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New oxidative pathways for the synthesis of α-hydroxy ketones—the α-hydroxylation and ketohydroxylation

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Abstract—α-Hydroxy ketones serve as versatile intermediates in organic chemistry. Although this functional group combination allows a variety of synthetic manipulation, catalytic methods for the selective generation of this structural motif, via oxidation of carbonyl compounds (α-hydroxylation) or olefins (ketohydroxylation), have recently been developed. The present review gives a brief overview of the recent developments in the field of catalytic α-hydroxylations and ketohydroxylations, with a focus on the latter reaction.

Contents

1. Introduction

Asymmetric synthesis is a key methodology in modern organic chemistry.[1] Various strategies for the formation of isomerically pure organic compounds have been developed. Stereocentres present in the starting material are used to direct the trajectory of an incoming reagent (substrate induction) or chiral reagents lead to stereochemical differentiation at the reactive centre (reagent induction). If no enantiomerically pure starting material is available, an asymmetric synthesis of a more complex molecule starts with the formation of a new stereocentre by reaction of an achiral substrate with a chiral reagent. If the reaction can be performed in a catalytic fashion, small amounts of chiral catalyst are needed to give large amounts of enantiomerically enriched products. If the subsequent transformations can be done using the substrate induction of a newly formed stereocentre an efficient asymmetric synthesis is possible.

With regard to the synthetic considerations mentioned above, a high level of substrate induction is necessary to transform an isomerically pure starting material into an isomerically pure product. Several functional groups display a high substrate induction.[2] Most of

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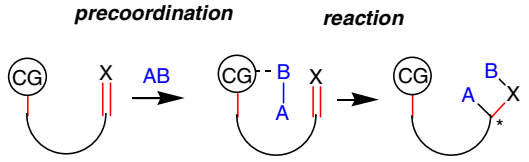


Figure 1. Mode of operation in privileged synthons.

them possess coordinating properties allowing a temporary binding of the incoming achiral reagent via, for example, van-der-Waals-interactions. This pre-coordination of the reagent via the coordinating group *CG* (Fig. 1) can be used to induce a high level of stereoselectivity, especially if the reacting functional group is located proximal to the coordinating group. Such a combination of directing functional group and a functionalizable achiral moiety can be regarded as a '*privileged synthon*'.[3]

The hydroxyl group has frequently been used as a reagent directing group, for example, for the selective elaboration of aldol products.[4] A structurally related motif that fulfills all the criteria of a privileged synthon is the α-hydroxy ketone (acyloin). Several selective transformations of this compound class have been developed and indicate that this motif is ideal for the creation of structural diversity and complexity as exemplified in Figure 2.

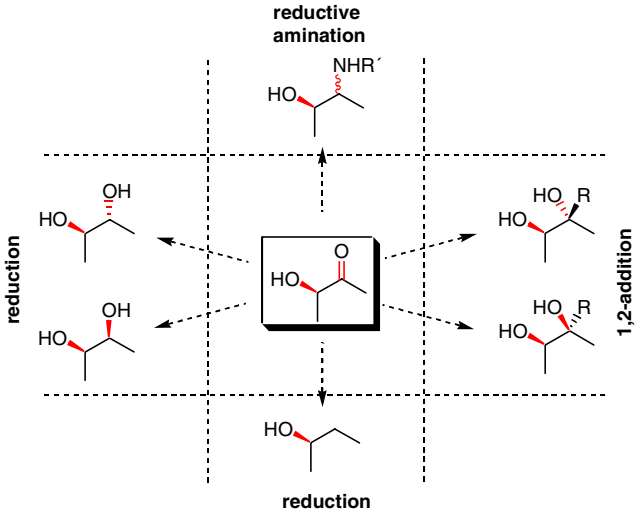


Figure 2. The acyloin as a privileged synthon in asymmetric synthesis.

A variety of α-ketol syntheses have been reported in the literature. In a classical acyloin condensation, the C,C-bond is formed, a process, which has been elaborated in an asymmetric fashion via bio- or organocatalysts.[5] The following paragraphs, however, summarize oxidative pathways towards α-hydroxy ketones.

Two main synthetic routes have been described in the past three years. In the catalytic α-hydroxylation of ketones, a carbonyl compound is transformed into an enolate or enamine with subsequent oxidation of the C,C-double bond to provide access to α-hydroxylated products (*path A*, Fig. 3). The ketohydroxylation of olefins on the other side introduces three C,O-bonds in one step (*path B*, Fig. 3).

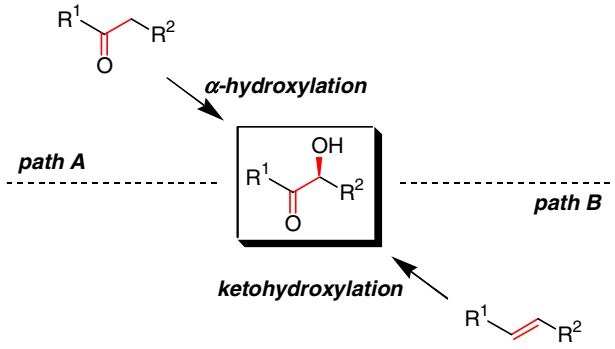
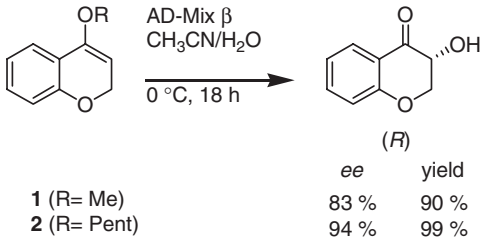


Figure 3. Oxygen transfer routes towards α-hydroxy ketones.

Herein, we report recent advances in both fields of acyloin synthesis with a focus on the newly developed ketohydroxylation.

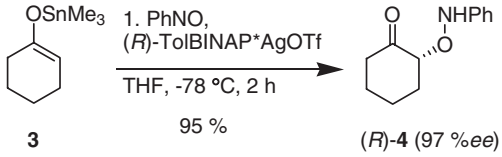
2. The catalytic α-hydroxylation of ketones

The two-step procedure of enolate generation and subsequent oxidation of the resulting double bond has been known in organic chemistry for decades.[6] Various oxidizing agents can be used for non-stereoselective C,O-bond formation, with *m*-CPBA being the most prominent. The era of stereoselective α-hydroxylations started with the stoichiometric use of chiral oxidizing agents with sultam-based oxaziridines being the most successful.[6] The first catalytic α-hydroxylations were reported in 1988 by Shioiri et al.[7] They observed moderate to good enantioselectivities in the oxidation of branched ketones in the presence of alkaline peroxide solution and catalytic amounts of cinchona-based chiral phase transfer catalysts. The breakthrough, however, was achieved in 1993 when the Sharpless group succeeded in the asymmetric dihydroxylation of silyl enol ethers. This method proved to be quite general and broadly applicable for the synthesis of a variety of enantiomerically enriched acyloins.[8] This procedure has recently been further elaborated upon. Marcune showed that longer unbranched aliphatic substituents on the enol ether oxygen improved the enantioselectivity (Scheme 1).[9]



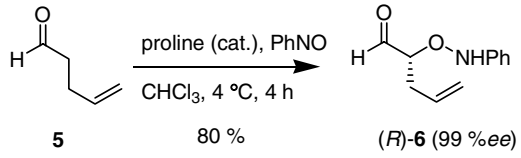
Scheme 1. The asymmetric dihydroxylation of alkyl enol ethers.

An alternative catalytic approach towards α-hydroxylated products was recently developed by Yamamoto. An enantiopure Ag(I)-BINAP-catalyst allowed the asymmetric formation of a new C,O-bond at the α-position of tin enolates using nitrosobenzene as the oxygen source. A variety of new and unprecedented cyclic and acyclic α-hydroxy ketones are accessible in good to excellent enantioselectivities (Scheme 2).[10]



Scheme 2. The Ag-catalyzed asymmetric α-oxygenation of tin enolates.

Whereas the selectivities in these α-hydroxylations are very good, both of the processes mentioned so far represent multi-step syntheses involving the preformation of isomerically pure enol ethers. A solution to this synthetic drawback has recently been presented by various groups, who reported independently on the direct asymmetric L-proline catalyzed α-oxygenation of ketones.[11] The combination of an in-situ formation of chiral enamides and the use of Yamamoto's nitrosobenzene as an oxygen source allowed the synthesis of a variety of acyloins in one step without the need to preform the active enolate (Scheme 3).



Scheme 3. The proline-catalyzed asymmetric α-oxygenation.

The proposed mechanism is closely related to proline-catalyzed aldol reactions (Fig. 4). It starts with the condensation between carbonyl compound **ii** and proline **i** as the initial step in the catalytic cycle. The π-facial selective addition of the incoming nitrosobenzene **iv** is the consequence of coordination between the carboxyl group and the nitrogen part of the electrophile in the cyclic transition state **v**. The observed oxygenated products **vii** are released via a concluding hydrolysis of **vi**.[12]

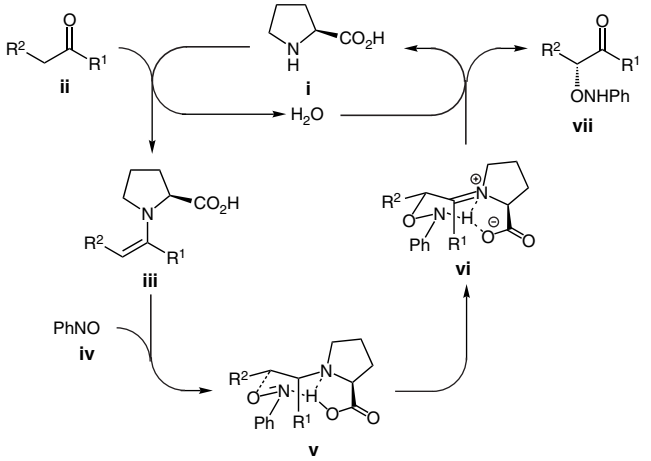
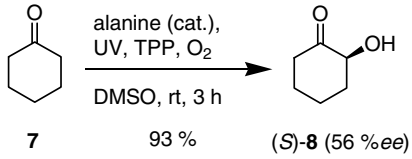


Figure 4. Mechanistic proposal for the proline-catalyzed α-oxygenation.

Recent reports on asymmetric α-oxygenations have demonstrated that this method possesses the potential to become a powerful new synthetic tool in organic chemistry. However, the C,O-bond formation by O-alkylation of nitrosobenzene possesses a drawback. Cleavage of the N,O-bond is necessary if manipulations at the oxygen are planned. The inherent epimerization potential of some α-hydroxy ketones, however, might cause problems in this cleavage reaction. Hence, most products were isolated after reduction to the corresponding alcohols. A solution to this problem was recently discovered by Córdova et al.[13] They were able to directly oxidize the α-carbon with molecular oxygen in the presence of alanine as a catalyst. Although the enantioselectivities were only moderate, this reaction represents a promising new alternative to the use of nitrosobenzene (Scheme 4).



Scheme 4. The alanine-catalyzed aerobic asymmetric α-oxygenation.

3. The ketohydroxylation of olefins

The direct formation of acyloins from olefins via a '*ketohydroxylation*', that is, a process in which three C,O-bonds are formed in one step, has not been elaborated as much as the transfer of two oxygens to a C,C-double bond, for example, epoxidation or dihydroxylation (Fig. 5).[14] With regard to recent progress in the field of olefin metathesis,[15] the ketohydroxylation seems to be a promising new alternative route towards α-hydroxy ketones complementing the acyloin syntheses developed so far.

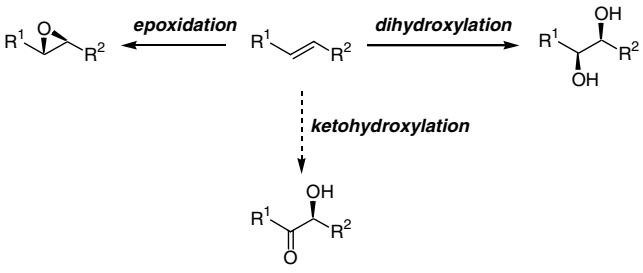
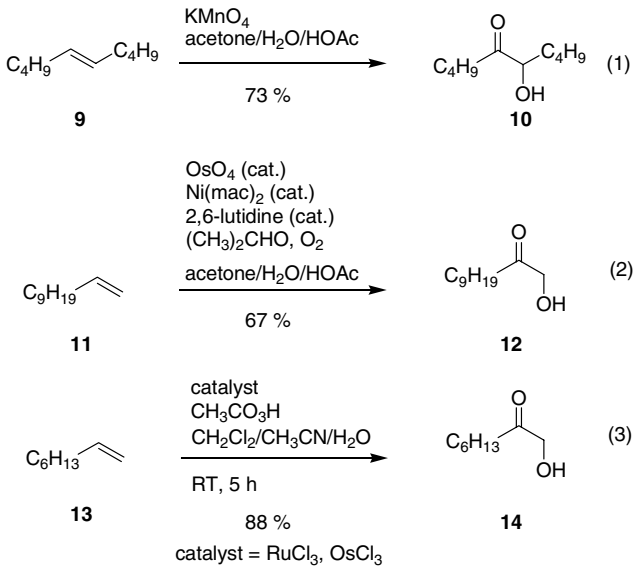


Figure 5. Oxidative transformations of olefins.

Several synthetic attempts towards a ketohydroxylation have been published.[14] The stoichiometric use of

$KMnO_4$ under slightly acidic conditions represents one of the earliest examples (Eq. 1, Scheme 5).[14f] The first catalytic version was published in 1989 by Mukaiyama et al. (Eq. 2, Scheme 5).[14e] They used a bimetallic system of OsO_4 and a Ni-catalyst to perform a two-step one-pot oxidation sequence of dihydroxylation and subsequent mono-oxidation of the diol. Interestingly, oxygen in the presence of *iso*-butyraldehyde served as the stoichiometric reoxidant. Another interesting procedure was published by Murahashi et al.[14c,d] The use of $RuCl_3$ in the presence of stoichiometric amounts of peracids generated a Ru(V)-oxo species that oxidized several olefins to acyloins in moderate to good yield (Eq. 3, Scheme 5). From a mechanistic point of view, the reaction was thought to proceed via an initial epoxidation, subsequent hydrolytic ring-opening and β-hydride elimination as the final oxidizing step.



Scheme 5. Ketohydroxylation of olefins.

3.1. The RuO_4-catalyzed ketohydroxylation

3.1.1. Scope and limitations. Although these methods proved successful for the direct preparation of α-hydroxy ketones, the use of toxic metal catalyst combinations and the lack of stereocontrol represent severe drawbacks of the known methods. Hence, a process that could introduce three C,O-bonds in one step with full control of regio- and stereochemistry would be an interesting synthetic alternative to the methods known so far. The research in our group focuses on the use of highly oxidized ruthenium-species, such as RuO_4, as versatile catalysts in organic synthesis.[16] This reagent, although known in organic synthesis since 1953,[17] has mainly been used for the oxidative degradation of olefins or aromatic compounds.[18] It is isoelectronic to OsO_4 but possesses a significantly higher redox potential. It is for this reason that we envisioned RuO_4 to fulfill all the requirements necessary for the introduction of three C–O-bonds in one step (Fig. 6).

Our mechanistic proposal is based upon the idea of using the concerted character of the initial [3+2]-cycloaddition between an olefin and RuO_4 and its direct translation of π-bond geometry into the relative configuration as a stereoinducing step in the reaction. In the related dihydroxylation, this cyclization event is followed by an oxidation to **viii** and a subsequent nucleophilic addition of water to the metal centre in **ix** (Fig. 6). A subsequent second nucleophilic addition of water furnishes the *syn*-diol **xiii** and regenerates the active catalyst. If a nucleophile that adds faster to the metal centre in **viii** than water while acting as an oxidant, is used a new mechanistic pathway might be possible (Fig. 6). Upon the addition of such a nucleophilic reoxidant to the metal centre in **x** a Ru-peroxo-ester **xii** is formed, which collapses to give the desired α-hydroxy ketone **xv** and RuO_4. Stereocontrol can be achieved if the Ru–O-bond, which is cleaved in the first step of the ketohydroxylation, generates a hydroxyl group that does not undergo epimerization by the catalyst or under the reaction conditions. If this mechanistic scenario could be realized the stereochemical rules obtained in the related OsO_4-catalyzed dihydroxylation could be applied to the RuO_4-catalyzed ketohydroxylation as well.

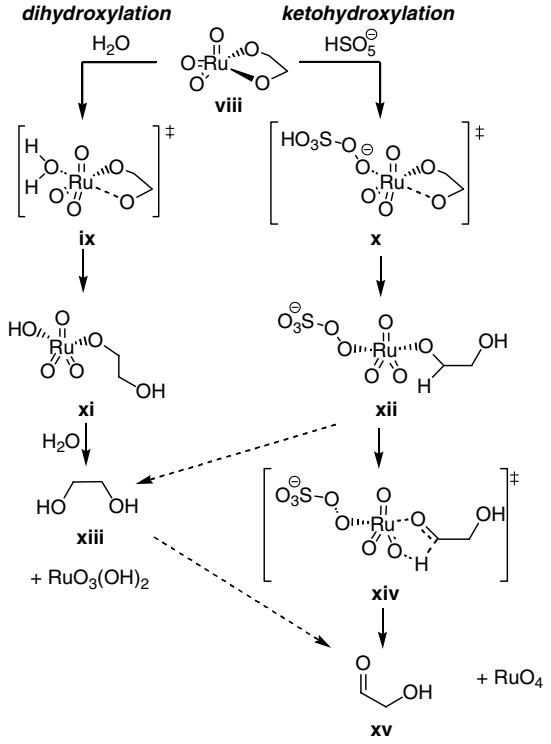
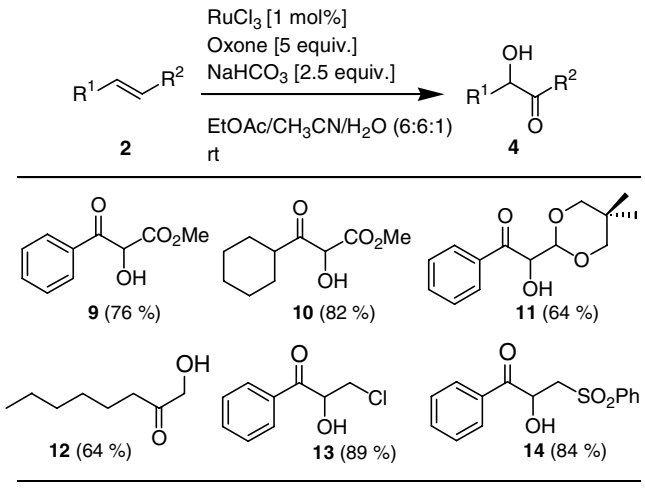


Figure 6. Mechanistic dichotomy in RuO_4-catalyzed oxidation of olefins.

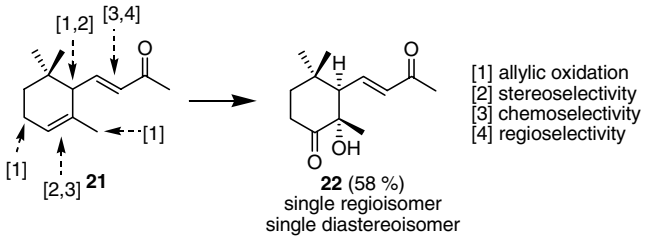
In the related RuO_4-catalyzed dihydroxylation (flash-dihydroxylation) originally discovered by Shing in 1994,[19] protons or Lewis-acids were found to accelerate the nucleophilic addition of water.[20] Consequently, Oxone ($2\,KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), a stable, commercially available, inexpensive and acidic reoxidant proved to successfully oxidize olefins in the presence of $RuCl_3$ to

give α-hydroxy ketones in good to excellent yields and moderate to excellent regioselectivities.[21,22] This is a remarkable result since this reagent combination has been used in the past for the oxidative cleavage of olefins.[23] However, under strictly buffered conditions, a variety of olefins can be transformed into the corresponding α-hydroxy ketones (Scheme 6).[24]



Scheme 6. The RuO_4-catalyzed ketohydroxylation.

Apart from scope and limitations, the chemoselectivity, that is, the relative reactivities between differently substituted olefins, or olefins and various functional groups were explored in detail.[24b] Not surprisingly, RuO_4 was found to act as an electrophilic oxidizing agent. Electron rich olefins react faster. With regard to the high redox potential of RuO_4, the observed chemoselectivity is remarkable and renders this oxidation reaction to be synthetically valuable as shown in Scheme 6. The ketohydroxylation of α-ionone **21**, which cannot only undergo oxidation of the C–C-double bond, but is also prone towards allylic oxidation, gives rise to isomerically pure acyloin **22** out of several possible side products (Scheme 7).[24b]



Scheme 7. Ketohydroxylation of α-ionone **21**.

The electrophilicity of RuO_4 in the oxidation reactions allows the selective oxidation of a C,C-double bond in the presence of a variety of functional groups.[24b] The dehydrogenation of primary aliphatic amines or alcohols, for example, proved to be slow on the timescale of the ketohydroxylation. Hence, it is possible to selectively form an acyloin in the presence of unprotected primary, aliphatic alcohols. On the other hand, allylic or benzylic primary alcohols or amines, N-, S- and O-containing five-membered heterocycles are oxidized much faster than olefins. These groups are incompatible with the RuO_4-catalyzed oxidations of olefins.[24b]

3.1.2. Stereoselectivity issues

3.1.2.1. Diastereoselectivity. Since the initial [3+2]-cycloaddition serves as the stereoinducing step in the ketohydroxylation, the diastereoselectivity of the reaction should follow the rules developed by Kishi for the related OsO_4-catalyzed dihydroxylation.[25] This original model has been elaborated further by Stork et al.[26] and Vedejs[27] and shows the addition of OsO_4 to occur predominantly *anti* to an allylic electronwithdrawing group. Frenking and co-workers[28] and Strassner and Drees[29] independently calculated the mechanistic pathway for the related oxidation of olefins in the presence of RuO_4 and indicated an initial [3+2]-cycloaddition event to take place. Hence, Kishi's rules are applicable towards ketohydroxylation under RuO_4-catalysis (Fig. 7).

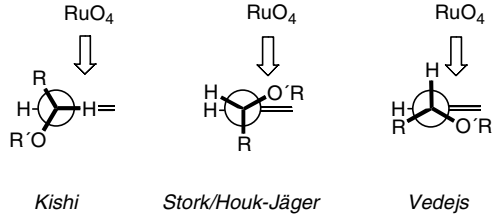


Figure 7. Stereoselectivity models for RuO_4-catalyzed oxidation of olefins.

Several experiments verified this theoretical assumption.[11b] The selectivities depend largely on the electronwithdrawing character and the steric bulk of the allylic stereogenic substituent. As in the related OsO_4- or RuO_4-catalyzed dihydroxylations, the diastereoselectivity in the oxidation of cyclic olefins is good to excellent. The selectivity in the ketohydroxylation of acyclic olefins, however, is only moderate (Fig. 8).[24]

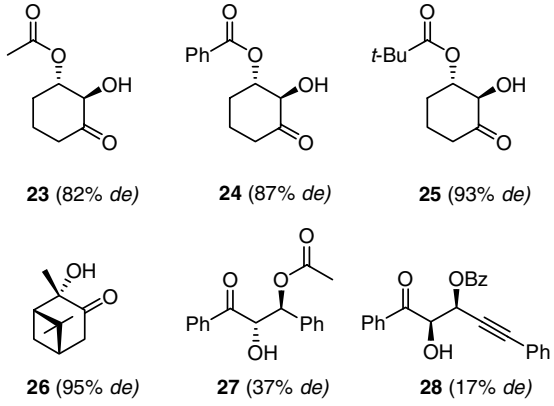


Figure 8. Diastereoselectivity in RuO_4-catalyzed ketohydroxylations.

3.1.2.2. Enantioselectivity—the catalytic mono-oxidation. Whereas an asymmetric RuO_4-catalyzed ketohydroxylation has not yet been developed, a short two-step procedure consisting of asymmetric dihydroxylation

and concomitant RuO_4-catalyzed selective mono-oxidation of the intermediate enantioenriched *vic*-diol allows the synthesis of isomerically pure α-hydroxy ketones with predictable absolute configurations. When we started our research on the acyloin synthesis, we were surprised to find that no regioselective catalytic mono-oxidation of enantiopure *vic*-diols had been developed. Based upon the assumption that a condensation between a *vic*-diol and RuO_4 could lead to a Ru(VIII)-ester, the subsequent nucleophilic addition of Oxone should follow the mechanistic pathway of the ketohydroxylation and result in the formation of an α-hydroxy ketone (Fig. 9).[30]

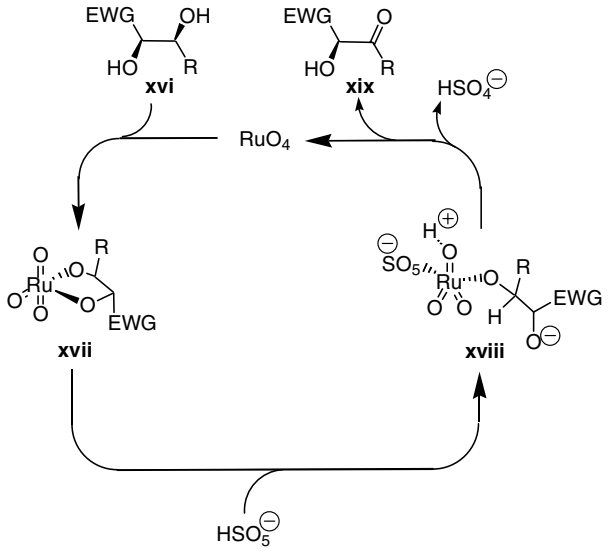
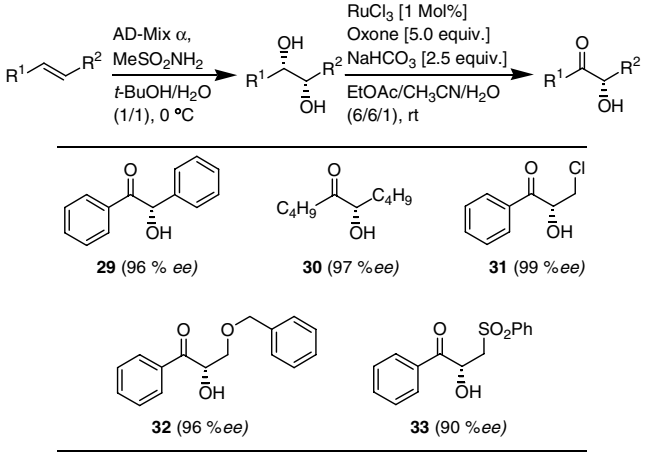


Figure 9. Mechanism of the RuO_4-catalyzed mono-oxidation.

Indeed, upon treating enantioenriched *vic*-diols, accessible via the asymmetric Sharpless dihydroxylation, with the combination of $RuCl_3$/Oxone/$NaHCO_3$, various enantioenriched α-hydroxy ketones were obtained (Scheme 8).[30]



Scheme 8. The RuO_4-catalyzed mono-oxidation.

We were pleased to find that the regioisomeric ratio was identical to the one observed in the ketohydroxylation of the corresponding olefins. Furthermore, several acyloins proved to be stable against epimerization under the acidic reaction conditions and conserved the enantiomeric excess obtained in the initial dihydroxylation process. Hence, this protocol allows the simple and efficient preparation of a variety of enantioenriched α-hydroxy ketones with predictable regioselectivities and absolute configuration and complements the acyloin synthesis developed so far by using olefins as ketol surrogates.[30]

4. Conclusion

α-Hydroxy ketones possess the potential to serve as privileged synthons in asymmetric synthesis. A number of transformations have been developed allowing the regio- and enantioselective formation of this structural motif. This report summarizes recent advances in two new oxidative pathways towards α-hydroxy ketones, the direct α-hydroxylation of ketones and the RuO_4-catalyzed ketohydroxylation of olefins. These transformations have been developed within the past three years and allow fast and selective access towards unsymmetrical α-hydroxy ketones, which are not accessible by alternative methods. Whereas the proline-catalyzed direct α-oxygenation displays a high level of enantiocontrol an asymmetric ketohydroxylation awaits to be developed. On the other hand, the latter proved to be broadly applicable, a fact that needs to be confirmed for the proline-catalyzed α-oxygenation. Thorough investigations on the scope and limitations as well as on chemo- and stereoselectivity issues rendered the RuO_4-catalyzed ketohydroxylation to be synthetically valuable. Furthermore, both reactions are complementary to each other and towards the existing acyloin syntheses and offer the opportunity to build up higher structural complexity in just a few steps starting from simple olefins or carbonyl compounds.

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