Stereoselective syntheses of functionalized cyclic ethers via (Schiff-base)vanadium(V)-catalyzed oxidations*,**

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Abstract: (Schiff-base)vanadium(V) complexes catalyze the oxidation of Br⁻ (formation of Br₂) and the stereoselective synthesis of functionalized tetrahydrofurans from substituted bishomoallylic alcohols. In both instances, tert-butyl hydroperoxide (TBHP) serves as primary oxidant. The oxidation of Br⁻ was applied as the key step for stereo- and 6-endo-selectively constructing the 2,2,3,5,6,6-substituted tetrahydropyran nucleus of the marine natural product alysiapyranoid A starting from an adequately substituted bishomoallylic alcohol. In the absence of Br⁻, 1-alkyl-, 1-vinyl-, and 1-phenyl-5,5-dimethyl-substituted bishomoallylic alcohols are selectively oxygenated to furnish 2,5-cis-configured tetrahydrofurans as major products. 2- or 3-substituted ω,ω-dimethyl-substituted bishomoallylic alcohols afford trans-disubstituted tetrahydrofurans under these conditions. Oxidation of substituted 4-penten-1-ols, i.e., substrates with a terminal π-bond, proceeds with a preference for formation of trans-disubstituted tetrahydrofurans. According to data from (i) ⁵¹V NMR spectroscopy, (ii) mass spectrometry, (iii) a structure-selectivity survey, (iv) competition kinetics, and (v) a stereochemical analysis, the oxygen atom transfer onto a bishomoallylic alcohol occurs in a peroxide- and alkenol-loaded (Schiff-base)vanadium(V) complex.

Keywords: Vanadium; oxidation; tert-butyl hydroperoxide; tetrahydrofuran; tetrahydropyran; bromide; bromoperoxidase.

INTRODUCTION

In recent years, a remarkable number of tetrahydrofuran- and tetrahydropyran-derived secondary metabolites have been isolated from terrestic and marine organisms (Fig. 1) [1]. A considerable fraction of these compounds exhibits notable cytotoxic and/or antibiotic properties [2,3]. This circumstance has brought about a growing demand of functionalized cyclic ethers, which, however, cannot be covered from natural sources alone [4–6]. The invention of methods for stereoselectively constructing hydroxylated or halogenated heterocycles from alkenols, in particular via transition metal-catalyzed oxidations, has therefore received considerable attention [7–12]. However, none of the procedures reported so far has provided a solution for a longstanding problem: the control of diastereoselectivity and regioselectivity in the ring closing and the heteroatom functionalization step by means of the applied auxiliary and not by the selected substrate or the oxidant [10,13].

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**Dedicated to Prof. Dr. Bernd Giese on the occasion of his 65th birthday.
The prerequisite for the formation of functionalized cyclic ethers from alkenols is the availability of an adequately strong oxidant that is able to chemoselectively oxidize the olefinic $\pi$-bond (Fig. 1). In view of this consideration, tert-butyl hydroperoxide (TBHP) has been selected for conducting (Schiff-base)vanadium(V)-catalyzed oxidations in organic media. It is a comparatively strong oxidant ($E^\circ = 1.20$ V vs. NHE, CH$_3$OH/C$_6$H$_6$) that was discovered by Milas almost 70 years ago [18,19]. The commercially available 5.5 M solution of TBHP in nonane corresponds to a satisfactory active oxygen atom content of 11 %. tert-Butanol is obtained as major co-product from oxygenation reactions and can easily be removed via distillation (bp = 83 °C). TBHP is readily soluble in organic solvents and thermally surprisingly stable under neutral conditions. A major advantage of TBHP compared to H$_2$O$_2$ is the fact that it is less sensitive to metal contamination and does not react with most organic compounds in the absence of metal-catalysts [20,21]. Activation of TBHP for an application in selective oxidation reactions is attainable using transition-metal complexes, either via high-valent oxometal compounds or peroxide intermediates (Scheme 1). The third pathway for peroxide activation involves single electron transfer from the transition-metal complex [X–M$^{n+}$] onto TBHP, which is followed by homolytic cleavage of the O=O bond and free radical-based transformations [10,20].

![Fig. 1](image1.png)

Fig. 1 Selection of biologically active natural products with a tetrahydrofuran or a tetrahydropyran subunit [14–17].

The results of a screening survey [22] indicated that reagents formed by in situ mixing TBHP and a vanadium(V) complex with a dibasic tridentate Schiff-base auxiliary [23–27] constitute powerful but selective oxidants for chemo-, regio-, and stereoselectively converting bishomoallylic alcohols I into functionalized tetrahydrofurans II (Scheme 2) [22,28]. In the presence of Br$-$ and one equivalent of H$^+$ per oxidizable halide ion, the selectivity of this system entirely changes from $\pi$-bond oxygenation to Br$^-$ oxidation. In the latter case, the reaction furnishes products of selective bromocyclization, i.e. heterocycles III (Scheme 2) [29].
In view of this background, it is the aim of this review to summarize the principles, the mechanisms, and some of the more recent applications of (Schiff-base)vanadium(V)-catalyzed oxidations in the stereoselective synthesis of heteroatom-functionalized cyclic ethers, with a focus on the formation of natural products and structurally closely related derivatives thereof (Fig. 1).

**Scheme 2** Reagent-controlled divergence of reaction channels in oxidation catalysis: The stereoselective formation of hydroxymethyl-substituted tetrahydrofurans II or bromocyclization products III. \( R^E, R^Z = \text{H, alkyl, phenyl} \). \([\text{O}] = \text{TBHP / VOL(OEt)}; [\text{Br}^+] = \text{pyBr/TBHP/VOL(OEt)} \) (see Scheme 3 for structure formulae of vanadium complexes).

In view of this background, it is the aim of this review to summarize the principles, the mechanisms, and some of the more recent applications of (Schiff-base)vanadium(V)-catalyzed oxidations in the stereoselective synthesis of heteroatom-functionalized cyclic ethers, with a focus on the formation of natural products and structurally closely related derivatives thereof (Fig. 1).

**Scheme 3** Preparation of (Schiff-base)vanadium(V) complexes 1–4 [23,28]. \( m = 1–4 \), \( q = 0,1 \).
Table 1 Selected spectroscopic data of (Schiff-base)vanadium(V) complexes 1–4 [28,29].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$^{51}$V NMR $\delta$ [ppm] (CDCl$_3$)</td>
<td>$-529$</td>
<td>$-538$</td>
<td>$-542/-545$</td>
<td>$-562/-573$</td>
</tr>
<tr>
<td>2</td>
<td>$^{51}$V NMR $\delta$ [ppm] (CDCl$_3$ + TBHP)</td>
<td>$-571$</td>
<td>$-578$</td>
<td>$-574/-578$</td>
<td>$-$</td>
</tr>
<tr>
<td>3</td>
<td>$\nu_{V=O}$ [cm$^{-1}$]</td>
<td>990</td>
<td>991</td>
<td>997</td>
<td>987</td>
</tr>
<tr>
<td>4</td>
<td>$\lambda_{\text{max}}$ [nm] (lg $\varepsilon$)</td>
<td>659 (2.40)</td>
<td>652 (2.39)</td>
<td>652 (2.06)</td>
<td>652 (2.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>361 (3.80)</td>
<td>435 (2.44)</td>
<td>437 (1.91)</td>
<td>437 (1.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>341 (3.78)</td>
<td>359 (4.07)</td>
<td>345 (3.74)</td>
<td>350 (3.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>242 (4.16)</td>
<td>269 (4.48)</td>
<td>272 (4.22)</td>
<td>251 (4.25)</td>
</tr>
</tbody>
</table>

$^a$Not determined.

The analytical data were supplemented by results from single-crystal X-ray diffraction analysis, e.g., for 1,2-aminoindanol-derived complex 3 (Fig. 2) [28]. Coordination compound 3 crystallizes in space group $P\overline{2}1\overline{2}1\overline{2}1$ and exhibits (C)-configuration at vanadium [30–32]. The central ion is located 0.52 Å above the NO$_3$ plane in a distorted square pyramidal coordination polyhedron. The V–O distance decreases along the series V1–O$_2$ = 1.855(2) Å, V1–O$_3$ 1.815(3) Å, V1–O$_4$ 1.777(2) Å, to V1–O$_1$ = 1.586(2) Å. The observed long distance of V1–N$_1$ = 2.106(3) Å has been attributed to the well-known low affinity of neutral imino nitrogens to vanadium(V) [33]. The bond angles toward vanadium decrease in going from O$_2$–V1–O$_4$ [94.0(1)$^\circ$, phenolato to ethanolato oxygen], via O$_3$–V1–O$_4$ [91.8(1)$^\circ$, aminoalcoholato to ethanolato oxygen], N$_1$–V1–O$_2$ [82.7(1)$^\circ$, imine nitrogen to phenolato oxygen] to N$_1$–V1–O$_3$ [77.0(1)$^\circ$, imine nitrogen to aminoalcoholato oxygen].

Complexes VOL$_3$(OEt) (3) and VOL$_4$(OEt) (4), which were prepared from enantiomerically pure chiral ligands ($H_2L^{40}$), exhibit in CDCl$_3$ solution two $^{51}$V NMR resonances (Table 1). In view of the fact that the central ion in vanadium(V) reagents 1–4 constitutes a stereogenic center (for 1 and 3, see Fig. 3), it is likely that the two $^{51}$V NMR signals originate from diastereomers with respect to the absolute configuration at vanadium [10,34–37].

Fig. 2 Geometry of (Schiff-base)vanadium(V) complex (C)-3 in the solid state ($P\overline{2}1\overline{2}1\overline{2}1$) [28,30].
Treatment of VOL₁(OEt)(EtOH) (1) with a 1.5 molar excess of TBHP in CDCl₃ at 61 °C provides a brown solution, which is characterized by a highfield-shifted ⁵¹V NMR signal at δ = –571. In combination with additional analytical data from earlier studies [23,38], the resonance at –571 ppm has been assigned to (tert-butyl peroxy)vanadium(V) complex ⁵ (Scheme 4). In a more recent study, the in situ formation of a tert-butyl peroxy complex starting from VOL₂(OEt) (2) has been confirmed by results from ESI-MS investigations [29]. In view of this information, a highfield shift of ~40 ppm (⁵¹V NMR) upon addition of an excess of TBHP to a solution of a (Schiff-base)vanadium(V) coordination compound in CDCl₃ has been interpreted as evidence for the in situ formation of a (tert-butyl peroxy)(Schiff-base)vanadium(V) complex in general.

In the absence of a reducing agent, peroxy complex ⁵ decomposes into the oxo-bridged dimer ⁶ (Scheme 4), which has been characterized by X-ray diffraction [28]. If treated with 6-methyl-5-hepten-2-ol (7), peroxy complex ⁵ selectively delivers its active oxygen atom to the alkenol substrate, to provide in a stoichiometric reaction 77 % of pityol (cis:trans = 95:5) and 14 % of vittatol (cis:trans = 49:51) (Scheme 4). It should be noted that pityol or vittatol are not formed from substrate 7 and TBHP alone. The cis-isomers of the latter two ethers have been isolated from insect volatiles of the elm bark beetle Ptleobius vittatus. Their significance as pheromones and their application in bark beetle traps are under current investigation [14].

The reaction between (tert-butyl peroxy)(Schiff-base)vanadium(V) complex ⁵ and thianthrene-S-oxide (8) affords bis-S-oxide ⁹ as major product. On the basis of a quantitative analysis of all thianthrene-S-oxide-derived products, an Adam 𝜓SO value of 0.2 has been calculated for this reaction (reference data: 𝜓SO = 1.0 for NaOH/H₂O₂; 𝜓SO = 0.0 for TBHP/HClO₄) [29,40,41]. This information classifies peroxy complex ⁵ as electrophilic oxidant thus being suited to oxidize typical nucleophiles such as Br⁻. The latter reaction affords an electrophilic brominating reagent, which has been trapped by chlorodimedone (10) to provide 77 % of 2-bromo-2-chlorodimedone (11) (Scheme 4) [29,42].
Suitable conditions for the synthesis of functionalized tetrahydrofurans from substituted bishomoallylic alcohols in catalytic reactions were established by modifying (i) the amount of complex \( \text{VOL}^1(\text{OEt})(\text{EtOH}) \), (ii) the solvent, (iii) the reaction temperature, and (iv) the primary oxidant. Thus, 1.5 equiv. of TBHP, 10 mol % of catalyst \( \text{VOL}^1(\text{OEt})(\text{EtOH}) \) (1), a temperature of 20 °C and \( \text{CHCl}_3 \) as solvent were found to be adequate in order to convert 5-methyl-1-phenyl-4-hexen-1-ol (12) into 81 % of 2,5-disubstituted tetrahydrofuran \( \text{rac} \)-13 (\( \text{cis}:\text{trans} = 98:2 \)) and 14 % of tetrahydropyran \( \text{rac} \)-14 (\( \text{cis}:\text{trans} = 46:54 \)). In addition, 1–3 % of other oxidation products were formed, isolated, and characterized (not shown in Scheme 5) [28]. Under these conditions, a turnover of 98 % for substrate 12, a combined yield of 95 % for cyclic ethers \( \text{rac} \)-13 and \( \text{rac} \)-14, and a peroxide efficiency of 65 % is achieved. Other primary oxidants, such as \( \text{H}_2\text{O}_2 \), CHP, UHP, and PhIO were found to be less efficient in this reaction.

In further studies, it was noted that the stereoselectivity for the (Schiff-base)vanadium(V)-catalyzed oxygenation of 1-phenyl-substituted bishomoallylic alcohols is critically dependent on the substitution pattern at the olefinic \( \pi \)-bond (Scheme 6). For example, oxidation of 1-phenyl-4-penten-1-ol (15) and \( (E) \)-1-phenyl-4-hexen-1-ol \( (E) \)-(16) with TBHP in the presence catalyst 1 (10 mol %) affords \( \text{trans} \)-configured 2,5-substituted tetrahydrofurans as major products (\( \text{cis}:\text{trans} = 39:61 \) for \( \text{rac} \)-17, \( \text{cis}:\text{trans} = 40:60 \) for \( \text{rac} \)-18 along with 14 % of 2-\( \text{trans},6\)-\( \text{trans} \)-configured tetrahydropyran \( \text{rac} \)-19).

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The reaction of the (Z)-configured alkenol (Z)-16 under these conditions proceeds with a marked preference for formation of the cis-diastereomer of rac-18 (cis:trans = 90:10) [28,43]. In view of the side-chain configuration, it is important to note that unlike-isomer of rac-18 is formed from (E)-16, while (Z)-16 furnishes exclusively the corresponding like-stereoisomer.

1-Amino-2-indanol-derived complex VOL3(OEt) (3) was the most selective oxidation catalyst (stereoselectivity, regioselectivity, and chemoselectivity) out of a larger set of vanadium(V) compounds and was therefore applied for the conversion of 2- or 3-substituted bishomoallylic alcohols with TBHP into the corresponding functionalized tetrahydrofurans (Tables 2 and 3). All these oxidations proceeded trans-selectively. In general, the selectivity and the efficiency for product formation from ω,ω-dimethyl-substituted substrates (entries 3 and 4 in Tables 2 and 3) was superior to reactions starting from substrates with terminal π-bonds (entries 1 and 2 in Tables 2 and 3).

Table 2 Formation of cyclic ethers from 2-substituted bishomoallylic alcohols [28].

<table>
<thead>
<tr>
<th>Entry</th>
<th>R2</th>
<th>R</th>
<th>20–23 [%] (cis:trans)</th>
<th>24–27 [%] (cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(CH3)2</td>
<td>H</td>
<td>20</td>
<td>90 (29:71)</td>
</tr>
<tr>
<td>2</td>
<td>C6H5</td>
<td>H</td>
<td>21</td>
<td>43 (36:64)</td>
</tr>
<tr>
<td>3</td>
<td>CH(CH3)2</td>
<td>CH3</td>
<td>22</td>
<td>90 (19:81)</td>
</tr>
<tr>
<td>4</td>
<td>C6H5</td>
<td>CH3</td>
<td>23</td>
<td>55 (9:91)</td>
</tr>
</tbody>
</table>

* Racemates.
* Not detected (1H NMR).

Scheme 6 Diastereoselection caused by the substitution pattern at olefinic π-bonds. [O] = TBHP, VOL2(OEt)(EtOH) (1) (10 mol %), CHCl3, 20 °C [28,43].
Table 3 Conversion of 3-substituted bishomoallylic alcohols into β-hydroxylated cyclic ethers [28].

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^3$</th>
<th>$R$</th>
<th>28–31 [%] (cis:trans)</th>
<th>32–35 [%] (cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(CH$_3$)$_3$</td>
<td>H</td>
<td>28</td>
<td>61 (&lt;2:98)</td>
</tr>
<tr>
<td>2</td>
<td>C$_6$H$_5$</td>
<td>H</td>
<td>29</td>
<td>43 (40:60)</td>
</tr>
<tr>
<td>3</td>
<td>CH(CH$_3$)$_2$</td>
<td>CH$_3$</td>
<td>30</td>
<td>54 (&gt;2:98)</td>
</tr>
<tr>
<td>4</td>
<td>C$_6$H$_5$</td>
<td>CH$_3$</td>
<td>31</td>
<td>76 (&gt;2:98)</td>
</tr>
</tbody>
</table>

*a*Racemates.

*b*Not detected (*$^1$H NMR).

Enantioselective tetrahydrofuran syntheses starting from prochiral bishomoallylic alcohols, TBHP and catalyst VOL$_3$(OEt) (3) have so far not been accomplished [28]. On the other hand, some noteworthy selectivities have been observed in (Schiff-base)vanadium(V)-catalyzed oxidations of dienols, such as (S,S)-bisabolol (36), (R)-linalool (40), and its twofold higher homologue 38 (Scheme 7). All compounds gave rise to well-defined regioselectivities, as seen in the formation of (–)-epi-bisabolol oxide B (37) and the twofold higher homologue rac-39 of furanoid linalool oxide 41 [28,43,44].

Scheme 7 Vanadium(V)-catalyzed oxidation of (S,S)-bisabolol (36), tertiary alkenol 38 and (R)-linalool (40). [O] = TBHP, VOL$_3$(OEt) (3) (10 mol %), CHCl$_3$, 20 °C [28,43,44].

The selective oxygenation of (R)-Linalool (40) at positions 6,7 is, to my knowledge, the first example for a vanadium(V)-catalyzed oxidation at the bishomoallylic rather than at the allylic π-bond of this substrate [44,45]. The straightforward synthetic access to enantiomerically pure furanoid linalool oxides cis-41 and trans-41 has been opened a new perspective for a short synthesis of hitherto unknown
derivatives of the natural product cyclocapitelline (Scheme 8) [16,44]. For example, oxidation of purified isomers cis-41 and trans-41 with RuCl$_3$ and NaIO$_4$ in a two-phase system of C$_2$H$_4$Cl$_2$/H$_2$O affords the corresponding lactol from cis-41 and a hydroxyaldehyde from trans-41. Treatment of these products with tryptamine provides Schiff-bases, which were cyclized in the presence of trifluoroacetic acid in a Pictet–Spengler-type reaction. Dehydrogenation of the cyclization products gave rise to β-carbolines cis-42 and trans-42 in satisfactory yields (Scheme 8).

\[ \text{cis-41} \quad \xrightarrow{\text{a-d}} \quad 14\% \quad \text{cis-42} \]
\[ [\alpha]_{D}^{25} = -32.9 \quad \text{(c 0.57, CHCl}_3) \]

\[ \text{trans-41} \quad \xrightarrow{\text{a-d}} \quad 21\% \quad \text{trans-42} \]
\[ [\alpha]_{D}^{25} = -50.5 \quad \text{(c 0.50, CHCl}_3) \]

Scheme 8 Formation of derivatives of cyclocapitelline from furanoïd linalool oxides cis-41 and trans-41. Reagents and conditions: (a) RuCl$_3$, NaIO$_4$, C$_2$H$_4$Cl$_2$, H$_2$O; (b) tryptamine, CH$_2$Cl$_2$; (c) CF$_3$CO$_2$H, CH$_2$Cl$_2$; (d) Pd/C, xylene [44].

MECHANISTIC INVESTIGATIONS

The oxidation of 1-phenyl-5-methylhexenol 12 with TBHP in the presence of a (Schiff-base)vanadium(V) complex, e.g., o-aminophenol-derived catalyst 1, affords 2-(1-hydroxy-1-methylethyl)-5-phenyltetrahydrofuran rac-(13) and 2,2-dimethyl-6-phenyltetrahydropyran-3-ol rac-(14) as major products (Scheme 5). Treatment of 2-methyl-6-phenyl-2-hexene (43) under these conditions furnishes 87 % of epoxide 44. Oxidation of well-defined mixtures of substrates 12 and 43 in a set of competition experiments provides tetrahydrofuran 13 (cis/trans-isomers), tetrahydropyran 14 (cis/trans-isomers), and epoxide 44 (Scheme 9). A numerical analysis of likewise obtained kinetic data has been performed using a reaction model, which is based on a direct and irreversible oxygen atom transfer from peroxo complex 5 to substrates 12 and 43 under pseudo first-order conditions. The slope of a linear correlation between the ratios of ([13]+[14])/[44] and [12]/[43] then corresponds to the relative rate constant $k_{\text{rel}} = k_2/k_1 = 120 \pm 20$ (20 °C, CHCl$_3$) thus pointing to a rate-enhancing effect of the OH group for the oxygenation of 12 (see below).
The model for rationalizing the origin of the selectivity in alkenol oxygenation using the combination of TBHP and a (Schiff-base)vanadium(V)-catalyst has been supplemented by a concise stereochemical analysis starting from enantiomerically pure substrates \((R)\)-12 and \((S)\)-12 (both >99 % ee). The two alkenols were epoxidized under Shi-conditions [46] to provide \((1R,4R)\)-45 in 94 % yield (76 % de, \(^1\)H-NMR, Scheme 10) from alkenol \((R)\)-12 [47] and \((1S,4R)\)-45 in 96 % yield (64 % de, \(^1\)H NMR) from \((S)\)-12. Assignment of the \((R)\)-configuration at the stereocenter which was constructed in the Shi-epoxidation was based on (i) the general face selection rule for this well-established method [48] and (ii) a correlation of epoxyalcohol configurations with the geometry of rearranged products 13 and 14 (see below). Treatment of epoxyalcohol \((1R,4R)\)-45 with 10 mol % of vanadium(V) complex 3 or with 1 equiv of \(p\)-toluenesulfonic acid (TsOH) quantitatively affords 2,5-cis-configured tetrahydrofuran \((2S,5R)\)-13 and 3,6-cis-configured tetrahydropyran \((3R,6R)\)-14 in a ratio of 91:9. The vanadium(V)- or the acid-catalyzed rearrangement of epoxyalcohol \((1S,4R)\)-45 yields 2,5-trans-disubstituted tetrahydrofuran \((2S,5S)\)-13 and 3,6-trans-substituted tetrahydropyran \((3R,6S)\)-14 in a ratio of 39:61. Since the major component in one sample [e.g., \((1R,4R)\)-45] constituted the enantiomer of the minor in the second probe [e.g., \((1S,4S)\)-45], the by-products from each epoxide isomerization were readily identified.

Scheme 9 Competition kinetics: oxygenation of alkenol 12 vs. olefin 43.

Scheme 10 Diastereoselective conversion of alkenols \((R)\)-12 and \((S)\)-12 into cyclic ethers 13 and 14. Reagents and conditions: (a) Shi-epoxidation [46]; (b) TsOH (1 equiv) or VOL\(^3\)(OEt) (3) (10 mol %), CDCl\(_3\) [28].

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The information from the structure-selectivity survey, competition kinetics, and the stereochemical analysis match with a unified model (Scheme 11). According to this mnemonic device, the observed diastereoselectivities originate from a selective oxygen atom transfer in (tert-butyl peroxy)vanadium(V) complex 46. Evidence for formation of intermediate 46 has been deduced from the result of the competition experiments that point to a rate-enhancing effect of the hydroxyl group in the oxygenation of substrate 12 (Scheme 9). A syn-selective oxygen atom transfer in “loaded” peroxy complex 46 onto one of the diastereotopic faces is feasible, if the alkenol chain adopts preferentially a chair-like folding (chair-46) or the geometry of gauche-46. On the basis of nonbonding interactions, the former should be favored upon an approach of the reacting entities, thus leading to the like-configured (epoxy-alcohol)vanadium(V) complex like-47. Rearrangement of like-47 and elimination of vanadium(V) complex 48 provides cis-disubstituted tetrahydrofuran cis-13 as major and tetrahydropyran cis-14 as minor product. It should, however, be noted that free epoxyalcohols have so far not been detected in reaction mixtures obtained by mixing a bishomoallylalkohol, TBHP, and a (Schiff-base)vanadium(V) catalyst. Substrate oxygenation in intermediate gauche-46 occurs with an opposite facial selectivity, if compared to the formation of like-47 from chair-46, thus leading to synthesis of trans-substituted heterocycles trans-13 and trans-14. The reaction starting from chair-46 is in most instances favored. Exception to this guideline are 1-substituted 4-penten-1-ols (e.g., 15), (E)-1-phenyl-4-hexen-1-ol (E)-(16), and 3-substituted bishomoallylic alcohols, which obviously are oxidized via the pathway that starts from gauche-46 [22,28].

Scheme 11 Stereochemical model for correlating the facial selectivity of \( \pi \)-bond oxygenation in “loaded” peroxy complex 46 with the geometry of likewise formed cyclic ethers 13 and 14; \([V]\) corresponds to the transition-metal fragment VOL\(^m\), e.g., VOL\(^1\) (see Scheme 3).

**SCHIFF-BASE)\textit{VANADIUM(V)}-CATALYZED OXIDATION OF BROMIDE AND ITS APPLICATION IN THE SYNTHESIS OF APLYSIAPYRANOID A**

The fact that Br\(^-\) is selectively oxidized by TBHP out of a mixture of the halide and a bishomoallylic alcohol has considerably extended the scope of (Schiff-base)vanadium(V)-catalyzed oxidations for se-
lective syntheses of β-heteroatom-functionalized cyclic ethers [29]. According to data from a mechanistic study, Br₂ is formed as electrophilic brominating reagent with a slow but steady rate starting from Br⁻ and a (tert-butyl peroxy)(Schiff-base)vanadium(V) complex. This step is followed by a non-vanadium-dependent process, i.e., bromocyclization of an alkenol substrate [29,49]. The stereo- and regioselectivities in such ring closures therefore resemble those of many relevant examples from the literature [50] because the principles of substrate control [51] and not of transition metal-directed heteroatom transfer apply in the final step of this sequence. Since the primary event, i.e., the in situ generation of Br₂, takes profit from the principles of catalysis and thus does not require an on-site storage and handling of elemental Br₂, it is expected that this procedure opens new perspectives in organic synthesis [52]. This vision has been recently supported by reports on enantioselective syntheses of all naturally occurring muscarine alkaloids [53] and (±)-2-epi-magnosalicin—the 2-epimer of the antiallergic natural product (±)-magnosalicin—using this methodology [29,54]. More recently, the (Schiff-base)vanadium(V)-catalyzed oxidation of Br⁻ has been applied as key step in the synthesis of the heterocyclic core of the marine natural product aplysiapyranoid A using the 1,2-disconnection approach [55,56]. Thus, methyl (E)-2-(1-hydroxy-1-methylethyl)-5-phenyl-4-hexenoate (49) was treated in the initial step on a 15 g-scale with TBHP, pyridinium hydrobromide (pyHBr), and 5 mol % of catalyst VOL¹(OEt)(EtOH) (1) to furnish 43 % of 6-endobromocyclized product 50 (3,5-cis:3,5-trans = 80:20) besides 15 % of tetrahydrofuran 51 (cis:trans = 66:34, Scheme 12). Substituents at C5 and C6 in both diastereomers of 50 exhibit relative trans-configuration. Formation of 5-(1-phenyl-1-hydroxy-1-ethyl)-substituted tetrahydrofurans or the corresponding tetrahydropyranyls as side products, which might have originated from a competing direct vanadium(V)-catalyzed oxygenation of substrate 49, was not observed [55]. It is further worth mentioning that attempts to convert alkenol 49 using the state-of-the-art reagent for conducting 6-endoselective bromocyclizations, i.e., 2,4,4,6-tetrabromocyclohexa-2,5-dienone, failed to afford yields of target product 50 that exceeded 20 %.

Scheme 12 Application of the (Schiff-base)vanadium(V)-catalyzed oxidation of Br⁻ in the 6-endoselective bromocyclization of styrene-derived alkenol 49 [55].

Saponification of methyl ester 50 with LiOH in a solution of aqueous dimethoxyethane provides upon neutralization a carboxylic acid (3,5-cis:3,5-trans = 80:20, 93 %), which was converted with N-(hydroxy)pyridine-2(1H)thione and diisopropylcarbodiimide (DIC) into mixed anhydride 52 (Scheme 13). Photolysis of pyridinethione 52 in the presence of BrCCl₃ affords dibromide 53 (3,5-cis:3,5-trans = 50:50, 52 % starting from the carboxylic acid derivative of 50). For completion of the synthesis, the 3,5-trans-diastereoisomer 3,5-trans-53 was purified and subsequently oxidized with the combination of RuCl₃ and NaIO₄ [57], to afford a crude carboxylic acid that was esterified with MeOH/DIC in CH₂Cl₂ to yield ester 54. The latter compound was reduced with DIBAH in hexanes/CH₂Cl₂ to afford aldehyde 55. Treatment of this product with CrCl₂ and CHCl₃ furnished aplysiapyranoid A as target compound [58].
(Schiff-base)vanadium(V) complexes are useful reagents for an activation of TBHP via intermediate formation of peroxy complexes, e.g., 5. These compounds are electrophilic oxidants that are able to stereoselectively convert alkenols into functionalized cyclic ethers via a peroxy mechanism (Scheme 14). The stereoselectivities in this transformation generally are predictable using a stereochemical model, thus allowing a general application of this method in natural product synthesis. The reactivity of (tert-butyl peroxy)(Schiff-base)vanadium(V) complexes is further applicable for the oxidation of bromide (Scheme 14), in order to induce synthetically useful bromocyclizations in a second, non-vanadium-dependent step, as documented in the total synthesis of the marine natural product aplysiapyranoid A.

**Scheme 13** Completion of the synthesis of rac-applysiapyranoid A. Reagents and conditions: (a) LiOH, DME, H₂O; (b) N-(hydroxy)pyridine-2(1H)-thione, DIC, CH₂Cl₂; (c) BrCCl₃, hv, C₆H₆, 20 °C; (d) chromatography; (e) RuCl₃, NaIO₄, CH₃CN, CCl₄, H₂O; (f) CH₃OH, DIC, CH₂Cl₂; (g) DIBAH, hexanes, CH₂Cl₂; (h) CrCl₂, CHCl₃, THF [55].

**SUMMARY AND CONCLUSION**

(Schiff-base)vanadium(V)-catalyzed oxidations
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References

32. The stereodescriptors C and A refer to clockwise and anticlockwise [30,31]. The assignment of the absolute configuration in square pyramidal complexes is performed as follows: (i) The four atoms in the plane of the coordination polyhedron are ranked according to the CIP convention. (ii) The reference projection requires a view on top of the atom that in combination with the central ion defines a $C_4$ axis. A C-configuration is associated with a clockwise arrangement of the four atoms in the plane of the square pyramid in decreasing CIP-hierarchy 1–2–3–4. If the atoms with CIP hierarchy 1 and 2 are bound in opposite and not in vicinal coordination sites, the direction for configuration assignment that proceeds via the atom with the hierarchy 3 is preferred thus leading to the sequence 1–3–2 instead of going from 1 via 4 to 2 and then on to 3. The latter error unfortunately has been made in earlier contributions from my group [10,22,28]. In all instances, the opposite configuration from of what has been reported in these papers is correct in order to agree with the IUPAC convention.