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Chemo and regioselective oxidation of secondary alcohols in vicinal diols

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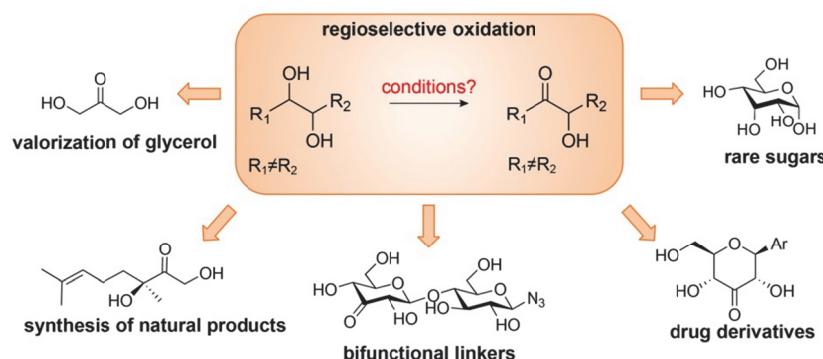
Abstract Oxidation of secondary hydroxyl groups in vicinal diols enables the straightforward functionalization of biomolecules and biomaterials. The resulting hydroxy ketone can for example be used to form derivatives, such as the epimeric alcohol and imines, and it may be employed for chemical probe synthesis. Regioselectivity becomes an essential factor when this strategy is applied on compounds containing multiple hydroxyl groups, such as carbohydrates. Large advances have been made in this field in the past decade, which led to the development of novel methodologies that enable selective oxidation of secondary hydroxyl groups of 1,2-diols in complex molecules and that have complementary regioselectivities. We here discuss these recent advances as well as some of the limitations. Future research should focus on addressing these issues, which will eventually lead to methods for the chemo and regioselective oxidation of complex oligosaccharides.

Key words 1,2-diols, chemoselectivity, oxidation, chelates, glycosides, palladium, regioselectivity

Introduction. Oxidation of alcohols is one the most well studied reactions in organic chemistry and even up to this day, new and improved methods are being reported, highlighting the need and desire for faster, more efficient and especially more selective methods. The chemo and/or regioselective oxidation of complex molecules that have multiple oxidation sensitive groups is still not an easy feat and in particular 1,2-diols prove to be challenging substrates. Side reactions, like C-C bond fission, tautomerization of the resulting α-hydroxy ketone (or carbonyl transposition) and over-oxidation, are commonly observed for these substrates.

Vicinal diols are commonly found in natural products with carbohydrates being the prime example and oxidation of these diols into α-hydroxy ketones forms an attractive means to functionalize and modify these natural products. To achieve this, the field has largely relied on protecting group strategies. All hydroxyl groups in the substrate except for the hydroxyl group of interest are protected and the latter is subsequently oxidized using conventional methods. Regioselective approaches overcome the need of laborious protecting group manipulations. These may therefore be applied for the late stage functionalization of vicinal diol-containing natural products, in a similar fashion as C-H activation has been used to block metabolism to generate metabolites, to synthesize probe molecules and for structure-activity relationship studies.[1]

Key to the successful application of oxidation chemistry in complex biomolecules is the ability to use the inherent differences in reactivity of the various hydroxyl groups. Selective oxidation of the more accessible primary alcohol of a (vicinal) diol is readily achieved with a number of sterically hindered oxidizing agents, such as TEMPO, and these methods have shown to be highly selective.[2,3] Furthermore, ruthenium(PPh₃)(OH) salen complexes have been described for the aerobic oxidation of primary alcohols under ambient conditions.[4] Obtaining selectivity for secondary alcohols in vicinal diols is less straightforward, even though secondary alcohols have a lower oxidation potential. As highlighted by Arterburn, the Corey-Kim oxidation[5], Swern type oxidations[6], dimethyldioxirane[7] and several transition metal catalysts in combination with an oxidant are effective methods for the chemoselective oxidation of the secondary alcohol, although the selectivity varies.[8] For more complex substrates that contain multiple secondary alcohol groups, the selectivity is often significantly lower. Chelation control has been used to improve the chemo and regioselectivity for 1,2-diols over the remaining hydroxyl groups.[9]

Pushed by the need for more sustainable oxidation methods, the focus of the field shifted to the development of catalytic oxidation reactions that preferably employ dioxygen or hydrogen peroxide as the (co)oxidant and water as a solvent. In this review, we discuss the recent advances made in the field with a particular emphasis on the chemoselective oxidation of non-activated secondary hydroxyl groups in vicinal diols. Benzylic vicinal diols readily oxidize with high selectivity and will therefore not be discussed. Both modified procedures of

well-known oxidation methods and novel oxidation methods will be discussed. Special attention will be given to oxidation methods that are based on chelation control. These methods often show increased selectivity and enhanced rates for the oxidation of vicinal diols and are therefore often more selective in the oxidation of substrates bearing multiple hydroxyl groups. These methods are inherently suitable for the application in more complex molecules such as in carbohydrate chemistry and the synthesis of renewables from feedstocks.

General methods to oxidize simple vicinal diols

The methods that have an inherent preference for secondary alcohols have been successfully applied on simple vicinal diols. However, these methods have their limitations, such as harsh conditions, the use of toxic reagents and small substrate scopes. In the past decade, several modified procedures that address these issues have been developed. A limitation of most DMSO-based oxidation methods is that these require strictly anhydrous conditions and consequently, the use of these methods is limited to compounds that are soluble in aprotic solvents. To oxidize 1,2-diols in aqueous solutions with DMSO, the group of Konwar developed a modified procedure which employs *in situ* generated HI, formed from hydrazine and iodine, to activate DMSO.[10] Hydroxyacetone and dihydroxyacetone can be synthesized from glycerol and 1,2-propanediol in moderate yields using this procedure.

Also chromium-based reagents have shown to be suitable oxidants for the oxidation of the secondary alcohol in simple 1,2-diols. Grinding (±)-3-chloro-1,2-propanediol with one equivalent of pyridinium fluorochromate at room temperature in the absence of solvent results in the selective oxidation of the secondary alcohol and 1-hydroxy-3-chloropropanone can be isolated in 87% yield.[11] Stoichiometric amounts of the highly toxic chromium-based oxidant are needed to achieve full oxidation, however. To lower the amount of chromium reagent required, a method that employs catalytic amounts of 3,5-dimethylpyrazolium fluorochromate (DmpzHFC) **1** in combination with hydrogen peroxide as the co-oxidant has been developed by Chaudhuri and co-workers (Figure 1).[12,13] Oxidation of (±)-3-chloro-1,2-propanediol using this modified procedure gave the resulting α-hydroxy ketone in a comparable yield as the stoichiometric procedure and again, exclusive oxidation of the secondary position was observed. In order to completely abandon chromium oxidants, Garonne and coworkers studied if iron(III) reagents could be used instead. Hydrogen peroxide in the presence of a catalytic amount of FeBr₃ oxidized octane-1,2-diol, both in acetonitrile and under solvent free conditions, to the keto product with complete selectivity.[14] Since this method only was tested on octane-1,2-diol, Bauer and coworkers aimed to develop a broadly applicable approach for the iron-catalyzed chemoselective oxidation. They screened several iron (II) complexes that can oxidize alcohols using H₂O₂ as an oxidant for their activity and their selectivity for secondary alcohols over primary alcohols.[15] Bis(picolyl)amine iron(II) catalyst **3** showed excellent activity at room temperature (Figure 2). Using hydrogen peroxide (2.6 eq) as the internal oxidant, a range of diols including several vicinal diols could be oxidized in good yields (75 – 84%) within 15 minutes. Longer reaction times led to oxidation of the primary hydroxyl group as well.

Farnetti and coworkers applied iron catalyst **3** in the oxidation of glycerol.[16] Initial experiments led to 46% overall conversion and approximately a one-to-one mixture of dihydroxyacetone and formic acid was obtained. Lowering the reaction temperature, excess of H₂O₂ and using a 10% solution of H₂O₂ increased the selectivity for dihydroxyacetone, albeit at the expense of the conversion (∼20%).
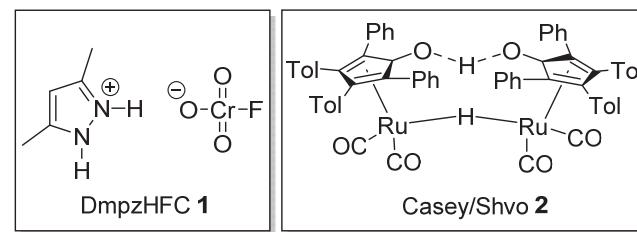

Figure 1, Overview of oxidation catalyst.
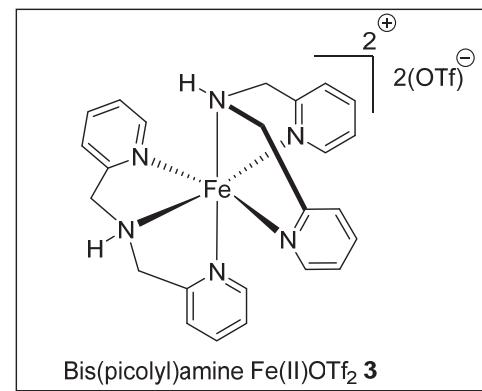
Figure 2, Bis(picolyl)amine Fe(II)OTf₂ **3**

Besides iron and chromium reagents, also polyoxometalates have been used as catalysts for the chemoselective oxidation of vicinal diols with hydrogen peroxide. Wang demonstrated that Na₄H₃[SiW₉Al₃(H₂O)₃O₃₇]·12H₂O is an excellent, recyclable catalyst.[17] Full conversion is reached within 10 h by performing the reaction neat with hydrogen peroxide as the co-oxidant. Upon complete conversion, the reaction mixture is extracted with an organic solvent and the aqueous layer can be reused for a successive oxidation reaction.

Finally, ruthenium-based methods have been developed to oxidize vicinal diols. Plietker utilized *in situ* generated RuO₄ for the synthesis of enantiopure α-hydroxy ketones starting from alkenes.[18] Asymmetric Sharpless dihydroxylation of the alkene followed by a regioselective catalytic monooxidation of the isolated vicinal diol using 1 mol% of RuCl₃ in combination with an internal oxidant gives the desired α-hydroxy ketones in high isolated yields (∼90%) and high ee's within 1 hour. The nature of the oxidant has a large effect on the outcome of the reaction. NaIO₄ and NaBrO₃ gave a large amount of C-C bond fission, while Oxone gave the desired α-hydroxy ketone as major product.

More recently, the catalytic dehydrogenation of 1,2- and 1,3-diols with Casey/Shvo catalyst **2** was studied, with the aim to convert lignocellulose into useful fine chemicals (Figure 1).[19] When Ford and coworkers performed the reaction in a closed vessel, low conversions were obtained (∼0.25%). However, refluxing the reaction mixture in diglyme under air resulted in a
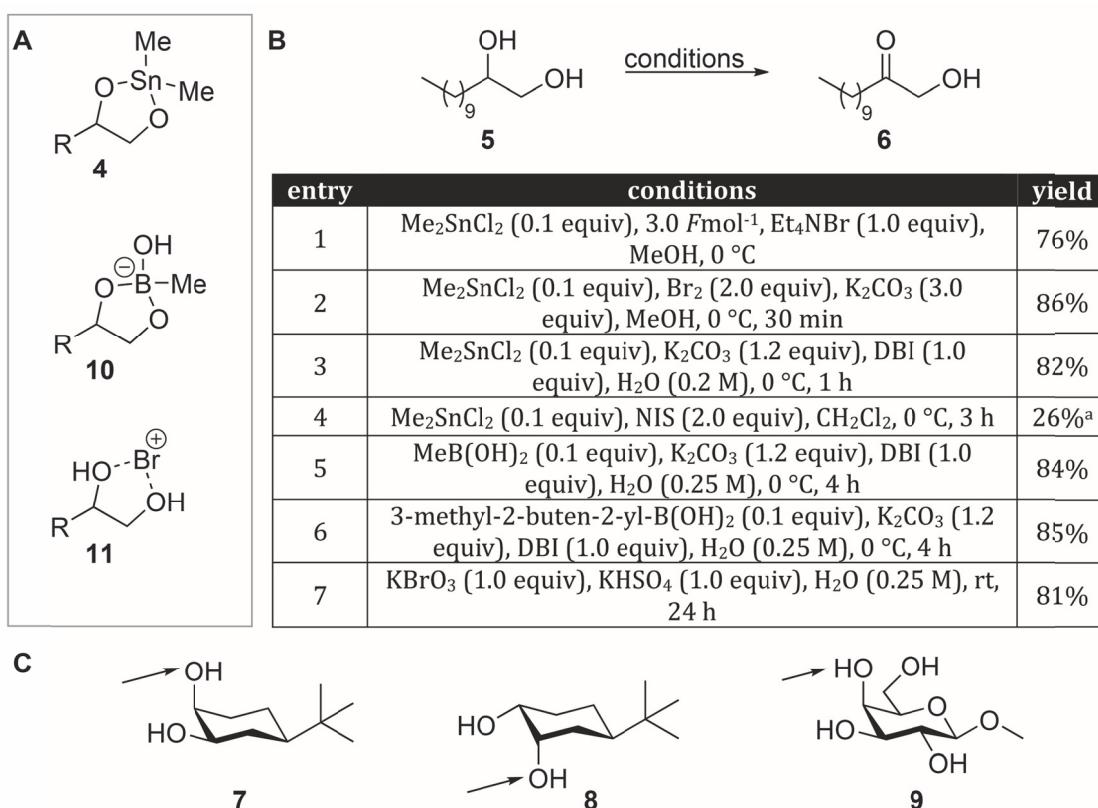
Scheme 1, overview of chelation-controlled oxidation methods. (A) Proposed modes of chelation. (B) Oxidation of the model substrate 1,2-dodecanediol with different methods. [a] Low yields are obtained when oxidizing dodecanediol **5** with NIS, but yields for the oxidation of 1,2,6-hexanetriol with NIS or bromine are comparable. (C) Selectivity in vicinal secondary diols of cyclic substrates. Arrows indicate the alcohol functionality that is preferentially oxidized. For cyclohexane diols see ref [20] and for galactosides see ref [21].

significant increase (~40% conversion) and they therefore hypothesized that the elevated temperatures facilitate the elimination of H_2 from the catalyst. By employing cyclohexanone, as a hydrogen acceptor, the conversion towards the α-hydroxy ketone increased further to 64% within 10 minutes. Again simple vicinal diols (1,2-propanediol and 1,2-butanediol) were tested and these showed isolated yields around ~70%.

Other reagent combinations and catalysts have been reported to selectively oxidize secondary alcohols in the presence of primary alcohols. Examples include the polymeric phosphotungstate catalyst reported by Uozumi and co-workers,[22] 2-iodoxybenzoic acid (IBX) oxidations in the presence of a catalytic amount cyclodextrin,[23] IBX oxidations under phase transfer conditions,[24] oxidations using a combination of TEMPO-TBAB-H_5IO_6 on wet alumina,[25] and finally oxidations with bromide salts in the presence of peroxides,[26–28] but most of these methods have not been employed for the oxidation of aliphatic vicinal diols.

While most of the methods that have a preference for secondary diols can be applied on simple substrates that contain 1,2-diols, the oxidation of substrates that contain more hydroxyl groups either has not been studied or the methods are not suitable for these substrates.

Chelation-controlled oxidation

Reagents that chelate to or coordinate vicinal diols have been used to enhance the selectivity for the secondary hydroxyl unit of a vicinal diol over the other hydroxyl groups in the molecule of interest. Already in early 70's, David *et al.* showed that stannyl ethers and stannylene acetals (compound **4**, Scheme 1A), formed by refluxing di- and triorganotin compounds with 1,2-diols can be oxidized to α-hydroxy ketones with halonium oxidants.[9]

In cyclic substrates, stannylenes also have shown to improve the regio- and stereoselectivity. The axial hydroxyl group of *cis*-diols in cyclic substrates is more accessible for the oxidant and is therefore preferentially oxidized over the equatorial hydroxyl group. This stereoselectivity has been exploited for the regioselective oxidation of monosaccharides.[29,30] Arabinosides, galactosides and mannosides have been successfully converted into the corresponding C2 and C4 ketoglycosides using stoichiometric amounts of (bis)tributyltin oxide and bromine.[29] To lower the amount of toxic organostannanes being used, Onomura and coworkers developed an electrochemical oxidation method.[31] A catalytic amount of dibutyltin oxide (10 mol%) gave good conversion, but the stannylene acetal still had to be generated *in situ* prior to oxidation, due to the poor solubility of dibutyltin oxide. In the past decade, a variety of trialkyl and dialkyl organotin compounds have been screened for their ability to mediate the oxidation of vicinal diols without preheating the reaction mixture.[20] All of the organotin derivatives studied by Onomura and coworkers oxidized cyclic diols in reasonable to good yields in methanol, but only a subset was suitable for the oxidation of acyclic diols. Of these, dimethyltin dichloride proved to have the best catalytic activity, most likely due to its increased solubility in methanol compared

to dibutyltin oxide and its higher reactivity for tin acetal formation. With this catalyst, 1,2-Dodecanediol **5** is efficiently converted into corresponding hydroxymethyl ketone **6** using electrochemically generated "Br+" (Scheme 1B, entry 1) or reagents like bromine and dibromoisocyanuric acid (DBI), as oxidants (Scheme 1B, entry 2 and 3). Oxidation of diol **5** with NIS gave ketone **6** in low yields (Scheme 1B, entry 4), but this oxidant has successfully been applied to 1,2,6-hexanetriol.

The selection of the oxidant largely depends on the solvent being used in the reaction. NIS generally gives the highest yields in ethyl acetate, dichloromethane and acetonitrile, while a combination of bromine and potassium carbonate is the reagent system of choice in methanol.[20] Finally, DBI or bromine are the most suitable oxidants for the oxidation of 1,2-diols in water.[32] As little as 0.5 mol% of dimethyltin dichloride is sufficient to synthesize α-hydroxy ketones from simple linear diols in methanol,[20] but catalyst loadings up to 10 mol% are needed to oxidize more complex diols or to perform the reaction in water.[32] The regio-, chemo- and stereoselectivity of reactions performed with a catalytic amount of organotin are comparable to those with preformed organostannanes. The secondary hydroxyl group of 1,2-diols is exclusively oxidized. Primary and tertiary hydroxyl groups and 1,3-diols do not react, and the axial hydroxyl group of *cis*-diol motifs in cyclic substrates **7** and **8** is oxidized preferentially (Scheme 1C).[20]

Muramatsu recently demonstrated that catalytic tin-mediated oxidation is also applicable on a range of glycosides.[21] Dioctyltin dichloride rather than dimethyltin dichloride gives the best yields for glycosides. Trimethylphenylammonium tribromide ([TMPhA]+ Br3-) in THF/MeOH in the presence of 2 mol% of organotin and K_2CO_3 converts glycosides containing an axial hydroxyl at the C4, such as galactoside **9**, into the corresponding 4-keto products with excellent selectivity (Scheme 1C). Protecting the C3-OH in galactosides with a benzyl group completely blocked oxidation,[21] which underlines the importance of the presence of a 1,2-diol system and thus chelation.[20] Oxidation of glucosides and mannosides using the same conditions gave the expected keto products, albeit in lower yields than the stoichiometric procedure described by Tsuda.[29] However, a mixture of oxidation products is obtained when the glycoside bears two axial hydroxyl groups, as in arabinose.

In the search for more environmentally benign alternatives for the organotin compounds, Onomura and coworkers explored the feasibility of using boronic acids to activate 1,2-diols in water.[33] They hypothesized that boronate esters (see Scheme 1A, structure **10** for the chelation mode) that can be formed *in situ* by reacting 1,2-diols with boronic acids, would react in a similar fashion with halonium reagents as the corresponding stannylene acetals. Both cyclic and acyclic 1,2-diols could indeed be oxidized with either DBI or electrochemically generated "Br+" using 4-methoxyphenyl boronic acid (only tested on 1,2-cyclooctanediol), methylboronic acid or 3-methyl-2-buten-2-yl boronic acid as catalyst (Scheme 1B, entry 5 and 6). Scale up of this procedure is hampered by the low solubility of DBI in water and its high cost. Inspired by the work of Ishii *et al.* who showed that hypobromous acid can be generated *in situ* using sodium bromate and sodium bisulfite,[34] Onomura and coworkers applied a similar reagent combination in the boronic acid-mediated oxidation of 1,2-diols.[35] Potassium bromate and

potassium hydrogensulfate were used rather than the reagents reported by Ishii to minimize the effect of the addition order and the pH on hypobromous acid formation. Remarkably, the secondary alcohol of vicinal diols was not only oxidized in the presence of the methylboronic acid catalyst, but also in its absence (Scheme 1B, entry 7). It was therefore postulated that the formed bromonium species transiently interacts with the diol (Scheme 1A, structure **11**), thereby activating the diol and facilitating oxidation of the secondary alcohol.

Many transition metal catalyst systems have been reported to oxidize primary and secondary mono-alcohols, pronounced examples being the Pd(OAc)₂/pyridine system of Uemura[36], the Pd(OAc)₂ neocuproine system of Sheldon[37], and the Pd-NHC system of Sigman[38]. The ligands used in these systems play an essential role in the oxidation reaction. They stabilize the catalyst to prevent palladium black formation, lower the energy barrier for β-hydride elimination and facilitate alkoxide formation by proton-coupled ligand exchange.[39] Based on this, novel systems have been developed that have improved catalytic activity and that enable chelation-controlled regioselective oxidation of 1,2-diols (Scheme 2 and Figure 3).

The group of Lee explored the use of NHC ligands to both stabilize and activate the palladium for oxidation chemistry.[40] The neutral Pd-NHC (η³-allyl) complexes showed excellent selectivity for the secondary hydroxyl of 1,2-diols, with complex **12** being the most efficient catalyst (Scheme 2A). Although the reaction is performed at 80 °C with 20 bar of air, only minimal amounts of palladium black are formed and 74% conversion of 1,2-propanediol **13** into hydroxyacetone **14** was achieved in 5 h using only 1 mol% of catalyst (Scheme 2B). 1,3-Diols are also oxidized by **12**, albeit far less efficiently,[40] and it has therefore been recently proposed that the catalyst may form the corresponding chelate **15** (Scheme 2C). For similar catalysts, chelation is initiated by proton-coupled ligand exchange of the η³-allyl ligand by one of the hydroxyl functionalities, thereby forming a palladium alkoxide. The remaining hydroxyl of the vicinal diol coordinates to palladium and expels propene, which is favorable for 1,2-diols and may thus explain the regioselectivity.[41]

Waymouth and coworkers pioneered the use of cationic palladium complexes that have an open coordination site and a basic acetate ligand for the oxidation of alcohols.[42] They showed that this dimeric catalyst **16** dissociates in solution and that the resulting monomeric catalyst reacts with alcohols to form aldehydes and ketones under mild conditions using air as the co-oxidant (Scheme 2A). When the same catalyst was applied on vicinal diols, a dramatic increase in reaction rate and selectivity was observed.[43] Glycerol **17** was converted into dihydroxyacetone **18** in 92% yield and >95% selectivity within 15 minutes using 2.5 mol% of catalyst, benzoquinone as the internal oxidant and DMSO as solvent (Scheme 2B). Primary and secondary alcohols and 1,3-diols react only slowly under these conditions.

The large difference in reactivity between 1,2-diols and other alcohols is caused by differences in ligand-exchange. Upon binding to the vacant coordination site, the 1,2-diol rapidly forms a relatively stable palladium-alkoxy chelate **19** (Scheme 2C and 2D).[44] Subsequent β-hydride elimination gives the hydroxy ketone products. Both DFT calculations and

A

12   **16**   **20**   **21**

B

13 : R = CH$_3$
17 : R = CH$_2$OH

14 : R = CH$_3$
18 : R = CH$_2$OH

C

15

19

entry	SM	conditions	yield
1	13	Pd-NHC **12** (1 mol%), air (20 bar), toluene/DMSO (19 : 1, 0.05 M), 80 °C, 5 h	74%[a]
2	17	Benzoquinone (3 equiv), [(neocuproine)PdOAc]$_2$OTf$_2$ **16** (2.5 mol%), CH$_3$CN/H$_2$O (10 : 1), rt, 4 h	92%
3	17	Benzoquinone (1.15 equiv), [(PyOx)PdOAc]$_2$OTf$_2$ **20** (2.2 mol%) CH$_3$CN/H$_2$O (10 : 1), 55 °C, 24 h	87%

D
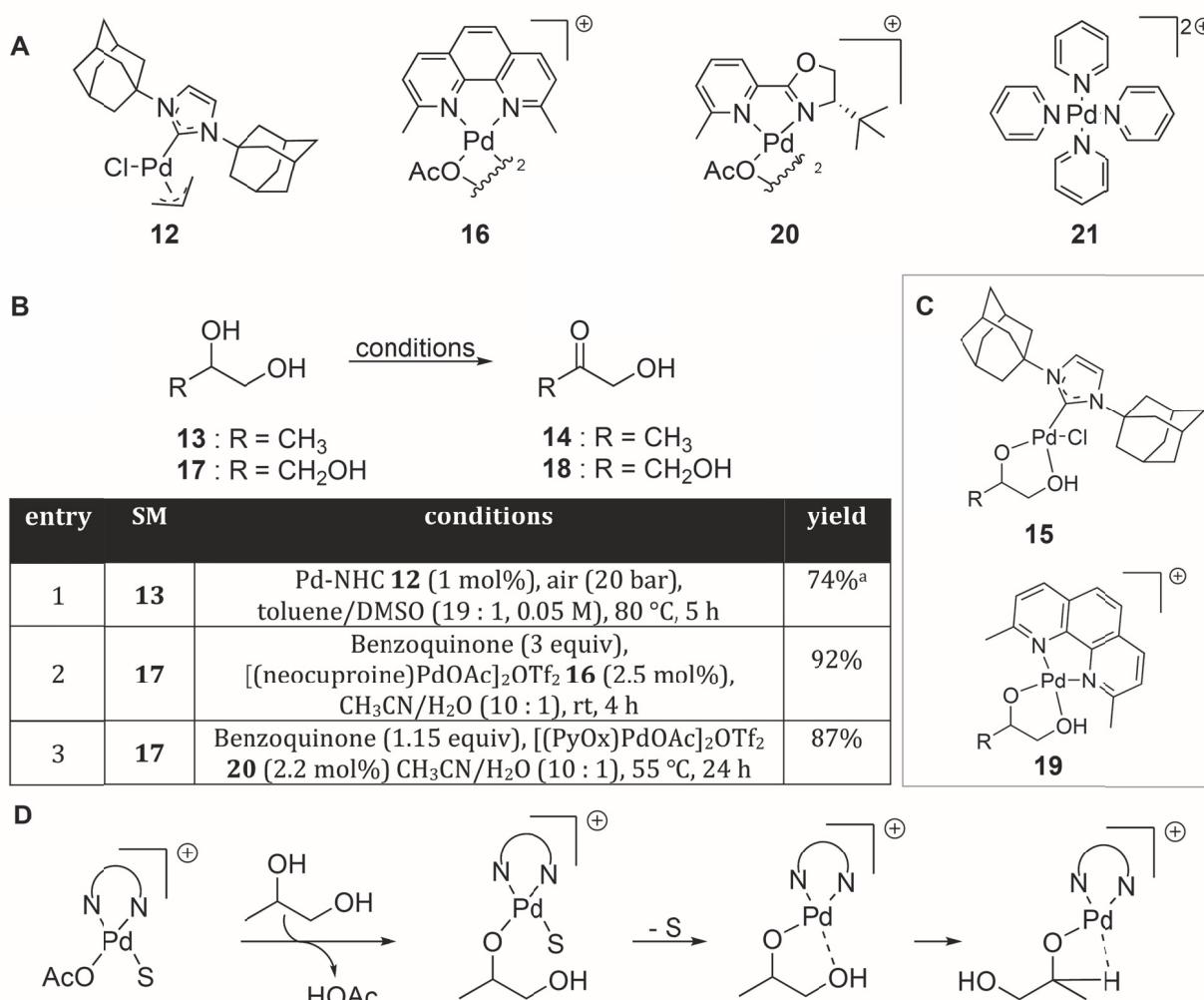
Scheme 2, Overview of palladium catalyzed chelation-controlled oxidations. (A) Structures of palladium catalysts **12**, **16**, **20** and **21**. (B) oxidation of the linear substrates 1,2-propanediol and glycerol. [a]Conversion, no isolated yields. (C) Proposed chelation modes of palladium catalysts **12** and **16**. (D) mechanism of chelation of **16** followed by subsequent oxidation. S is a solvent molecule.

experimental results with tetraol substrates, like threitol and erythritol, indicate that β-hydride elimination is favored for secondary alcohols and that this step determines the regioselectivity. Benzoquinone or oxygen oxidizes the palladium hydride formed after β-hydride elimination thereby regenerating the active catalyst.[44] Other cationic palladium complexes, such as pyOX-ligand **20** (Scheme 2A), which was designed for enantioselective oxidation, give similar regioselectivities and yields for 1,2-propanediol and glycerol (Scheme 2B).[45] In the enantioselective oxidation reactions, however, only moderate e.e.'s were obtained. Even though harsher conditions are required, also bis-cationic palladium pyridyl complex **21** (Scheme 2A) selectively oxidizes the secondary alcohol of 1,2-propanediol.[41]

Interestingly, Waymouth and workers revealed that **16** can also be used to discriminate between two secondary alcohols (Figure 3). Palladium catalyst **16** oxidized cyclohexanediols **7** and **8** with the same selectivity as organotin catalysts; that is, the axial alcohol of a cyclic cis-diol is preferentially oxidized over the equatorial one (Figure 3).[44] At the same time, we demonstrated that palladium catalyst **16** enables selective oxidation of one of the three contiguous secondary alcohol groups in glycosides. Reacting methyl glucoside **22** (both the alpha and the beta-

epimer) with **16** in CH$_3$CN/H$_2$O gave a single product, which turned out to be the 3-keto glucoside (Figure 3).[46] Changing the solvent system to DMSO/dioxane or DMSO led to a significant rate enhancement, as was also reported for glycerol, but it did not affect the selectivity. All of the studied glucose-configured saccharides react at the C3 position, independent of the substituent at the anomeric position. Thioglucosides, azidoglucosides and C-glucosides give the C3 keto product.[46–48] Waymouth and coworkers recently extended the scope of the reaction and demonstrated that xylosides, fucosides **23,** rhamnosides **24**, arabinosides **25**, 6-deoxyglucosides and also conformationally locked 1,6-anhydropyranose give selective oxidation at the C3 position (Figure 3).[49] In contrast to cyclohexane diols **7** and **8**, the equatorial C3-OH predominantly gets oxidized in glycosides that bear an axial substituent at C2 or at C4. Clearly, stereoelectronic effects in the substrate dominate the regioselectivity.

Not only monosaccharides can be selectively oxidized by Waymouths catalyst **16**, but also more complex di- and oligosaccharides.[46,48] The reaction takes place exclusively at the terminal glucose residue, even in oligoglucosides up to heptamers (Figure 3, structure **26**). Internal oxidation is not
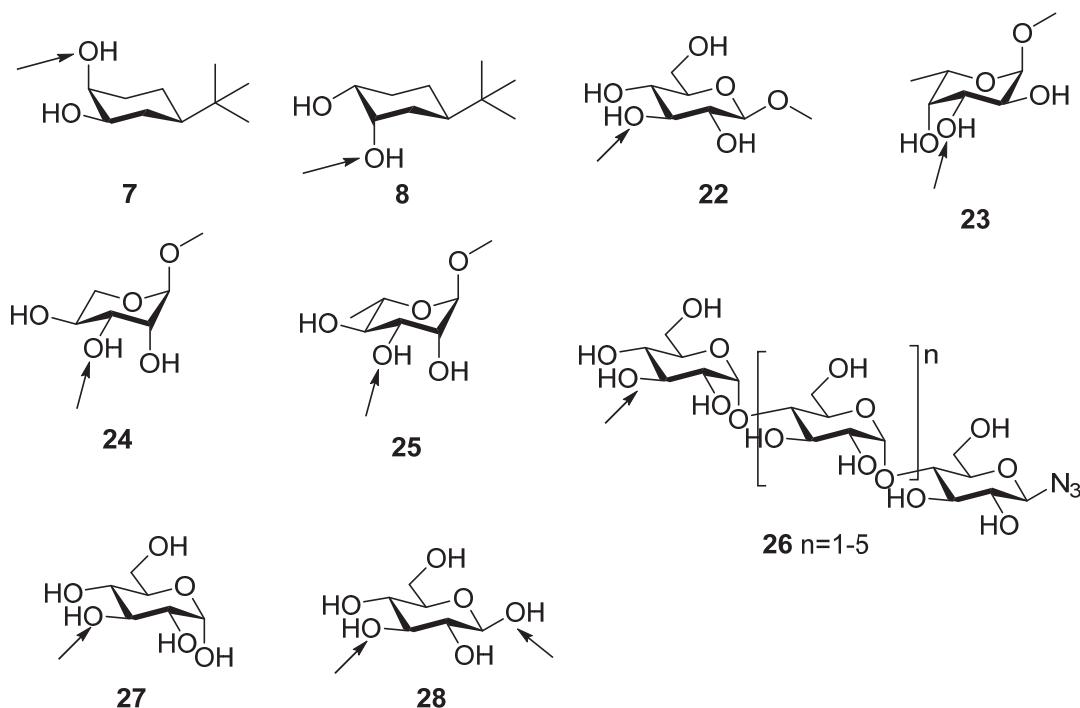
Figure 3, The selectivity of palladium catalyzed oxidation of vicinal, cyclic secondary diols. The hydroxyl group that is oxidized is indicated by an arrow. For oxidation of cyclohexane diols **7** and **8** see ref [44]. Oxidation of glucosides **22** see ref [46] and ref [49]. Oxidation of fucoside **23**, arabinoside **24** and rhamnoside **25** see ref [49].

observed and this method thus allows the straightforward synthesis of oligosaccharide derivatives.[48]

Besides glucosides and oligosaccharides, we recently showed that also reducing carbohydrates can be oxidized with **16**.[50] We initially reasoned that the hemiacetal in reducing carbohydrates would be oxidized preferentially by the catalyst and we therefore protected the anomeric position as an acetal. Unpublished results with galactosides and mannosides suggested that there may be a difference in reaction rate between *cis*- and *trans*- diols groups and we hypothesized that we could exploit this difference in the oxidation of α-glucose **27** (Figure 3). Our established reaction conditions gave the C3-oxidized product in a surprisingly clean manner. Apparently, palladium catalyst **16** (Scheme 2) has such a high preference for *trans* vicinal diols, presumably due to a more favorable O-Pd-O bite angle, that oxidation of the axial anomeric alcohol in α-glucose is prevented. This hypothesis is further supported by the results with β-glucose **28**, which has a *trans* configured diol at C1-C2 (Figure 3). Simultaneous oxidation at C1 and C3 is observed when using this substrate and to successfully oxidize reducing sugars, it is therefore essential that conditions minimizing mutarotation are used.

A major practical hurdle in the oxidation of glycosides is the tedious purification of the keto products, which is hampered by their polarity, the solvent used in the oxidation reaction and the use of benzoquinone. The latter issue can be addressed by using oxygen as co-oxidant. However, competing oxidation of the methyl groups in the neocuproine ligand inhibits the catalyst and consequently higher catalyst loadings are required to achieve full conversion.[42,46] The two methyl groups play an essential role in the dissociation of the dimeric complex into the catalytically active monomeric species and can therefore not be omitted. Waymouth and coworkers demonstrated that catalyst

inactivation can be minimized using ligands that are less oxidation sensitive. Palladium complexes of (2-trifluoromethyl)-4-methyl-1,10 phenanthroline showed an approximately 2-fold increase in turn-over numbers (TON) and turn over frequencies (TOF) (after 24 h) compared to catalyst **16**.[51] We showed that deuteration of the methyl groups in neocuproine has a similar effect on the catalyst stability and also leads to an approximate 2-fold increase in TON and TOF.[52] Besides improvements in the catalyst, also the reaction conditions have been optimized. Waymouth and coworkers recently showed that sacrificial reductants that react with peroxides, such as 2,5-diisopropylphenol have a beneficial effect on the catalyst lifetime, when oxygen is used as a co-oxidant.[49] Lowering the amount of benzoquinone simplifies purification and improves the selectivity. Finally, Waymouth showed that depending on the substrate, trifluoroethanol or acetonitrile/water can be used as solvents in the oxidation reaction. Although this greatly simplifies the work-up procedure, it comes at the cost of epimerization of some of the products.[49]

Applications

The regioselective oxidation of vicinal diols has been applied in wide range of research fields. It has been used for the valorization of glycerol, a major side-product of the production of biodiesel. Palladium catalyst **16** and iron-based catalyst **3** convert glycerol selectively into dihydroxyacetone. This added value building block forms a starting point for the synthesis of fine chemicals and it can be applied in cosmetics.

In organic synthesis, regioselective oxidation reactions have been employed to functionalize diols in partly protected intermediates to synthesize chemical probes[53] and to synthesize natural products. We exploited the excellent regioselectivity of catalyst **16** for the protection group free synthesis of the

Colorado potato beetle pheromone.[54] Using this catalyst, we could obtain the pheromone in 80% yield over three steps. Other natural products containing an alpha hydroxymethyl ketone moiety may be synthesized in a similar fashion.

When applied on (partly) saccharides, regioselective oxidation enables the synthesis of rare monosaccharides, the synthesis of aminoglycosides, straightforward synthesis of derivatives of glycosylated natural products and the synthesis of oligosaccharide-based bifunctional linkers. D-Allose can be obtained in only two steps form α-D-glucose by regioselective oxidation of the C3 with palladium catalyst **16** and subsequent stereoselective reduction.[50] In a similar fashion, 3-aminoglycosides, like the natural product derivative methyl 3-*epi*-kanosamine, can be synthesized by regioselective oxidation followed by oxime formation and concomitant reductive amination. Palladium catalyst **16** has also been employed to synthesize drug derivatives.[55] Analogues of the C-glycoside dapagliflozin, an inhibitor of the glucose transporter SGLT-2, have been prepared using palladium catalyst **16**.[47] Finally, we used regioselective oxidation of olgisaccharides in combination with Shoda's method to functionalize the anomeric alcohol into azides for the synthesis of 1,4-glucan-based linker molecules. We demonstrated that the azide and ketone in these bifunctional linker molecules can be used to prepare bioconjugates.[48]

Conclusions and future directions

In the past decade, large advances have been made in the regioselective oxidation of vicinal diols. This has led to the development of methods that are environmentally more benign and that can be used to oxidize relatively simple 1,2-diols with excellent selectivities. Although insightful, the real potential of regioselective oxidation lies in the ability to modify more complex molecules, like monosaccharides, oligosaccharides and glycosylated natural products and this exemplified by the recent patent on the selective modification of natural products using oxidation.[39] In particular chelation-controlled oxidation methods show great promise in this field. The complementary regioselectivities of organotin mediated and palladium-catalyzed oxidation reactions have enabled selective oxidation of the C4 and C3 position of monosaccharides. It has been proposed that the difference in regioselectivity is caused by the fact that steric factors play an important role in organotin reactions and that stereoelectronic effects in the substrate seem to dominate the selectivity when using cationic palladium complexes.

To fully exploit the potential of regioselective oxidation reactions, methods that enable selective modification of specific glycoside residues within in a complex oligosaccharide will have to be developed. Future research should therefore not only focus on determining the regioselectivity within an monosaccharide of interest, but it should also direct at establishing the difference in reaction rates between glycosides (i.e. glucose *vs* mannose, glucose *vs* galactose) for each oxidation method. The large variations in yields and reaction times for differently configured glycosides in both organotin mediated and cationic palladium catalyzed oxidation already suggest that there may be difference in the reaction rate. These differences may be more pronounced when the reaction is performed with other cationic palladium complexes, such as **20**, and other organotin catalyst, such as di-*tert*-butyltin dichloride.

Besides improving the substrate selectivity, also purification methods should be simplified. Using oxygen as a co-oxidant addresses this issue in part, but comes at the cost of oxidative degradation of the ligand. Even though sacrificial reductants and novel ligands have led to increased turnover numbers for the palladium-catalyzed oxidation reaction, further improvements are required when using air as the co-oxidant.

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Biosketches

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