN/sodium phophate buffer}]{NaClO_2, \text{ cat. } NaClO, \text{ cat. TEMPO}} R\text{-}CO_2H$$

In 1999, Epp and Widlanski described[5] the oxidation of alcohols to carboxylic acids using catalytic TEMPO, with bis(acetoxy)iodobenzene—$PhI(OAc)_2$, commonly referred as BAIB—as secondary oxidant in an acetonitrile–aqueous buffer mixture. This procedure for the oxidation of primary alcohols possesses the distinctive advantage of producing the rather benign iodobenzene and acetic acid as side compounds. Furthermore, in contrast to other oxidation procedures, it is possible to perform the oxidation of Epp and Widlanski in the absence of metallic salts.

Procedure of Epp and Widlanski for oxidation of primary alcohols to carboxylic acids

$$R\text{-}CH_2OH \xrightarrow[\text{MeCN/aqueous buffer}]{\text{cat. TEMPO, } PhI(OAc)_2} R\text{-}CO_2H$$
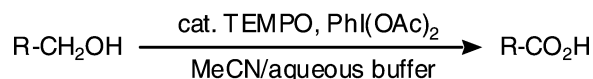
Mechanism

The available experimental data are consistent with a mechanism,[4, 6] as shown below, in which the secondary oxidant transforms TEMPO, or a related stable radical, in an oxoammonium salt that operates as the primary oxidant, transforming the alcohol into the corresponding aldehyde. This results in the formation of a hydroxylamine that is oxidized to a TEMPO radical, thus completing the catalytic cycle.
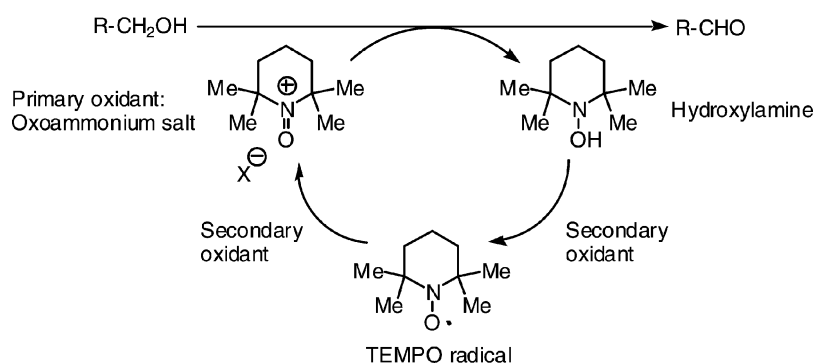
The catalytic cycle can in fact be more complex, because TEMPO radicals can dispro-portionate into oxoammonium salts and hydroxylamines under acidic catalysis.[6a]

The aldehyde, in the presence of water, equilibrates with the corresponding hydrate that can be oxidized via a similar mechanism to the corresponding acid, as shown below.

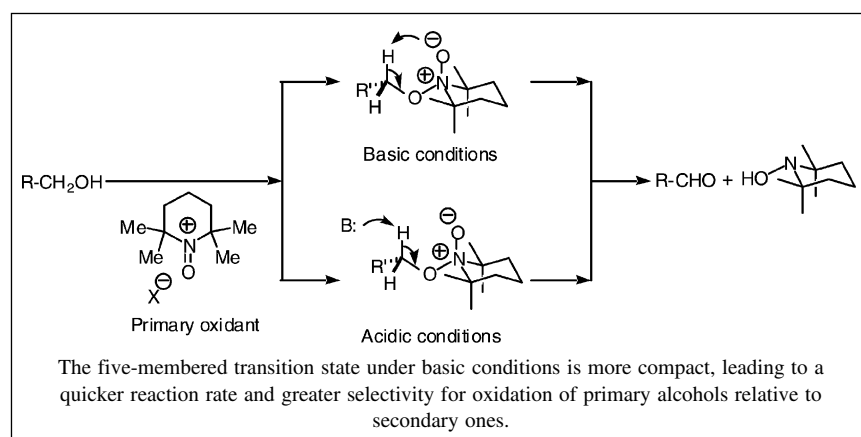R-CHO $\xrightarrow{\text{+H}_2\text{O}}$ R–C(OH)(OH)–H $\longrightarrow$ R-CO$_2$H
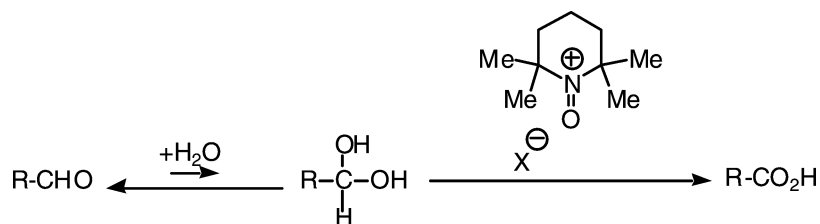
The oxoammonium salt operates as primary oxidant in a catalytic cycle as above

Interestingly, TEMPO inhibits the oxidation of aldehydes to carboxylic acids when this oxidation proceeds via a radical mechanism. That is why Anelli's oxidation can be carried out under air and be easily stopped at the aldehyde stage with no competing overoxidation due to the presence of gaseous oxygen.[7]

While in all TEMPO-mediated oxidations of primary alcohols to carboxylic acids, oxoammonium salts are the primary oxidants for the transformation of alcohols into aldehydes, the subsequent oxidation of aldehydes to carboxylic acids may sometimes be effected by the oxidant present in excess rather than by oxoammonium salts. In such cases, the secondary oxidant for the transformation of alcohols into aldehydes is the primary oxidant for the oxidation of aldehydes to carboxylic acids.

The oxidation of primary alcohols with oxoammonium salts can work either via a compact five-membered transition state under basic conditions or via a linear transition state under acidic conditions, as shown below. Under basic conditions the oxidation is quicker and possesses a greater selectivity for primary alcohols versus secondary ones.

R-CH$_2$OH $\longrightarrow$ $\longrightarrow$ R-CHO + HO-N

Primary oxidant

Basic conditions

Acidic conditions

B:

The five-membered transition state under basic conditions is more compact, leading to a quicker reaction rate and greater selectivity for oxidation of primary alcohols relative to secondary ones.

Stoichiometric Oxidants

The most common stoichiometric oxidants in TEMPO-mediated transformations of primary alcohols into carboxylic acids are sodium hypochlorite (NaOCl)—Anelli's oxidation—,[3] sodium chlorite (NaClO$_2$)—Zhao's modification of Anelli's oxidation—,[4] and PhI(OAc)$_2$—oxidation of Epp and Widlanski.[5] Other stoichiometric oxidants less commonly used include MCPBA,[2] Ca(ClO)$_2$ (swimming pool bleach),[8] *t*-BuOCl,[9] CuCl−O$_2$,[10] NaBrO$_2$,[11] Cl$_2$,[12] Br$_2$[12], and trichloroisocyanuric acid.[13] It is possible to perform the oxidation under electrochemical conditions in the presence of catalytic TEMPO.[14]

Amino 1-Oxyl Radicals

TEMPO and analogue compounds can be prepared starting with a simple condensation of ammonia with acetone,[15] and their cost is quite affordable. They are stable radicals because they are flanked by two quaternary carbons that provide a bulky environment. For these reasons, TEMPO and analogue compounds, that is, 2,2,6,6-tetramethylpiperidine-1-oxyl radicals, are almost exclusively employed in oxidations mediated by amino 1-oxyl radicals.
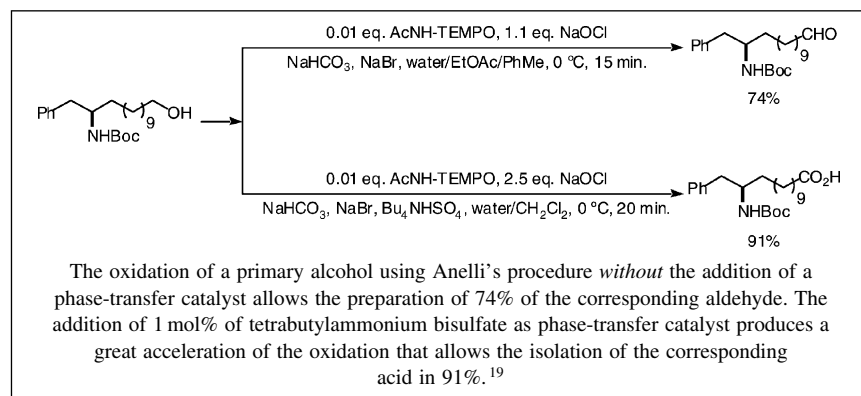
> TEMPO is a volatile compound soluble in organic solvents and water. It can be recovered by extraction with Et$_2$O[14] or by azeotropic distillation with water.[16]

Although some differences in the chemical behavior of different TEMPO derivatives were noticed,[17] the selection of a particular derivative is normally dictated by price and convenience. As far as the authors are aware, no profound study of the efficacy of different TEMPO derivatives in the oxidation of alcohols has been carried out.

> TEMPO entrapped within a silica matrix has been employed as a recyclable catalyst in the selective oxidation of primary alcohols using NaOCl as stoichiometric oxidant.[18]

6.2. Anelli's Oxidation

In 1987, Anelli *et al.* made a key contribution to TEMPO-mediated oxidations by showing that the very cheap reagent chlorine bleach (aqueous NaOCl) can function very effectively as a stoichiometric oxidant for alcohols in the presence of traces of 4-MeO-TEMPO.[3] They established a protocol involving a reaction run at 0 °C in a biphasic CH$_2$Cl$_2$–water mixture in the presence of excess of NaOCl, NaHCO$_3$, KBr, and catalytic 4-MeO-TEMPO for oxidation to aldehydes. Under these conditions the oxidation to acids is quite slow. If the acid is desired, it is advisable to add a phase-transfer catalyst to speed up the oxidation.

The oxidation of a primary alcohol using Anelli's procedure *without* the addition of a phase-transfer catalyst allows the preparation of 74% of the corresponding aldehyde. The addition of 1 mol% of tetrabutylammonium bisulfate as phase-transfer catalyst produces a great acceleration of the oxidation that allows the isolation of the corresponding acid in 91%.[19]

The following experimental data are relevant regarding Anelli's oxidation:

- Primary alcohols are transformed into the corresponding aldehydes—with no need to add a phase-transfer catalyst—normally in only about 3 minutes. The oxidation of benzyl alcohols possessing electron donating groups in the aromatic ring can be much slower, a fact that can be explained by the presence of a negative charge in the transition state for the oxidation involving oxoammonium salts under basic conditions.

- The addition of some KBr produces a substantial acceleration of the oxidation, because of the generation of HOBr.[20] This reagent is formed from HOCl and KBr, and is apparently a much better oxidant for the regeneration of oxoammonium salts than HOCl.

- The reaction is rather slow at the pH of commercial bleach (ca. 12.7), being much quicker at a pH of ca. 8.6, generated by the addition of $NaHCO_3$ as buffer. This fact can be explained assuming that at a very high pH the regeneration of the oxoammonium salt, rather than the oxidation of the alcohol by the oxoammonium salt via a five-membered transition state, becomes rate-determining. At a very basic pH the concentration of HOBr, which is the oxidant regenerating the oxoammonium salt, becomes very low relative to the concentration of the hypobromite anion (BrO^-).

- The reaction can fail in substrates possessing a high hydrophilicity. Apparently, the oxidation takes place in the organic phase, where such substrates are present in a very low concentration.

- The oxidation can be substantially accelerated by the addition of quaternary ammonium salts as a phase-transfer catalyst. Thus, while in the absence of phase-transfer catalyst the reaction is easily stopped at

the aldehyde stage, the addition of catalytic amounts of a quaternary ammonium salt normally allows the oxidation to carboxylic acid to be completed in 5 minutes at $0\,°C$. As in the oxidation to aldehydes, electronic effects can be very important, and oxidations yielding benzoic acids possessing electron donating groups can be much slower.

- Somehow unexpectedly, the reaction speed decreases by increasing the temperature, a fact due to the decomposition of oxoammonium salts, which are very stable at $0\,°C$, but decompose very quickly in the presence of water at $25\,°C$.
- The transformation of aldehydes into carboxylic acids is apparently mediated by oxoammonium salts, rather than by some other oxidant in excess; for, in the absence of TEMPO radicals, this reaction is rather slow.

The above facts are illustrated in the following scheme:

Oxidation of primary alcohols into carboxylic acids by Anelli`s procedure
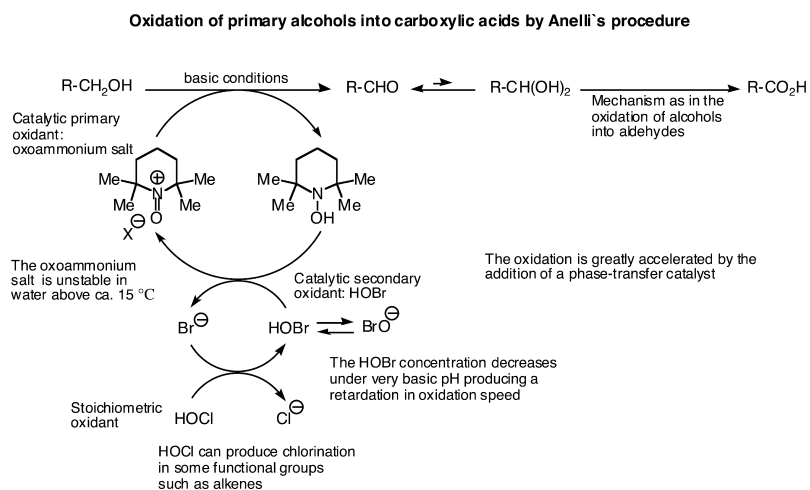
Solvent

Anelli's oxidation is most often carried out in a biphasic system consisting of CH_2Cl_2 and water. As the oxidation takes place in the organic phase, this biphasic system fails in water-soluble substrates. That is why when Anelli's oxidation is applied to sugars, water is normally employed as the sole solvent.[21] Furthermore, acetone/water is a solvent combination quite often utilized,[22] while

MeCN/water[23] and EtOAc/water[24] are less used. When water or an aqueous mixture is employed as solvent, the reaction may fail in lipophilic substrates because of lack of solubility.[25]
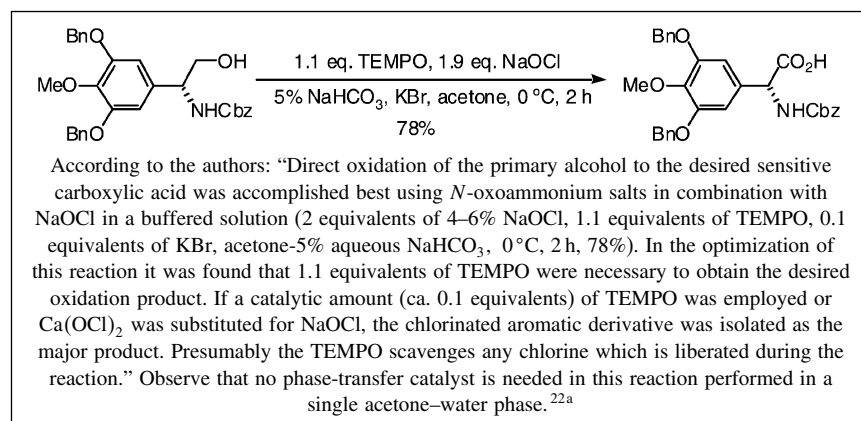

The primary alcohols, in a cyclodextrin possessing the secondary alcohols protected as methyl ethers, are oxidized in a monophasic MeCN–water mixture providing 93% of the corresponding heptacarboxylate. Under these conditions there is no oxidation in substrates where the secondary alcohols are protected as benzyl or allyl ethers, due to their much greater lipophilicity.[25]

Catalyst

Simple TEMPO is usually employed as catalyst in the Anelli's oxidation of primary alcohols to acids, although other TEMPO derivatives such as 4-MeO-TEMPO,[3, 26] 4-HO-TEMPO,[27] or 4-AcNH-TEMPO[19] are equally effective. A trace quantity of 1 mol% of catalyst is normally enough for an efficient oxidation, although because of the low price of TEMPO and its very easy elimination during the workup, the use of ca. 4–10 mol% is common. TEMPO is sometimes added in amounts as high as 1–1.5 equivalents; this may help to prevent side reactions produced by excess of HOCl.[22a,b, 28]

According to the authors: "Direct oxidation of the primary alcohol to the desired sensitive carboxylic acid was accomplished best using *N*-oxoammonium salts in combination with NaOCl in a buffered solution (2 equivalents of 4–6% NaOCl, 1.1 equivalents of TEMPO, 0.1 equivalents of KBr, acetone-5% aqueous NaHCO₃, 0 °C, 2 h, 78%). In the optimization of this reaction it was found that 1.1 equivalents of TEMPO were necessary to obtain the desired oxidation product. If a catalytic amount (ca. 0.1 equivalents) of TEMPO was employed or Ca(OCl)₂ was substituted for NaOCl, the chlorinated aromatic derivative was isolated as the major product. Presumably the TEMPO scavenges any chlorine which is liberated during the reaction." Observe that no phase-transfer catalyst is needed in this reaction performed in a single acetone–water phase.[22a]

Phase-Transfer Catalyst

Although no phase-transfer catalyst is needed in oxidations carried out in a single phase—such as in water, MeCN/water, or acetone/water— an ammonium salt such as n-Bu$_4$NCl,[29] n-Bu$_4$NBr,[30] n-Bu$_4$NHSO$_4$,[19] or Aliquat® 336 (tricaprylylmethylammonium chloride)[31] is normally added in oxidations performed in a biphasic CH$_2$Cl$_2$/water mixture.

pH

Commercial chlorine bleach is prepared by reacting chlorine with an aqueous NaOH solution, and contains ca. 3–6% of NaOCl. Excess of NaOH is employed to stabilize the NaOCl, which otherwise would disproportionate into NaCl and NaClO$_3$. This results in bleach possessing a pH between 11 and 13, which is too basic for a normal Anelli's oxidation. The addition of NaHCO$_3$ allows lowering the pH to a value of ca. 8.6–10, which is normally ideal for Anelli's oxidations. Some NaOH is sometimes added additionally to fine tune the pH to a value of ca. 10.[25, 32]

Figure 3 shows the influence of pH on the rate of oxidation of methyl α-D-glucopyranoside. There is a very sharp increase in speed from pH 8 to pH 10, while a higher pH produces no further acceleration of reaction speed.

The generation of carboxylic acid during the oxidation may cause a lowering of pH that produces a decrease of oxidation speed and of selectivity
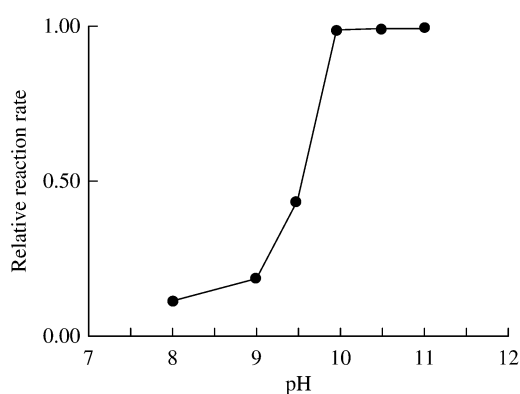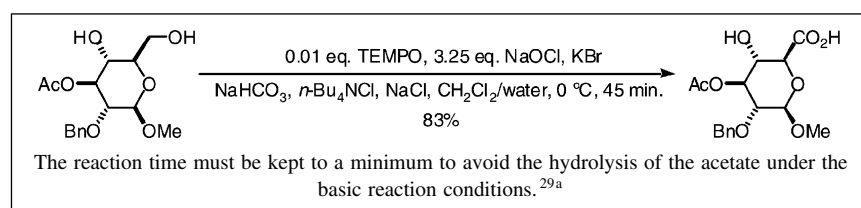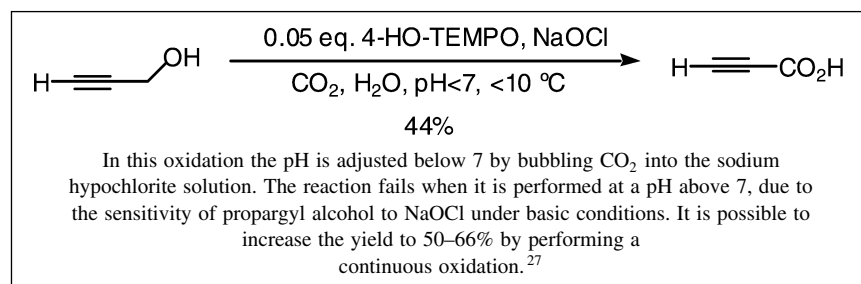

Figure 3. Influence of pH on the rate of oxidation of methyl α-D-glucopyranoside using 0.007 eq. of TEMPO, 2.2 eq. of a 15% NaOCl solution, and 0.4 eq. of NaBr at 2 °C, adding 4 M HCl to adjust the pH.[6b] Reprinted from Carbohydrate Research, Vol.269, Nooy, A.E.J.; Besemer, A.C.; van Bekkum, H., "Highly selective nitroxyl radical-mediated oxidation of primary alcohol groups in water-soluble glucans," pages 89–98, ©1995, with permission from Elsevier.

for oxidation of primary alcohols versus secondary ones. This may be avoided by continuous adjustment of the pH by addition of NaOH.[21b, 33]

Some functional groups, such as esters, may be sensitive to the mildly basic pH normally used in Anelli's oxidations, and in some cases it may be necessary to adjust the precise reaction conditions to avoid interferences.[29a]

0.01 eq. TEMPO, 3.25 eq. NaOCl, KBr

NaHCO$_3$, n-Bu$_4$NCl, NaCl, CH$_2$Cl$_2$/water, 0 ℃, 45 min.

83%

The reaction time must be kept to a minimum to avoid the hydrolysis of the acetate under the basic reaction conditions.[29a]

In some cases, Anelli's oxidation must be carried out under acidic conditions to obtain an optimum yield.[27]

0.05 eq. 4-HO-TEMPO, NaOCl

CO$_2$, H$_2$O, pH<7, <10 ℃

44%

In this oxidation the pH is adjusted below 7 by bubbling CO$_2$ into the sodium hypochlorite solution. The reaction fails when it is performed at a pH above 7, due to the sensitivity of propargyl alcohol to NaOCl under basic conditions. It is possible to increase the yield to 50–66% by performing a continuous oxidation.[27]
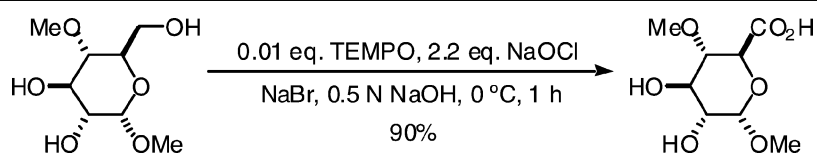
Selectivity

One of the most useful features of the oxidation of primary alcohols to carboxylic acids under Anelli's conditions is the great selectivity achieved for the oxidation of primary alcohols versus secondary ones.[8, 9b, 34] This selectivity is the result of the steric hindrance around the oxoammonium functionality in the oxoammonium salts derived from TEMPO-like radicals, resulting in a much easier attack by the relatively less hindered primary alcohols.
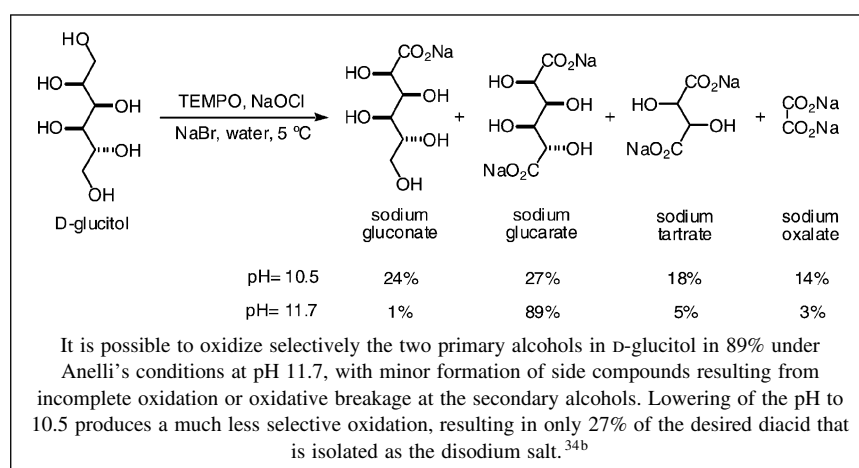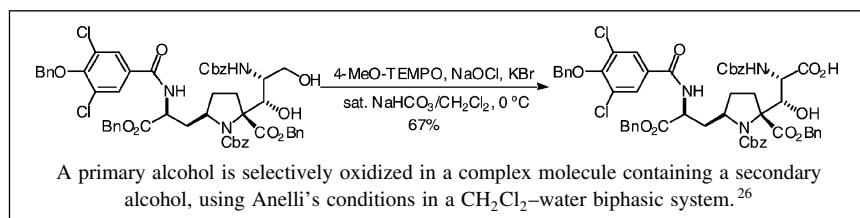

Research needed

The employment of amino oxyl radicals, yielding oxoammonium salts with a greater steric hindrance than those derived from TEMPO-like radicals, in the selective oxidation of primary alcohols must be investigated.

Treatment of the starting triol under Anelli's conditions in water at pH 10–11 allows the selective oxidation of the primary alcohol in 90%. The use of gaseous oxygen in the presence of platinum on carbon under Heyns' conditions provides a more modest 50% yield of the desired carboxylic acid.[9a]

Under basic conditions there is a compact and sterically demanding five-membered transition state for the oxidation of alcohols with oxoammonium salts, while under acidic conditions a less sterically demanding linear transition state operates. This results in both greater oxidizing speed and greater selectivity for oxidation of primary alcohols under Anelli's conditions at high pH. Furthermore, under less basic conditions hypohalous acids may compete with oxoammonium salts for the direct oxidation of alcohols[6b] resulting in even less selectivity. In fact, under acidic conditions the selectivity greatly decreases and secondary alcohols may even be oxidized more rapidly.[6a]

---

	sodium gluconate	sodium glucarate	sodium tartrate	sodium oxalate
pH= 10.5	24%	27%	18%	14%
pH= 11.7	1%	89%	5%	3%

It is possible to oxidize selectively the two primary alcohols in D-glucitol in 89% under Anelli's conditions at pH 11.7, with minor formation of side compounds resulting from incomplete oxidation or oxidative breakage at the secondary alcohols. Lowering of the pH to 10.5 produces a much less selective oxidation, resulting in only 27% of the desired diacid that is isolated as the disodium salt.[34b]

A primary alcohol is selectively oxidized in a complex molecule containing a secondary alcohol, using Anelli's conditions in a CH_2Cl_2–water biphasic system.[26]

6.2.1 General Procedure for Oxidation of Primary Alcohols to Carboxylic Acids by Anelli's Oxidation

A mixture of 1 equivalent of alcohol with ca. 0.002–0.1—typically 0.01—equivalent of TEMPO (MW 156.25),[a,b] ca. 1.75–8—typically 2—equivalents of NaOCl (MW 74.44),[c] ca. 0.1–0.7 equivalent of KBr (MW 119.01),[d] and ca. 0.05–0.12—typically 0.06—equivalent of a phase-transfer catalyst[e] in a biphasic buffered[f,g] system containing water and CH_2Cl_2,[h] is vigorously stirred at 0 °C[i] until most of the starting alcohol is consumed.[j] The reaction mixture is optionally quenched by addition of methanol or ethanol. When the reaction is carried out using a mixture of acetone and water, the removal of acetone *in vacuo* may facilitate the rest of the workup. The elimination of acetone sometimes causes the crystallization or precipitation of the sodium salt of the acid that can be isolated by filtration. Generally, the remainder of the workup of the reaction can be made according to three alternative protocols:

Workup A: The reaction mixture is optionally washed with an organic solvent like Et_2O or CH_2Cl_2. When the product—even as a sodium carboxylate—is very lipophilic, it may be convenient to adjust the pH above 12 by the addition of concentrated NaOH before the washing with an organic solvent. The pH is brought to ca. 2–6 by the addition of hydrochloric acid or 10% aqueous citric acid. WARNING: this may cause the evolution of poisonous chlorine gas. The mixture is extracted with an organic solvent like EtOAc or CH_2Cl_2. The collected organic phases can be optionally washed with water or brine. The organic phase is dried with Na_2SO_4 or $MgSO_4$ and concentrated, giving a crude acid that may need further purification. This workup may not be suitable for products like many sugars, possessing a very low solubility in organic solvents. The acidification sometimes causes the precipitation or crystallization of the acid that can be isolated by simple filtration. Alternatively, in the case of organic acids with a high solubility in water, the precipitation of the organic acid from an acidic aqueous phase may be induced sometimes by addition of an organic solvent miscible with water such as ethanol.

Workup B: The reaction mixture is fractioned between EtOAc and water. The organic phase is separated and can be optionally washed with

water, 10% HCl, or brine. The organic phase is dried with Na_2SO_4 or $MgSO_4$ and concentrated, giving a crude acid that may need further purification. This workup is suitable for lipophilic organic acids possessing a very low solubility in water even when present as sodium salts.

 Workup C: The reaction mixture is optionally neutralized by the addition of hydrochloric acid. The solvent is removed either by concentration at reduced pressure or lyophilization. The resulting residue containing the desired acid—either free or as a sodium salt contaminated with inorganic salts—is purified by chromatography.

[a] Other TEMPO derivatives such as 4-AcO-TEMPO (MW 214.28), 4-HO-TEMPO (MW 172.24), or 4-AcNH-TEMPO (MW 213.30) are equally effective.

[b] A quantity as high as 1–1.5 equivalents of TEMPO is sometimes employed in order to mitigate some side reactions induced by the stoichiometric oxidant, such as unwanted chlorinations.[22a,b, 28]

[c] Sodium hypochlorite is sold as a ca. 3–13% aqueous solution (chlorine bleach) containing some NaOH to provide a pH of 11–13, which helps to stabilize the reagent against disproportionation in NaCl and $NaClO_3$. Household bleach is perfectly effective.

[d] KBr is added to generate HOBr, which is a more effective secondary oxidant than HOCl. Failure to add KBr leads to a slower oxidation that nevertheless may prove useful. NaBr is equally effective.

[e] Quaternary ammonium salts such as n-Bu$_4$NCl (MW 277.9),[29] n-Bu$_4$NBr (MW 322.37),[30] n-Bu$_4$NHSO$_4$ (MW 339.53),[19] or Aliquat® 336 (tricaprylylmethylammonium chloride, MW 404.17)[31] are used as phase-transfer catalysts. Failure to add a phase-transfer catalyst results in a much slower reaction that may lead to isolation of aldehyde. No phase-transfer catalyst is needed when the oxidation is performed in a monophasic system.

[f] The addition of bleach causes the mixture to reach a very basic pH that may prove detrimental for many substrates. Thus, although the oxidation velocity increases under basic conditions, the pH is normally lowered to ca. 8.5–10 in order to attain a good balance of oxidation speed versus base-induced deleterious side reactions. The optimum pH is very substrate dependent. When the selective oxidation of a primary alcohol in the presence of a secondary one is desired, a pH as high as 11.7 may be advisable.[34b] On the other hand, in oxidations occurring in the presence of esters the pH must be lowered to 8–9 to avoid unwanted hydrolysis.

[g] The pH is normally lowered to 8.6–10 by the addition of an aqueous solution of $NaHCO_3$ possessing a concentration between 5% and saturation. A higher pH can be adjusted by the subsequent addition of aqueous NaOH. A final fine tuning of the pH can require the addition of some HCl. A phosphate buffer is sometimes used. The formation of carboxylic acid in the course of the oxidation leads to lowering of pH as the reaction proceeds, causing a decrease in the oxidation rate. This can be avoided by the sequential addition of some aqueous NaOH.

[h] A ca. 7:2 to 3:5 water:CH_2Cl_2 mixture is normally employed. Normally, ca. 15–60 mL of solvent mixture is used per mmol of alcohol. Sometimes, ca. 2–19 mL of brine per mmol of alcohol is also added. The reaction can also be performed in a monophasic system consisting of water, water:acetone (ca. 3:4 to 7:4), or water:MeCN (ca. 29:26 to 9:5). In a water:CH_2Cl_2 biphasic system the oxidation takes place in the organic phase, therefore, this system is very suitable for lipophilic substrates but fails in substrates—like most sugars—possessing a high solubility in water. In such cases the oxidation is best carried out in water or in a monophasic solvent mixture.
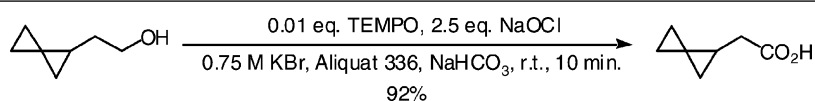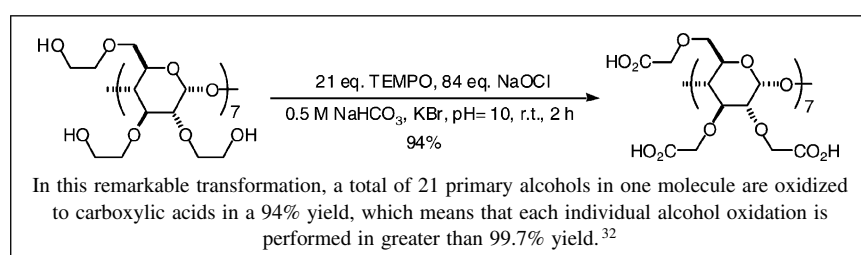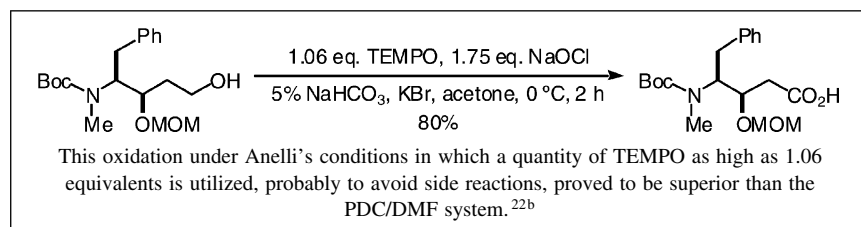
An attempted oxidation using Jones reagent resulted in extensive decomposition due to the acid-sensitivity of the spiro system. The employment of Anelli's oxidation under mildly basic conditions allowed the isolation of the desired acid in very good yield.[31a]
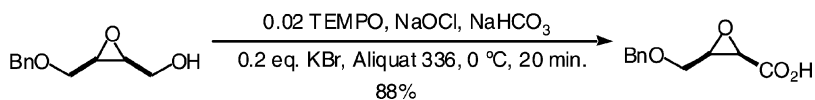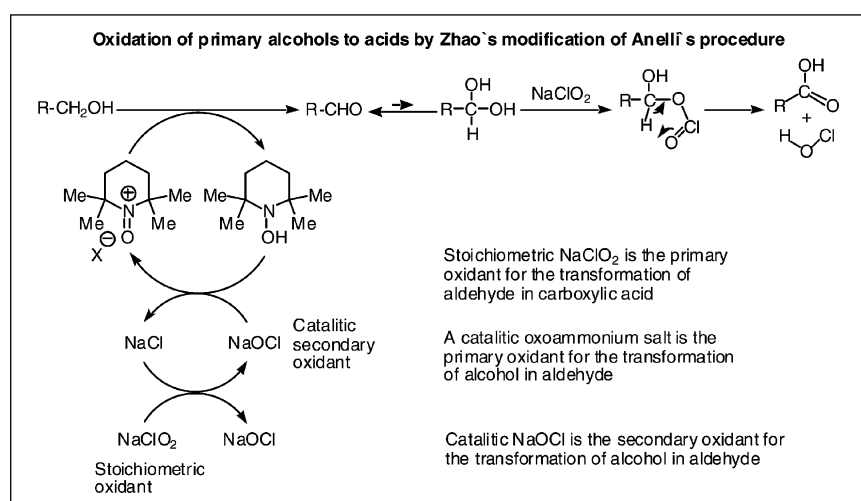

According to the authors: "Oxidation of the hydroxymethyl function to a carboxylic acid, without simultaneous oxidation of the benzyl to a benzoyl group, proved to be a challenging problem. Neither pyridinium dichromate in dimethylformamide nor Jones oxidation gave the desired product in acceptable yield. Oxidation with ruthenium tetraoxide predictably gave a mixture of the benzyl- and the benzoylepoxy acids. The problem was overcome by oxidation with hypochlorite in the presence of catalytic amounts of oxoammonium salt generated from 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, free radical). The product, (2R, 3R)-3-(benzyloxy)methyloxirane-2-carboxylic acid, was obtained in excellent yield (88%) and high purity."[31b]

According to the authors: "Problems were encountered in the attempted oxidation of the primary alcohol to a carboxylic acid. After screening of various oxidation methods, the oxoammonium salt mediated oxidation using a couple TEMPO-NaOCl was selected for further optimization. Chlorination of the electron-rich aromatic ring was found to be the major side reaction. However, when the reaction temperature was carefully maintained between −5 °C and 0 °C, the desired acid was obtained in good yield."[35]

This oxidation under Anelli's conditions in which a quantity of TEMPO as high as 1.06 equivalents is utilized, probably to avoid side reactions, proved to be superior than the PDC/DMF system.[22b]

In this remarkable transformation, a total of 21 primary alcohols in one molecule are oxidized to carboxylic acids in a 94% yield, which means that each individual alcohol oxidation is performed in greater than 99.7% yield.[32]

6.3. Zhao's Modification of Anelli's Oxidation

In 1999, Zhao *et al.* published[4] a variation of Anelli's procedure for the transformation of primary alcohols into carboxylic acids, in which side reactions induced by the presence of sodium hypochlorite were lessened by using this reagent in catalytic rather than stoichiometric quantity. In this modified procedure sodium chlorite ($NaClO_2$) is employed as stoichiometric oxidant, which serves both to regenerate NaOCl and to operate as the primary oxidant[36] for the transformation of the intermediate aldehyde into carboxylic acid. The mechanism represented in the following scheme indicates the catalytic cycles in this oxidation:

Oxidation of primary alcohols to acids by Zhao`s modification of Anelli`s procedure

Stoichiometric $NaClO_2$ is the primary oxidant for the transformation of aldehyde in carboxylic acid

A catalitic oxoammonium salt is the primary oxidant for the transformation of alcohol in aldehyde

Catalitic NaOCl is the secondary oxidant for the transformation of alcohol in aldehyde

Interestingly, there is no need for sodium chlorite to regenerate directly NaOCl by oxidation of NaCl, because as soon as some aldehyde is formed, the aldehyde is very quickly oxidized by sodium chlorite resulting in the formation of NaOCl. Thus, NaOCl is in fact regenerated via oxidation of the aldehyde. If the reaction is carried out in the absence of added NaOCl, there is a long induction period during which $NaClO_2$ generates the aldehyde in a very inefficient way. Once some aldehyde is formed, it is very quickly oxidized by $NaClO_2$, resulting in the formation of NaOCl that is very efficient in the generation of an N-oxoammonium salt, resulting in a very quick acceleration of the whole oxidation.

Zhao *et al*. optimized the reaction conditions seeking to minimize unwanted chlorinations rather than increasing the oxidation speed. This resulted in an oxidation protocol involving the simultaneous addition of $NaClO_2$ and catalytic NaOCl in the form of dilute bleach to a stirred mixture kept at 35 °C, containing the alcohol, acetonitrile, an aqueous phosphate buffer at pH 6.7, and catalytic TEMPO. WARNING: sodium chlorite and bleach must not be mixed before being added to the reaction, because the resulting mixture is unstable. Subsequent authors tended to follow very closely the original oxidation protocol of Zhao *et al*.

Zhao's modification of Anelli's oxidation is reported[4] to give generally better yields of carboxylic acids than the original Anelli's procedure. WARNING: Zhao's procedure involves the use of stoichiometric $NaClO_2$, which is a very powerful oxidant that can explode in the presence of organic matter. Therefore, Zhao's procedure must be employed, particularly on a big scale, only on substrates for which it proves to be clearly superior.

6.3.1 General Procedure for Oxidation of Primary Alcohols to Carboxylic Acids by Zhao's Modification of Anelli's Oxidation

WARNING: $NaClO_2$ and NaOCl must not be mixed before being added to the reaction because the resulting mixture is unstable.

Approximately, from 2 to 5—typically 2—equivalents of aqueous ca. 1.1–2 M $NaClO_2$ (MW 90.44)[a] and ca. 0.02–0.32—typically 0.02—equivalent of NaOCl (MW 74.44) contained in ca. 0.28–0.65%—typically 0.30%—bleach[b] are slowly[c] added over a vigorously stirred mixture, kept at a certain temperature between room temperature and 45 °C,[d] typically 35 °C, containing 1 equivalent of the alcohol, ca. 0.07–0.125—typically 0.1—equivalent of TEMPO (MW 156.25), acetonitrile,[e] and a phosphate buffer at pH 6.6–6.8.[f,g] The resulting mixture is stirred at a certain temperature between 35 and 50 °C until most of the starting alcohol is consumed.[h]
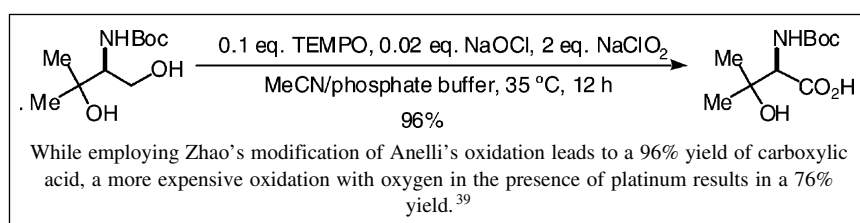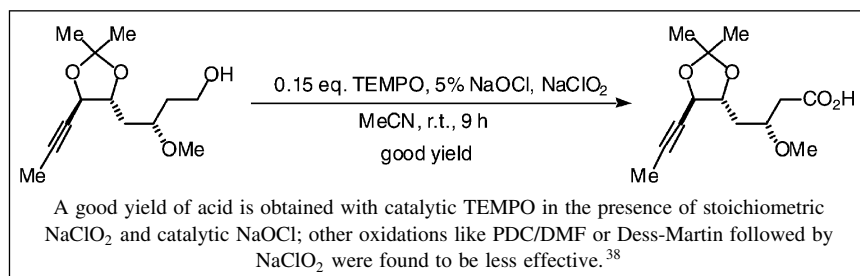
The reaction mixture is cooled to room temperature. At this point the addition of some (cold) water may help to carry out the rest of the workup.

The reaction mixture is basified to pH 8–9 by the addition of 0.05–2 M NaOH, and is quenched by mixing with a cold sodium sulfite (Na_2SO_3) aqueous solution, followed by stirring for 30 minutes. The mixture is washed with an organic solvent such as methyl *t*-butyl ether (MTBE), EtOAc, or Et_2O. The organic solutions must be checked for the presence of product, because very lipophilic organic acids can be washed away by organic solvents even from very basic aqueous solutions. The aqueous phase is acidified to a pH of 2–4 by the addition of 1–2 M HCl and extracted with an organic solvent such as EtOAc, Et_2O, MTBE, or CH_2Cl_2. If the organic phase from the washing of the aqueous basic solution contains product, all organic phases must be united for further workup. After optionally washing the organic phase containing the product with water and brine, it is dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a crude acid that may need further purification. The workup can be simplified by avoiding the quenching with sodium sulfite and the washing of the basified aqueous solutions with an organic solvent. This may lead to a more impure crude product.

[a] WARNING: $NaClO_2$ can explode in contact with organic matter.

[b] Household chlorine bleach is perfectly effective. The desired concentration of NaOCl is normally attained by diluting commercial bleach with some water.

[c] The $NaClO_2$ and NaOCl solutions can be added either simultaneously or sequentially beginning with $NaClO_2$. The addition is normally performed over a period between 15 minutes and 2 hours.

[d] Zhao *et al*. recommend a temperature of 35 °C. Other researchers utilize a slightly higher temperature of ca. 45–50 °C. It must be mentioned that the oxoammonium salts primary oxidants are unstable in hot water and increasing the temperature may lead to decreased reaction rate.

[e] A quantity of ca. 2.2–11.5—typically 5—mL of acetonitrile per mmol of alcohol is normally employed.

[f] An amount of ca. 1.7–5.5—typically 3.75—mL of phosphate buffer per mmol of alcohol is normally used.

[g] A phosphate buffer at pH 6.8 (35 °C) consists of an aqueous solution containing 0.025 M Na_2HPO_4 and 0.025 M KH_2PO_4.

[h] It normally takes between 4 and 24—typically 5—hours.
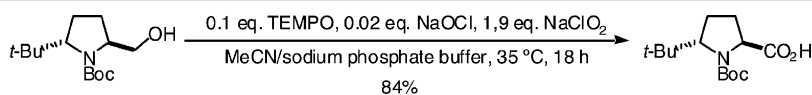
Although the oxidation could be carried out in 86% yield using $RuCl_3$ and $NaIO_4$, Zhao's modification of Anelli's procedure was preferred on a big scale.[37]

A good yield of acid is obtained with catalytic TEMPO in the presence of stoichiometric NaClO$_2$ and catalytic NaOCl; other oxidations like PDC/DMF or Dess-Martin followed by NaClO$_2$ were found to be less effective. [38]

While employing Zhao's modification of Anelli's oxidation leads to a 96% yield of carboxylic acid, a more expensive oxidation with oxygen in the presence of platinum results in a 76% yield. [39]

6.4. Oxidation of Epp and Widlanski

In 1997, Margarita, Piancatelli *et al*. reported[6c] the oxidation of alcohols to *aldehydes* and ketones using catalytic TEMPO in the presence of 1.1 equivalents of bis(acetoxy)iodobenzene (BAIB)—that is, PhI(OAc)$_2$—as stoichiometric secondary oxidant. According to the authors, under those conditions no noticeable overoxidation to carboxylic acid is detected, even when the reaction is carried out without employing an inert atmosphere and a dry solvent. In fact, Margarita and Piancatelli described one successful oxidation to aldehyde in which a MeCN:water (1:1) mixture is utilized as solvent. Two years later, Epp and Widlanski reported[5] that it is possible to obtain a carboxylic acid from a primary alcohol using the procedure of Margarita and Piancatelli, when the reaction is performed with at least 2 equivalents of BAIB in the presence of excess of water. They reported a successful protocol for the oxidation of primary alcohols to carboxylic acids involving 2.2 equivalents of BAIB and catalytic TEMPO in MeCN:water (1:1). This oxidation procedure for the obtention of carboxylic acids is rather unique, because it is carried out in the total absence of any inorganic salt and the by-products are the rather innocuous iodobenzene and acetic acid.
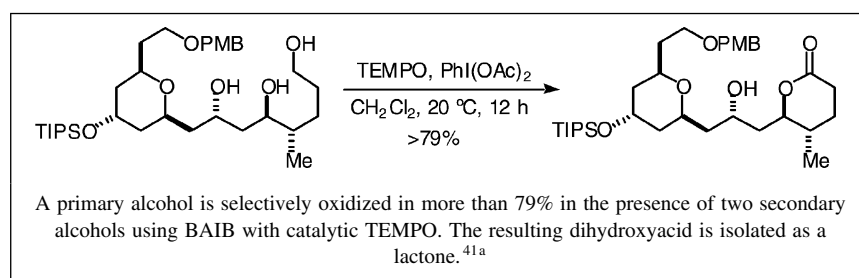
Mechanism

A mechanism consistent with the experimental facts is shown in the following scheme.

Oxidation of primary alcohols to acids by the procedure of Epp and Widlanski
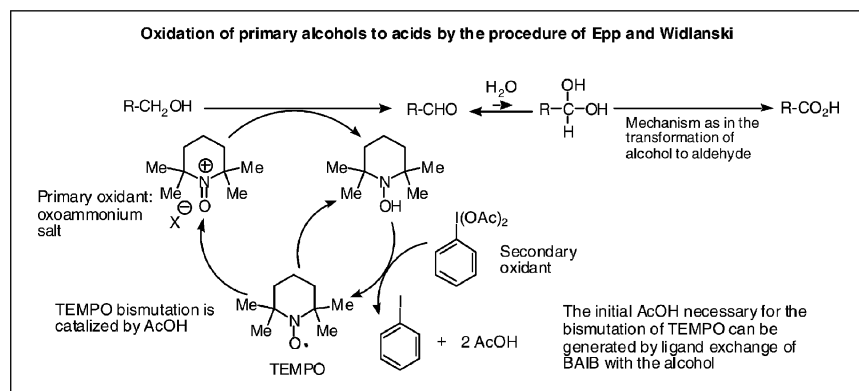
Apparently, BAIB does not oxidize directly TEMPO to the corresponding oxoammonium salt primary oxidant. Rather, TEMPO suffers an AcOH-catalyzed bismutation to an oxoammonium salt and hydroxylamine, the latter being oxidized to TEMPO by BAIB, resulting in the generation of AcOH. The initial AcOH necessary for the formation of the first molecules of oxoammonim salt can be generated by ligand exchange of PhI(OAc)$_2$ with the alcohol.

Selectivity

Although at the time of this writing the reports of selective oxidation of primary alcohols in the presence of secondary ones with TEMPO/BAIB are rather scarce,[40] it seems that this oxidation system shows a great potential for this selective transformation. The resulting hydroxyacids are very often isolated as lactones, and TEMPO/BAIB is a very good reagent for the conversion of 1,4- and 1,5-diols to lactones.[40b, 41]

A primary alcohol is selectively oxidized in more than 79% in the presence of two secondary alcohols using BAIB with catalytic TEMPO. The resulting dihydroxyacid is isolated as a lactone.[41a]

6.4.1 General Procedure for Oxidation of Primary Alcohols to Carboxylic Acids by the Protocol of Epp and Widlanski

Approximately, from 0.2 to 0.3—typically 0.2—equivalent of TEMPO (MW 156.25) and ca. 2.2–4.2—typically 2.2—equivalents of bis(acetoxy)iodobenzene[a] (BAIB, MW 322.1) are added to a solution of the alcohol in a MeCN:water (1:1) mixture,[b,c] containing ca. 0.06–0.28 mmol of alcohol per mL of mixture. The resulting mixture is stirred at room temperature[d] until most of the alcohol or the intermediate aldehyde is consumed.[e] The carboxylic acid sometimes precipitates from the reaction mixture and can be very easily isolated in high purity by simple filtration. Otherwise, the reaction can be optionally quenched by addition of 5–10% aqueous $Na_2S_2O_3$ and the rest of the workup can proceed according to two alternative protocols:

   Workup A:

   The reaction mixture is concentrated, giving a crude acid containing iodobenzene[f] and other by-products that must be separated for example by chromatography.

   Workup B:

   The reaction mixture can be optionally acidified by the addition of hydrochloric acid. It is extracted with an aqueous solvent such as EtOAc or Et_2O. The organic phase can be optionally washed with water and brine. The resulting organic solution is dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a crude carboxylic acid that may need further purification.

[a] BAIB possesses the following ^{1}H-NMR (δ, $CDCl_3$, ppm): 8.13–7.45 (m, 5H, ArH), 2.01 (s, 6H, $MeCO_2$).[42]

[b] A CH_2Cl_2:water mixture can also be employed.[43]

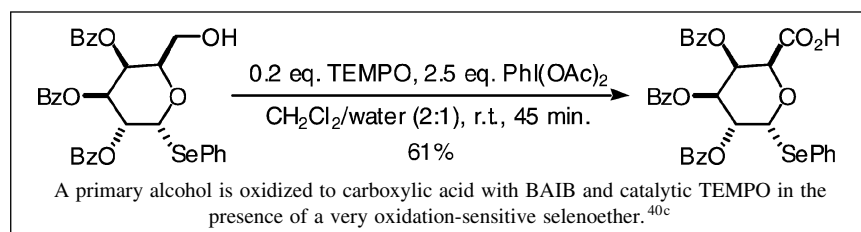[c] It is sometimes beneficial to add 1 or 2 equivalents of $NaHCO_3$ to the reaction mixture.[5]

[d] Better yields are sometimes obtained performing the reaction at 0 °C, a temperature at which the oxoammonium salt primary oxidant shows a greater stability in the presence of water.

[e] It normally takes between half an hour and 1 day.

[f] Iodobenzene possesses the following ^{1}H-NMR (δ, $CDCl_3$, ppm): 8.19 (s, 1H), 7.81 (s, 1H).[44]
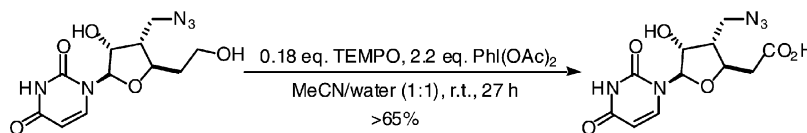
A primary alcohol is selectively oxidized in the presence of a secondary alcohol and a sensitive uracil residue, using BAIB and catalytic TEMPO.[40a]

A primary alcohol is oxidized to carboxylic acid with BAIB and catalytic TEMPO in the presence of a very oxidation-sensitive selenoether.[40c]
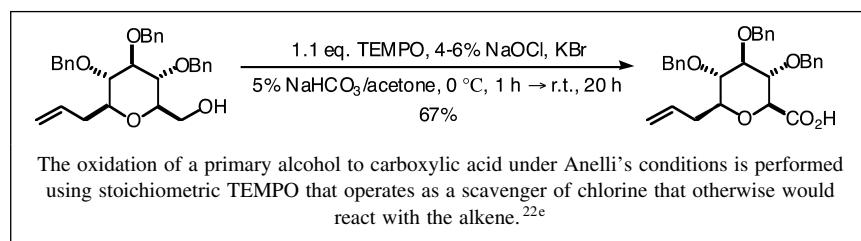
6.5. Functional Group and Protecting Group Sensitivity to TEMPO-Mediated Oxidations

The transformation of primary alcohols into acids using Anelli's protocol involves more severe conditions than the analogous oxidation of alcohols to aldehydes and ketones.[22e]

TEMPO-mediated oxidations using Anelli's protocol are normally performed at a pH of ca. 8.6–10. This moderately basic pH is compatible with acid-sensitive functional groups and with most base-sensitive ones. Esters normally resist[40c, 45] the conditions of Anelli's oxidation, including the very base-sensitive acetate esters.[25] However, it is sometimes advisable to minimize the reaction time to prevent hydrolysis of acetates.[29a] Not surprisingly, esters are fully compatible with the almost neutral conditions of TEMPO-mediated oxidations by the method of Epp and Widlanski.[40c, 46]

Normally, Anellis's oxidation is not compatible with the presence of olefins, because usually they react very easily with NaOCl. Nevertheless, there is one report[22e] in which a primary alcohol is oxidized to acid in the presence of an alkene due to the use of stoichiometric—rather than catalytic—TEMPO that, therefore, is able to act as a chlorine scavenger.

Alkynes remain unchanged under TEMPO-mediated oxidations.[4, 47]

The oxidation of a primary alcohol to carboxylic acid under Anelli's conditions is performed using stoichiometric TEMPO that operates as a scavenger of chlorine that otherwise would react with the alkene.[22e]

Olefins conjugated with carbonyl groups are much less reactive against HOCl, and, therefore, remain unchanged under TEMPO-mediated oxidations.[34a, 48]

It is possible to transform primary alcohols into acids in the presence of sulfides and selenides, which fail to react in spite of their general sensitivity to oxidation.[40c]
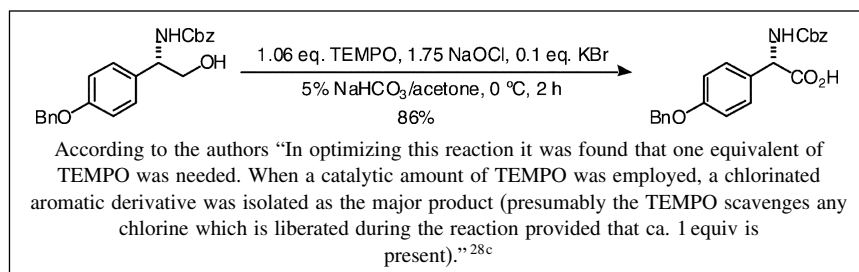
Formation of neither lactones nor lactols has been reported when 1,4-[8, 9b, 34a, 49] and 1,5-diols[8, 14, 34b, 50] are oxidized under TEMPO-mediated conditions, unless the condition of Epp and Widlanski are used. In this case, good yields of lactones can be obtained.[40b, 41]
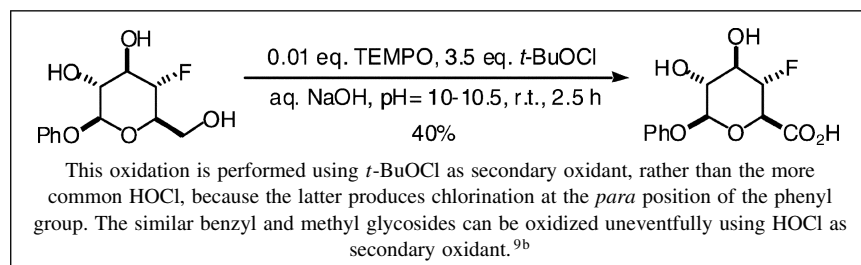
6.6. Side Reactions

A very common lateral reaction in oxidations under Anelli's protocol is the chlorination of aromatic rings and alkenes, due to the presence of HOCl. This reaction can be mitigated by:
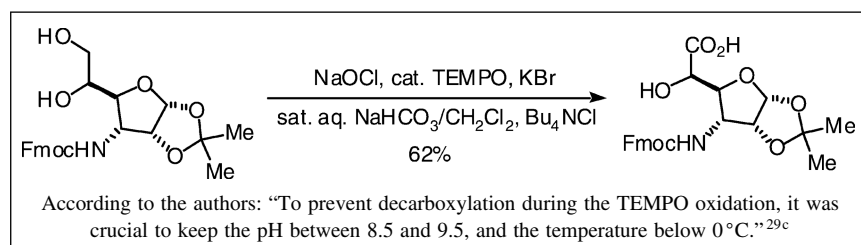
- Addition of a stoichiometric quantity of TEMPO, which acts as scavenger of chlorine.[22a, 28c]
- Addition of a secondary oxidant different from NaOCl, such as t-BuOCl.[9b]
- Lowering the reaction temperature to -5 to $0\,°C$.[35]
- Using Zhao's modification of Anelli's oxidation, in which $NaClO_2$— a much weaker chlorinator than HOCl—serves as stoichiometric secondary oxidant; HOCl being present in catalytic quantities and, therefore, much less able to produce undesired chlorinations.[4]

For obvious reasons, no chlorinations are possible in TEMPO-mediated oxidations performed under the protocol of Epp and Widlanski, in which $PhI(OAc)_2$ is used as secondary oxidant, rather than HOCl.

According to the authors "In optimizing this reaction it was found that one equivalent of TEMPO was needed. When a catalytic amount of TEMPO was employed, a chlorinated aromatic derivative was isolated as the major product (presumably the TEMPO scavenges any chlorine which is liberated during the reaction provided that ca. 1 equiv is present)."[28c]

This oxidation is performed using *t*-BuOCl as secondary oxidant, rather than the more common HOCl, because the latter produces chlorination at the *para* position of the phenyl group. The similar benzyl and methyl glycosides can be oxidized uneventfully using HOCl as secondary oxidant.[9b]

Sometimes, carboxylic acids obtained by Anelli's oxidation suffer *in situ* decarboxylation. This can be avoided by proper adjustment of pH and maintaining low temperature.[29c]

According to the authors: "To prevent decarboxylation during the TEMPO oxidation, it was crucial to keep the pH between 8.5 and 9.5, and the temperature below 0 °C."[29c]

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