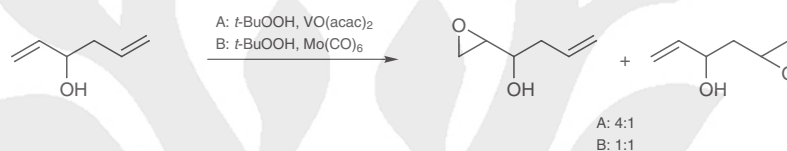

37.2	Product Class 2: Epoxides (Oxiranes)	
<hr/>		
37.2.1	Synthesis from Alkenes by Metal-Mediated Oxidation H. Adolfsson	
<hr/>		
37.2.1.2	Synthesis Mediated by Group 5 Metals	236
37.2.1.2.1	Method 1: Vanadium-Mediated Epoxidation with Alkyl Hydroperoxides	236
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Asymmetric Epoxides 5; General Procedure Using Catalyst 3:^[28]

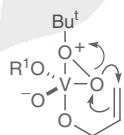
Ti complex **3** (1.8 mg, 1 μ mol) and alkene (0.1 mmol) were dissolved in an appropriate solvent (1.0 mL) under N_2 . After addition of 30% aq H_2O_2 (0.101 mmol), the mixture was stirred at rt for the appropriate time (12–48 h). The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel, pentane/Et₂O 40:1).

37.2.1.2 Synthesis Mediated by Group 5 Metals

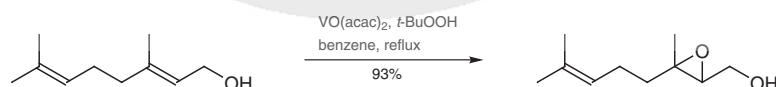
Epoxidation reactions mediated by group 5 metals are dominated by vanadium-based catalysts. In similarity to group 4 metals, the heavier elements (niobium and tantalum) are infrequently employed as catalysts. The discovery that vanadium complexes, in combination with alkyl hydroperoxides, participate in alkene epoxidation was made in the early 1970s.^[31,32] Although 3-chloroperoxybenzoic acid was known to oxidize more reactive isolated alkenes, it was revealed that allylic alcohols are converted into the corresponding epoxides with the same rate or even faster than simple double bonds when vanadium(V) or molybdenum(VI) catalysts are employed in the reaction (Scheme 8).^[31]

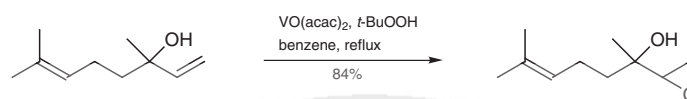
Scheme 8 Vanadium- and Molybdenum-Catalyzed Epoxidation of Allylic Alcohols^[31]

The mechanism for such a process is explained with a structure as depicted in Scheme 9. The allylic alcohol and the alkyl hydroperoxide are incorporated into the vanadium coordination sphere and the oxygen transfer from the peroxide to the alkene takes place in an intramolecular fashion (as described in Section 37.2.1.1.2 for the titanium tartrate catalyst).^[31,33]

Scheme 9 Proposed Structure for the Vanadium Complex Prior to Oxygen Transfer from the Peroxide to the Allylic Alkene^[33,35]**37.2.1.2.1****Method 1: Vanadium-Mediated Epoxidation with Alkyl Hydroperoxides**

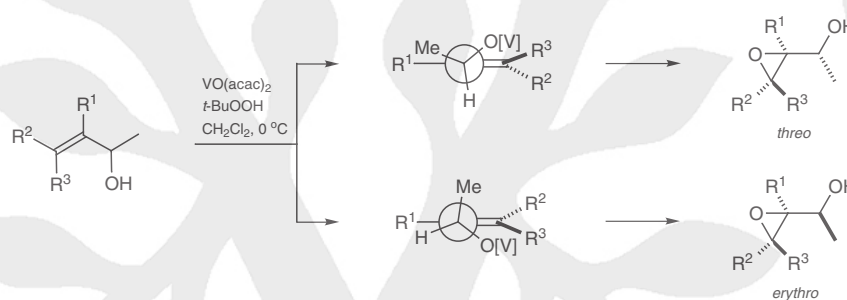
The vanadium-catalyzed epoxidation of allylic alcohols using alkyl hydroperoxides as terminal oxidants proceeds readily at or below room temperature. The epoxidation selectivity for a number of simple alkenes, as well as in more complex diene systems has been systematically investigated. The oxidation of (2*E*)-3,7-dimethylocta-2,6-dien-1-ol and 3,7-dimethylocta-1,6-dien-3-ol using *tert*-butyl hydroperoxide and catalytic amounts of bis(acetylacetonato)oxovanadium(IV) result in high yields of only one out of two possible regioisomeric epoxide products (Scheme 10).^[32]

Scheme 10 Regioselective Epoxidation Using a Vanadium Catalyst^[32]



When the epoxidations are carried out on differently substituted acyclic allylic alcohols, an interesting trend regarding the stereoselectivity of the reaction is revealed.^[34–36] As shown in Scheme 11, the epoxidation of secondary allylic alcohols proceeds in most cases with rather high stereoselectivity. The stereochemical rationale for the outcome of the reactions has been explained as follows: in the transition state for the epoxidation reaction, the coordinated substrate must orientate the alkene for a linear backside attack on the peroxide formed when *tert*-butyl hydroperoxide reacts with the vanadium complex. This results in a boat-like folding conformation of the alkene where the dihedral O–C–C angle becomes close to 50°. The various intramolecular steric interactions which thereby occur control the stereochemical outcome of the epoxidation. In comparison to epoxidations of the corresponding alkenes using 3-chloroperoxybenzoic acid, the vanadium-catalyzed reactions in most cases proceed with higher stereoselectivity, often favoring the opposite stereoisomer.^[35]

Scheme 11 Stereoselective Epoxidation of Allylic Alcohols Catalyzed by Bis(acetylacetonato)oxovanadium(IV)^[34]



R ¹	R ²	R ³	Ratio (<i>threo</i> / <i>erythro</i>)	Ref
H	H	H	20:80	[34]
Me	H	H	5:95	[34]
H	Me	H	29:71	[34]
H	H	Me	71:29	[34]
H	Me	Me	86:14	[34]

The corresponding epoxidations of secondary homoallylic and bis(homoallylic) alcohols employing the bis(acetylacetonato)oxovanadium(IV)-*tert*-butyl hydroperoxide system proceed with equally high levels of diastereomeric control.^[37,38] More recently, Tumas and coworkers reported on an efficient and selective epoxidation of allylic, homoallylic, and bis-(homoallylic) alcohols using triisopropoxyoxovanadium(V) and *tert*-butyl hydroperoxide in liquid carbon dioxide.^[39] The reactivity of the vanadium catalyst in liquid carbon dioxide was demonstrated to be as high as in chlorinated solvents (e.g., dichloromethane), which demonstrates the “green” potential of this system.

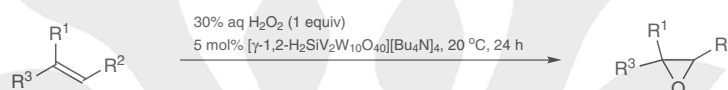
Mimoun and coworkers have demonstrated that stoichiometric amounts of vanadium(V) peroxo complexes containing Schiff-base ligands mediate the epoxidation of unfunctionalized alkenes in moderate to good yields.^[40]

for references see p 273

37.2.1.2.1.1 Variation 1: With Hydrogen Peroxide

The oxidation of simple alkenes such as cyclohexene using monovanadium complexes and hydrogen peroxide as terminal oxidant predominantly results in allylic oxidations instead of epoxide formation. However, when vanadium is incorporated into polyoxometalates, the results are significantly improved. The tetrabutylammonium salt of a polyoxometalate with the composition $[\gamma\text{-}1,2\text{-H}_2\text{SiV}_2\text{W}_{10}\text{O}_{40}]^{4-}$ acts as a highly active and selective epoxidation catalyst employing aqueous hydrogen peroxide as terminal oxidant.^[41,42] The catalyst, which has a bridging divanadyl core $[\text{VO}-(\mu\text{-OH})_2\text{-VO}]$ catalyzes the stereospecific epoxidation of a wide range of unfunctionalized alkenes and dienes, as well as hydroxy-functionalized alkenes, in the presence of only 1 equivalent of oxidant per degree of unsaturation. The limitation of this system appears to be *E*-disubstituted alkenes, which show poor reactivity (*E*-oct-2-ene gives only 6% yield of the epoxide under the conditions presented in Scheme 12). Mechanistic studies and density functional theory calculations indicate severe steric interactions between the substituents of such substrates and the polyoxometalate framework.^[43]

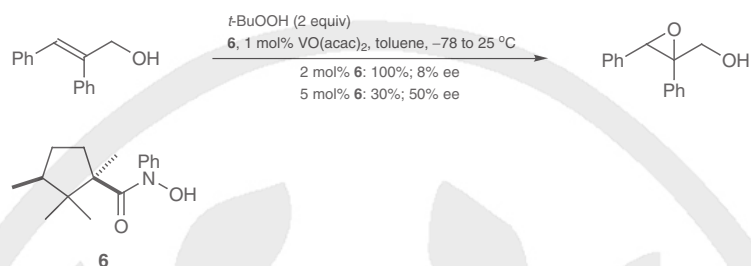
Scheme 12 Polyoxometalate-Catalyzed Epoxidation of Alkenes^[41]



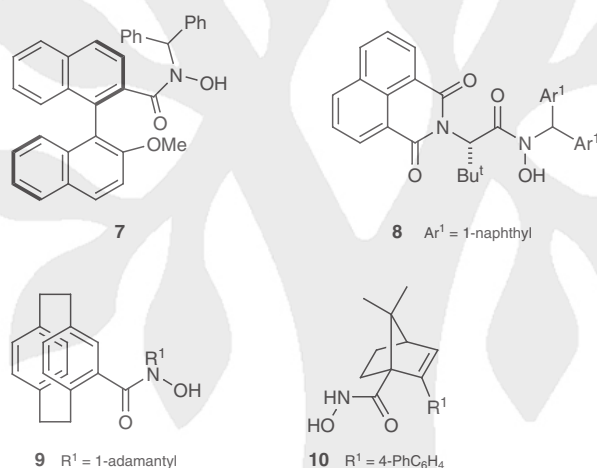
R ¹	R ²	R ³	Selectivity (%)	Ratio (<i>syn</i> / <i>anti</i>)	Yield (%)	Ref
H	H	Bu	99	–	92	[41]
(CH ₂) ₄ Me	Me	H	99	–	90	[41]
Ph	H	H	99	–	88	[41]
CHOH(CH ₂) ₃		H	95	12:88	87	[41]

37.2.1.2.2 Method 2: Vanadium-Mediated Asymmetric Epoxidation

The asymmetric epoxidation catalyzed by vanadium was reported as early as 1977. The study performed showed that the hydroxamic acid **6** was the most promising ligand in the reaction; it further revealed the importance of using a specific ratio between the vanadium catalyst precursor and the chiral ligand (Scheme 13).^[33] A fivefold excess of ligand **6** gives considerably better enantioselectivity than the reaction performed with only two ligands per vanadium. The yield, however, is much better in the latter case, which indicates a system that suffers from a ligand-decelerating effect (LDC). This is a direct contradiction to the titanium-catalyzed asymmetric epoxidations discussed in Section 37.2.1.1, and it highlights one of the difficulties that can be encountered during the development of protocols for asymmetric reactions.

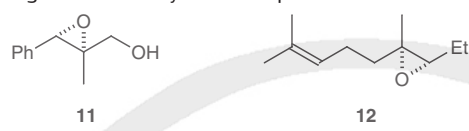
Scheme 13 Vanadium-Catalyzed Asymmetric Epoxidation Using a Hydroxamic Acid Ligand^[33]

While the titanium-catalyzed epoxidation reaction was flourishing, the pioneer version of the reaction remained undeveloped. New discoveries in vanadium-catalyzed asymmetric epoxidation were not revealed until 1999.^[44] In the epoxidation of various allylic alcohols, the hydroxamic acid **7** (Scheme 14) was presented as the best ligand for vanadium, allowing enantiomeric excesses up to 94%.^[44,45]

Scheme 14 Chiral Ligands Employed in the Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols^[44,45,47–49]

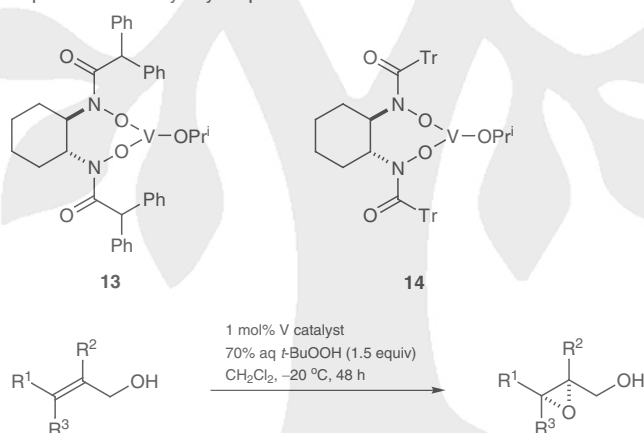
The promising results using hydroxamic acid **7** as a ligand in vanadium-catalyzed asymmetric epoxidations inspired reinvestigation of this epoxidation system.^[46] A number of different chiral hydroxamic acids **8–10** have been prepared (Scheme 14), and vanadium complexes based on these ligands have been used in the asymmetric epoxidation of allylic alcohols. A comparison of their catalytic activity for two different substrates, to give epoxides **11** and **12**, is presented in Table 3.

for references see p 273

Table 3 Comparison of the Performances Shown by Vanadium Complexes with Various Ligands in the Asymmetric Epoxidation Reaction^[45,47–49]


VO(OiPr) ₃ (mol%)	Ligand (mol%)	Oxidant	Reaction Time	Temp (°C)	Epoxide 11		Epoxide 12		Ref
					ee (%)	Yield (%)	ee (%)	Yield (%)	
5	7 (7.5)	TrOOH	2–3 d	–20	91	96	66	80	[45]
1	8 (1.5)	<i>t</i> -BuOOH	3–6 h	0	95	97	81	95	[47]
5	9 (7.5)	<i>t</i> -BuOOH	3 d	–20	71	85	45	89	[48]
5	10 (7.5)	<i>t</i> -BuOOH	1 d	0	55	86	46	83	[49]

As is evident in Table 3, none of the vanadium catalysts are as efficient and selective as the corresponding titanium–tartrate system used in the Sharpless asymmetric epoxidation. However, Yamamoto has presented some highly interesting results using novel *C*₂-symmetric bis(hydroxamic acid) ligands for the vanadium-catalyzed epoxidation of a series of allylic alcohols (Scheme 15).^[50] The design and use of a bidentate bis(hydroxamic acid) ligand for vanadium was believed to further stabilize the vanadium complex, e.g. **13** and **14**, and thereby avoid the rapid ligand exchange often occurring in these systems. Moreover, the use of a *C*₂-symmetric ligand would better facilitate a chiral encapsulation about the catalyst.

Scheme 15 Enantioselective Epoxidation of Allylic Alcohols Using Vanadium Catalysts and Aqueous *tert*-Butyl Hydroperoxide^[50]

R ¹	R ²	R ³	Catalyst	ee (%)	Yield (%)	Ref
Ph	Ph	H	13	97	91	[50]
Ph	Me	H	13	97	84	[50]
Ph	H	H	13	97	53 ^a	[50]
H	H	Ph	14	97	24 ^b	[50]
Me	H	CH ₂ CH=CMe ₂	14	95	62	[50]

^a Reacted 60 h.^b Reacted 120 h.