ORGANIC LETTERS

2004
Vol. 6, No. 2
289−291

Alkenes as Ketol Surrogates–A New Approach toward Enantiopure Acyloins

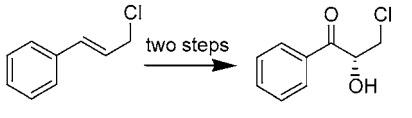
Bernd Plietker*

Organische Chemie II, Fachbereich Chemie, Universität Dortmund, Otto-Hahn-Str. 6, D-44221 Dortmund, Germany

plietker@pop.uni-dortmund.de

Received November 20, 2003

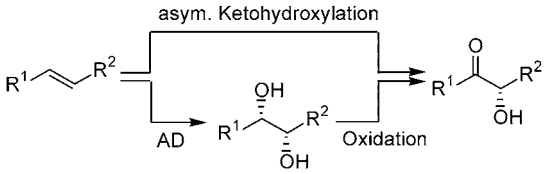
ABSTRACT



Enantiopure α-hydroxy ketones are important building blocks in organic synthesis. This paper describes the use of cyclic ruthenates for the first catalytic regioselective oxidation of *vic*-diols to α-ketols. The combination of $RuCl_3$/Oxone/$NaHCO_3$ was used in a two-step sequence of asymmetric dihydroxylation and regioselective monooxidation for the synthesis of a broad scope of enantiopure acyloins.

Transition-metal-catalyzed oxidations have become one of the most important synthetic tools in organic chemistry.[1] Whereas the asymmetric synthesis of hydroxy groups,[2] epoxides,[3] or *vic*-diols[4] has been in[5] the center of research for more than 20 years, the development of an enantioselective oxidation protocol to build up α-hydroxy ketones (acyloins) attracted considerably less attention.[2] The recent progress in the asymmetric catalytic α-hydroxylation of carbonyl compounds[5] prompted us to report our complementary approach toward enantioenriched acyloins by using alkenes as ketol surrogates. Recently, we reported the direct and regioselective ruthenium-catalyzed ketohydroxylation of simple alkenes.[6] While a direct enantioselective version of this reaction is under current investigation, a two-step protocol of osmium-catalyzed asymmetric dihydroxylation and concomitant regioselective monooxidation under ruthenium catalysis could furnish enantiomerically enriched acyloins with predictable regioselectivity and absolute configuration (Scheme 1).

Scheme 1. Ketohydroxylation vs Diyhdroxylation−monooxidation



To the best of our knowledge, a regioselective catalytic monooxidation of *vic*-diols has not been reported so far. Apparently, the electronic bias in favor of one of the two hydroxyl groups is too low for a successful differentiation.[7] Within the course of mechanistic studies on the ketohydroxylation, a monooxidation of diols using the same cata-

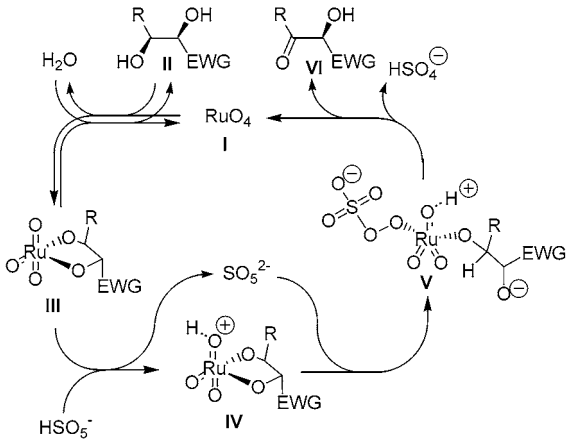
(1) *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; p 81.
(2) Zhou, P.; Chen, B. C.; Davies, F. A. *Asymmetric Oxidation Reactions;* Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; p 128.
(3) (a) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 231. (b) Katsuki, T. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 287.
(4) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 357.
(5) (a) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038. (c) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (d) Zhoung, G.; *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem., Int. Ed.* **2003**, *42*, 4247.

(6) Plietker, B. *J. Org. Chem.* **2003**, *68*, 7123.

10.1021/ol0362663 CCC: $27.50
Published on Web 12/19/2003

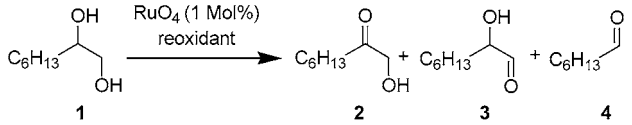
lytic system was observed.[6] Cyclic ruthenates are envisioned to be key intermediates in both monooxidation and ketohydroxylation (Scheme 2). If Oxone reacts as a nucleophilic

Scheme 2. Regioselective monooxidation−A Proposal



reoxidant in either process, the oxidation of unsymmetrical *vic*-diols should furnish acyloins with high regioselectivity. Hence, diol **1** was oxidized with RuO_4 in the presence of different reoxidants (Table 1).

Table 1. Influence of Reoxidant on Product Distribution



entry	reoxidant	**2**:**3**:**4**[a]	conversion [%][a]
1	NaOCl	41:4:55	75
2	$NaIO_4$	12:0:88	98
3	$K_2S_2O_8$	n.d.	21
4	$KBrO_3$	15:0:85	47
5	Oxone/$NaHCO_3$	92:0:8	96

[a] Determined by GC integration.

Apart from Oxone, neither of the common reoxidants could be used for a selective monooxidation of diol **1**. Using a combination of Oxone/$NaHCO_3$ α-hydroxy ketone **2** was formed exclusively. This result corresponds to the product distribution obtained in the direct ketohydroxylation of 1-octene.[6] From a mechanistic point of view a simple oxidation of the secondary alcohol in **3** by RuO_4 was ruled out on the basis of the results in separate control experiments on the oxidation of 2-octanol to 2-octanone. The reaction proceeds with either oxidation system. However, the use of reoxidants other than Oxone in the oxidation of the corresponding glycol **1** resulted in a predominant formation of fission product **4**.

Diols are known to react with ruthenium(VIII)-oxide **I** in a reversible condensation reaction to give cyclic ruthenates **III** or **IV**,[8] which are proposed intermediates in the related ketohydroxylation.[6] Our working model is based upon the assumption that the strongly electron-withdrawing ruthenium in **III** or **IV** sets an electronic bias, thus orchestrating the irreversible addition of SO_5^{2-} with a preferred trajectory leading to the cleavage of the less electron-rich of the two Ru−O bonds in **III** or **IV** (Scheme 2). The resulting peroxo ester **V** reacts via a β-hydride elimination to furnish ketol **VI** and regenerates RuO_4 **I**. The observed product distribution indicates the existence of cyclic ruthenates such as **III** or **IV**. Fission products such as **4** can be obtained via a competing electrocyclic fragmentation of **III** or **IV**.[9] Recently, we found a significant rate acceleration in the related ruthenium-catalyzed dihydroxylation by addition of protic acids.[9] Ruthenate **III** can be activated for a nucleophilic addition via a protonation pathway in analogy to the acid-catalyzed saponification of carboxylates. The combination of protonation of **III** and nucleophilic character of SO_5^{2-} accelerates the nucleophilic addition of the reoxidant to the metal center in **IV** resulting in the observed high regioselectivity for the monooxidaton process.

With these results in hand, we investigated the oxidation of enantioenriched *vic*-diols derived from simple alkenes via an asymmetric Sharpless dihydroxylation. Apart from the regioselectivity, the scope and limitation as well as the question whether the acidic reaction media could lead to an epimerization are important issues that have to be addressed. The results are outlined in Table 2. Different alkenes were transformed into the corresponding enantioenriched acyloins with remarkably high regioselectivity. The enantiomeric excess of both diol and ketol was determined by chiral HPLC. *Importantly, an acid-assisted epimerization of* α*-ketols was not observed in any case within the time frame of the monooxidation.* The assignment of absolute configuration is based upon comparison with the literature or the mnemonic device.[4] A broad scope of functional groups is tolerated. Acetates or chlorides can be oxidized in high yields and excellent regioselectivities.

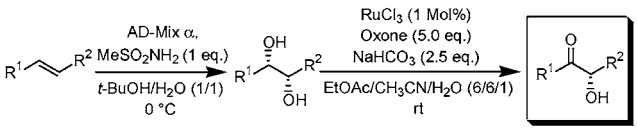
Interestingly, electron-rich diols are oxidized more slowly than electron-poor substrates. Whereas the reaction of diol **6** (entry 3, Table 2) proceeded within 1 h, the oxidation of sulfone **10** (entry 7, Table 2) was complete after 30 min. Since the initial condensation between RuO_4 **I** and diol **II** appears to be a reversible process (which is a basic requirement in the dihydroxylation), the hydrolysis of more electron-rich ruthenates **III** eventually outcompetes the irreversible nucleophilic attack of oxone (Scheme 2).[9] This hypothesis is further underlined by the fact that a reduction of the total

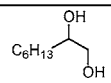
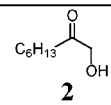
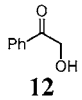
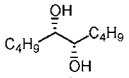
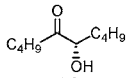
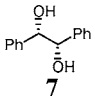
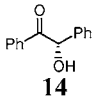
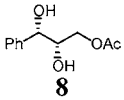
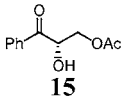
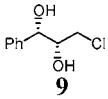
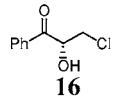
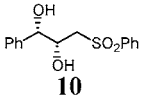
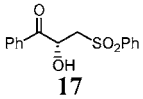
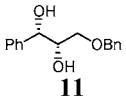
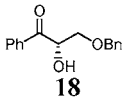
(7) (a) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600. (b) Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Rosa, A. *Tetrahedron Lett.* **1996**, *37*, 115. Desymmetrisation of *meso*-diols: (c) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *J. Org. Chem.* **1999**, *64*, 7492 and references therein.

(8) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(9) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353.

Table 2. Preparation of Enantiopure α-Hydroxyketones



entry	diol	*ee* [%][b]	yield [%][c]	ketol[a]	time [h]	*ee* [%][b]	yield [%][c]
1	 **1**	-	-	 **2**	0.5	-	94
2	 **5**	-	-	 **12**	1	-	91
3	 **6**	97	81	 **13**	1	97	89
4	 **7**	97	89	 **14**	1	96	92
5	 **8**	98	59[d]	 **15**	0.5	98	89
6	 **9**	99	85[d]	 **16**	0.5	99	88
7	 **10**	91	94	 **17**	0.5	90	87
8	 **11**	96	81	 **18**	0.5	96	76

[a] The reactions were performed on a 2 mmol scale using 1 mol % $RuCl_3$ (as a 0.1 M solution in water), 5.0 equiv of Oxone and 2.5 equiv of $NaHCO_3$ in EtOAc (12 mL)/CH_3CN (12 mL)/H_2O (2 mL) at room temperature. [b] Determined by chiral HPLC using Chiracel columns. [c] Isolated yield. [d] The dihydroxylation was performed in the presence of 3 equiv. $NaHCO_3$ under buffered conditions.

amount of water by a factor of 2 compared to the dihydroxylation leads to significantly shorter reaction times.

In this paper, we describe the first regioselective catalytic monooxidation of *vic*-diols. This new protocol allows the synthesis of a variety of unsymmetrical acyloins without the use of inert gas atmosphere or dry solvents. Based upon this method, a two-step procedure for the preparation of enantioenriched acyloins from simple alkenes has been developed. The well-established asymmetric Sharpless dihydroxylation creates two new stereocenters by a direct translation of double-bond geometry to relative configuration, whereas the cyclic nature of the corresponding ruthenates in combination with the use of Oxone as a nucleophilic reoxidant sets an electronic bias for the regioselective oxidation without loss of enantiomeric excess. The regioselectivity can be predicted by analyzing the electronic environment of the intermediate Ru−O bonds with the less electron-rich oxygen ending up in the hydroxy group of the product. This method provides a convenient and new access to enantiopure acyloins and complements the most recently developed α-hydroxylation protocols[5] by using alkenes as ketol surrogates. The results provide further indications for the proposed mechanism of the related ketohydroxylation.[6] With regard to a future asymmetric development of the latter reaction, it is important to note that (i) the asymmetric [3 + 2]-cycloaddition of a group-(VIII)-metal oxide creates two new stereocenters with defined relative and absolute configuration and that (ii) the obtained enantiopure α-hydroxy ketones do not epimerize under the acidic reaction conditions.

Acknowledgment. The author thanks Prof. Dr. N. Krause for generous support and the Fonds der Chemischen Industrie for a Liebig fellowship. Further financial support by the Deutsche Forschungsgemeinschaft and the Fonds zur Förderung des wissenschaftlichen Nachwuchses im Fachbereich Chemie der Universität Dortmund is gratefully acknowledged.

Supporting Information Available: Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0362663