Transition-Metal Catalyzed Oxidations. 7. Zirconium-Catalyzed Oxidation of Primary and Secondary Alcohols with Hydroperoxides

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A new procedure for the oxidation (dehydrogenation) of primary and secondary alcohols employing $Zr(O\text{-}t\text{-}Bu)_4$ or $Zr(O\text{-}n\text{-}Pr)_4$/*tert*-butyl hydroperoxide/3 Å molecular sieves is presented. Secondary alcohols—if not severely sterically hindered—are usually converted quantitatively to the corresponding ketones. Esters or acids can be byproducts in the reaction of primary alcohols. However, the aldehydes are obtained in good yield by lowering the reaction temperature, decreasing the amount of TBHP or replacing TBHP by cumene hydroperoxide (CHP), and/or exchanging the catalyst $Zr(O\text{-}t\text{-}Bu)_4$ by $Zr(O\text{-}n\text{-}Pr)_4$ or silica gel-supported $Zr(OR)_x$. A remarkable selectivity of equatorial alcohol groups (e.g., **11** and **13**) is observed in contrast to chromium(VI)-based oxidations. Strongly chelating substrates such as furfuryl alcohol (**18**) or 1,2-diol **25** that prevent hydride transfer in the six-membered transition state **A** are not converted.

In connection with current investigations[1,2] on the use of activated forms of oxygen (e.g., hydroperoxides) in organic synthesis (review[3]), we discovered the transition-metal-catalyzed dehydrogenation of benzylic alcohols to the corresponding carbonyl compounds.[4] The detection of small amounts of acetone in the $Ti(O\text{-}i\text{-}Pr)_4$-catalyzed oxidation of benzylic alcohols with *tert*-butyl hydroperoxide (TBHP) indicated that *non*activated alcohols could also be oxidized by this system. Previously, mainly d^5, d^6, and d^7 elements such as vanadium,[5] molybdenum,[6−12] tungsten,[10,11,6] and ruthenium,[13−15] were investigated in connection with related oxidations. With exception of the $ZrO(OAc)_2$/TBHP system[16] for the oxidation of allylic and primary alcohols, the catalytic ability of the d^4 elements is less well known. However, most elements of this group would offer considerable advantages such as low or no toxicity, low cost, and ease of separation from reactants after acidic workup.[17] The zirconium alkoxides in particular are known to possess a high ligand exchange rate.[17] In addition, their decomposition of TBHP is virtually nonexistent even at elevated temperatures[18] and would thus be particularly well suited for the use as oxidation catalysts.

We now report on the extension of our previous communication (oxidation of benzylic alcohols[4]) using zirconium alkoxides as the catalysts and hydroperoxides such as TBHP or cumene hydroperoxide (CHP) in the oxidation of nonactivated primary and secondary alcohols to the corresponding aldehydes and ketones.

Analogously to the Sharpless epoxidation,[19] a rapid exchange of *tert*-butyl alcohol by the substrate alcohol and TBHP is required to form the mixed zirconium complex and hydride transfer occurs then via the postulated six-membered transition state **A** (Scheme 1; it is not known whether **A** is monomeric or dimeric). Peroxides or peresters cannot exchange with *tert*-butyl alcohol and therefore do not serve as oxidation reagents in this reaction type. The hydride is transferred to the activated O−O bond of the hydroperoxide leading to the oxidized ketone or aldehyde, *tert*-butyl alcohol, and the zirconium species **B**. The mixed zirconium complex is then regenerated by reaction of **B** with substrate and TBHP, releasing 1 mol of water. The metal atom in transition state **A** serves at least three purposes: (1) coordination of the substrate and the hydride acceptor TBHP; (2) activation of the O−O bond of TBHP; (3) activation of the H−C bond of the substrate.

Thus, properties of the metal center, both as a Lewis acid and an electron donor in the corresponding alcoholate, are required to minimize the activation energy of the hydride transfer. Similar to the Meerwein−Ponndorf−Verley and the Oppenauer reaction, group three (e.g.,

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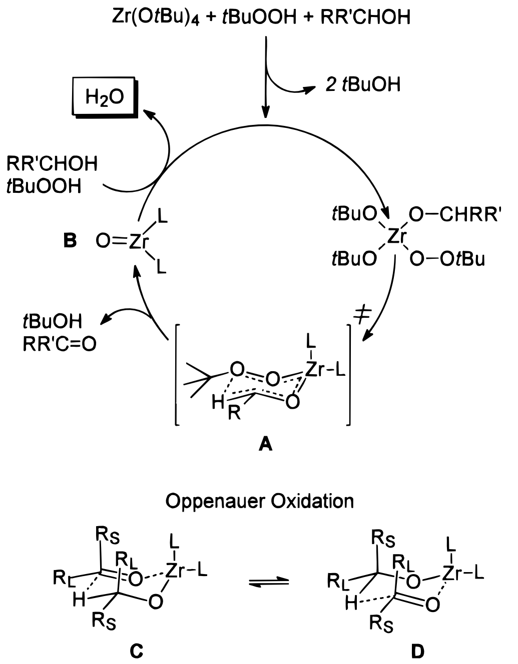
Table 1. TBHP Oxidation of Primary and Secondary Alcohols

entry	substr	catalyst	*T* [°C]	time [h]	conv [%]	products
			Primary Alcohols			
1	**1**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	60	2	>98	aldehyde/acid (4:1)
2	**1**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	20	96	aldehyde/acid (9:1)
3	**2**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	22	70[a]	aldehyde
4	**3**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	6	>98	aldehyde/acid (1:1)
5	**4**	$\mathrm{Zr(O\text{-}\mathit{t}\text{-}Bu)_4}$	60	1	>99	aldehyde
6[b]	**4**	$\mathrm{SiO_2/Zr(OR)_\mathit{x}}$	80	22	49	aldehyde
			Secondary Alcohols			
7	**5**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	4	>99	2-octanone
8	**6**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	6	95	cyclopentanone
9[b]	**6**	$\mathrm{SiO_2/Zr(OR)_\mathit{x}}$	80	5	>99	cyclopentanone
10	**7**	$\mathrm{Zr(O\text{-}\mathit{t}\text{-}Bu)_4}$	60	0.3	>99	cyclohexanone
11	**7**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	60	1	>99	cyclohexanone
12	**7**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	4	>99	cyclohexanone
13[b]	**7**	$\mathrm{SiO_2/Zr(OR)_\mathit{x}}$	80	4	>99	cyclohexanone
14	**8**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	60	2	>99	2-methylcyclohexanone
15	**9**	$\mathrm{Zr(O\text{-}\mathit{t}\text{-}Bu)_4}$	60	23	38	menthone
16	**9**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	60	23	84[c]	menthone
17	**10**/11[d]	$\mathrm{Zr(O\text{-}\mathit{t}\text{-}Bu)_4}$	60	0.3	>99	4-*tert*-butylcyclohexanone
18	**10**/11[d]	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	5	>99	4-*tert*-butylcyclohexanone
19[b]	**10**/11[d]	$\mathrm{SiO_2/Zr(OR)_\mathit{x}}$	80	5	>99	4-*tert*-butylcyclohexanone
20	**12**/13[e]	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	7	>99	3,3,5-trimethylcyclohexanone
21	**14**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	17	96[f]	ketone
22	**15**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	80	85[c,f]	ketone
23	**16**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	17	90[f]	ketone
24	**17**	$\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$	20	17	92[f]	ketone

[a] The reaction was stopped before byproducts could be detected by GC. [b] $\mathrm{SiO_2/Zr(OR)_\mathit{x}}$: silica gel-supported zirconium catalyst.[30] [c] Addition of further oxidant and catalyst (altogether 3.5 equiv of TBHP and 0.3 mol of $\mathrm{Zr(O\text{-}\mathit{n}\text{-}Pr)_4}$ for **15** and 0.5 mol for **9**). [d] Ratio of *cis*- and *trans*-4-*tert*-butylcyclohexanol = ca. 3:7. [e] Ratio of *cis*- and *trans*-3,3,5-trimethylcyclohexanol = 17:83. [f] Isolated yields.

Scheme 1. Zirconium-Mediated Hydride Transfer to TBHP



aluminum) or group four elements such as titanium, zirconium,[17,20] or the rare earth metals[21,22] are particularly well suited for this process. The analogy to the Oppenauer oxidation is shown in Scheme 1 (transition state models **C** and **D**). A carbonyl compound activated by complexation to the metal center accepts the hydride from the alcohol activated by alcoholate formation.[21,23] But there are also remarkable differences between the two reactions. Whereas in the Oppenauer oxidation the equilibrium is determined by the redox potential of the carbonyl/alcohol pairs, the hydride transfer to the O–O acceptor is essentially *irreversible*. The oxidation to carbonyl compounds can thus occur *quantitatively* provided that the process is kinetically possible using an appropriate catalyst posessing the correct balance of Lewis acidity and basicity in the transition state **A**.

The goal of the present investigation is the elaboration of a high-yielding, operationally simple, and enviromentally safe *catalytic* method using commercially available reagents for the oxidation of alcohols to replace reagents containing toxic heavy metals such as chromium(VI).[24] For that purpose the scope and limitations of the reaction were carefully established with a variety of different catalytic systems and substrates.

The titanium- or zirconium-catalyzed TBHP oxidation of benzylic alcohols to aldehydes and ketones is very rapid, and the water formed during the reaction did not significantly decrease the process of dehydrogenation[4] (see also kinetic data in the Experimental Section, Table 4). However, hydride abstraction from *non*activated primary and secondary alcohols is a much slower process, and in our initial experiments, the reactions usually stopped after ca. 20% conversion due to hydrolysis of the transition metal alkoxide by the water formed. Rigorous removal of the water was therefore a prerequisite for higher conversion rates. In fact, the conversion drastically increased (see Table 1) after addition of powdered 4 Å molecular sieves or highly activated alumina (see General Procedure). In addition, in analogy to the recently described reinvestigation of the Meerwein–Ponndorf–Verley (MPV) reaction,[20] the use of nonpolar solvents such as tetrachloromethane, cyclohexane, or toluene also accelerated the reaction. Furthermore, the nature of the catalyst was of great importance. Figure

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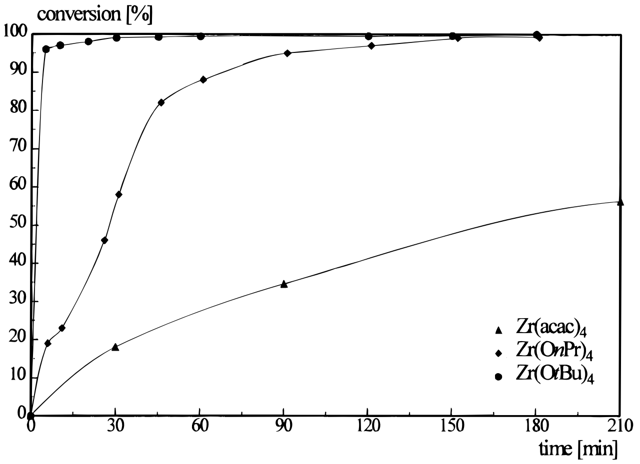


Figure 1. Oxidation of cyclohexanol with different zirconium catalysts (conditions: 10 mol % catalyst, 2 equiv of TBHP, CCl_4, $T = 20$ °C; for $Zr(acac)_4$ $T = 60$ °C).

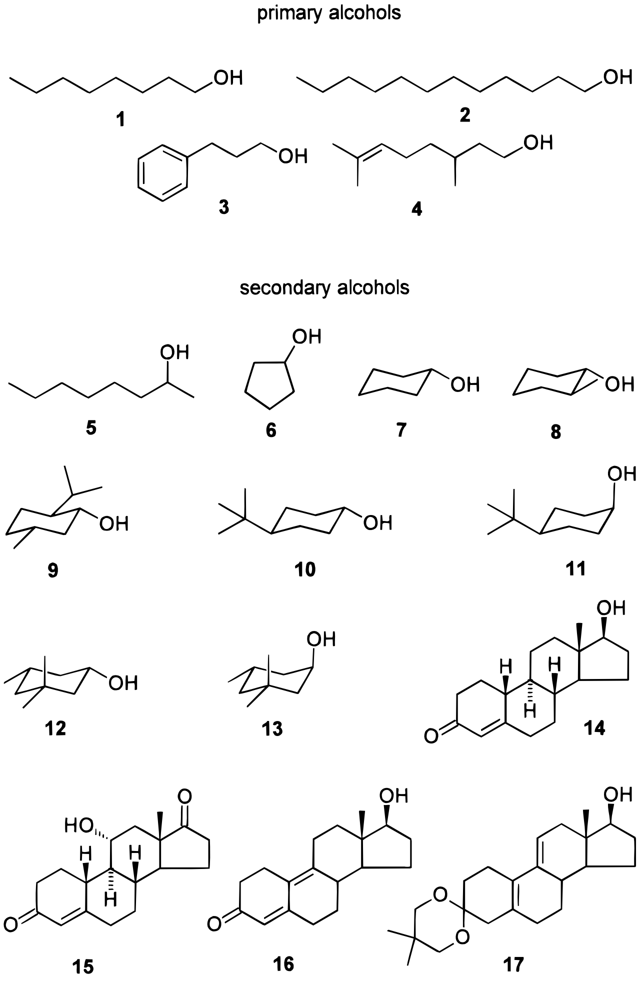
1 shows a comparison of the efficiency of $Zr(acac)_4$, $Zr(O\text{-}n\text{-}Pr)_4$, and $Zr(O\text{-}t\text{-}Bu)_4$ in the oxidation of cyclohexanol with 2 equiv of TBHP, demonstrating the superiority of $Zr(O\text{-}t\text{-}Bu)_4$ as the catalyst in this system (for kinetic data for $Zr(O\text{-}n\text{-}Pr)_4$ and $Zr(O\text{-}t\text{-}Bu)_4$ see the Experimental Section, Table 6). The superior catalytic activity of $Zr(O\text{-}t\text{-}Bu)_4$ is caused by a number of special properties: (1) the increase of alcohol exchange rate from primary to secondary to tertiary alcohol ligands,[25] (2) the monomeric nature of $Zr(O\text{-}t\text{-}Bu)_4$ in contrast to the oligomeric primary and secondary alkoxides of zirconium,[26,27] and (3) the inertness of *tert*-butyl alcohol in contrast to primary or secondary alcohols of the catalyst which compete with the substrate during the oxidation.

The low activity of $Zr(acac)_4$ already observed by Kaneda et al.[5] may be attributed to the decreased exchange rate of the more strongly bound chelated acetylacetonate ligand in addition to electron-withdrawing effects. However, $Zr(acac)_4$ is a very effective catalyst in the oxygenation of the more nucleophilic and reactive phenols to *o*-quinones[28,29] or α-ketols.[1] Interestingly, the sensitivity to hydrolysis parallels the catalytic efficiency. A less-water-sensitive heterogeneous silica-supported zirconium -catalyst, originally prepared by Inada et al. for MPV reactions,[30] also showed considerable activity and even an increased selectivity in the TBHP oxidation (see Table 1).

After establishing optimum reaction conditions with cyclohexanol as the substrate, we selected a number of primary (**1**−**4**), secondary (**5**−**17**) (Scheme 2), benzylic (**18**−**24**), and allylic alcohols (**31** and **33**) and 1,2- (**25**), 1,3- (**26** and **27**), and 1,4-diols (**29**) (Scheme 3) to investigate the scope and limitation of the new oxidation procedure.

Primary Alcohols. In many cases the transition-metal-catalyzed oxidations with hydroperoxide succeeded with secondary alcohols but show low reactivity with primary alcohols [e.g., $VO(acac)_2$].[5] In contrast, the primary alcohols 1-octanol (**1**) and 1-dodecanol (**2**) rapidly oxidized at 60 °C using the optimized system $Zr(O\text{-}n\text{-}Pr)_4$/TBHP/toluene to the corresponding aldehydes (Table 1, entries 1, 2, and 4). However, under prolonged reaction times and with an excess of TBHP as the oxidant, formation of carboxylic acids was observed. Carboxylic acid formation can be considerably decreased by lowering the reaction temperature (entry 2) or stopping the reaction (TLC monitoring) at lower conversion rates (70%, entry 3). In the last two cases, the less reactive ($Zr(O\text{-}n\text{-}Pr)_4$/TBHP) system can also be recommended. No overoxidation was observed in the slightly more hindered *β*-branched primary alcohol citronellol (**4**) (entry 5) which was converted quantitatively to the corresponding aldehyde. Not surprisingly the isolated double bond of citronellol (**4**) was not affected. Apparently, the heterogenous silica gel-supported zirconium catalyst $SiO_2/Zr(OR)_x$[30] is not sufficiently reactive for primary alcohols (entry 6).

Scheme 2



Secondary Alcohols. Thirteen secondary alcohols (**5**−**17**) were selected to test the influence of steric hindrance on the oxidation rate (Table 1). The yields of the corresponding ketones were essentially quantitative by GC (TLC for the steroids **14**−**17**) with exception of the sterically hindered menthol **9** and the strongly hindered 11-hydroxy steroid **15**. In the case of these severely hindered alcohols the yields could be raised to 84 and 85% by portionwise addition of more catalyst $Zr(O\text{-}n\text{-}Pr)_4$ and TBHP (see entries 16 and 22 and footnote c). The data show that $Zr(O\text{-}t\text{-}Bu)_4$ is the more active

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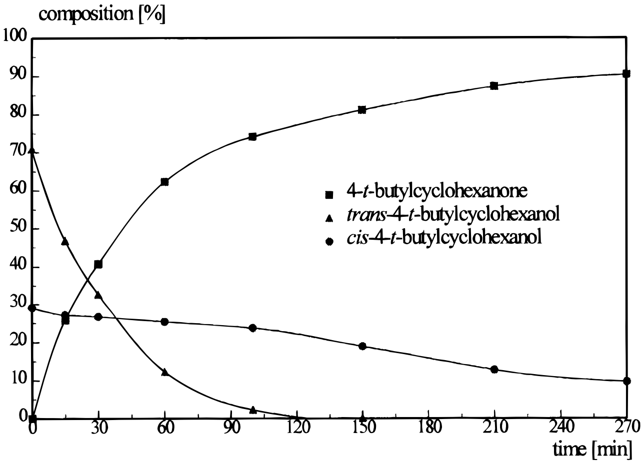
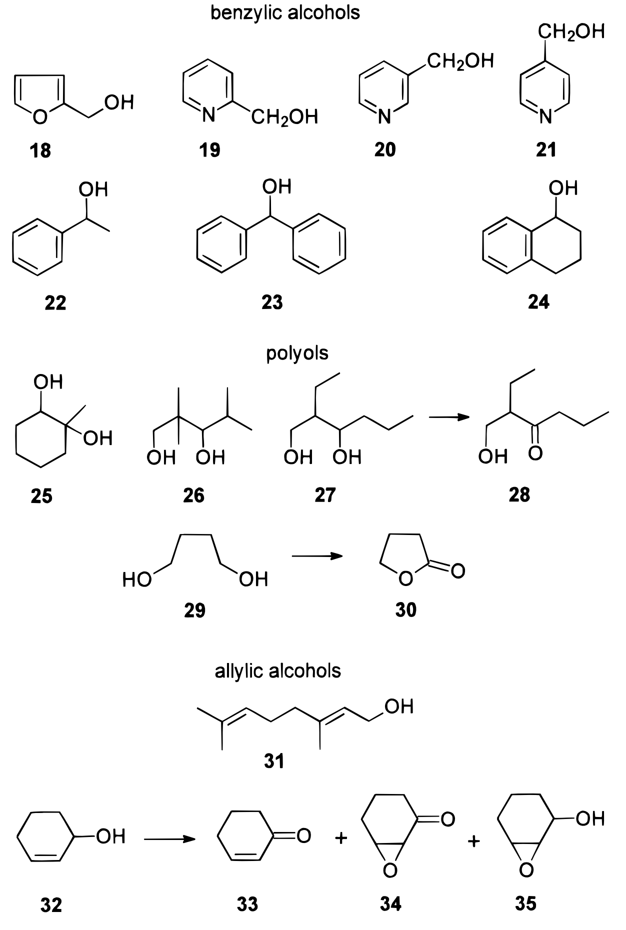


Figure 2. Oxidation of a *cis/trans*-mixture of 4-*tert*-butylcyclohexanol with Zr(O-*n*-Pr)$_4$.

Scheme 3



catalyst, but in many cases the less expensive Zr(O-*n*-Pr)$_4$ and also the heterogenous silica gel-supported zirconium catalyst can be used if longer reaction times and higher temperatures are acceptable.

A very interesting observation, which demonstrates the stereoselectivity of the system, was made during the oxidation of *trans*- and *cis-tert*-butylcyclohexanols **10** and **11** (as a 7:3 mixture). Figure 2 shows that the *trans*-isomer **10** (equatorial hydroxyl group) is rapidly converted into the ketone whereas the oxidation of *cis-tert*-butylcyclohexanone proceeds much slower. This effect is in contrast to chromium(IV) oxidations where the axial alcohol **11** is generally oxidized more rapidly.[31] This result was rationalized by relief of steric 1,3-strain in the rate-determining step.[31] The reverse selectivity in our case can perhaps be explained by developing 1,3-diaxial strain of the axial R of the secondary alcohol and ligand L on the zirconium (see Scheme 1), raising the energy of transition state **A**. This complementary selectivity of the zirconium-catalyzed dehydrogenation, in contrast to most of the other oxidations, can be preparatively very useful. For example, the thermodynamically less stable *cis*-alcohol can be obtained in pure form after 1 h of reaction time by separation from the 4-*tert*-butylcyclohexanone. During this time only 5% of the cis-isomer (**11**) was consumed while the trans-isomer (**10**) was completely oxidized to the ketone. The selectivity for equatorial alcohols is a general feature as confirmed by the oxidation of the trimethylcyclohexanols **12** and **13** (as a 17:83 mixture). In this case the *cis*-isomer (**12**) is completely converted to the ketone after 1 h, yielding a mixture of 43% ketone and 57% of the pure *trans*-3,3,5-trimethylcyclohexanol (**13**).

Benzylic Alcohols. Next we investigated the benzylic alcohols **18**–**24** including those with heteroatoms (**18**–**21**). As expected, furfuryl alcohol (**18**) did not react at all and 2-(hydroxymethyl)pyridine (**19**) reacted only very slowly, indicating a strong chelation of these alcohols to the zirconium center (Table 2, entries 1 and 2). Model considerations showed that hydride abstraction was impossible in these chelates and the reaction of **19** most probably occurred from the low equilibrium concentration of nonchelated substrate. However, 3- and 4-(hydroxymethyl)pyridines **20** and **21**, which failed to react with the titanium alkoxide/TBHP system,[4] were rapidly oxidized with Zr(O-*t*-Bu)$_4$/TBHP to mixtures of the corresponding aldehydes and *tert*-butyl esters (ca. 10–20%). Fortunately, the ester formation was entirely suppressed using the sterically more hindered cumene hydroperoxide (CHP) (entries 5 and 9) as hydride acceptor, and the corresponding aldehydes were formed in quantitative yield. In these cases the heterogeneous SiO$_2$/Zr(OR)$_x$ catalyst was also active, but much longer reaction times and higher temperatures were required. Finally, the reactive secondary benzylic alcohols **22**–**24** were also oxidized to the ketones quantitatively, even at 0 °C (entries 11–14).

Polyols. Experiences with the chelating alcohols **18** and **19** suggest that similar factors may operate in polyols. In fact, almost no conversion was observed with the 1,2-diol **25** (e.g., VO(acac)$_2$ system cleaved the C–C bond[5] of 1,2-diols). The 1,3-diol **27** has a primary and a secondary hydroxy group. Usually, sterically unhindered secondary hydroxy groups react approximately 2–10 times faster than primary alcohols as deduced from a competition experiment with 1- and 2-octanols (see Experimental Section, kinetic data Table 5). However, both hydroxyl groups in **27** are severely hindered and the reaction is very slow, yielding 85% of the corresponding hydroxy ketone **28** after 5 d (Table 3). The severely hindered 1,3-diol **26** is converted only very slowly, yielding 40% of the corresponding primary hydroxy aldehyde and mixtures of products after a very long reaction time. A number of oxidation modes are possible with the 1,4-diol **29**, yielding the dialdehyde, the aldehyde acid, or the lactone **30** which could in fact be identified as the major product (ca. 50%, entry 4).

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Table 2. Oxidation of Benzylic Alcohols

entry	substr	catalyst	oxidant	*T* [°C]	time [h]	convn [%]	products
1	**18**	Zr(O-*t*-Bu)$_4$	TBHP	60	26		
2	**19**	Zr(O-*t*-Bu)$_4$	TBHP	60	26	ca. 60	aldehyde/*t*-Bu ester[a]
3	**20**	Zr(O-*t*-Bu)$_4$	TBHP	20	1	>99	aldehyde/*t*-Bu ester[a]
4	**20**	Zr(O-*n*-Pr)$_4$	TBHP	20	1	>99	aldehyde/*t*-Bu ester[a]
5	**20**	Zr(O-*t*-Bu)$_4$	CHP	60	1	>99	aldehyde
6	**20**	SiO_2/Zr(OR)$_x$	TBHP	80	19	70	aldehyde
7	**21**	Zr(O-*t*-Bu)$_4$	TBHP	20	1	>99	aldehyde/*t*-Bu ester[a]
8	**21**	Zr(O-*n*-Pr)$_4$	TBHP	20	1	>99	aldehyde/*t*-Bu ester[a]
9	**21**	Zr(O-*t*-Bu)$_4$	CHP	60	1	>99	aldehyde
10	**21**	SiO_2/Zr(OR)$_x$	TBHP	80	19	65	aldehyde
11	**22**	Zr(O-*t*-Bu)$_4$	TBHP	0	3	>99	acetophenone
12	**23**	Zr(O-*t*-Bu)$_4$	TBHP	0	4	95	benzophenone
13	**24**	Zr(O-*t*-Bu)$_4$	TBHP	0	1	>99	tetralone
14	**24**	Zr(O-*n*-Pr)$_4$	TBHP	0	5	98	tetralone

[a] The ratio of aldehyde/ester depends on the rection conditions (see Experimental Section).

Table 3. Oxidation of Polyols and Allylic Alcohols

entry	substr	catalyst	*T* [°C]	time [h]	convn [%]	products
1	**25**	Zr(O-*n*-Pr)$_4$	20	2 d		
2	**26**	Zr(O-*n*-Pr)$_4$	20	2 d	40	hydroxyaldehyde
3	**27**	Zr(O-*n*-Pr)$_4$	20	5 d	85	**28**
4	**29**	Zr(O-*n*-Pr)$_4$	60	2	>99	50% of **30**
5	**31**	Zr(O-*t*-Bu)$_4$	20	0.5	>99	2,3-epoxygeraniol
6	**31**	Zr(O-*n*-Pr)$_4$	20	0.5	>99	2,3-epoxygeraniol
7	**31**	SiO_2/Zr(OR)$_x$	80	22	70	2,3-epoxygeraniol/citral (2:1)
6	**32**	Zr(O-*n*-Pr)$_4$	60	1	>99	**33**:**34**:**35** = 1:1:4
7	**32**	Zr(O-*n*-Pr)$_4$	20	1.5	>99	**33**:**34**:**35** = 2:1:1
8	**32**	Zr(O*n*-Pr)$_4$	−20	24	>99	**33**:**34**:**35** = 10:0.5:1

Allylic Alcohols. Allyl alcohols can be valuable test systems for checking the oxygenation versus dehydrogenation pathway since epoxidation can be a major pathway (e.g., Sharpless[19] reaction). The primary allyl alcohol geraniol (**31**) and the secondary 2-cyclohexenol (**32**) were selected as test systems. The less easily dehydrogenated primary allyl alcohol **31** showed only epoxidation with the zirconium alkoxide catalysts but ca. 30% of aldehyde was formed with the heterogeneous SiO_2/Zr(OR)$_x$. The situation reversed with the secondary allyl alcohol where ca. 85% of the dehydrogenation product **33** was formed at −20 °C, together with the epoxides **34** and **35**. These results suggest that the zirconium alkoxides are more suitable for the dehydrogenation process than their titanium analogues.

In summary, secondary alcohols, not too sterically hindered, can be quantitatively converted to the corresponding ketones with the dehydrogenation system Zr(OR)$_4$/TBHP/4 Å molecular sieves. Good yields of aldehydes can also be obtained by lowering the reaction temperature, decreasing the amount of TBHP, and changing the catalyst (Zr(O-*t*-Bu)$_4$ to Zr(O-*n*-Pr)$_4$ or SiO_2/Zr(OR)$_x$).

Experimental Section

For general remarks and instrumentation used, see ref 32; assignments in the NMR spectra are based on DEPT or COLOC experiments. Unless otherwise noted all alcohols were obtained commercially and used without further purification. Powdered 3 Å molecular sieves (Fluka) were activated by being heated in a vacuum at 300 °C and 0.1 Torr for 8 h. Dichloromethane was distilled from calcium hydride and tetrachloromethane from P_4O_{10} under nitrogen. Solutions of anhydrous TBHP in dichloromethane were prepared from 70% aqueous *tert*-butyl hydroperoxide (Fluka) according to the procedure described by Sharpless et al.[33] Solutions of cumene hydroperoxide (CHP) (80% solution in cumene, Fluka) were stored for 14 h over molecular sieves prior to use. Zr(O-*n*-Pr)$_4$ (70% solution in 1-propanol, Fluka) was distilled by bulb-to-bulb distillation (the propanol had to be removed rigorously). Zr(O-*t*-Bu)$_4$ and Zr(acac)$_4$ (Fluka) were used without further purification.

General Procedure for Homogenous Catalysis. All reactions were carried out under an atmosphere of dry nitrogen or argon. In general, the reactions were run in oven-dried 25 mL two-necked round-bottomed flasks, equipped with a magnetic stirring bar and a rubber septum. In a typical procedure a mixture of the alcohol (1.5 mmol, see Tables), anhydrous TBHP (solution in CH_2Cl_2, 3 mmol), and 3 Å of powdered freshly activated molecular sieves (0.6 g) in CH_2Cl_2, CCl_4, or toluene (3 mL) was vigorously stirred for 10 min at 20, 60, or 80 °C (toluene) (see tables). The reaction was started by addition of the catalyst (0.15 mmol, syringe). Different methods of workup were used.

A. Acidic Workup. The reaction mixture was diluted with CH_2Cl_2 (5 mL), the molecular sieves were removed by filtration, hydrochloric acid (10%, 10 mL) was added, and the mixture was stirred for 30 min. The phases were separated, the organic layer was extracted with 5% HCl (2 × 5 mL), the aqueous extracts were washed with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over a mixture of $MgSO_4$ and Celite for 30 min and filtered through a pad of Celite. The filtrate was directly used for GC analysis or the solvent and excess TBHP were removed at reduced pressure and the residue was purified by bulb-to-bulb distillation, column chromatography, or crystallization and analyzed by NMR (see tables). Alternatively, the TBHP can be removed by stirring the mixture with an aqueous solution of Fe_2SO_4 (see ref 33).

B. Neutral Workup. For substrates sensitive to acids (see entry 24 in Table 1) water was used to quench the reaction, the organic phase was washed with brine (3 × 20 mL), and workup was continued as described under A.

C. Workup for Water-soluble Products. The reaction mixture was diluted with CH_2Cl_2 (15 mL), the reaction was quenched by additon of water (2 mL), and the solution was stirred for 1 h. Stirring was maintained while $MgSO_4$ (4 g) and celite (2 g) were added. The mixture was filtered through

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Table 4. Rates at $t = 0$ and Reaction Times for 50% Conversion ($t_{1/2}$) of the Dehydrogenation of Selected Primary and Secondary Alcohols

substr[a]	$-\mathrm{d}(c/c_0)$ ($t = 0$) [min^{-1}]	$t_{1/2}$ [min]	T [°C]	observ time [min]
1	0.009		20	120
2	0.006		20	240
4	0.011	296	20	495
6	0.009	73	20	210
7	0.029	24	20	180
8	0.006	66	20	345
10/11	0.017	46	20	240
22	0.040	327	0	420
23	0.025	135	0	240
24	0.186	13	0	270

[a] Catalyst Zr(O-*n*-Pr)$_4$, solvent CCl$_4$.

Table 5. Kinetic Data for the Competitive Oxidation of 1 and 5

time [min]	convn 1 [%][a]	convn 2 [%][a]	c_1/c_2
0	0	0	1
15	8.3	12.2	1.05
30	13.7	20.3	1.09
60	26.2	35.9	1.16
120	39.5	65.3	1.74
210	51.6	91.7	6.00
270	57.9	94.9	8.40

[a] c_1 = concentration of 1-octanol, c_2 = concentration of 2-octanol.

a pad of Celite, the drying agents were washed carefully with CH$_2$Cl$_2$ (3 × 10 mL), and workup was continued as described under A.

General Procedure for the Heterogenous Catalysis. To a mixture of alcohol (1.5 mmol), CCl$_4$ (5 mL), TBHP (solution in CH$_2$Cl$_2$, 3 mmol), and powdered, activated 3 Å molecular sieves (300 mg) was added the silica gel-supported zirconium catalyst (see ref 30) at 20 °C. The reaction mixture was heated to 80 °C, and the conversion was monitored by TLC and/or GC. The catalyst and the molecular sieves were separated by filtration, the solvent was removed under reduced pressure, and the crude product was purified by bulb-to-bulb distillation, column chromatography, or crystallization and analyzed by GC and NMR spectroscopy.

General Analytic Procedures and Kinetics. All reactions were monitored by TLC and/or GC (examples in the tables are the result of at least two experiments). For GC, samples of 0.01 mL were taken from the reaction mixtures, diluted with CH$_2$Cl$_2$ (1.25 mL), washed with H$_2$O (0.5 mL), and dried with Na$_2$SO$_4$. Special care was taken to keep the temperature constant (20 °C). The aldehydes and ketones obtained by oxidation were identified by comparison of their ^{1}H and ^{13}C NMR data or their retention times/R_f values with authentic samples.

The nature of the catalyst changed continuously during the reaction time, and rate orders or constants were difficult to determine. Instead, the rate v at $t = 0$ ($\mathrm{d}(c/c_0)/\mathrm{d}t$ for $t = 0$) and the time at 50% conversion ($t_{1/2}$) were determined to compare the reactions quantitatively. The kinetic data were fitted using TechPlot for Windows,[34] and the $\mathrm{d}(c/c_0)/\mathrm{d}t$ values were calculated for $t = 0$ from the functions resulting from the fit. The square of the correlation coefficient r^2 ranged between 0.98 and 1.00. Selected examples are shown in Table 4, demonstrating the increased rate at $t = 0$ for primary, secondary, and benzylic alcohols.

Competitive Oxidation of 1-Octanol and 2-Octanol. A mixture of 1-octanol (1 mmol) and 2-octanol (1 mmol) was dissolved in CCl$_4$ (3 mL) (Table 5). TBHP (solution in CH$_2$Cl$_2$, 4 mmol) and powdered, activated 3 Å molecular sieves (0.6 g) were added at 20 °C, and the reaction was started by addition of Zr(O-*n*-Pr)$_4$ (1 M in CH$_2$Cl$_2$, 0.2 mL, 0.2 mmol). The conversion was monitored for 6.5 h.

Table 6. Comparision of the Kinetic Data of the Dehydrogenation by Zr(O-*n*-Pr)$_4$ and Zr(O-*t*-Bu)$_4$

substr	Zr(OR)$_4$	$-\mathrm{d}(c/c_0)/\mathrm{d}t$ [min^{-1}]	$t_{1/2}$ [min]	T [°C]	observ time [min]
7	R = *n*-Pr	0.029	24	20	180
7	R = *t*-Bu	0.748	0.9	20	180
22	R = *n*-Pr	0.040	327	0	180
22	R = *t*-Bu	0.440	1.7	0	180
23	R = *n*-Pr	0.025	135	0	240
23	R = *t*-Bu	0.384	1.9	0	240

Finally, the efficiency of the catalysts Zr(O-*n*-Pr)$_4$ and Zr(O-*t*-Bu)$_4$ was compared quantitatively as shown in Table 6.

Catalytic Oxidation of Steroids (alcohols 14−17). A solution of the steroid (0.5 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with TBHP (solution in CH$_2$Cl$_2$, 1.25 mmol) and Zr(O-*n*-Pr)$_4$ (1 M in CH$_2$Cl$_2$, 0.1 mL, 0.1 mmol) at 20 °C as described in the general procedure for homogenous catalysis. After 90 min the same amounts of TBHP and catalyst were added a second time. The reactions were monitored by TLC (ethyl acetate: CH$_2$Cl$_2$ = 1:1) and worked up (procedure A) after the times indicated in Table 1. If necessary, the crude products were purified by column chromatography (ethyl acetate:CH$_2$Cl$_2$ = 1:1) and crystallization from ethyl acetate/cyclohexane.

Oxidation of 17α-hydroxy-19-norandrost-4-en-3-one (14) to 19-norandrost-4-ene-3,17-dione: mp 162.5−163 °C; lit.[35] mp 162−164 °C; ^{13}C NMR δ = 14.04 (q, 18-C), 21.87 (t), 25.91 (t), 26.84 (t), 30.12 (t, 7-C), 31.57 (t), 35.47 (t), 35.95 (t), 36.70 (t), 40.00 (d, 8-C), 42.58 (d, 9-C), 47.88 (s, 13-C), 49.72 (d, 14-C), 50.31 (d, 10-C), 124.93 (d, 4-C), 166.30 (s, 5-C), 199.73 (s, 3-C), 220.43 (s, 17-C).

Oxidation of 17α-hydroxyestra-4,9-dien-3-one (16) to estra-4,9-diene-3,17-dione: mp 125.2−126.5 °C; lit.[36] mp 130−131 °C; lit.[37] mp 119−121 °C; ^{13}C NMR δ = 13.45 (q, 18-C), 22.15 (t), 25.42 (t), 26.12 (t), 26.76 (t), 30.94 (t), 31.71 (t), 36.11 (t), 37.26 (t), 38.96 (d, 14-C), 47.74 (s, 13-C), 51.39 (d, 8-C), 122.65 (d, 4-C), 126.42 (s, 10-C), 145.23 (s), 157.07 (s), 199.78 (s, 3-C), 219.95 (s, 17-C).

Oxidation of 11*β*-hydroxy-19-norandrost-4-ene-3,17-dione (15) to 19-norandrost-4-ene-3,11,17-trione: mp 192−194 °C; lit.[38] mp 185−190 °C; ^{13}C NMR δ = 14.86 (q, 18-C), 21.44 (t), 28.54 (t), 29.84 (t), 34.79 (t), 36.20 (d, 8-C), 36.30 (t), 37.14 (t), 40.56 (d, 14-C), 49.45 (d, 10-C), 49.85 (t), 51.78 (s, 13-C), 60.43 (d, 9-C), 126.52 (d, 4-C), 164.75 (s, 5-C), 200.13 (s, 3-C), 208.71 (s, 11-C), 216.83 (s, 17-C).

Oxidation of 17α-hydroxy-3,3-(2,2-dimethyltrimethylene-1.3-dioxy) 5(10),9(11)-estradiene (17) to (2,2-dimethyltrimethylene-1,3-dioxy)-5(10),9(11)-estradien-17-one: mp 129−133 °C (*n*-hexane), lit.[39] 139−140 °C; ^{1}H NMR δ = 0.78 (18- CH$_3$), 0.79 and 0.98 (2 s, 2 × 3 H, 2 × dioxolane CH$_3$), 1.1−2.4 (m, 18 H), 3.2−3.6 (m, 4 H, dioxolane CH$_2$), 5.45 (s, broad, 1 H, 11-H); ^{13}C NMR δ = 15.11 (q, 18-C), 22.71 (q, dioxolane CH$_3$), 23.21 (q, dioxolane CH$_3$), 23.94 (t), 27.11 (t), 27.23 (t), 30.50 (s, dioxolane-C), 31.16 (t), 33.99 (t), 36.36 (t), 37.83 (d, 14-C), 41.73 (t), 46.52 (s, 13-C), 47.80 (d, 8-C), 70.57 (t, 2 dioxolane CH$_2$), 97.48 (s, 3-C), 116.92 (d, 11-C), 126.41 (s), 130.02 (s), 137.30 (s), 221.88 (s, 17-C).

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