# The $RuO_4$-Catalyzed Ketohydroxylation, Part II: A Regio-, Chemo- and Stereoselectivity Study[‡]

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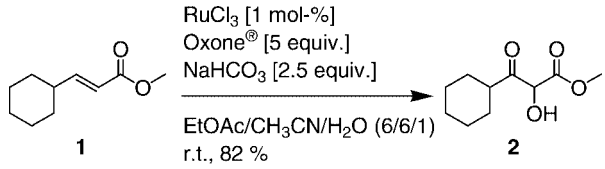
**Keywords:** Ruthenium / Oxidation / Oxone® / Acyloin / Hydroxy ketone

The direct $RuO_4$-catalyzed ketohydroxylation of olefins is a new and convenient method for the preparation of a wide range of symmetrical and unsymmetrical α-hydroxy ketones. Since reactions in which two different functional groups are introduced in one step always involve regio-, chemo- and stereoselectivity issues, this paper gives a full account of investigations of various selectivity aspects in the ketohydroxylation. Stereoselectivity issues were examined in the final part of the present report. The Kishi rules, known from $OsO_4$-catalyzed dihydroxylations, are found to be valid for the $RuO_4$-catalyzed ketohydroxylation and lead to moderate to good diastereomeric ratios in the oxidation of olefins possessing an allylic center of chirality. Furthermore, competition experiments between different substituted olefins led to a reactivity profile applicable to the prediction of which is the most reactive of different C=C double bonds present in a molecule.



## Introduction

Catalytic oxidations are an important research field in organic synthesis.[1] The use of only small amounts of an active oxidant and stoichiometric amounts of a reoxidant, that is not hazardous or poisonous, fulfills both economical and ecological requirements.[2] It is in line with these arguments that synthetic organic chemistry possesses an increasing demand for transformations that are highly chemo-, regio- and stereoselective. Among the catalytic oxidations developed to date, oxygen transfer to a C=C double bond occupies an important place.[3] However, whereas the formation of one C–O bond (hydratization)[4] or two C–O bonds (epoxidation[5] dihydroxylation[3]) has been the focus of oxidation chemistry for more than twenty years, the direct introduction of three C–O bonds at a time has been essentially neglected. However, this transformation results in the formation of α-hydroxy ketones, which are an important substructure found in a variety of biologically active natural products. When we started our research in this field only a few reports had described the formation of acyloins from olefins by using either stoichiometric amounts of $KMnO_4$[6] or catalytic amounts of toxic Ni and Os catalysts.[7] One report by Murahashi dealt with a ruthenium(III)- or osmium(V)-catalyzed oxidation of olefins to α-ketols.[8] From a mechanistic point of view, stable intermediates like diols or epoxides are formed in situ in all of these procedures, hence the formation of an acyloin is a consequence of a subsequent second oxidation of these intermediates. Recently, we reported the first $RuO_4$-catalyzed direct ketohydroxylation of alkenes (Scheme 1).[9] The simple combination of $RuCl_3$, Oxone® (potassium peroxomonosulfate), and $NaHCO_3$ resulted in the clean formation of a variety of α-hydroxy ketones.




Scheme 1. The ruthenium-catalyzed ketohydroxylation.

The higher oxidation rate of olefins under the ketohydroxylation conditions compared to the oxidation rate of diols means that this process is a *direct transformation without the formation of intermediate diols*. The formation of intermediate epoxides can be excluded. The treatment of the latter compounds resulted in the formation of a complex mixture of products with only trace amounts of the desired α-hydroxy ketone.[9a]

A simplified mechanistic proposal is shown in Figure 1. After a [3+2] cycloaddition of ruthenium tetraoxide (**I**) to the double bond, the resulting ruthenium(VI) compound **III** is oxidized to ruthenate **IV**. After activation by protonolysis $SO_5^{2-}$ adds to the metal center in **V** with concomitant cleavage of one of the two metal–oxygen bonds. The resulting mixed peroxoruthenate **VI** then rearranges to give acyloin **VII** and regenerate the active catalyst.

[‡] Part I: B. Plietker, *J. Org. Chem.* **2004**, *69*, 8287.

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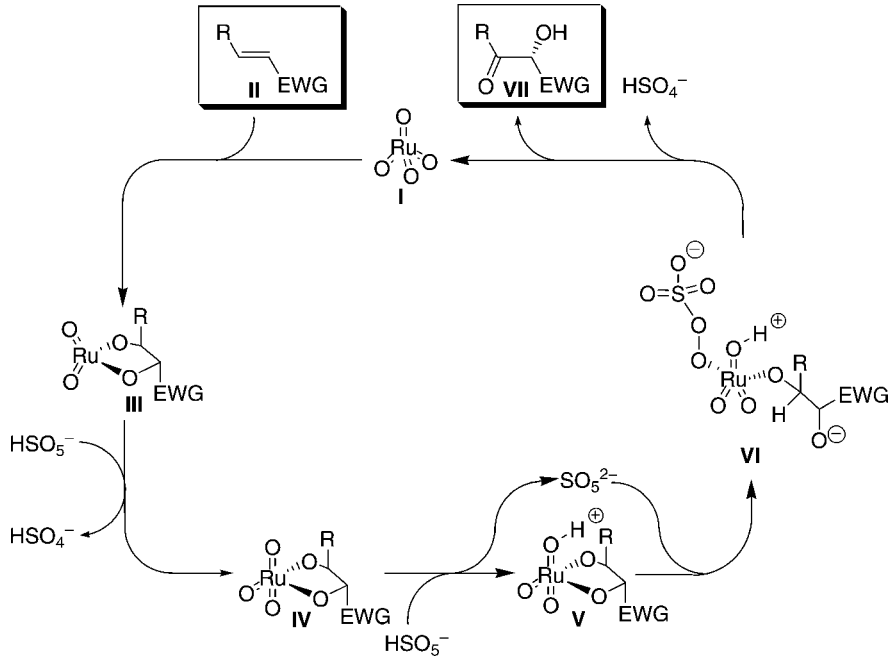



Figure 1. Mechanistic proposal for the ketohydroxylation.

The stereocenter in the final product is formed by a concerted [3+2] cycloaddition between the catalyst and the isomerically pure (*E*)- or (*Z*)-olefin. Hence, the original π-bond geometry is translated into the relative configuration of the stereocenters in **III**. Since the final center of chirality is already introduced at an early stage of the mechanism the control of π-facial selectivity in the initial [3+2] cycloaddition is key for the successful development of an asymmetric oxidation.

The present report concludes our studies on the $RuO_4$-catalyzed ketohydroxylation. Whereas preceding publications dealt with the exploration of its scope and limitation, the present manuscript tries to shed light on the field of selectivity. Selectivity is an important process that needs to be investigated in detail prior to the application of this new reaction in the synthesis of complex molecules or the development of an asymmetric ketohydroxylation. However, much to our surprise, although $RuO_4$ has been known as an oxidant in organic chemistry for more than 50 years, to the best of our knowledge no comprehensive study on selectivity issues in the most common sense has been published to date. It is due to this lack of knowledge that this powerful oxidant never gained as much attention from synthetic chemists as the less-reactive well characterized $OsO_4$. It is in line with our research focus to close this knowledge gap by analyzing the factors that influence the selectivity in $RuO_4$-catalyzed oxidations.

Stereoselectivity studies will be presented in the first part of this report, and the second part will focus on chemoselectivity issues. The results of various competition experiments led to a ranking of relative reactivities between various functional groups vs. olefins, and between different substituted olefins. The empirical reactivity rules can be used for a prediction of the chemoselectivity in the $RuO_4$-catalyzed oxidation of polyunsaturated systems. Various examples will be presented in order to evaluate the obtained data.

## Results and Discussion

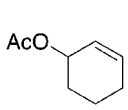
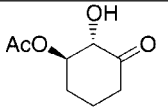
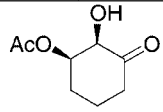
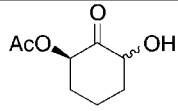
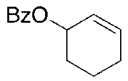
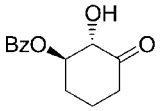
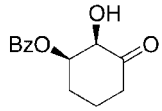
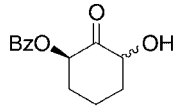
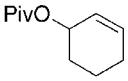
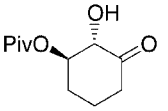
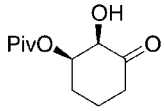
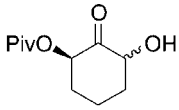
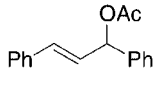
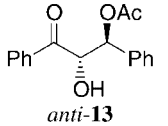
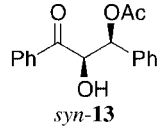
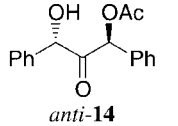
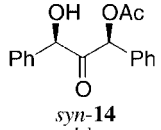
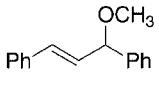
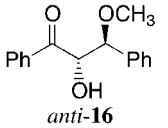
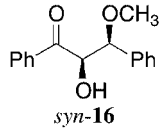
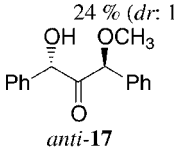
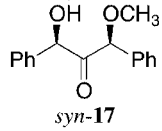
### Stereoselectivity

In the related osmium-catalyzed dihydroxylation, the [3+2] cycloaddition of the metal-oxo species to the double bond is directed *anti* to the allylic noncoordinating oxygen-containing stereocenters (Kishi rules).[10] Shing and our group have observed good simple diastereoselectivities in $RuO_4$-catalyzed dihydroxylations.[11] If, in analogy to osmium-catalyzed oxidations, an initial [3+2] cycloaddition between ruthenium(VIII) oxide is involved in the ketohydroxylation the diastereoselectivities should follow Kishi's rules. One parameter that influences the stereochemical outcome of the oxidation is the size of the substituent at the stereocenter. Kishi observed a decrease in selectivity with acetates. In order to prove the analogies between the Os- and Ru-catalyzed oxidations different substituted olefins were prepared and ketohydroxylated under standard conditions. The obtained regio- and stereoisomeric mixtures were subsequently analyzed by HPLC (Table 1).

The simple diastereoselectivity of the ketohydroxylation follows the Kishi rules. Cyclic olefins can be oxidized to give the corresponding acyloins in good to excellent diastereomeric ratios. As known from dihydroxylations, large substituents shield one face of the π-bond thereby forcing the $RuO_4$ to perform the [3+2] cycloaddition *anti* to the substituent (entries 1–3, Table 1, Figure 2). Furthermore, if the substituent at the stereocenter is electron withdrawing the observed good diastereoselectivity is accompanied by a

Table 1. Diastereoselecitivities in the ketohydroxylation of chiral alkenes.

| Entry | Alkene[a] | Acyloin[b] Regioisomer 1 *anti* | Regioisomer 1 *syn* | Regioisomer 2 *anti* | Regioisomer 2 *syn* | Yield [%][c] |
|---|---|---|---|---|---|---|
| 1 |  **3** |  *anti*-**4** 82 % |  *syn*-**4** 8 % |  **5** 10 % | | 76 |
| 2 |  **6** |  *anti*-**7** 89 % |  *syn*-**7** 6 % |  **8** 5 % | | 69 |
| 3 |  **9** |  *anti*-**10** 86 % |  *syn*-**10** 3 % |  **11** 11 % | | 73 |
| 4 |  **12** |  *anti*-**13** 52 % |  *syn*-**13** 24 % |  *anti*-**14** |  *syn*-**14** 24 % (*dr*: 1.8 : 1.0)[e] | 71[d] |
| 5 |  **15** |  *anti*-**16** 48 % |  *syn*-**16** 14% |  *anti*-**17** 29 % |  *syn*-**17** 9 % | 83[d] |

[a] All reactions were performed on a 2 mmol scale in a solvent mixture of ethyl acetate(12 mL)/acetonitrile (12 mL)/water (2 mL) at 0 °C using 1 mol-% $RuCl_3$ (as a 0.1 M stock solution in water), 5.0 equiv. of Oxone®, and 2.5 equiv. of $NaHCO_3$. [b] Percentages are calculated as the amount of product in the crude product mixture based upon HPLC integration. [c] Combined isolated yield. [d] Reactions were performed at room temperature. [e] Obtained as an inseparable mixture. The diastereomeric ratio was determined by $^1H$ NMR spectroscopy.

good regioselectivity. The oxidation of acyclic olefins, however, is more complex.

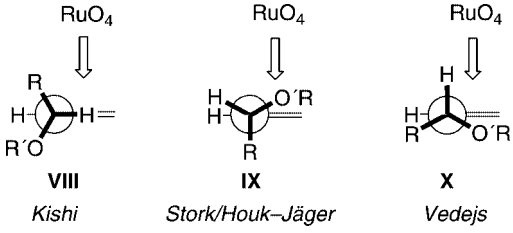



Figure 2. Mechanistic proposal for the ketohydroxylation.

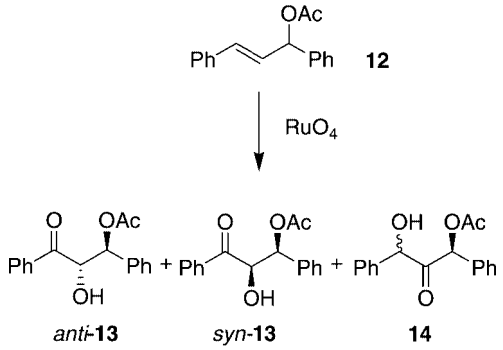
Three different models have been proposed in the literature to try to understand the effect of substitution on the stereoselectivity. According to Houk the "*inside alkoxy effect*" directs the incoming $RuO_4$ *trans* to the biggest substituent, with the C–O bond being coplanar to the C=C double bond. However, due to the additional degree of freedom diastereoselectivities are generally lower.[10b] The oxidation of allylic acetate **12** and allyl methyl ether **15** resulted in the formation of a mixture of four diastereo- and regioisomers that were separable by HPLC (entries 4 and 5, Table 1). This observation clearly limits the number of parameters able to improve the selectivity in $RuO_4$-catalyzed ketohydroxylations. The regioselectivity is usually high if one electron-withdrawing substituent is present proximal to the C=C double bond. However, the substituents known to induce the highest diastereoselectivity in both osmium- and ruthenium-catalyzed dihydroxylations are ethers. This compound class does not possess the electron-withdrawing character necessary for a regioselective ketohydroxylation. In these cases the higher diastereoselectivity is achieved at the expense of the regioselectivity (entry 5, Table 1).

Earlier results obtained in the ketohydroxylation of cyclic olefins indicated that the reaction temperature plays a key role in the product-forming steps. Whereas higher temperatures increase the amount of scission products lower temperatures favor the nucleophilic addition of the oxidant at

the metal center. We envisioned the temperature to be an important parameter for both product distribution and diastereoselectivity due to the lower structural flexibility of the olefin at lower temperature. In order to test this hypothesis allyl acetate **12** was oxidized at different temperatures following the standard protocol. The diastereoselectivities of the crude reaction mixtures were analyzed by GC integration, and are listed in Table 2.

Table 2. Temperature effects in the ketohydroxylation of **12**.




| Entry[a] | *T* [°C] | *anti*-**13**:*syn*-**13**:**14**[b] | Time [min] | Yield [%][c] |
|---|---|---|---|---|
| 1 | 20 | 2.2:1.0:1.0 | 10 | 71 |
| 2 | 0 | 3.4:1.0:0.6 | 30 | 64 |
| 3 | –10 | 4.7:1.0:0.3 | 60 | 62 |

[a] All reactions were performed on a 2 mmol scale in a solvent mixture of ethyl acetate(12 mL)/acetonitrile (12 mL)/water (2 mL) at the given temperature using 1 mol-% $RuCl_3$ (as a 0.1 M stock solution in water), 5.0 equiv. of Oxone®, and 2.5 equiv. of $NaHCO_3$. [b] Determined by GC integration of the crude mixture. [c] Combined isolated yield.

A temperature decrease has a beneficial influence on both the regio- and diastereoselectivity of the ketohydroxylation. Although longer reaction times are needed the stereoselective outcome and the shift in the regioselectivity are remarkable and prove the hypothesis that the ketohydroxylation is a kinetically controlled reaction. At 0 °C or below almost no scission products were detectable. Furthermore, the amount of undesired regioisomer **14** decreased significantly. As already observed before, the reaction temperature seems to play a key role in this reaction by allowing a more selective oxidation, albeit at the expense of conversion. A careful analysis of the temperature effects seems to be an important prerequisite for the successful and selective ketohydroxylation of olefins.

At this point we turned our attention to whether the obtained diastereoselectivities are a result of substrate induction by the stereocenter or whether the primary diastereomeric ratio of the ketohydroxylation is somewhat different, with the observed diastereomeric ratio being a result of a fast, acid-catalyzed keto–enol tautomerism between the thermodynamically favored 1,2-*anti* and the less favored 1,2-*syn* product, in which one of the two substituents is axially oriented (Figure 3).

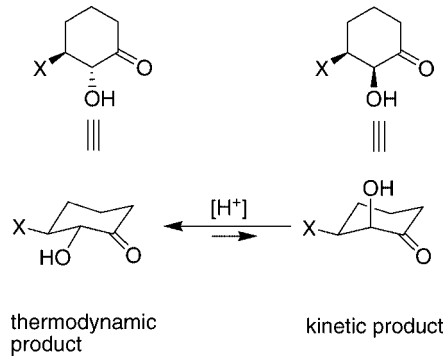



Figure 3. Acid-catalyzed isomerization via keto–enol tautomerism in cyclic acyloins.

In order to analyze the stability of cyclic α-hydroxy ketones the ketohydroxylation of **3** was followed by GC. Conversions and diastereomeric excesses are shown in Figure 4.

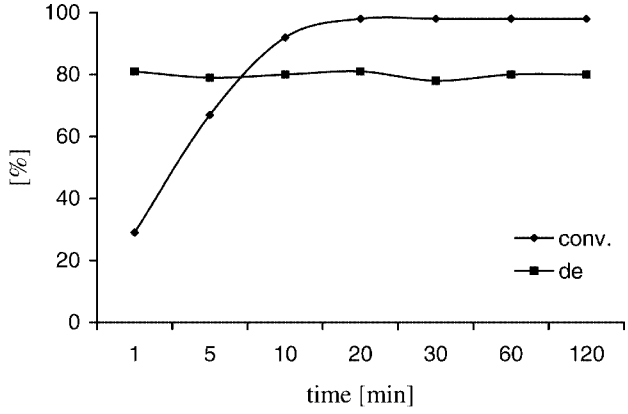


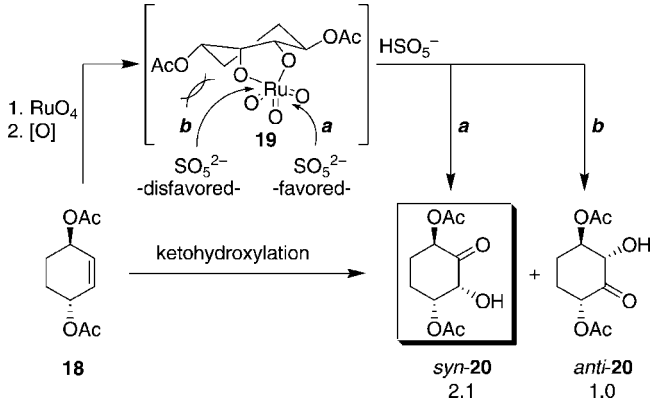

Figure 4. *de* vs. time plot for the ketohydroxylation of olefin **3**.

No epimerization was observed under the ketohydroxylation conditions, thus indicating that the diastereoselectivities obtained in the ketohydroxylation of **3** reflect the stereoinduction of the acetate. Hence, an acid-catalyzed epimerization of acyloins **4** seems not to be problematic during the ketohydroxylation process of olefin **3**.[12] However, the equilibrium between the keto and enol structures depends on the stability of the enol. 1,3-Dicarbonyl compounds, for example, are known to undergo a fast epimerization due to the favorable formation of a conjugated enol. Thus, with regard to the stereoselectivity, the enolization tendency of the product and the electron-withdrawing properties of the olefin substituents in the starting material determine the regio- and stereoselective outcome of the reaction. Certain α-hydroxy ketones, however, prove to be very stable against epimerization.

Apart from these primary substituent effects both regio- and stereoselectivity can be influenced by a second stereocenter present in the molecule. The oxidation of *trans*-cyclohexenyl diacetate (**18**) illustrates this dichotomy. Due to the relative configuration of the two stereocenters the initial [3+2] cycloaddition must occur in an anti-Kishi sense, i.e. *syn* to one of the two substituents, to give ruthen-

ate **19**. If the subsequent addition of the peroxomonosulfate at the metal center in **19** follows an $S_N2$ pathway the Ru–O bond *trans* to the incoming nucleophile is cleaved. The *syn*-oriented substituent, however, blocks one trajectory of the incoming nucleophile (path b), hence the addition of the nucleophile from the sterically less-hindered side, leading to the formation of the 1,2-*syn* product **20** (path a), is preferred, whereas the $S_N2$ reaction leading to the formation of the thermodynamically preferred *anti*-**20** (path b) is disfavored. As a result of this steric interaction *syn*-product **20** is obtained in moderate selectivities. Interestingly, the two diastereomers of **20** are regioisomers. This reaction illustrates the regio- and stereoselective dilemma in $RuO_4$-catalyzed ketohydroxylations. Future work will focus on solving this issue (Scheme 2).




Scheme 2. Ketohydroxylation of *trans*-cyclohexenyl diacetate (**18**).

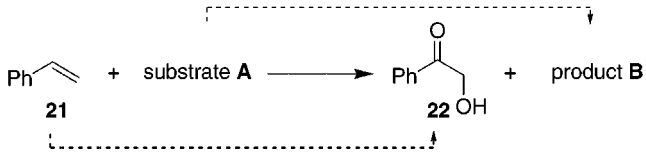
The results obtained in these studies serve as a good base for the development of an asymmetric ketohydroxylation. The detailed knowledge of substituent effects and product stability is an important prerequisite for future work in this field and complements the results obtained in the catalytic monooxidation of *vic*-diols.

## Chemoselectivity

Although $RuO_4$ is known to act as a powerful oxidant in a variety of oxidation reactions, i.e. the oxidation of alcohols to aldehydes or carboxylic acids, amines to imines or nitriles, sulfides to sulfones, alkynes to 1,2-diketones, or different aromatic groups to carboxylic acids,[13] to the best of our knowledge no comprehensive study on the relative reactivities between different oxidizable functional groups and C=C double bonds has been published. However, in order to apply the ketohydroxylation to the synthesis of complex α-hydroxy ketones a profound knowledge of these relative reactivities is of paramount importance.

In order to shed light on this field we started our investigation with different cross experiments aimed towards a better understanding of the relative reactivities of different oxidizable functional groups and olefin **21** (Table 3). Whereas the oxidation of alcohol **23** to the corresponding aldehyde **24** is faster than the ketohydroxylation of styrene **21** (entry 1, Table 3) the subsequent oxidation of **24** to benzoic acid **25** is much slower (entry 2, Table 3). The dehydrogenation of amines is a slow process, as can be seen in the competition experiments employing benzylamine **26** (entry 3, Table 3) or *N*-methylbenzylamine **28** (entry 4, Table 3). Thus, it is possible to selectively oxidize a C=C double bond with $RuO_4$ in the presence of free amines or aldehydes. Sulfides, however, are more reactive. The oxidation of styrene (**21**) in the presence of diphenylsulfide **30** led to a mixture of three products, with the sulfoxide **31** being the major product (entry 5, Table 3). Alkynes and aromatic systems are less reactive than styrene (**21**; entries 6 and 7, Table 3); heteroaromatic substrates, however, are oxidized in a vigorous reaction to give the corresponding carboxylic acid derivatives (entry 8, Table 3).

Table 3. Relative reactivities between olefin **21** and functional groups.




| Entry[a] | A | B | 22 : B[b,c] |
|---|---|---|---|
| 1 | Ph–OH **23** | Ph–CHO **24** | 2.1 : 97.9 (81 %) |
| 2 | **24** | Ph-$CO_2$H **25** | 87.8 : 12.2 (67 %) |
| 3 | Ph–$NH_2$ **26** | Ph-CN **27** | 91.2 : 8.8 (89 %) |
| 4 | Ph–NHCH$_3$ **28** | Ph–NCH$_3$ **29** | 97.2 : 2.8 (69 %) |
| 5 | Ph–S–Ph **30** | Ph–S(=O)–Ph **31** (4.8) + Ph–S(=O)$_2$–Ph **32** (1.0) | 36.1 : 63.9 (93 %) |
| 6 | Ph–≡ **33** | Ph–C(=O)–C(=O) **34** | 98.3 : 1.7 (93 %) |
| 7 | Ph– **35** | Ph–C(=O) **36** | 99.2 : 0.8 (93 %) |
| 8 | Ph–furan **37** | Ph-$CO_2$H **25** | 2.1 : 97.9 (87 %) |

[a] All reactions were performed using 2 mmol of olefin **21** and substrate in a solvent mixture of ethyl acetate(12 mL)/acetonitrile (12 mL)/water (2 mL) at room temperature using 1 mol-% $RuCl_3$ (as a 0.1 M stock solution in water), 5.0 equiv. of Oxone®, and 2.5 equiv. of $NaHCO_3$ and stopped after 20 min. [b] The product ratio was determined by GC integration. [c] Conversion of the more reactive starting material is given in parentheses and is referenced to *n*-dodecane as internal standard.

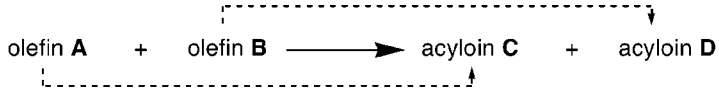
Knowing the relative reactivities between functional groups and olefins we turned our attention towards an examination of the chemoselectivity between different C=C double bonds. Various olefins were oxidized under the stan-

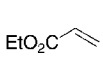
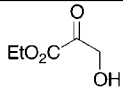
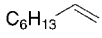
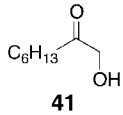
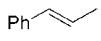
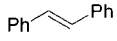
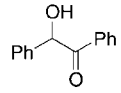
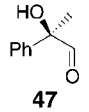
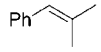
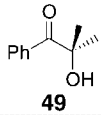
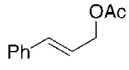
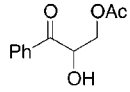
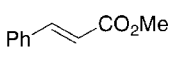
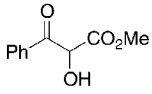
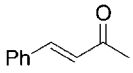
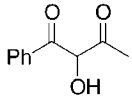
  

dard reaction conditions in competition experiments. The results are outlined in Table 4.

We were pleased to find that the ketohydroxylation is very chemoselective. The electronic influences of the substituents are responsible for the different reactivity: +I,+M substituents increase the reactivity of the olefins, whereas –I,–M substituents decrease the reactivity. One –I,+M substituent, however, generates the most reactive olefin. Hence,

Table 4. Relative reactivities between mono-, di-, and trisubstituted olefins.




| Entry[a] | A | B | C | D | C : D[b,c] |
|---|---|---|---|---|---|
| 1 |  |  |  |  | 98.9 : 1.1 (69 %) |
| | **21** | **38** | **22** | **39** | |
| 2 | **21** |  | **22** |  | 91.8 : 8.2 (67 %) |
| | | **40** | | **41** | |
| 3 | **38** | **40** | **39** | **41** | 1.2 : 98.8 (89 %) |
| 4 | **21** |  | **22** |  | 3.3 : 96.7 (91 %) |
| | | **42** | | **43** | |
| 5 | **21** |  | **22** |  | 10.9 : 91.1 (76 %) |
| | | **44** | | **45** | |
| 6 | **21** |  | **22** |  | 92.0 : 8.0 (43 %) |
| | | **46** | | **47** | |
| 7 | **21** |  | **22** |  | 97.6 : 2.4 (94 %) |
| | | **48** | | **49** | |
| 8 | **42** | **44** | **43** | **45** | 67.0 : 33.0 (68 %) |
| 9 | **42** |  | **43** |  | 97.1 : 2.9 (87 %) |
| | | **50** | | **51** | |
| 10 | **44** | **50** | **45** | **51** | 97.9 : 2.1 (79 %) |
| 11 | **42** |  | **43** |  | 98.2 : 1.8 (84 %) |
| | | **52** | | **53** | |
| 12 | **44** | **52** | **45** | **53** | 99.1 : 0.9 (92 %) |
| 13 | **50** | **52** | **51** | **53** | 97.2 : 2.8 (82 %) |
| 14 |  | **52** |  | **53** | 13.4 : 86.6 (62 %) |
| | **54** | | **55** | | |
| 15 | **54** | **37** | **55** | **38** | 8.2 : 91.8 (57 %) |

[a] All reactions were performed using 2 mmol of each olefin under the conditions listed in Table 1. [b] The product ratio was determined by GC integration. [c] Conversion of the more-reactive olefin is given in parentheses and is referenced to *n*-dodecane as internal standard.

styrene (**21**) reacts exclusively in the presence of ethyl acrylate (**38**) or 1-octene (**40**; entries 1 and 2, Table 4). The beneficial influence of alkyl substituents is evident by the fact that 1-octene possesses a higher reactivity than ethyl acrylate (entry 3, Table 4). Subsequently, the influence of a second substituent on the reactivity was investigated. Whereas 2-methylstyrene (**42**) reacts faster than styrene (entry 4, Table 4), 1-methylstyrene (**46**) shows no conversion (entry 6, Table 4). 2-Methylstyrene (**42**) is more reactive than *trans*-stilbene (**44**; entry 8, Table 4). Apparently, one –I,+M substituent increases the reactivity of an olefin whereas a second substituent of this kind decreases the reactivity. However, the chemoselectivity in this cross experiment indicated that the ketohydroxylation might be problematic in cases where electronically similar olefins are present. –I,–M substituents decrease the reactivity and allow the exclusive oxidation of the more electron-rich double bond (entries 8–13, Table 4). It is noteworthy that electron-rich trisubstituted double bonds are among the most unreactive C–C bonds − only very electron-poor olefins are oxidized slower (entry 15, Table 4).

The results obtained so far are summarized in the following reactivity chart (Figure 5).

In order to evaluate the results obtained in the cross experiments different dienes were synthesized and oxidized under the ketohydroxylation conditions. The oxidation of allyl cinnamate [**56**; see equation (1) in Scheme 3], which possesses two electronically similar disubstituted C=C double bonds, could lead to the formation of up to four different α-hydroxy ketones (**57**–**60**). However, product **57** was obtained as the major compound in the chemo- and regioselective oxidation of the more electron-rich allylic moiety (Scheme 3). In a further test experiment, bisallyl ether **61** was treated with $RuCl_3$ and Oxone® under buffered conditions [see equation (2) in Scheme 3]. We were pleased to find that the electron-rich 1,2-disubstituted double bond in **61** was predominantly oxidized to give acyloin **62** in moderate yield (Scheme 3). The lower yield might be due to an acid-assisted cleavage of the labile allyl protecting group and subsequent oxidation of the resulting allylic alcohol.[14]

In a final experiment, α-ionone **66**, which possesses an exocyclic disubstituted but electron-poor olefin and an endocyclic trisubstituted but electron rich C–C bond was oxidized. This substrate possesses several further problematic properties. Apart from the fragmentation of one or two C=C double bonds the endocyclic trisubstituted olefin can easily be shifted in the presence of acid to the thermodynamically favorable tetrasubstituted conjugated position. Furthermore, the double allylic activated tertiary C–H bond at C-1 is prone to undergo oxidation to the tertiary alcohol. However, the ketohydroxylation of α-ionone **66** led to the formation of α-hydroxy ketone **67** in diastereo- and regioisomerically pure form in moderate yield (Scheme 4). The conversion stopped at 70% conversion. The reisolated starting material proved to be α-ionone **66** in isomerically pure form. No shift of the double bond was observed. This result is remarkable since it demonstrates that an acid-assisted isomerization of the endocyclic, nonconjugated, trisubstituted C=C double bond into a conjugated, tetrasubstituted double bond and the oxidation of the labile tertiary C–H bond are slow under the ketohydroxylation conditions.

The application of the qualitative rules obtained in the cross experiments allows us to make a prediction about which is the more reactive π-bond and a very selective oxidation using $RuCl_3$ and Oxone®. Moreover, since the reaction conditions for keto- and dihydroxylation are almost identical the obtained general chemoselectivity rules can also be applied to the $RuO_4$-catalyzed dihydroxylations. The results obtained in these experiments prove $RuO_4$-catalyzed oxidations to be highly selective. In certain cases the selectivity can be improved by a simple variation of the pH and reaction temperature.

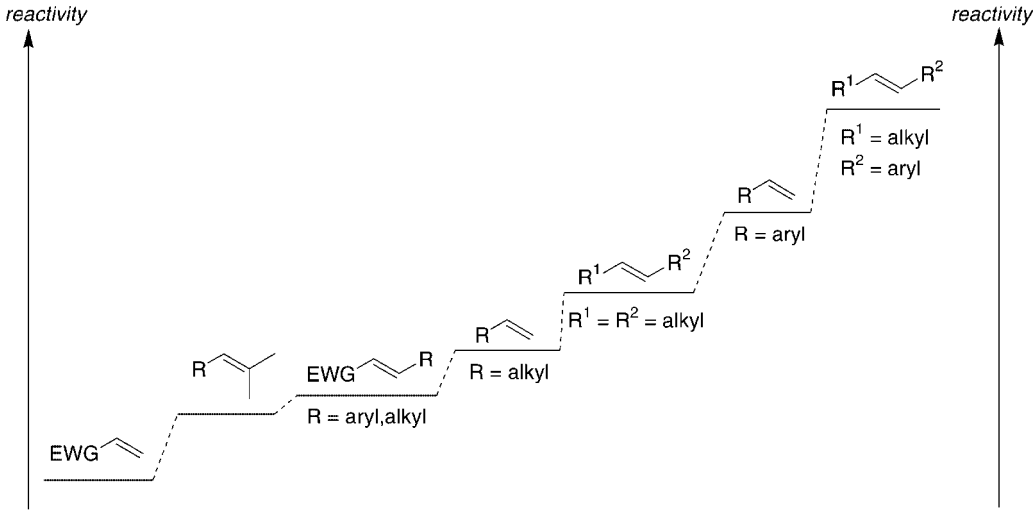
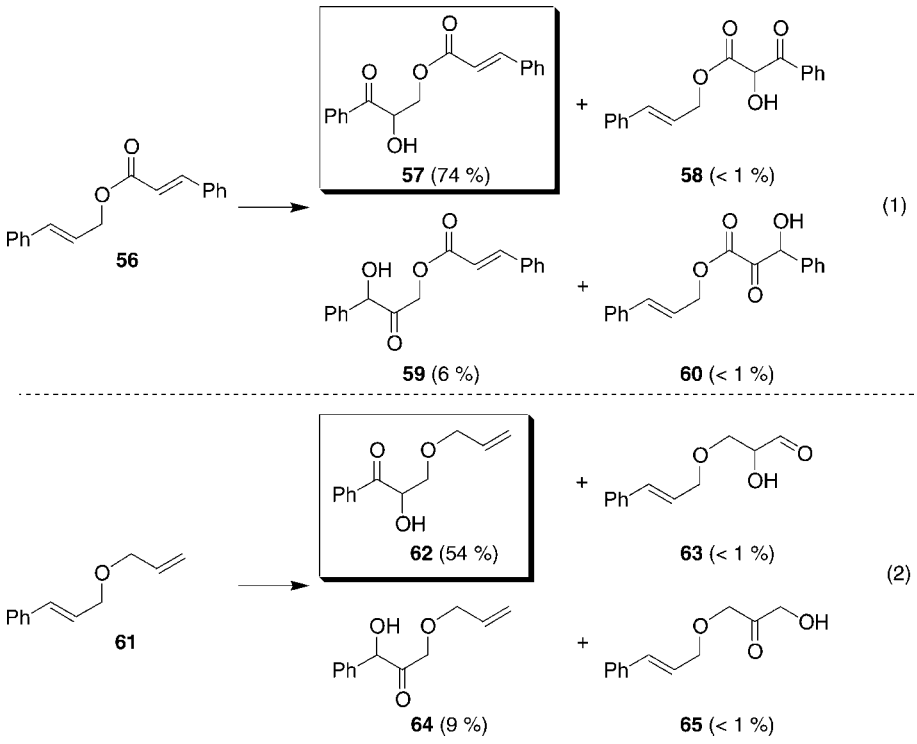
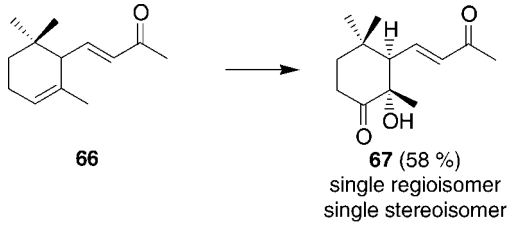



Figure 5. Reactivity profile for ketohydroxylations.




Scheme 3. Chemoselective ketohydroxylation of bis-unsaturated compounds **56** and **61**: $RuCl_3$ (1 mol-%), Oxone® (5 equiv.), $NaHCO_3$ (2.5 equiv.), EtOAc/$CH_3CN$/$H_2O$ (6:6:1), room temp.




Scheme 4. Chemoselective ketohydroxylation of α-ionone **66**: $RuCl_3$ (1 mol-%), Oxone® (5 equiv.), $NaHCO_3$ (2.5 equiv.), EtOAc/$CH_3CN$/$H_2O$ (6:6:1), room temp.

## Conclusions

The present report summarizes investigations on the selectivity of $RuO_4$-catalyzed ketohydroxylations. Although this reagent has been known as an oxidant in organic chemistry for more than fifty years, to the best of our knowledge no comprehensive study on stereo- and chemoselectivity issues has been published so far. In order to close this knowledge gap and get a deeper understanding of the reactivity and selectivity of this powerful oxidant various competition experiments were performed. The obtained data led to the development of empirical rules that allow the prediction of the most reactive functional group within a complex molecule. Furthermore, detailed investigations on the diastereoselectivity of the ketohydroxylation were performed and confirmed $RuO_4$ to be the active oxidant. The Kishi rules known from the related osmium-catalyzed dihydroxylation can be applied to the ketohydroxylation process as well. However, substituents at the chiral center known to induce good levels of diastereoselectivity usually possess a lower electron-withdrawing ability and lead to a lower regioselectivity. This selectivity dilemma can be influenced by a simple variation of the reaction temperature. A lower temperature proved to be beneficial for both regio- and stereoselectivity in the ketohydroxylation of acyclic olefins.

Contrary to common opinion, $RuO_4$, although very reactive, can act as a very selective oxidant. The stereochemical outcome of the reaction follows the Kishi rules and can be improved by lowering the reaction temperature. The empirical rules derived from various cross experiments are useful for the prediction of the chemoselectivity in $RuO_4$-catalyzed oxidations of unsaturated systems. First examples of the successful oxidation of polyfunctionalized complex organic molecules have been presented. Further work will be based on these findings and will be oriented towards the development of asymmetric $RuO_4$-catalyzed oxidation reactions.

## Experimental Section

**General Remarks:** $RuCl_3$ was obtained from Aldrich. A stock solution was prepared assuming a formula of $RuCl_3 \cdot 2H_2O$ and dissolving the catalyst (2.44 g, 10 mmol) in 100 mL of water (0.1 M). The deep brown solution can be stored on the bench for weeks without loss of activity. In cases where the regioselectivity of the oxidation was better than 90:10 only the spectroscopic data of the major isomer are reported. The order of compounds in the spectroscopic data refers to the order of elution during column chromatography or HPLC.

**General Procedure for the Ketohydroxylation:** A 100-mL round-bottomed flask equipped with magnetic stirring bar and overpressure

valve was charged with $NaHCO_3$ (420 mg, 5 mmol). A 0.1 M aqueous solution of $RuCl_3$ (200 μL, 0.02 mmol) was added and the suspension was diluted with $H_2O$ (1.8 mL), $CH_3CN$ (12 mL), and ethyl acetate (12 mL). Oxone® (6.1 g, 10 mmol) was added in one portion to the resulting brownish suspension (gas evolution!) resulting in the formation of a bright yellow suspension. At this point the reaction mixture was cooled to the desired temperature. The olefin (2 mmol) was then added in one portion. The course of the reaction was followed by TLC. After complete conversion the mixture was diluted with ethyl acetate (20 mL). The resulting suspension was filtered, the filtrate was washed with 10 mL of sat. $Na_2SO_3$ solution, and dried with $Na_2SO_4$. Filtration and evaporation under reduced pressure gave the crude product, which was purified by flash column chromatography under the given conditions.

**(1*R**,2*S**)-2-Hydroxy-3-oxocyclohexyl Acetate (*anti*-4):**[8c] Following the general procedure a mixture of regio- and diastereomeric acyloins **4** and **5** was obtained in a ratio of *anti*-**4**:*syn*-**4**:**5** of 10.2:1.0:1.3 (by HPLC integration) as a colorless oil within 10 min (261 mg, 1.52 mmol, 76%). Purification by HPLC led to the isolation of isomer *anti*-**4** (206 mg,1.20 mmol, 60%) as a colorless oil; $R_f$ = 0.23 (pentane/ethyl acetate, 1:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.70 (ddd, $J$ = 14.8, 10.0, 4.8 Hz, 1 H), 4.13 (d, $J$ = 10.0 Hz, 1 H), 3.66 (s, 1 H), 2.55 (ddd, $J$ = 14.0, 4.8, 2.8 Hz, 1 H), 2.33 (ddd, $J$ = 14.0, 5.6 Hz, 1 H), 2.12–2.23 (m, 1 H), 2.08 (s, 3 H), 1.98–2.04 (m, 1 H), 1.66–1.77 (m, 1 H, $CH_2$), 1.47–1.58 (m, 1 H, $CH_2$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.3, 170.4, 78.6, 77.2, 38.5, 29.1, 21.2, 20.7 ppm. IR (film): $\tilde{\nu}$ = 3460 cm$^{-1}$ (br. w), 2951 (m), 2872 (m), 1733 (s), 1730 (s), 1376 (m), 1245 (s), 1109 (m), 1035 (m).

**(1*R**,2*S**)-2-Hydroxy-3-oxocyclohexyl Benzoate (*anti*-7):** Following the general procedure a mixture of regio- and diastereomeric acyloins **7** and **8** was obtained in a ratio of *anti*-**7**:*syn*-**7**:**8** of 17.8:1.2:1.0 (by HPLC integration) as a colorless oil within 10 min (323 mg, 1.38 mmol, 69%). Purification by HPLC led to the isolation of isomer *anti*-**7** (288 mg, 1.22 mmol, 61%); $R_f$ = 0.13 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.05 (d, $J$ = 8.4 Hz, 2 H), 7.53 (dd, $J$ = 8.4 Hz, 1 H), 7.41 (dd, $J$ = 8.4 Hz, 2 H), 4.99 (ddd, $J$ = 10.0, 4.8 Hz, 1 H), 4.33 (d, $J$ = 10.0 Hz, 1 H), 2.60 (ddd, $J$ = 14.0, 4.0, 2.1 Hz, 1 H), 2.40 (ddd, $J$ = 14.0, 6.4 Hz, 1 H), 2.37 (m, 1 H), 2.07 (m, 1 H), 1.88 (m, 1 H), 1.64 (m, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.2, 165.8, 133.1, 129.9, 129.7, 128.3, 78.6, 77.6, 38.4, 29.1, 21.1, 20.6 ppm. IR (film): $\tilde{\nu}$ = 3466 cm$^{-1}$ (br.), 2952 (m), 2872 (m), 1731 (s), 1717 (s), 1451 (m), 1274 (s), 1112 (s), 713 (s). $C_{13}H_{14}O_4$ (234.25): calcd. C 66.66, H 6.02; found C 66.58, H 6.06.

**(1*R**,2*S**)-2-Hydroxy-3-oxocyclohexyl 2,2-Dimethylpropionate (*anti*-10):** Following the general procedure a mixture of regio- and diastereomeric acyloins **10** and **11** was obtained in a ratio of *anti*-**10**:*syn*-**10**:**11** of 28.7:1.0:3.7 (by HPLC integration) as a colorless oil within 10 min (312 mg, 1.46 mmol, 73%). Purification by HPLC led to the isolation of isomer *anti*-**10** (255 mg, 1.09 mmol, 54%); $R_f$ = 0.15 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.74 (ddd, $J$ = 10.5, 4.5 Hz, 1 H), 4.18 (d, $J$ = 10.5 Hz, 1 H), 2.57 (d, $J$ = 14.0 Hz, 1 H), 2.36 (ddd, $J$ = 14.0, 6.5 Hz, 1 H), 2.13–2.19 (m, 1 H), 2.01–2.07 (m, 1 H), 1.71–1.78 (m, 1 H), 1.53–1.59 (m, 1 H), 1.22 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.4, 177.7, 78.7, 77.1, 38.8, 38.4, 28.9, 27.0, 20.6 ppm. IR (film): $\tilde{\nu}$ = 3457 cm$^{-1}$ (br.), 2960 (m), 2872 (m), 1733 (s), 1708 (s), 1481 (m), 1461 (m), 1398 (m), 1367 (m), 1283 (s), 1161 (s), 734 (s). $C_{11}H_{18}O_4$ (214.26): calcd. C 61.66, H 8.47; found C 61.69, H 8.46.

**Ketohydroxylation of 1,3-Diphenylallyl Acetate (12):** Following the general procedure a mixture of regio- and diastereomeric acyloins **13** and **14** was obtained in a ratio of *anti*-**13**:*syn*-**13**:**14** of 2.4:1.0:1.0 (by HPLC integration) as a colorless oil within 20 min (403 mg, 1.42 mmol, 71%). Separation of the isomers was performed by HPLC.

***Fraction 1*:** A mixture of diastereomers *anti*-**14** and *syn*-**14** was obtained.

**3-Hydroxy-2-oxo-1,3-diphenylpropyl Acetate (14):** Colorless oil. $R_f$ = 0.42 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.42 (m, $H_{arom.}$), 7.20–7.25 (m, $H_{arom.}$), 7.11–7.17 (m, $H_{arom.}$), 6.96–6.99 (m, $H_{arom.}$), 5.99 (s, 1 H, 1-$H_{anti}$), 5.97 (s, 1 H, 1-$H_{syn}$), 5.42 (d, $J$ = 3.5 Hz, 1 H, 3-$H_{syn}$), 5.01 (d, $J$ = 5.0 Hz, 1 H, 3-$H_{anti}$), 3.97 (d, $J$ = 5.0 Hz, 1 H, $OH_{anti}$), 3.91 (d, $J$ = 3.5 Hz, 1 H, $OH_{syn}$), 2.10 (s, 3 H, $OAc_{anti}$), 2.04 (s, 3 H, $OAc_{syn}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 204.8, 203.4, 170.3, 169.8, 136.9, 136.2, 132.5, 132.4, 129.8, 129.3, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 78.8, 77.5, 76.9, 20.5, 20.4 ppm. IR (film): $\tilde{\nu}$ = 3475 cm$^{-1}$ (br.), 3032 (m), 1739 (s), 1731 (s), 1495 (m), 1455 (m), 1232 (s), 1035 (m), 1028 (m), 749 (m), 699 (s). $C_{17}H_{16}O_4$ (284.10): calcd. C 71.82, H 5.67; found C 71.87, H 5.64.

***Fraction 2*: (1*S**,2*R**)-2-Hydroxy-3-oxo-1,3-diphenylpropyl Acetate (*syn*-13):**[15] Colorless oil. $R_f$ = 0.41 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.05 (d, $J$ = 7.6 Hz, 2 H), 7.65 (dd, $J$ = 7.6 Hz, 1 H), 7.54 (dd, $J$ = 7.6 Hz, 1 H), 7.21–7.22 (m, 3 H), 7.06–7.09 (m, 2 H), 7.11 (d, $J$ = 3.2 Hz, 1 H), 5.57 (dd, $J$ = 7.2, 3.2 Hz, 1 H), 3.63 (d, $J$ = 7.2 Hz, 1 H), 2.11 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 198.8, 169.5, 136.6, 134.1, 129.8, 128.9, 128.5, 128.4, 128.3, 126.9, 75.6, 75.1, 20.7 ppm. IR (film): $\tilde{\nu}$ = 3468 cm$^{-1}$ (br. w), 3064 (m), 1741 (s), 1686 (s), 1451 (m), 1372 (m), 1233 (s), 1028 (m), 756 (m), 733 (m), 699 (s).

***Fraction 3*: (1*S**,2*S**)-3-Hydroxy-2-oxo-1,3-diphenylpropyl Acetate (*anti*-13):**[15] Colorless oil. $R_f$ = 0.30 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.07 (d, $J$ = 6.4 Hz, 2 H), 7.67 (dd, $J$ = 6.4 Hz, 1 H), 7.56 (dd, $J$ = 6.4 Hz, 2 H), 7.23–7.28 (m, 3 H), 7.08–7.12 (m, 2 H), 6.14 (d, $J$ = 4.6 Hz, 1 H), 5.60 (d, $J$ = 4.6 Hz, 1 H), 3.66 (s, 1 H), 2.13 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 197.8, 170.5, 134.5, 129.1, 128.9, 128.6, 128.0, 127.4, 77.0, 75.1, 21.0 ppm. IR (film): $\tilde{\nu}$ = 3464 cm$^{-1}$ (br.), 3065 (m), 1736 (s), 1685 (s), 1451 (m), 1374 (m), 1235 (s), 1117 (m), 1029 (m), 758 (m), 733 (m), 698 (s).

**Ketohydroxylation of 1,3-Diphenylallyl Methyl Ether (15):** Following the general procedure a mixture of regio- and diastereomeric acyloins **16** and **17** was obtained in a ratio of *anti*-**16**:*syn*-**16**:*anti*-**17**:*syn*-**17** of 5.3:3.2:1.6:1.0 (by HPLC integration) as a colorless oil within 20 min (425 mg, 1.66 mmol, 83%). Separation of the isomers was performed by HPLC.

***Fraction 1*: (2*R**,3*S**)-2-Hydroxy-3-methoxy-1,3-diphenylpropan-1-one (*syn*-16):**[16] Colorless oil. $R_f$ = 0.33 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.91 (d, $J$ = 10.5 Hz, 2 H), 7.60 (dd, $J$ = 10.5 Hz, 1 H), 7.49 (dd, $J$ = 10.5 Hz, 2 H), 7.31 (m, 3 H), 7.23 (m, 2 H), 5.15 (dd, $J$ = 7.5, 4.0 Hz, 1 H), 4.53 (d, $J$ = 4.0 Hz, 1 H), 3.74 (d, $J$ = 7.5 Hz, 1 H), 3.09 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.9, 133.8, 128.8, 128.7, 128.5, 128.3, 127.5, 84.3, 57.4, 36.4 ppm. IR (film): $\tilde{\nu}$ = 3468 cm$^{-1}$ (br.), 3062 (m), 2932 (m), 1686 (s), 1597 (m), 1450 (m), 1263 (m), 1092 (s), 978 (m), 756 (m), 700 (s), 577 (m).

***Fraction 2*: (1*S**,3*S**)-1-Hydroxy-3-methoxy-1,3-diphenylpropan-2-one (*anti*-17):** Colorless oil. $R_f$ = 0.33 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27–7.34 (m, 8 H), 7.10–7.17 (m, 2 H), 5.61 (s, 1 H), 4.55 (s, 1 H), 3.09 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.7, 136.5, 134.1, 128.7, 128.6, 128.5, 128.4, 127.9, 127.7, 85.7, 57.2, 36.3 ppm. IR (film): $\tilde{\nu}$ = 3463 cm$^{-1}$ (br), 2930 (m), 1725 (s), 1452 (m), 1097 (m), 1049 (m), 698 (m).

$C_{16}H_{16}O_3$ (256.30): calcd. C 74.98, H 6.29; found C 74.95, H 6.29.

***Fraction 3*: (2*S**,3*S**)-2-Hydroxy-3-methoxy-1,3-diphenylpropan-1-one (*anti*-16):**[16] Colorless oil. $R_f$ = 0.32 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.81 (d, $J$ = 8.5 Hz, 2 H), 7.57 (dd, $J$ = 8.5 Hz, 1 H), 7.42 (dd, $J$ = 8.5 Hz, 2 H), 7.21–7.27 (m, 3 H), 7.08–7.12 (m, 2 H), 5.36 (dd, $J$ = 7.0, 5.0 Hz, 1 H), 4.48 (d, $J$ = 5.0 Hz, 1 H), 3.52 (d, $J$ = 7.0 Hz, 1 H), 3.22 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 199.7, 136.3, 135.2, 133.9, 128.8, 128.7, 128.4, 128.3, 127.6, 85.7, 76.3, 57.4, 36.3 ppm. IR (film): $\tilde{\nu}$ = 3465 cm$^{-1}$ (br), 2934 (m), 2825 (m), 1683 (s), 1597 (s), 1450 (m), 1278 (m), 1107 (s), 976 (m), 757 (m), 701 (s), 569 (m).

***Fraction 4*: (1*R**,3*S**)-1-Hydroxy-3-methoxy-1,3-diphenylpropan-2-one (*syn*-17):** Colorless oil. $R_f$ = 0.32 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27–7.37 (m, 5 H), 7.18–7.25 (m, 3 H), 7.11–7.16 (m, 2 H), 5.17 (s, 1 H), 4.76 (s, 1 H), 4.10 (s, 1 H), 3.15 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 206.5, 137.5, 134.9, 129.2, 129.1, 129.0, 128.1, 127.9, 85.6, 57.1, 36.3 ppm. IR (film): $\tilde{\nu}$ = 3466 cm$^{-1}$ (br), 3062 (m), 2933 (m), 2827 (m), 1719 (s), 1493 (m), 1455 (m), 1199 (m), 1101 (m), 1048 (m), 747 (m), 699 (s). $C_{16}H_{16}O_3$ (256.30): calcd. C 74.98, H 6.29; found C 75.00, H 6.29.

**Ketohydroxylation of (1*R**,4*R**)-4-Acetoxycyclohex-2-enyl Acetate (18):** Following the general procedure a mixture of diastereoisomeric acyloins *syn*-**20** and *anti*-**20** (2.1:1.0) was obtained (326 mg, 1.52 mmol, 76%) at room temperature within 15 min, which was separated by HPLC (pentane/ethyl acetate).

***Fraction 1*: (1*R**,3*R**,4*R**)-4-Acetoxy-3-hydroxy-2-oxocyclohexyl Acetate (*syn*-20):** Colorless oil; $R_f$ = 0.28 (pentane/ethyl acetate, 1:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.46 (m, 1 H), 5.21 (m, 1 H), 4.60 (d, $J$ = 4.0 Hz, 1 H), 1.95–2.18 (m, 4 H), 2.10 (s, 3 H), 2.01 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 205.1, 171.5, 171.1, 76.9, 76.8, 75.1, 28.4, 27.9, 24.4, 22.3 ppm. IR (film): $\tilde{\nu}$ = 3452 cm$^{-1}$ (br), 2941 (m), 2856 (m), 1738 (s), 1736 (s), 1721 (s), 1367 (m), 1233 (s), 1048 (m), 1022 (m). $C_{10}H_{14}O_6$ (230.21): calcd. C 52.17, H 6.13; found C 52.16, H 6.15.

***Fraction 2*: (1*R**,3*S**,4*R**)-4-Acetoxy-3-hydroxy-2-oxocyclohexyl Acetate (*anti*-20):** Colorless oil; $R_f$ = 0.28 (pentane/ethyl acetate, 1:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.23 (ddd, $J$ = 12.4, 6.8, 2.0 Hz, 1 H), 4.71 (ddd, $J$ = 10.8, 10.0, 4.0 Hz, 1 H), 4.27 (dd, $J$ = 10.8, 2.0 Hz, 1 H), 3.51 (s, 1 H), 2.20–2.32 (m, 2 H), 2.15 (s, 3 H), 2.10 (s, 3 H), 1.63–1.82 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 202.6, 171.7, 171.3, 79.0, 77.8, 75.6, 27.6, 26.6, 22.5, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3469 cm$^{-1}$ (br), 2932 (m), 1734 (s), 1730 (s), 1709 (s), 1458 (m), 1374 (s), 1236 (s), 1027 (s). $C_{10}H_{14}O_6$ (230.21): calcd. C 52.17, H 6.13; found C 52.19, H 6.12.

**2-Hydroxy-3-oxo-3-phenylpropyl 3′-Phenylacrylate (57):** Yield: 438 mg (1.48 mmol, 74%); colorless oil; $R_f$ = 0.28 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.99 (m, 2 H), 7.59–7.63 (m, $J$ = 16.0 Hz, 2 H), 7.44–7.51 (m, 3 H), 7.33–7.37 (m, 4 H), 6.37 (d, $J$ = 16.0 Hz, 1 H), 5.37 (dd, $J$ = 6.0, 3.6 Hz, 1 H), 4.68 (dd, $J$ = 12.0, 3.6 Hz, 1 H), 4.23 (dd, $J$ = 12.0, 6.0 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 198.7, 166.1, 145.9, 137.3, 134.6, 133.6, 130.6, 129.2, 129.0, 128.8, 127.4, 117.2, 72.2, 67.0 ppm. IR (film): $\tilde{\nu}$ = 3463 cm$^{-1}$ (br), 1714 (s), 1636 (s), 1450 (m), 1311 (m), 1281 (m), 1169 (s), 980 (m), 768 (s). $C_{18}H_{16}O_4$ (296.32): calcd. C 72.96, H 5.44; found C 73.01, H 5.41.

**3-Allyloxy-2-hydroxy-1-phenylpropan-1-one (62):** Yield: 222 mg (1.08 mmol, 54%); colorless oil; $R_f$ = 0.28 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.93 (d, $J$ = 8.0 Hz, 2 H), 7.63 (dd, $J$ = 8.0 Hz, 1 H), 7.50 (dd, $J$ = 8.0 Hz, 2 H), 5.75 (m, 1 H), 5.08–5.21 (m, 3 H), 3.94 (m, 2 H), 3.80 (dd, $J$ = 10.0, 2.5 Hz, 1 H), 3.72 (dd, $J$ = 10.0, 4.5 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 199.5, 134.1, 134.0, 133.9, 128.8, 128.6, 117.2, 73.7, 72.6, 72.5 ppm. IR (film): $\tilde{\nu}$ = 3789 cm$^{-1}$ (br), 2960 (m), 1689 (s), 1598 (m), 1449 (m), 1235 (m), 1119 (s), 692 (m). $C_{12}H_{14}O_3$ (206.24): calcd. C 69.88, H 6.84; found C 69.92, H 6.86.

**(2*S**,3*R**)-2-Hydroxy-2,4,4-trimethyl-3-(3′-oxo-but-1′-enyl)cyclohexanone (67):** Yield: 260 mg (1.16 mmol, 58%); colorless oil; $R_f$ = 0.18 (pentane/ethyl acetate, 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.84 (dd, $J$ = 15.6, 10.4 Hz, 1 H), 6.19 (d, $J$ = 16.0 Hz, 1 H), 2.78 (ddd, $J$ = 14.4, 5.6 Hz, 1 H), 2.42 (ddd, $J$ = 14.4, 3.2 Hz, 1 H), 2.26 (s, 3 H), 2.23 (d, $J$ = 10.4 Hz, 1 H), 1.85 (ddd, $J$ = 14.0, 5.6, 3.2 Hz, 1 H), 1.64 (ddd, $J$ = 14.0, 3.6 Hz, 1 H), 1.36 (s, 3 H), 1.19 (s, 3 H), 0.88 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 212.6, 197.9, 141.5, 135.4, 62.3, 41.5, 34.7, 34.4, 31.9, 28.5, 23.3, 21.5, 14.6 ppm. IR (film): $\tilde{\nu}$ = 3475 cm$^{-1}$ (br), 2962 (m), 2858 (m), 1716 (s), 1672 (s), 1361 (m), 1256 (m), 1123 (m), 1055 (m), 987 (m). $C_{13}H_{20}O_3$ (224.14): calcd. C 69.61, H 8.99; found C 69.56, H 8.93.

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