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The RuO_4-Catalyzed Ketohydroxylation. Part 1. Development, Scope, and Limitation

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A new straightforward oxidation of C,C-double bonds to unsymmetrical α-hydroxy ketones using catalytic amounts of $RuCl_3$ and stoichiometric amounts of Oxone under buffered conditions has been developed, a reaction for which we coined the expression "ketohydroxylation". The transformation allows the direct formation of α-hydroxy ketones (acyloins) from olefins without intermediate formation of *syn*-diols. The present paper will provide detailed information starting with the underlying concept and the subsequent development of the reaction. The effect of base, solvent stoichiometry, and temperature will be discussed resulting in an improved mechanistic model that might help to explain the influence of different reaction parameters on reactivity and selectivity in RuO_4-catalyzed oxidations of C,C-double bonds. Furthermore, an improved workup procedure allows the recovery of the ruthenium catalyst by precipitation while simplifying the overall product purification. The second part of the paper focuses on exploration of scope and limitation. A variety of substituted olefins are oxidized to α-hydroxy ketones in good to excellent regioselectivities and yield. Cyclic substrates proved to be problematic to oxidize; however, a careful analysis of temperature effects resulted in the development of a successful protocol for the ketohydroxylation of cyclic substrates by simply decreasing the reaction temperature.

Introduction

Chiral α-oxygenated carbonyl compounds (acyloins) are useful building blocks in organic synthesis and structural motifs in a variety of biological active natural products. The macrolides amphidinolides T1−T4, for example, differ only in the regio- and stereochemical arrangement of the α-hydroxy ketone (Figure 1).[1]

Given the importance of these macrocyclic compounds with regard to their biological activity[1d] a both regio- and stereoselective access toward α-hydroxy ketones is of high synthetic interest. Different retrosynthetic approaches have been investigated in the past. Consequently, asymmetric protocols for the benzoin condensation[2] and the α-hydroxylation of carbonyl compounds[3−5] have been developed giving rise to a variety of enantiomerically enriched acyloins. With regard to recent progress in the field of olefin metathesis[6] we envisioned the direct asymmetric oxidation of olefins to α-hydroxy ketones to

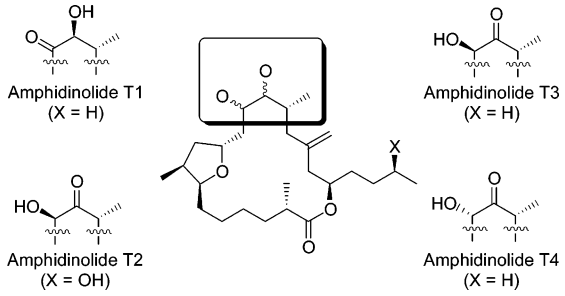

FIGURE 1. Acyloin substructure in amphidinolides T1−T4.

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be a synthetically interesting transformation. However, whereas the dihydroxylation of alkenes has been in the center of research for more than 30 years[7] the direct oxidation of a C,C-double bond to an α-hydroxy ketone has almost been neglected.[8−11] Based upon results obtained during investigations in RuO_4-catalyzed dihydroxylations,[12] we recently reported a new RuO_4-catalyzed direct ketohydroxylation of olefins. This reaction, although not enantioselective at the moment, represents a first and important step toward the development of the attempted asymmetric direct oxidation of olefins to α-hydroxy ketones.[13] The present paper gives a full account on the basic ideas and the subsequent development of this new direct oxidation reaction. Furthermore, the workup procedure was significantly improved compared to our original report. Whereas an aqueous workup allows the removal of the catalyst, we were able to reisolate different ruthenium−oxo compounds by simple centrifugation or filtration during an anhydrous workup. The reisolated catalyst was used in different runs during the ketohydroxylation and proved to be catalytically active. The second part will provide a full account of the scope and limitations of this new catalytic process with a special focus on functional group tolerance and temperature effects in the oxidation of cyclic olefins.

Results and Discussion

Concept. RuO_4 is isoelectronic to OsO_4. Hence, both cyclic ruthenates and osmates are primary intermediates in the oxidation of C,C-double bonds.[14] The hydrolysis of these compounds furnishes *vic*-diols. From a mechanistic point of view, the hydrolysis proceeds via a nucleophilic addition of water to the metal center while cleaving one of the two metal−oxygen bonds. A subsequent second nucleophilic attack furnishes the desired diol. In osmium-catalyzed dihydroxylations the hydrolysis is the rate-limiting step.[15] Hence, different promoters for an accelerated hydrolysis have been identified. Akashi[16] reported on the beneficial influence of tetra-*n*-alkylammonium acetates while Sharpless[17] described the accelerated dihydroxylation using stoichiometric amounts of sulfonamides. In either reaction, the promoter represents a better nucleophile than water facilitating the initial metal−oxygen bond cleavage in the osmate. As an alternative to the addition of an external promoter a fine-tuning of the pH value can lead to an accelerated hydrolysis. Recently, we reported the acid-accelerated ruthenium-catalyzed dihydroxylation.[12] The addition of catalytic amounts of H_2SO_4 resulted in a dramatic increase in the rate of hydrolysis.[18]

Our concept for the development of a direct RuO_4-catalyzed ketohydroxylation is based upon the following facts and ideas:

(i) RuO_4 is less expensive and toxic compared to OsO_4.

(ii) During the initial [3 + 2]-cycloaddition of RuO_4 to the C,C-double bond two stereocenters with defined relative configuration are generated. This introduction of stereoinformation differs significantly from the Murahashi protocol,[11] in which the final stereocenter is introduced via a nucleophilic addition of water to a planar carbocation. Whereas a stereoselective addition of this type is difficult to control, our protocol introduces the center of chirality at an early stage of the catalytic cycle. With regard to an asymmetric ketohydroxylation the problem of stereoselectivity is finally reduced to an enantioselective [3 + 2]-cycloaddition.

(iii) In analogy to the osmium-catalyzed dihydroxylation the nucleophilic addition of water, i.e., the hydrolysis, should occur at the stage of an ruthenium(VIII)−ester **III** (Figure 2). The results obtained for the ruthenium-catalyzed dihydroxylation clearly indicated that an accelerated nucleophilic addition might be achieved at pH < 7.[12]

(iv) If the addition of an alternative nucleophile is possible, the addition of a nucleophilic oxidant would result in highly reactive ruthenium(VIII)−peroxo ester **VI** (Figure 2) that could collapse to give the α-hydroxy ketone **VII** without corrupting the stereocenter in the final product. Figure 2 visualizes this mechanistic dichotomy.

Different problematic issues needed to be addressed during the development of the ketohydroxylation:

(i) The nucleophile has to add to the metal center faster than water.

(ii) The oxidation potential of the nucleophile has to be high enough to oxidize ruthenium(VI) to ruthenium(VIII).

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(iii) Unsymmetrical substituted double bonds can lead to complex mixtures of diols and regioisomeric acyloins.

Development. It is known that RuO_4 tends to cleave C,C-double bonds very fast.[12,19] However, intense investigations on the related ruthenium-catalyzed dihydroxylation carried out in our group indicated that the nucleophilic addition of water to the ruthenate is fast in a 3:3:1 mixture of ethyl acetate, acetonitrile, and water. Any other solvent combination facilitated the scission reaction.[12] Hence, we chose this ternary solvent mixture as a starting point. The development of the ketohydroxylation started with the search for an appropriate reoxidation system matching our criteria of a nucleophilic and oxidizing agent. To act as a nucleophile the oxygen part of the oxidant has to add to the metal center in ruthenate **III** (Figure 2). This process competes with the addition of water present in the reaction mixture. To accelerate the nucleophilic addition a 5-fold excess of the oxidizing agent was used whereas the amount of water was significantly lowered. Different reoxidation systems were tested. The acidic Oxone in combination with $NaHCO_3$ proved successful (Table 1).[19]

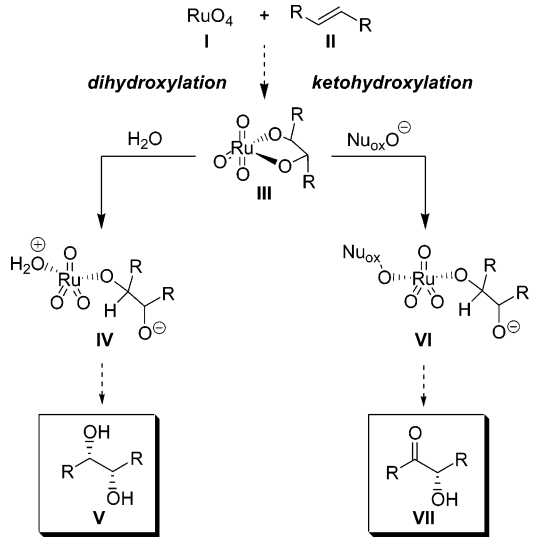

FIGURE 2. Nucleophilic addition of a reoxidant vs water.

These results are in line with our observations of a rate acceleration in ruthenium-catalyzed dihydroxylation by addition of Brönstedt acids.[12] Subsequently, we investigated the influence of the solvent stoichiometry on product distribution and reactivity. We envisioned the amount of water to be crucial for the outcome of the reaction. Water is needed in order to activate the Oxone; however, it competes in the nucleophilic addition. Hence, different solvent stoichiometries were tested. The results are listed in Table 2.

The amount of water determines the product distribution. More water favors the formation of scission products while less water pushes the selectivity toward the acyloin formation. Knowing the optimum solvent stoichiometry we investigated the influence of base on the reaction. Different basic salts as well as organic nitrogen bases were used under the standard reaction conditions. The results are listed in Table 3.

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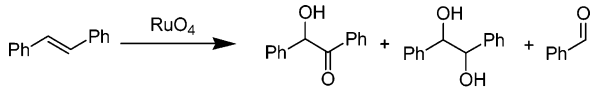
TABLE 1. Influence of Reoxidant



entry	reoxidant[a]	time	conversion[b] (%)	**2/3/4**[c] (%)
1	*t*-BuOOH, Et_4NOH	1 d	30	17:5:78
2	H_2O_2, Et_4NOH	1 d	12	n.d.
3	NaOCl	60 min	60	15:10:75
4	Oxone, $NaHCO_3$[d]	10 min	80	66:23:11

[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 room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water) and 5 equiv of reoxidant. [b] Determined by GC integration. [c] Percentage refers to the amount of product in the mixture. [d] 1.5 equiv $NaHCO_3$ was used.

TABLE 2. Influence of Solvent Stoichiometry

entry	EtOAc/CH_3CN/H_2O[a]	conversion[b] (%)	**2/3/4**[b] (%)
1	1:1:2	82	13:9:78
2	1:1:1	84	28:15:57
3	2:2:1l	81	49:10:41
4	3:3:1	80	66:23:11
5	6:6:1	83	75:7:18
6	6:3:1	51	n.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 room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water) and 5 equiv of reoxidant and stopped after 10 min. [b] Determined by GC integration.

TABLE 3. Influence of Base

entry	base[a]	conversion[b] (%)	**2/3/4**[b] (%)
1	$NaHCO_3$	83	75:7:18
2	Na_2CO_3[c]	12	n.d.
3	NaOH	8	n.d.
4	$CsCO_3$[c]	15	n.d.
5	Et_4NOH	19	n.d.
6	Et_3N	23	n.d.
7	pyridine	7	n.d.
8	DMAP	9	n.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 room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water), 5 equiv of reoxidant, and 1.5 equiv of base and stopped after 10 min. [b] Determined by GC integration. [c] 0.75 equiv of base was used.

A strong effect of the base on the reactivity of the system was observed. Whereas carbonates or organic nitrogen bases inhibit the reaction, $NaHCO_3$ gave good results. The influence of base is not clear at the moment; however, it was noted that in cases with low reactivity (entries 2−5, Table 3) the yellow color of the RuO_4 was not observed. Apparently, hydroxides or carbonates are too basic leading to a preferred formation of perruthenate RuO_4^-.[20] The inhibitory effect of the organic nitrogen bases (entries 6 and 7, Table 3), however, is not fully understood. Due to the known complexation ability of these bases with $RuCl_3$ the formation of catalytically inactive low valent ruthenium−base adducts might be possible.[21]

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TABLE 4. Influence of the Amount of Base

entry	$NaHCO_3$[a] (equiv)	conversion[b] (%)	**2/3/4**[b] (%)
1	0	58	48:15:37
2	1	38	61:23:16
3	2	79	81:12:7
4	2.5	96	98:0:2
5	3	81	86:6:8
6	4	73	41:3:56
7	5	86	21:6:73

[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 room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water), 5 equiv of Oxone, and the given amount of $NaHCO_3$ and stopped after 10 min. [b] Determined by GC integration.

TABLE 5. Temperature Effect

entry	T[a] (°C)	conversion[b] (%)	**2/3/4**[b] (%)
1	0	59	96:0:4
2	10	67	94:0:6
3	20	96	98:0 8
4	40	75	58:15:27
5	60	67	5:27:68

[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 room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water), 5 equiv of reoxidant, and 2.5 equiv of $NaHCO_3$ and stopped after 10 min. [b] Determined by GC integration.

With regard to the pH-dependent oxidation rate in RuO_4-catalyzed dihydroxylations[12] the influence of the stoichiometry Oxone/$NaHCO_3$ was investigated next (Table 4).

The reaction course changes drastically within the investigated pH range. There is an apparent maximum at a stoichiometry of Oxone/$NaHCO_3$ (2:1) (entry 4, Table 4). At higher base concentrations the hydrolysis of the less activated ruthenate is slow compared to the electrocyclic ring cleavage.[19] Hence, fission products such as **4** are formed predominantly. At lower pH values the reaction rate is accelerated; however, at a certain point the selectivity drops again. This observation might be explained by the fact that both the nucleophilic attack of SO_5^{2-} and of H_2O is accelerated leading to a mixture of diol, ketol, and aldehyde with the diol being cleaved in a concomitant step.[22] The influence of protons on the rate of the reaction underlines the hypothesis of the hydrolysis or any other nucleophilic addition being the rate-limiting step in either RuO_4-catalyzed oxidation.

In ruthenium-catalyzed dihydroxylations a strong interplay between temperature and selectivity was observed.[12] In general, electrocyclic fragmentations are faster at elevated temperature. Consequently, the influence of the temperature on the ketohydroxylation was investigated. The results are listed in Table 5.

The temperature influences the selectivity of the reaction. Whereas a temperature below 20 °C reduces the conversion without changing the selectivity, higher temperatures lead to a predominant formation of scission products. Furthermore, black precipitates of catalytically inactive ruthenium compounds responsible for the lower conversion are formed. At this point we reinvestigated the influence of solvent. The results are listed in Table 6.

(22) RuO_4 catalyzes efficiently the cleavage of *vic*-diols: see ref 12b.

TABLE 6. Solvent Effect

entry	solvent[a]	conversion[b] (%)	**2/3/4**[b] (%)
1	EtOAc	96	98:0:2
2	MTBE[c]	59	87:5:8
3	CH_2Cl_2	23	13:16:71
4	$CHCl_3$	17	n.d.
5	CCl_4	n.d.	n.d.
6	hexane	n.d.	n.d.
7	*tert*-butyl alcohol	89	0:27:73
8	acetone	84	65:18:17

[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 room temperature using 1 mol % $RuCl_3$ (as a 0.1 M stock solution in water), 5 equiv of reoxidant, and 2.5 equiv of $NaHCO_3$ and stopped after 10 min. [b] Determined by GC integration. [c] Methyl *tert*-butyl ether.

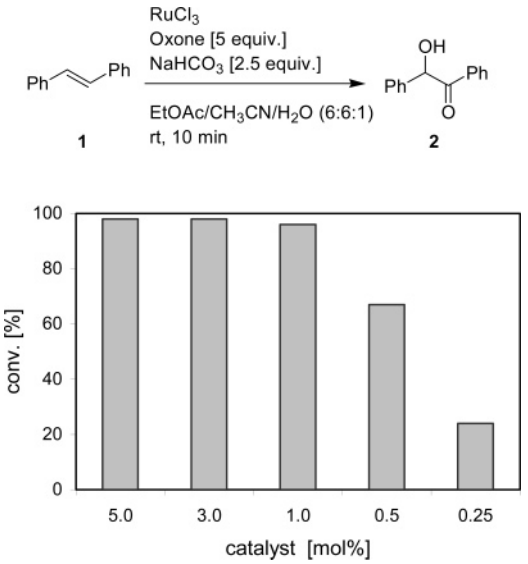


FIGURE 3. Optimization of catalyst concentration.

As in the dihydroxylation ethyl acetate proved to be the solvent of choice. *tert*-Butyl alcohol speeds up the addition of water rather than persulfate, whereas polar aprotic solvents lower the conversion and selectivity.

Having in hand the optimized conditions for the ketohydroxylation we finally investigated the amount of catalyst needed for an efficient oxidation. As can be seen in Figure 3 the conversion drops significantly at a catalyst concentration below 1 mol % (Figure 3).

In summary, the course of the reaction is influenced by the nature of the reoxidant, the pH value of the reaction medium, and the temperature.

Optimization of the Workup: Reisolation of the Catalyst. In most RuO_4-catalyzed oxidations the active catalyst is destroyed during the workup procedure by addition of reducing agents. However, due to the presence of acetonitrile in the reaction mixture it is impossible to remove the entire amount of catalyst during the workup. Hence, we were seeking an optimized workup that would allow the use of a minimum amount of solvent while reisolating the ruthenium catalyst by precipitation. Different from other oxidation reactions, we did not observe the formation of black ruthenium−oxo precipitates during the ketohydroxylation reaction. The organic layer had a yellow color even after complete conversion. This observation inspired us to develop an "anhydrous" work-

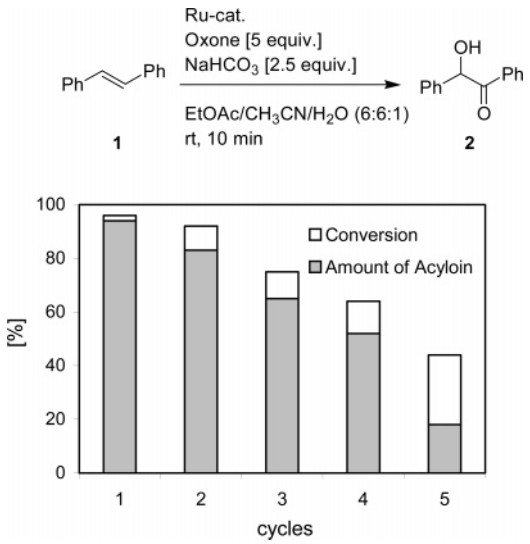


FIGURE 4. Activity of reisolated ruthenium compounds (reactions were performed on a 100 mmol scale).

up with the goal of reisolating the catalyst (vide infra). This new procedure allows the precipitation of ruthenium-oxo compounds upon evaporation of the solvent. The precipitates were removed by centrifugation and dried in a vacuum. Treating the purple-black solid with Oxone under the ketohydroxylation conditions resulted in a yellow organic layer. Although the activity and chemoselectivity drops after two reaction cycles, this procedure allows a partial recovery of an active ruthenium catalyst while simplifying the overall workup and product purification. Preliminary results on the activity of the reisolated ruthenium−oxo species in the oxidation of *trans*-stilbene **1** are shown in Figure 4.

The ketohydroxylation was performed on a 100-mmol scale. The yields and product distributions were identical to those obtained on a 2-mmol scale. Apart from this important result the activity of the recycled catalyst was analyzed. The amount of acyloin formed after four reisolation cycles is lower indicating that the reisolated catalyst might differ in the reactivity. However, the concept of reisolating the catalyst by precipitation appears to be promising. We are currently trying to develop a more selective "ruthenium scavenger" that allows the separation of the ruthenium catalyst directly from the product solution.

Mechanistic Proposal. The interplay of fragmentation, dihydroxylation, and ketohydroxylation is shown in the preliminary mechanistic proposal in Figure 5. The initial [3 + 2]-cycloaddition of ruthenium tetraoxide **I** to the double bond in **VIII** leads to ruthenium(VI) compound **IX**, which is oxidized to ruthenate **XII**. This compound can react in different ways. Apart from an electrocyclic fragmentation (path C) resulting in the formation of scission products **X** and **XI** the competing nucleophilic addition of water (path A) versus SO_5^{2-} (path B) determines the product composition. A low amount of water in the reaction combined with the excess of Oxone favors the addition of SO_5^{2-} to the metal center in **XIV**. Upon addition of SO_5^{2-} to the activated ruthenate **XIV** a mixed peroxoruthenate **XV** is formed, which collapses to give the desired α-hydroxy ketone **XVI** and RuO_4 **I**.

Apart from these productive mechanistic pathways a destructive background reaction is important in RuO_4-catalyzed oxidations as indicated in Figure 5: The condensation (path D) between diol **XIII** and **I** results in the formation of ruthenate **XII**, which can either be attacked by HSO_5^- or undergo an electrocyclic fragmentation (path C). Recently, we showed that the reaction according to path is much slower compared to the direct oxidation of olefins and is therefore most likely responsible for the formation of scission products in RuO_4-catalyzed oxidations after longer reaction times. How-

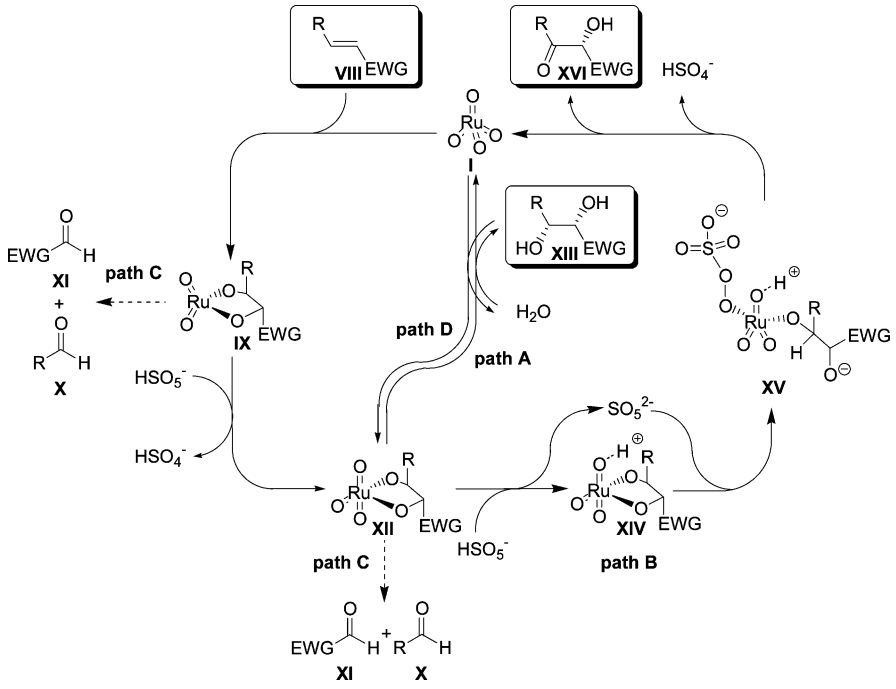
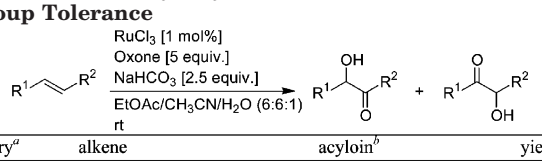
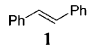
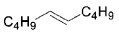
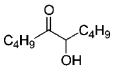
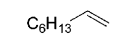
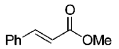
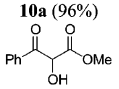
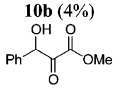
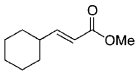
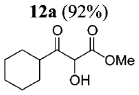
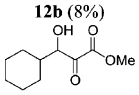
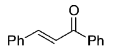
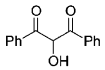
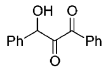
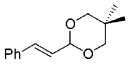
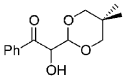
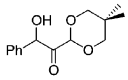
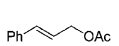
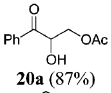
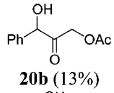
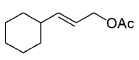
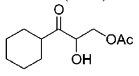
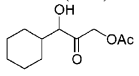
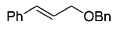
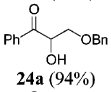
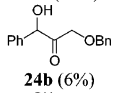
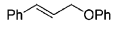
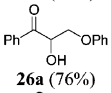
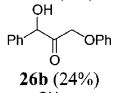
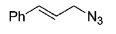
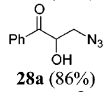
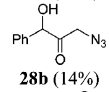
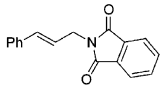
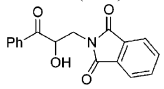


FIGURE 5. Mechanistic relationship between the ruthenium-catalyzed dihydroxylation (path A), ketohydroxylation (path B), fragmentation (path C), and mono oxidation (path D).

TABLE 7. Ketohydroylation of Olefins: Functional Group Tolerance



entry[a]	alkene	acyloin[b]	yield[%][c]
1	 **1**	 **2**	96
2	 **5**	 **6**	87
3	 **7**	 **8a**(97%)	 **8b** (3%)	66
4	 **9**	 **10a** (96%)	 **10b** (4%)	64
5	 **11**	 **12a** (92%)	 **12b** (8%)	76
6	 **13**	 **14a** (96%)	 **14b** (4%)	82
7	 **15**	 **16a** (97%)	 **16b** (3%)	54
8	 **17**	 **18a** (94%)	 **18b** (6%)	64
9	 **19**	 **20a** (87%)	 **20b** (13%)	68
10	 **21**	 **22a** (78%)	 **22b** (22%)	76
11	 **23**	 **24a** (94%)	 **24b** (6%)	86
12	 **25**	 **26a** (76%)	 **26b** (24%)	73
13	 **27**	 **28a** (86%)	 **28b** (14%)	68
14	 **29**	 **30a** (71%)	**30b** (29%)	84
15	**31**	**32a** (96%)	**32b** (4%)	89
16	**33**	**34a** (95%)	**34b** (5%)	84

[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 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 $NaHCO_3$. [b] Percentage in parentheses refers to the relative amount of regioisomer acccording to ^1H NMR integration of the crude product. [c] Combined isolated yield.

FIGURE 6. Ketohydroxylation (path A) vs fragmentation (path B) in strained bicyclic ruthenates.

ever, this reaction allows the regioselective conversion of enantiomerically enriched *vic*-diols to the corresponding acyloins without loss of enantiopurity.[9c] The electrocyclic fragmentation of **IX** or **XII** results in the formation of RuO_2 or a ruthenium(VI)−oxo species which can be reoxidized by Oxone to give catalytically active RuO_4.

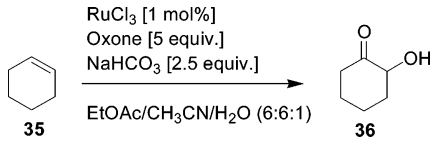
Scope and Limitations. Having in hand optimized conditions for the transformation of olefins to acyloins we turned our interest to an intense screening of scope and limitation. Apart from the question of functional group tolerance under acidic reaction conditions the regioselectivity was expected to be a problematic issue. However, we were pleased to find that the new developed ketohydroxylation can be applied to the oxidation of a wide variety of substrates. Depending on the electronic character of the functional group good to excellent regioselectivities were observed. Representative results are listed in Table 7.

Functional groups such as chlorides, acetates, or imides are tolerated. Surprisingly, even acetals can be oxidized under the conditions indicating that the reaction times are too short for the acetal hydrolysis to become a serious side reaction. Whereas the conversion is not strongly dependent on electronic properties of the C,C double bond the regioselectivity is. Electron-withdrawing groups direct the regioselectivity with the hydroxy group ending up proximal to the electron-withdrawing substituent. However, factors influencing the regioselectivity are currently under investigation.

The oxidation of cyclic systems was explored next. Whereas the reaction of acyclic substrates is a generally high-yielding process with the formation of only minor amounts of scission products, the fragmentation process becomes dominant in the ketohydroxylation of cyclic olefins. A possible explanation might be the ring strain in the *cis*-annulated bicyclic ruthenates **XVIII** formed upon [3 + 2]-cycloaddition between RuO_4 and the cycloalkene **XVII** (Figure 5). The tendency of cyclic ruthenates to undergo electrocyclic fragmentations is described in the literature. Calculations indicated that in contrast to the chemistry of the isoelectronic cyclic osmates the fragmentation pathway of ruthenates is thermodynamically favored.[14] The energy difference between hydrolytic pathway and fragmentation amplifies if strained bicyclic ruthenates are formed due to the release of ring strain. Hence, the product distribution reflects the competition between kinetic and thermodynamic control. This mechanistic dichotomy is illustrated in the simplified Figure 6.

The observations we made in the related RuO_4-catalyzed dihydroxylation proved indeed the fragmentation to be the thermodynamically preferred mechanistic pathway, thus decreasing the reaction temperature

TABLE 8. Oxidation of Cyclohexene 35 at Different Temperatures

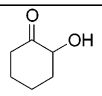
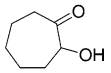
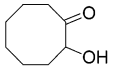
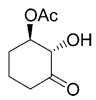
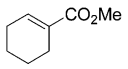
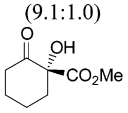
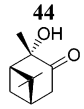


35 **36**

entry[a]	*T* (°C)	time (min)	conversion[b] (%)	yield[c] (%)
1	20	30	97	23
2	10	30	97	54
3	0	45	95	67
4	−10	60	95	72
5	−20	90	96	78

[a] All reactions were performed at the given temperature under the conditions listed in Table 7. [b] Determined by GC integration. [c] Isolated yield of **36**.

TABLE 9. Ketohydroxylation of Cyclic Compounds

entry[a]	alkene	acyloin[b]	T [°C]	yield [%][c]
1	 **35**	 **36**	-10	72 (23)
2	 **37**	 **38**	0	72 (37)
3	 **39**	 **40**	20	78
4	 **41**	 **42** (9.1:1.0)	20	79
5	 **43**	 **44**	0	78 (65)
6	 **45**	 **46** (>10:1)	0	64 (11)

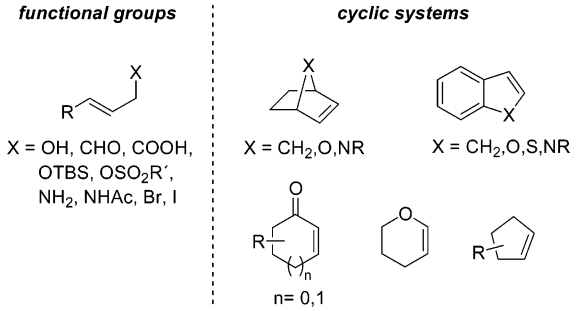
[a] All reactions were performed under the conditions listed in Table 7. [b] Diastereomeric ratio (according to ^{1}H NMR integration) is given in parentheses. Only the major stereoisomer is shown. [c] Isolated yield. The numbers in parentheses reflects the yield of the reaction at ambient temperature.

increased the rate of hydrolysis. We speculated that we could discriminate the scission reaction in the ketohydroxylation by simply lowering the temperature. The results are shown in Table 8.

Although the reaction times are longer the amount of fragmentation products decreased at lower temperature. Moreover, the reaction proceeds at temperatures below 0 °C, reflecting the fact that water is needed for the formation of RuO_4 from $RuCl_3$ but not essential for the ketohydroxylation. Different cyclic olefins were oxidized at room temperature or below as indicated in Table 9.

Cyclic systems can be ketohydroxylated in good yields and high regioselectivity. Six-, seven-, and eight-membered cyclic α-hydroxy ketones are stable under the

SCHEME 1. Problematic Substrates



reaction conditions. However, the influence of the ring strain is reflected in the yield. Whereas cycloheptene **37** (entry 2, Table 9) is oxidized in good yield, cyclohexene **35** was converted less efficiently (entry 1, Table 9). Cyclopentene reacted toward scission products. However, an efficient oxidation might be obtained with problematic cyclic substrates by lowering the reaction temperature. In this context it is important to note that the reaction even proceeds at temperature down to −20 °C albeit with significant longer reaction times. This temperature effect is exemplified in the oxidation of (1*S*)-(−)-α-pinene **45** (entry 6, Table 9). Due to the ring strain in the bicyclic olefin an efficient ketohydroxylation is not possible at room temperature. The fragmentation is the dominant pathway, which can be suppressed by lowering the temperature to 0 °C. Under these conditions, the desired α-hydroxy ketone **46** was obtained in good yield and excellent diastereomeric ratio. First results on the simple diastereoselectivity indicate that the initial [3 + 2]-cycloaddition between RuO_4 and the C,C-bond follows the Kishi rules developed for the related OsO_4-catalyzed dihydroxylation of olefins possessing a center of chirality in the allylic position.[23]

Limitations. Although a variety of different olefins are ketohydroxylated in good to excellent yields, certain limitations do exist. Due to the acidic conditions some acid-labile functional groups are not tolerated if the oxidation is slow. Furthermore, oxidizable heteroatoms can undergo competing side reactions. A survey of problematic functional groups is given in Scheme 1. It has to be emphasized that these functional groups were incorporated proximal to the C,C-double bond. The stability might vary in cases where the functional group is distal to the olefin moiety. Moreover, strained cyclic olefins tend to undergo electrocyclic fragmentations of the intermediate bicyclic ruthenates (vide supra).

These limitations indicate the need for further investigations directed toward the development of milder less acidic conditions allowing the oxidation of these substrates as well. However, decreasing the reaction temperature or increasing the catalyst concentration might lead to good results. Further work along these lines is currently being carried out in our laboratory.

Conclusion. The first ruthenium(VIII)-catalyzed ketohydroxylation has been developed. A careful analysis of the influence of different reaction parameters led to a protocol that allows the preparation of a variety of unsymmetrical acyclic and cyclic acyloins with predict-

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able and high regioselectivity starting from readily available olefins. The detailed knowledge of the interaction between temperature and chemoselectivity was used in the oxidation of different cycloalkenes. Whereas the oxidation of these substrates under the standard conditions is less selective, a decrease in the reaction temperature favors the kinetically preferred ketohydroxylation pathway, thus leading to good isolated yields of different cyclic α-hydroxy ketones. Furthermore, first results on the simple diastereoselectivity indicate that the Kishi rules known from OsO_4-catalyzed dihydroxylation can be applied to the ketohydroxylation reaction. However, detailed investigations regarding selectivity issues are of paramount importance in order to develop this new oxidation reaction into a broad applicable method. Hence, future work focuses on the development of general rules allowing the prediction of regio-, chemo-, and diastereoselectivity of the ketohydroxylation process. This work will be published in due course. With regard to the experimental setup it is important to note that no special precautions such as inert gas atmosphere or dry solvents is necessary. First experiments indicate that a scale-up of the procedure is possible. Furthermore, it is important to note that depending on the workup procedure a simple protocol for the reisolation of catalytically active ruthenium compounds has been developed.

Experimental Section

General Remarks. $RuCl_3$ was obtained from Aldrich. A stock solution was prepared by calculating with $RuCl_3(H_2O)_2$ and dissolving the catalyst (2.44 g, 10 mmol) in 100 mL water (0.1 M). The deep brown solution can be stored on the bench for weeks without loss of activity. Olefins **17**,[24] **21**,[25] **23**,[26] **25**,[27] **27**,[28] **29**,[29] and **33**[30] were prepared according to literature procedures. All other starting materials were purchased from commercial suppliers and used without further purification. In cases where the regioselectivity of the oxidation was better than 90:10 only the spectral data of the major isomer are reported. Regioselectivities were determined by GC or NMR integration of the crude product mixture.

General Procedure I. Ketohydroxylation: **Aqueous Workup**. 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 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, and the filtrate was washed with 10 mL of satd Na_2SO_3 solution and dried over Na_2SO_4. Filtration and evaporation under reduced pressure gave the crude product, which was purified by flash column chromatography under the given conditions.

General Procedure II. Ketohydroxylation: **Waterfree Workup and Reisolation of the Catalyst**. The initial procedure is the same as described above. After complete conversion the mixture was diluted with ethyl acetate (20 mL). The resulting suspension was filtered, and the filtrate was neutralized by addition of solid $NaHCO_3$. The solids were again removed by filtration and washed with ethyl acetate. The filtrate was concentrated in a vacuum. After reduction to ca. 20 mL of liquid the dissolved ruthenium catalyst precipitated and was separated by centrifugation. The solution containing the organic product was concentrated in a vacuum and purified via flash column chromatography under the given conditions. The reisolated dark ruthenium catalyst was dried under high vacuum and reused for another reaction without any further purification.

2-Hydroxy-1,2-diphenyl-ethanone (2).[31] Following the general procedure at room temperature, acyloin **2** (398 mg, 1.88 mmol, 94%) was obtained as a white solid within 10 min: mp 137 °C; R_f 0.57 (pentane/ethyl acetate, 3:1); IR (KBr) ν 3379 (br), 2932 (w), 1679 (s), 1206 (m), 1092 (m), 755 (s), 704 (s), 511 (s) cm^{-1}; ^1H NMR δ 7.92 (d, 2H, H_{arom}), 7.27−7.56 (m, 8H, H_{arom}), 5.92 (s, 1H, 2-H), 4.56 (s, 1H, OH); ^{13}C NMR δ 200.4, 140.5, 135.4, 130.6, 130.5, 130.3, 130.2, 130.0, 129.2, 77.6.

6-Hydroxydecan-5-one (6).[32] Following the general procedure at room temperature, acyloin **6** (299 mg, 1.74 mmol, 87%) was obtained as a colorless oil within 10 min: R_f 0.52 (pentane/ethyl acetate, 5:1); IR (film) ν 3480 (br), 2958 (s), 2873 (m), 1712 (s), 1466 (m), 1045 (m) cm^{-1}; ^1H NMR δ 4.16 (dd, J = 5.6, 2.8 Hz, 1H, 6-H), 3.42 (s, 1H, OH), 2.45 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 1.26−1.66 (m, 8H, CH_2), 0.91 (m, 6H, CH_3); ^{13}C NMR δ 214.0, 77.8, 39.0, 34.9, 28.4, 17.2, 23.9, 15.3.

2-Hydroxy-1-phenylethanone (8a).[33] Following the general procedure at room temperature, acyloin **8a** (180 mg, 1.32 mmol, 66%) was obtained as a white solid within 10 min: mp 88 °C; R_f 0.31 (pentane/ethyl acetate, 5:1); IR (KBr) ν 3430 (s), 3390 (s), 1683 (s), 1236 (m), 688 (m) cm^{-1}; ^1H NMR δ 7.92 (d, 2H, H_{arom}), 7.62 (dd, 1H, H_{arom}), 7.52 (dd, 2H, H_{arom}), 4.88 (s, 2H, 2-H), 3.52 (s, 1H, OH); ^{13}C NMR δ 199.8, 135.8, 134.8, 130.4, 129.2, 66.9.

1-Hydroxyoctan-2-one (10a).[34] Following the general procedure at room temperature, acyloin **10a** (184 mg, 1.28 mmol, 64%) was obtained as a colorless oil within 10 min: R_f 0.36 (pentane/ethyl acetate, 5:1); IR (film) ν 3426 (br), 2957 (s), 2930 (s), 2859 (s), 1722 (s), 1059 (m) cm^{-1}; ^1H NMR δ 4.21 (s, 2H, 1-H), 3.14 (s, 1H, OH), 2.37 (t, J = 7.6 Hz, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.21−1.38 (m, 6H, CH_2), 0.85 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR δ 210.0, 68.2, 38.5, 31.5, 28.9, 23.8, 22.5, 14.1.

2-Hydroxy-3-oxo-3-phenylpropionic Acid Methyl Ester (12a).[35] Following the general procedure at room temperature, acyloin **12a** (295 mg, 1.52 mmol, 76%) was obtained as a yellow oil within 30 min: R_f 0.43 (pentane/ethyl acetate, 4:1); IR (film) ν 3445 (br), 2956 (m), 2856 (s), 1749 (s), 1687 (s), 1449 (m), 1235 (s) cm^{-1}; ^1H NMR δ 8.08 (d, 2H, H_{arom}), 7.64 (t, 1H, H_{arom}), 7.51 (t, 2H, H_{arom}), 5.62 (s, 1H, 2-H), 4.31 (s, 1H, OH), 3.72 (s, 3H, OCH_3); ^{13}C NMR δ 195.1, 170.5, 136.2, 134.4, 131.5, 130.3, 77.8, 54.5.

2-Hydroxy-3-oxo-3-cyclohexylpropionic Acid Methyl Ester (14a).[13] Following the general procedure at room temperature, acyloin **14a** (328 mg, 1.64 mmol, 82%) was obtained as a colorless oil within 20 min: R_f 0.45 (pentane/ethyl acetate, 3:1); IR (film) ν 2933 (s), 2856 (s), 1749 (s), 1717 (s), 1450 (m), 1242 (m) cm^{-1}; ^1H NMR δ 4.86 (s, 1*H*, 3-H), 3.78

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(s, 3*H*), 2.77 (m, 1*H*), 1.61−1.83 (m, 5*H*), 1.22−1.45 (m, 5*H*); ^{13}C NMR δ 207.3, 169.0, 76.3, 53.2, 46.6, 29.3, 27.7, 25.6.

2-Hydroxy-1,3-diphenylpropan-1,3-dione (16a).[36] Following the general procedure at room temperature, acyloin **16a** (259 mg, 1.08 mmol, 54%) was obtained as a white solid within 60 min: mp 110 °C; R_f 0.59 (pentane/ethyl acetate, 7:1); IR (KBr) ν 3448 (br), 3064 (m), 1683 (s), 1597 (m), 1450 (m), 687 (m) cm^{-1}; ^{1}H NMR δ 7.99 (d, 4H, H_{arom}), 7.57 (dd, 2H, H_{arom}), 7.46 (dd, 4H, H_{arom}), 6.12 (s, 1H, 2-H), 4.68 (s, 1H, OH); ^{13}C NMR δ 197.1, 135.8, 135.5, 130.8, 130.3, 79.9.

2-(5,5-Dimethyl[1,3]dioxan-2-yl)-2-hydroxy-1-phenylethanone (18a). Following the general procedure at room temperature, acyloin **18a** (320 mg, 1.28 mmol, 64%) was obtained as a colorless oil within 10 min: R_f 0.31 (pentane/ethyl acetate, 3:1); IR (KBr) ν 3461 (br), 2956 (s), 2853 (s), 1685 (s), 1598 (m), 1471 (m), 1450 (m), 1270 (s), 1127 (s), 1119 (s), 1032 (s), 988 (s), 689 (m) cm^{-1}; ^{1}H NMR δ 7.98 (d, 2H, H_{arom}), 7.56 (dd, 1H, H_{arom}), 7.45 (dd, 2H, H_{arom}), 5.11 (m, 1H, 2-H), 4.70 (d, 1H, OH), 3.91 (m, 1H, 1-H), 3.51 (d, 2H), 3.42 (d, 2H), 0.81 (s, 3H), 0.61 (d, 3H); ^{13}C NMR δ 236.2, 133.9, 133.8, 129.5, 128.4, 101.9, 77.4, 76.8, 74.5, 37.1, 22.5, 21.7. Anal. Calcd for $C_{14}H_{18}O_4$ (250.29): C, 67.18; H, 7.25. Found: C, 67.18; H, 7.23.

Acetic Acid 2-Hydroxy-3-oxo-3-phenylpropyl Ester (20a).[37] Following the general procedure at room temperature, acyloin **20a** (283 mg, 1.36 mmol, 68%) was obtained as a colorless oil within 15 min: R_f 0.52 (pentane/ethyl acetate, 3:1); IR (film) ν 3463 (br), 3064 (w), 2957 (w), 2856 (w), 1742 (s), 1688 (s), 1378 (m), 1235 (s), 1047 (m), 702 (m); ^{1}H NMR δ 7.94 (dd, 2H, H_{arom}), 7.62 (ddd, 1H, H_{arom}), 7.49 (dd, 2H, H_{arom}), 5.28 (dd, J = 5.9, 3.2 Hz, 1H, 2-H), 4.53 (dd, J = 11.6, 3.2 Hz, 1H, 1-H), 4.09 (dd, J = 11.6, 5.9 Hz, 1H, 1-H), 3.93 (s, 1H, OH), 1.99 (s, 3H, CH_3); ^{13}C NMR δ 198.5, 170.9, 134.6, 133.5, 129.2, 128.7, 72.1, 66.9.

Ketohydroxylation of Acetic Acid 3-Cyclohexylallyl Ester (21). Following the general procedure at room temperature, a mixture of acyloin **22a** and **22b** (3.5:1.0) was obtained (326 mg, 1.52 mmol, 76%) as a colorless oil within 15 min, which was separated via HPLC (pentane/ethyl acetate). **Regioisomer 1: Acetic acid 2-hydroxy-3-oxo-3-cyclohexylpropyl ester (22a):** R_f 0.50 (pentane/ethyl acetate, 3:1); IR (film) ν 3463 (br), 2933 (s), 2856 (m), 1742 (s), 1736 (s), 1450 (m), 1378 (m), 1237 (s), 1060 (w) cm^{-1}; ^{1}H NMR δ 4.46 (dd, J = 4.0, 2.9 Hz, 1H, 2-H), 4.42 (dd, J = 12.0, 2.8 Hz, 1H, 1-H), 4.28 (dd, J = 12.0, 4.0 Hz, 1H, 1-H), 3.70 (m, 1H, OH), 2.56 (m, 1H, CH), 2.03 (s, 3H, C(O)CH_3), 1.71−1.90 (m, 3H, CH_2), 1.62−1.71 (m, 2H, CH_2), 1.41−1.52 (m, 1H, CH_2), 1.17−1.32 (m, 4H, CH_2); ^{13}C NMR δ 211.8, 174.9, 134.6, 73.8, 65.2, 46.4, 29.8, 27.3, 25.9, 25.2, 20.8. Anal. Calcd for $C_{11}H_{18}O4$ (214.26): C, 61.66; H, 8.47. Found: C, 61.69; H, 8.46. **Regioisomer 2: Acetic acid 3-cyclohexyl-3-hydroxy-2-oxopropyl ester (22b):** R_f 0.22 (pentane/ethyl acetate, 4:1); IR (film) ν 3481 (br), 2931 (s), 2856 (s), 1741 (s), 1734 (s), 1451 (m), 1375 (m), 1233 (s), 1065 (m) cm^{-1}; ^{1}H NMR δ 4.87 (d, J = 17.2 Hz, 1H, 1-H), 4.74 (d, J = 17.2 Hz, 1H, 1-H), 4.13 (m, 1H, 3-H), 2.87 (m, 1H, CH), 2.16 (s, 3H, C(O)CH_3), 1.63−1.81 (m, 4H, CH_2), 1.08−1.42 (m, 6H, CH_2); ^{13}C NMR δ 205.7, 171.2, 79.5, 66.2, 41.9, 29.8, 26.5, 26.0, 25.9, 25.4, 20.5Anal. Calcd for $C_{11}H_{18}O4$ (214.26): C, 61.66; H, 8.47. Found: C, 61.64; H, 8.49.

3-Benzyloxy-2-hydroxy-1-phenylpropan-1-one (24a).[9c] Following the general procedure at room temperature, acyloin **2** (440 mg, 1.72 mmol, 86%) was obtained as a colorless oil within 10 min: R_f 0.51 (pentane/ethyl acetate, 3:1); IR (KBr) ν 3464 (br), 3062 (m), 3030 (m), 2864 (m), 1685 (s), 1452 (s), 1235 (s), 1104 (s), 740 (m), 699 (s) cm^{-1}; ^{1}H NMR δ 7.90 (d, J = 7.5 Hz, 2H, H_{arom}), 7.62 (t, J = 7.5 Hz, 1H, H_{arom}), 7.49 (t, J = 7.5 Hz, 2H, H_{arom}), 7.27−7.36 (m, 1H, H_{arom}), 7.22 (m, 2H, H_{arom}), 7.13 (m, 2H, H_{arom}), 5.21 (t, J = 4 Hz, 1H, 2-H), 4.51 (d, J = 12.5 Hz, 1H, CH_2), 4.44 (d, J = 12.5 Hz, 1H, CH_2), 3.81 (dd, J = 10.5, 4 Hz, 1H, CH_2), 3.76 (dd, J = 10.5, 4 Hz, 1H, CH_2); ^{13}C NMR δ 199.7, 137.8, 134.1, 129.0, 128.8, 128.5, 128.2, 127.8, 127.7, 73.9, 73.7, 72.8.

Ketohydroxylation of (3-Phenoxypropenyl)benzene (25). Following the general procedure at room temperature, a mixture of acyloin **26a** and **26b** (3.2:1.0) was obtained (353 mg, 1.46 mmol, 73%) as a white solid within 10 min, which was separated via HPLC (pentane/ethyl acetate). **Regioisomer 1: 3-Phenyloxy-2-hydroxy-1-phenylpropan-1-one (26a):** mp 162 °C; R_f 0.36 (pentane/ethyl acetate, 3:1); IR (KBr) ν 3447 (br), 1684 (s), 1598 (s), 1496 (s), 1243 (s), 1121 (m), 754 (m), 690 (m) cm^{-1}; ^{1}H NMR δ 7.94 (dd, J = 8.1, 1.3 Hz, 2H, H_{arom}), 7.60 (ddd, J = 8.0, 1.4 Hz, 1H, H_{arom}), 7.48 (dd, J = 8.0 Hz, 2H, H_{arom}), 7.21 (m, 2H, H_{arom}), 6.90 (m, 1H, H_{arom}), 6.78 (m, 2H, H_{arom}), 5.39 (dd, J = 4.0 Hz, 1H, 2-H), 4.29 (dd, J = 9.6, 3.9 Hz, 1H, 3-H), 4.21 (dd, J = 9.6, 3.9 Hz, 1H, 3-H); ^{13}C NMR δ 199.1, 158.4, 134.3, 133.9, 129.5, 129.0, 128.7, 121.5, 114.8, 72.7, 70.6. Anal. Calcd for $C_{15}H_{14}O_3$ (242.27): C, 74.36; H, 5.82. Found: C, 74.33; H, 5.84. **Regioisomer 2: 1-Hydroxy-3-phenoxy-1-phenylpropan-2-one (26b):** mp 154 °C; R_f 0.36 (pentane/ethyl acetate, 3:1); IR (KBr) ν 3419 (br), 1724 (s), 1496 (s), 1224 (m), 1008 (m), 752 (m) cm^{-1}, 690 (m); ^{1}H NMR δ 7−31−7.39 (m, 5H, H_{arom}), 7.24 (dd, J = 8.0 Hz, 2H, H_{arom}), 6.96 (dd, J = 8 Hz, 1H, H_{arom}), 6.73 (d, J = 8.0 Hz, 2H, H_{arom}), 5.46 (s, 1H, 1-H), 4.57 (s, 2H, 3-H), 4.06 (s, 1H, OH); ^{13}C NMR δ 206.0, 157.4, 137.4, 129.8, 129.2, 129.1, 127.4, 122.1, 114.5, 77.5, 69.8. Anal. Calcd for $C_{15}H_{14}O_3$ (242.27): C, 74.36; H, 5.82. Found: C, 74.39; H, 5.79.

Ketohydroxylation of (3-Azidopropenyl)benzene (27). Following the general procedure at room temperature, a mixture of acyloin **28a** and **28b** (6.2:1.0) was obtained (329 mg, 1.72 mmol, 86%) as a colorless oil within 10 min, which was partially separated via HPLC (pentane/ethyl acetate, 3:1). **Regioisomer 1: 3-Azido-2-hydroxy-1-phenylpropan-1-one (28a):** R_f 0.32 (pentane/ethyl acetate, 3:1); IR (film) ν 3448 (br), 2108 (s), 1685 (s), 1267 (s), 1113 (m), 767 (m), 701 (m) cm^{-1}; ^{1}H NMR δ 7.85 (m, 2H, H_{arom}), 7.63 (m, 1H, H_{arom}), 7.49 (m, 2H, H_{arom}), 5.24 (dd, J = 3.4 Hz, 1H, 2-H), 3.68 (dd, J = 12.8, 3.4 Hz, 1H, H_{arom}), 3.41 (dd, J = 12.8, 3.4 Hz, 1H, H_{arom}); ^{13}C NMR δ 200.1, 135.9, 134.6, 130.6, 129.9, 74.9, 56.4. Anal. Calcd for $C_9H_9N_3O_2$ (191.19): C, 56.54; H, 4.74; N, 21.98. Found: C, 56.59; H, 4.71; N, 22.03. **Regioisomer 2: 3-Azido-1-hydroxy-1-phenylpropan-2-one (28b):** R_f = 0.31 (pentane/ethyl acetate, 3:1); IR (film) ν 3439 (br), 2107 (s), 1684 (s), 1269 (s), 1112 (m), 701 (m) cm^{-1}; ^{1}H NMR δ 7.38−7.44 (m, 3H, H_{arom}), 7.32−7.36 (m, 2H, H_{arom}), 5.23 (s, 1H, 1-H), 3.98 (d, J = 18.0 Hz, 1H, 3-H), 3.94 (d, J = 18.0 Hz, 1H, 3-H), 3.93 (s, 1H, OH); ^{13}C NMR δ 200.0, 138.3, 136.0, 130.8, 128.6, 79.8, 55.6. Anal. Calcd for $C_9H_9N_3O_2$ (mixture of regioisomers, 191.19): C, 56.54; H, 4.74; N, 21.98. Found: C, 56.52; H, 4.77; N, 21.94.

Ketohydroxylation of 2-(3-Phenylallyl)isoindole-1,3-dione (29). Following the general procedure at room temperature, an inseparable mixture of acyloin **30a** and **30b** (2.4:1.0) was obtained (496 mg, 1.68 mmol, 84%) as a white solid within 20 min. Analytical data are given for the mixture of **30a** and **30b**. **2-(2-Hydroxy-3-oxo-3-phenylpropyl)isoindole-1,3-dione (30a) and 2-(3-Hydroxy-2-oxo-3-phenylpropyl)isoindole-1,3-dione (30b):** mp 262 °C dec; R_f 0.13 (pentane/ethyl acetate, 4:1); IR (KBr) ν 3476 (br), 1769 (m), 1721 (s), 1691 (m), 1413 (m), 1387 (m), 1273 (m), 1093 (m), 970 (m), 718 (m), 698 (m) cm^{-1}; ^{1}H NMR δ 8.11 (m, 1H, $H_{arom,\mathbf{30a}}$), 7.83 (m, 4H, $H_{arom,\mathbf{30a}}$), 7.71 (m, 4H, $H_{arom,\mathbf{30a}}$), 7.61 (m, 1H, $H_{arom,\mathbf{30b}}$), 7.52 (m, 4H, $H_{arom,\mathbf{30b}}$), 7.42 (m, 4H, H_{arom}), 5.45 (m, 1H, 2-$H_{\mathbf{30a}}$), 5.29 (s, 1H, 3-$H_{\mathbf{30b}}$), 4.49 (d, J = 18.0 Hz, 1H, 1-$H_{\mathbf{30b}}$), 4.37 (d, J = 18.0 Hz, 1H, 1-$H_{\mathbf{30b}}$), 4.02 (dd, J = 14.0, 3.2 Hz, 1H, 1-$H_{\mathbf{30a}}$), 3.88 (s, 1H, $OH_{\mathbf{30b}}$), 3.84 (dd, J = 14.0, 3.2 Hz, 1H, 1-$H_{\mathbf{30a}}$), 3.76 (d, J = 7.6 Hz, 1H, $OH_{\mathbf{30a}}$); ^{13}C NMR δ 202.4, 199.0, 168.3, 167.5, 137.0, 134.6, 134.3, 134.2, 133.5, 132.1, 132.0, 129.4, 129.3, 129.2, 129.0, 127.5, 123.7, 123.5, 78.8, 71.3, 43.3, 42.8. Anal. Calcd for $C_{17}H_{13}NO_4$ (295.29): C, 69.15; H, 4.44; N, 4.74. Found: C, 69.11; H, 4.47; N, 4.76.

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3-Chloro-2-hydroxy-1-phenylpropan-1-one (32a).[9c] Following the general procedure at room temperature, acyloin **32a** (328 mg, 1.78 mmol, 89%) was obtained as a colorless oil within 20 min: R_f 0.59 (pentane/ethyl acetate, 3:1); IR (film) ν 3455 (br), 1680 (s), 1598 (m), 1450 (m), 1293 (s), 1098 (s), 705 (m) cm^{-1}; ^1H NMR δ 7.91 (d, J = 7.5 Hz, 2*H*, H_{arom}), 7.67 (t, J = 7.5 Hz, 1*H*, H_{arom}), 7.54 (t, J = 7.5 Hz, 2*H*, H_{arom}), 5.36 (t, J = 3.5 Hz, 1*H*, 2-H), 4.05 (s, 1*H*, OH), 3.94 (dd, J = 11.5, 3.5 Hz, 1H, 3-H), 3.77 (dd, J = 11.5, 3.5 Hz, 1H, 3-H); ^{13}C NMR δ 197.9, 134.5, 133.4, 129.2, 128.5, 72.6, 47.4.

2-Hydroxy-1-phenyl-3-(phenylsulfonyl)propan-1-one (34a).[9c] Following the general procedure at room temperature, acyloin **34a** (487 mg, 1.68 mmol, 84%) was obtained as a yellow oil within 30 min: R_f 0.59 (pentane/ethyl acetate, 5:1); IR (film) ν 3451 (br), 3064 (m), 1694 (s), 1692 (s), 1310 (s), 1151 (m), 1024 (m), 737 (m) cm^{-1}; ^1H NMR δ 7.95 (dd, 4H, H_{arom}), 6.56−7.67 (m, 6H, H_{arom}), 5.60 (dd, 1H, 2-H), 3.57 (dd, 1H, 3-H) cm^{-1}; ^{13}C NMR δ 236.3, 197.4, 139.6, 134.9, 134.2, 132.3, 129.4, 129.1, 128.5, 68.7, 61.2.

2-Hydroxycyclohexanone (36).[38] Following the general procedure at −10 °C, acyloin **36** (153 mg, 1.34 mmol, 67%) was obtained as a colorless oil within 60 min: R_f 0.21 (pentane/ethyl acetate, 4:1); IR (film) ν 3451 (br), 2969 (s), 1790 (s), 1761 (s), 1383 (m), 1097 (s) cm^{-1}; ^1H NMR δ 4.36 (ddd, 1H, J = 8.65, 5.21, 1.09 Hz, 1H, 2-H), 2.79 (d, J = 1.09 Hz, 1H, OH), 2.31−2.40 (m, 2H, CH_2), 1.66−2.15 (m, 6H, CH_2); ^{13}C NMR δ 203.0, 62.9, 39.3, 37.6, 27.0, 23.2.

2-Hydroxycycloheptanone (38).[39] Following the general procedure at 0 °C, acyloin **38** (184 mg, 1.44 mmol, 72%) was obtained as a colorless oil within 30 min: R_f 0.27 (pentane/ethyl acetate, 5:1); IR (film) ν 3466 (br), 2931 (s), 2858 (m), 1701 (s), 1454 (m), 1404 (m), 1272 (m), 1079 (s) cm^{-1}; ^1H NMR δ 4.26 (dd, J = 9.6, 3.6 Hz, 1H, 2-H), 2.65 (ddd, J = 17.6, 7.2, 1.2 Hz, 1H, CH_2), 2.43 (ddd, J = 17.6, 11.6, 4.0 Hz, 1H, CH_2), 2.01 (m, 1H, CH_2), 1.72−1.88 (m, 2H, CH_2), 1.51−1.68 (m, 3H, CH_2), 1.28−1.36 (m, 2H, CH_2); ^{13}C NMR δ 213.9, 77.2, 40.2, 33.9, 29.7, 26.8, 23.6.

2-Hydroxycyclooctanone (40).[39] Following the general procedure at room temperature, acyloin **40** (238 mg, 1.68 mmol, 78%) was obtained as a colorless oil: R_f 0.39 (pentane/ethyl acetate, 4:1); ^1H NMR δ 4.14 (dd, J = 6.4, 2.8 Hz, 1H, 2-H), 3.69 (s, 1H, OH), 2.66 (ddd, J = 12.0, 4.0 Hz, 1H, CH_2), 2.26−2.39 (m, 2H, CH_2), 1.89−2.04 (m, 2H, CH_2), 1.59−1.81 (m, 4H, CH_2), 1.29−1.38 (m, 2H, CH_2), 0.81−0.92 (m, 1H, CH_2); ^{13}C NMR δ 217.6, 76.3, 37.3, 29.4, 28.6, 25.5, 24.5, 22.2; IR (film) ν 3477 (br), 2930 (s), 2859 (s), 1703 (s), 1466 (m), 1447 (m), 1239 (m), 1110 (s), 947 (m) cm^{-1}.

(2*S,3*R**)-Acetic Acid 2-Hydroxy-3-oxocyclohexyl Ester (42).**[11c] Following the general procedure, a diastereomeric mixture (9.1:1.0, ^1H NMR integration) of acyloin **42** was obtained as a colorless oil within 10 min. Purification via flash-column chromatography led to the isolation of the major isomer in 79% yield: R_f 0.23 (pentane/ethyl acetate, 1:1); IR (film) ν 3460 (br w), 2951 (m), 2872 (m), 1733 (s), 1730 (s), 1376 (m), 1245 (s), 1109 (m), 1035 (m) cm^{-1}; ^1H NMR δ 4.70 (ddd, J = 14.8, 10.0, 4.8 Hz, 1H, 1-H), 4.13 (d, J = 10.0 Hz, 1H, 2-H), 3.66 (s, 1H, OH), 2.55 (ddd, J = 14.0, 4.8, 2.8 Hz, 1H, CH_2), 2.33 (ddd, J = 14.0, 5.6 Hz, 1H, CH_2), 2.12−2.23 (m, 1H, CH_2), 2.08 (s, 3H, $C(O)CH_3$), 1.98−2.04 (m, 1H, CH_2), 1.66−1.77 (m, 1H, CH_2), 1.47−1.58 (m, 1H, CH_2); ^{13}C NMR δ 207.3, 170.4, 78.6, 77.2, 38.5, 29.1, 21.2, 20.7.

1-Hydroxy-2-oxocyclohexanecarboxylic Acid Methyl Ester (44).[40] Following the general procedure, acyloin **44** (268 mg, 1.56 mmol, 78%) was obtained as a colorless oil: R_f 0.23 (pentane/ethyl acetate, 3:1); IR (film) ν 3451 (br w), 2959 (s), 2930 (m), 1731 (s), 1458 (m), 1275 (s), 1123 (m) cm^{-1}; ^1H NMR δ 3.76 (s, 1H, OH), 3.73 (s, 3H, OCH_3), 2.38 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 1.94 (m, 1H, CH_2), 1.79 (m, 1H, CH_2), 1.57 (m, 4H, CH_2); ^{13}C NMR δ 170.3, 109.2, 86.8, 52.3, 36.2, 27.3, 22.3, 21.4.

(1*S*,2*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.3.1]-heptan-3-one (46).[41] Following the general procedure, acyloin **46** (215 mg, 1.28 mmol, 64%) was obtained as a colorless oil: $[\alpha]_D$ = −39.6 (c = 0.56/$CHCl_3$); R_f 0.29 (pentane/ethyl acetate, 5:1); IR (film) ν 3445 (br), 2977 (s), 2923 (s), 1720 (s), 1371 (s), 1162 (s), 920 (m) cm^{-1}; ^1H NMR δ 2.58 (m, 2H, 4-H), 2.43 (m, 1H, 1-H), 2.30 (s, 1H, OH), 2.08 (m overlaid by d, J = 10.9 Hz, 2H, 5-H and 7-H), 1.65 (d, J = 10.8 Hz, 7-H), 1.35 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); ^{13}C NMR δ 214.2, 71.2, 49.7, 43.0, 39.1, 38.3, 28.5, 27.4, 25.4, 22.9.

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Supporting Information Available: ^1H NMR spectra of all acyloins. This material is available free of charge via the Internet at http://pubs.acs.org.

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