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19.5.12 Introduction of the Cyano Group by Addition to Alkynes

J. Podlech

General Introduction

Previously published information regarding this topic can be found in *Houben-Weyl*, Vol. 8, pp 265–268; Vol. E 5/2, pp 1410–1413; Vol. E 18/2, pp 812–816; and Vol. E 21, pp 2594–2595.

The hydrocyanation of alkynes is a significantly useful process since it generates highly versatile α,β -unsaturated nitriles (Michael systems) from easily accessible starting materials.^[1–4] Before suitable catalyst systems for the addition of hydrogen cyanide to alkynes were found, the uncatalyzed reactions needed high temperatures and yields were low. But despite this, thorough optimization of reaction conditions allowed the commercial synthesis of propenenitrile (acrylonitrile)^[5] to operate on a 10 000-ton scale as early as 1944.^[6–8] Since 1970, however, the importance of this process has declined in favor of alternatives that start from propene.^[9]

SAFETY: All the experiments described in the following account are highly hazardous. In particular, hydrogen cyanide is a highly toxic, volatile liquid (bp 27 °C) that is also susceptible to explosive polymerization in the presence of base catalysts. It should be handled only in a well-ventilated fume hood or drybox. Sensible precautions include not working alone and having available proper first aid equipment, hydrogen cyanide monitors, and Scott Air Packs. Hydrogen cyanide should be handled by teams of at least two technically qualified individuals who have received appropriate medical training for treating hydrogen cyanide poisoning [for details see *Prudent Practices for Handling Hazardous Chemicals in Laboratories*, National Academic Press: Washington, DC, (1981); pp 45–47]. Commercial hydrogen cyanide is stabilized with small amounts of strong acids such as sulfuric acid. Small amounts of uninhibited hydrogen cyanide may be obtained by vacuum transfer through Drierite. Uninhibited hydrogen cyanide should be stored cold. Excess hydrogen cyanide may be disposed of by burning or in the case of small amounts of hydrogen cyanide by adding to aqueous sodium hypochlorite (which converts it into the cyanate).^[10]

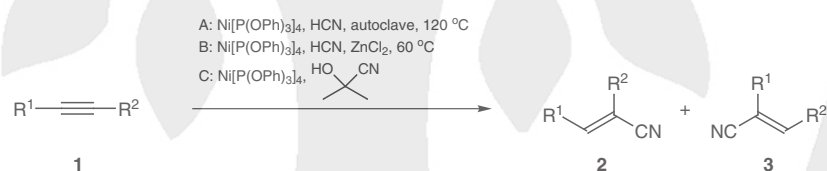
**19.5.12.1 Method 1:
Hydrocyanation of Alkynes**

Tetrakis(triphenyl phosphite)nickel(II) ($\text{Ni}[\text{P}(\text{OPh})_3]_4$), in the presence of excess triphenyl phosphite, is a catalyst that was developed for the hydrocyanation of alkenes {see Section 19.5.13 and *Science of Synthesis*, Vol. 1 [Compounds with Transition Metal–Carbon π -Bonds and Compounds of Groups 10–8 (Ni, Pd, Pt, Co, Rh, Ir, Fe, Ru, Os)] (Section 1.1.3.9)}; however, it also works well for similar reactions with alkynes **1** often giving isomeric unsaturated nitriles **2** and **3** (Scheme 1) with greater efficiency than either rhodium or palladium catalysts, for example.^[11] The catalyst is easy to prepare,^[12] and it can be kept for long periods if stored in the dark under dry nitrogen; it can even be weighed on an open balance immediately prior to use.^[2] The direct hydrocyanation of alkynes is carried out either in an autoclave (Method A),^[11,13–16] or at atmospheric pressure using the same catalyst in the presence of the Lewis acid zinc(II) chloride (Method B). In the latter case, hydrocyanation occurs at 60 °C with the slow addition of a solution of hydrogen cyanide to a solution of

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the catalyst, additional triphenyl phosphite, the alkyne, and the Lewis acid.^[11,13,17] For safety reasons hydrogen cyanide can be replaced by acetone cyanohydrin (2-hydroxy-2-methylpropanenitrile; Method C), and now the reaction can be carried out either at high pressure in benzene at 120 °C in an autoclave,^[11,13] or with rather more catalyst in toluene at reflux.^[16] The latter modification works satisfactorily when silylated alkynes are the substrates using a molar amount of the catalyst tetrakis(triphenyl phosphite)nickel(II), triphenyl phosphite, the silylalkyne, and acetone cyanohydrin in a ratio of 1:12:45:90.^[11,13,16,18–20] In most reactions a highly selective *syn* addition of hydrogen cyanide is observed,^[11,13] but there are exceptions and, for example, dimethyl acetylenedicarboxylate is hydrocyanated by Method C in an *anti* fashion.^[2,11] A low ratio of catalyst to substrate (ca. 1:90) is sufficient for reactions at 120 °C (Method A), but with increased amounts of catalyst the reactions occur at room temperature in moderate to good yields. For example, the hydrocyanation of hex-1-yne at 120 °C (catalyst/substrate 1:90) gives an 88% yield of products, whereas an identical yield is obtained in benzene at 25 °C with a catalyst to substrate ratio of 1:22.^[2] Although the high-pressure procedure (Method A) usually gives slightly better yields, selectivity control is improved by the presence of zinc(II) chloride (Method B). Regioselectivity is partly dependent on steric factors and moderate to high selectivity is observed with terminal alkynes (cyanide is introduced at the terminal carbon), whereas poor selectivity is exhibited by internal alkynes. Method A also allows compounds bearing both double and triple bonds to be selectively hydrocyanated at the alkyne bond; thus, for the alkyne **1** ($R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $R^2 = \text{Et}$) attack may occur at either alkynic carbon atom,^[14] but the clear 9:1 preference for the nitrile **3** ($R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $R^2 = \text{Et}$) is not understood. Indeed, steric effects may have low importance as a more bulky α,α' -bis(diphenylphosphino)-*o*-xylenenickel(0) catalyst still gives a product ratio of 3:1 in favor of **3** ($R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $R^2 = \text{Et}$). Other substrates, which have been hydrocyanated by Method A, include alkynol ethers,^[18,19] alkynols,^[17] and alkynamines;^[21,22] the products obtained from alkynamines have been used for the synthesis of unnatural amino acid derivatives.^[22,23]

Scheme 1 Hydrocyanation of Alkynes Using Tetrakis(triphenyl phosphite)nickel(II) and Hydrogen Cyanide or Acetone Cyanohydrin^[11,13–16]



R ¹	R ²	Method ^a	Ratio (2/3)	Yield (%) of 2 and 3	Ref
Ph	Ph	A	–	93 ^b	[11,13]
		B	–	82 ^b	[11,13]
		C	–	57 ^b	[11,13]
CO ₂ Me	CO ₂ Me	A	–	27 ^{b,c}	[11,13]
		B	–	5 ^{c,d}	[11,13]
Pr	H	A	3:22	60	[11,13]
		B	1:19	40	[11,13]
Bu	H	A	7:43	73	[11,13]
		B	1:24	33	[11,13]
(CH ₂) ₅ Me	H	A	7:43	60	[11,13]
		B	2:23	45	[11,13]

R ¹	R ²	Method ^a	Ratio (2/3)	Yield (%) of 2 and 3	Ref
Ph	H	A	49:1	48	[11,13]
		B	17:3	35	[11,13]
		C	–	16 ^b	[11,13]
t-Bu	H	A	22:3	15	[11,13]
		B	4:1	45	[11,13]
t-Bu	Me	B	9:1	78	[11,13]
CH ₂ CH=CH ₂	Et	A	1:9 ^c	41	[14]
TBDMS	H	A	7:13 ^f	57	[15,16]
TBDMS	Me	A	49:1 ^f	88	[15,16]
TBDMS	Ph	A	9:1 ^f	74	[15,16]
TMS	H	A	1:3 ^f	74	[15,16]
		C	1:3 ^g	75	[15,16]
TMS	Me	A	4:1 ^h	90	[15,16]
		C	4:1 ^g	87	[15,16]
TMS	Bu	A	18:7 ^h	94	[15,16]
		C	18:7 ^g	90	[15,16]
TMS	Ph	A	0:100 ^h	80	[15,16]
		C	0:100 ^g	81	[15,16]

^a Method A: 0.5 mol% Ni[P(OPh)₃]₄, autoclave, 120 °C; B: atmospheric pressure at 60 °C, slow addition of a solution of HCN to a solution of Ni[P(OPh)₃]₄ (2.5 mol%), additional ligand, the alkyne, and ZnCl₂; C: 0.5 mol% Ni[P(OPh)₃]₄, autoclave, 120 °C in benzene.

^b Only product 3 formed.

^c The *syn*-product is formed.

^d Slow addition of the alkyne and HCN to the catalyst system.

^e 1.8 mol% Ni[P(OPh)₃]₄.

^f 2.2 mol% Ni[P(OPh)₃]₄.

^g 2.2 mol% Ni[P(OPh)₃]₄, reflux in toluene.

^h 1.1 mol% Ni[P(OPh)₃]₄.

(E)-2,3-Diphenylprop-2-enitrile (3, R¹ = R² = Ph); Typical Procedure:^[11]

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Method A: Ni[P(OPh)₃]₄ (0.24 g, 0.2 mmol), P(OPh)₃ (0.8 g, 2.5 mmol), diphenylacetylene (1, R¹ = R² = Ph; 7 g, 39 mmol), HCN (1.25 mL, 32 mmol), and benzene (25 mL) (**CAUTION:** *carcinogen*) were placed in a stainless steel autoclave (75 mL). The vessel was heated at 120 °C for 18 h, then cooled, and the benzene was distilled off. Column chromatography (basic alumina, activity grade II, Et₂O/petroleum ether 1:9), followed by distillation, gave the title compound as colorless crystals; yield: 6.12 g (93%); mp 48–49 °C; bp 130 °C/0.01 Torr.

for references see p 331

**(tert-Butyldimethylsilyl)propenenitriles 2 (R¹ = TBDMS) and 3 (R¹ = TBDMS);
General Procedure for Method A:^[16]**

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Benzene (25 mL) (**CAUTION:** carcinogen), Ni[P(OPh)₃]₄ (0.24 g, 0.2 mmol), P(OPh)₃ (0.74 g, 2.4 mmol), the alkyne **1** (R¹ = TBDMS; 9.0 mmol), and HCN (0.21 g, 7.8 mmol) were placed in a stainless steel Koke-type autoclave and protected under a N₂ atmosphere. The vessel was heated to 120 °C for 18 h. It was then cooled, and most of the catalyst was removed by filtration, after the addition of pentane (15 mL). Removal of the solvents followed by distillation gave the title compounds.

(E)-2,4,4-Trimethylpent-2-enenitrile (2, R¹ = t-Bu; R² = Me) and (E)-2-tert-Butylbut-2-enenitrile (3, R¹ = t-Bu; R² = Me); Typical Procedure:^[11]

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Method B: A soln of HCN (1.25 mL, 32 mmol) in toluene (5 mL) was slowly added by means of a syringe pump to a mixture of Ni[P(OPh)₃]₄ (0.7 g, 0.54 mmol), P(OPh)₃ (0.75 g, 2.4 mmol), anhyd ZnCl₂ (0.14 g, 1 mmol), 4,4-dimethylpent-2-yne (**1**, R¹ = t-Bu; R² = Me; 2 g, 21 mmol), and toluene (25 mL) over 10 h at 60 °C. The toluene was removed by distillation, and bulb-to-bulb distillation gave the unsaturated nitriles (9:1 as determined by GLC) as a clear liquid; yield: 2.0 g (78%); bp 100 °C/25 Torr. The isomers could be separated by preparative GLC.

Hydrocyanation of Alkynes 1 Using Tetrakis(triphenyl phosphite)nickel(II)/Acetone Cyanohydrin; General Procedure for Method C:^[16]

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Toluene (50 mL), Ni[P(OPh)₃]₄ (0.24 g, 0.2 mmol), P(OPh)₃, a silylalkyne **1**, and acetone cyanohydrin in a molar ratio of 1:12:45:90 were placed in a predried 100-mL round-bottomed flask and protected under a N₂ atmosphere. The mixture was refluxed under a positive pressure of N₂ for 18 h. After cooling, most of the catalyst was removed by filtration after precipitation with pentane (15 mL). Removal of the solvents at reduced pressure gave a residue that was purified by distillation.

19.5.12.2

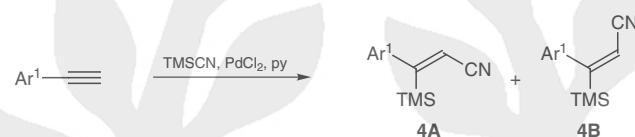
**Method 2:
Addition of Trimethylsilyl Cyanide or
Tributylstannanecarbonitrile to Alkynes**

Silylated or stannylated alkenes are very useful intermediates in organic synthesis since they can be used in the most powerful Stille-type cross-coupling protocols. Consequently, methods for the concomitant introduction of a cyano and a stannyl or silyl group are of great interest.

19.5.12.2.1 **Variation 1:**
Addition to Terminal Arylalkynes

The addition of trimethylsilyl cyanide to a terminal arylalkyne is possible using catalytic amounts of palladium(II) in the presence of a basic additive. The best results are obtained with palladium(II) chloride and pyridine.^[24] The cyano function is introduced vicinally to the aryl group in all cases (Scheme 2), but sterically undemanding arenes form *Z*-alkenes **4A** exclusively, while bulky arenes give a mixture of isomers **4A** and **4B** (although the *Z*-product is still favored). Yields range from 17–90%, and there is no advantage in using electron-rich over electron-poor alkynes.

Scheme 2 Addition of Trimethylsilyl Cyanide to Terminal Arylalkynes^[24]



Ar ¹	Ratio (4A / 4B) ^a	Yield ^b (%) of 4A	Ref
Ph	95:5	90	[24]
4-MeOC ₆ H ₄	95:5	90	[24]
4-FC ₆ H ₄	>95:5 ^c	38	[24]
4-ClC ₆ H ₄	94:6	47	[24]
4-BrC ₆ H ₄	>95:5 ^c	17 ^d	[24]
2-MeOC ₆ H ₄	83:17	85 ^e	[24]
2-ClC ₆ H ₄	81:29	23 ^e	[24]
1-naphthyl	71:29	68 ^e	[24]
2-naphthyl	93:7	54	[24]
2-thienyl	>95:5 ^c	39	[24]

^a Determined by gas chromatography.

^b Isolated yields.

^c Determined by ¹H NMR spectroscopy.

^d (*Z*)-2-(4-Cyanophenyl)-3-(trimethylsilyl)propenenitrile is also isolated in 19% yield.

^e A mixture of the isomeric products **4A**/**4B** is isolated.

(*Z*)-3-Phenyl-3-(trimethylsilyl)propenenitrile (4A, Ar¹ = Ph); Typical Procedure:^[24]

PdCl₂ (36 mg, 0.2 mmol) and pyridine (32 μL, 0.4 mmol) were added to a soln of phenylacetylene (0.55 mL, 5 mmol) and TMSCN (1.34 mL, 10 mmol) in toluene (10 mL). The mixture was refluxed with stirring for 20 h under N₂, the solvents were removed at reduced pressure, and the residue was purified by chromatography (silica gel, hexane/EtOAc 9:1), followed by bulb-to-bulb distillation; yield: 0.90 g (90%); bp 130–140 °C/25 Torr.

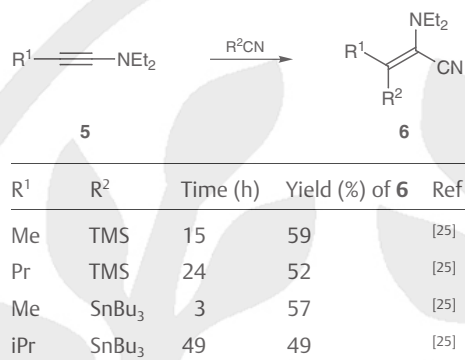
19.5.12.2.2 **Variation 2:**
Addition to Ynamines

Palladium catalysis is unsuitable for the addition of trimethylsilyl cyanide to dialkylaminoalkynes; however, the reaction times for the process are accelerated from 1–2 weeks to a matter of hours by a catalytic amount of iodotrimethylsilane. The stereo- and regiochemistries of the addition reactions of both trimethylsilyl cyanide and tributylstannane-

for references see p 331

carbonitrile to diethylaminoalkynes **5** are the same, giving the corresponding *E*-alkenes **6** bearing the cyano group geminal to the amino function as the only products (Scheme 3). Yields are usually about 50%.^[25]

Scheme 3 Addition of Trimethylsilyl Cyanide or Tributylstannanecarbonitrile to Ynamines^[25]



(2*E*)-2-(Diethylamino)-3-(trimethylsilyl)propenenitriles **6 (R² = TMS) or (2*E*)-2-(Diethylamino)-3-(tributylstannyl)propenenitriles **6** (R² = SnBu₃); General Procedure:**^[25]

A soln of either TMSCN or Bu₃SnCN (1.2 mmol) was added dropwise at rt to the ynamine (**5**; 1 mmol) in dry CH₂Cl₂ (2 mL). In the case of TMSCN addition, a catalytic amount of TMSI (ca. 5 mol%) is favorable. After the reaction was complete (monitoring by IR spectroscopy), the solvent was removed at reduced pressure and the residue was distilled or chromatographed (silica gel).

References

- [1] James, B. R., In *Comprehensive Organometallic Chemistry*, Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, (1982); Vol. 8, p 285.
- [2] Jackson, W. R.; Perlmutter, P., *Chem. Br.*, (1986) **22**, 338.
- [3] Casalnuovo, A. L.; RajanBabu, T. V., In *Transition Metals for Organic Synthesis*, Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, (1998); Vol. 1, p 91.
- [4] Huthmacher, K.; Krill, S., In *Applied Homogeneous Catalysis with Organometallic Compounds*, Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, (2000); p 465.
- [5] Parshall, G. W.; Ittel, S. D., In *Homogeneous Catalysis*, 2nd ed.; Wiley: New York, (1992); p 201.
- [6] Mowry, D. T., *Chem. Rev.*, (1948) **42**, 189.
- [7] Kurtz, P., DE 728 767, (1942); *Chem. Abstr.*, (1944) **38**, 2238.
- [8] Bradley, C. W.; Davis, H. S., US 2 385 327, (1945); *Chem. Abstr.*, (1946) **40**, 10102.
- [9] Hort, E. V.; Taylor, P., In *Encyclopedia of Chemical Technology*, 4th ed.; Kirk, R. E.; Othmer, D. F., Eds.; Wiley: New York, (1991); Vol. 1, p 195.
- [10] Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H., *J. Am. Chem. Soc.*, (1994) **116**, 9869.
- [11] Jackson, W. R.; Lovel, C. G., *Aust. J. Chem.*, (1983) **36**, 1975.
- [12] Levison, J. J.; Robinson, S. D., *Inorg. Synth.*, (1972) **13**, 105.
- [13] Jackson, W. R.; Lovel, C. G., *J. Chem. Soc., Chem. Commun.*, (1982), 1231.
- [14] Campi, E. M.; Jackson, W. R., *Aust. J. Chem.*, (1989) **42**, 471.
- [15] Fallon, G. D.; Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P., *J. Chem. Soc., Chem. Commun.*, (1985), 4.
- [16] Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P., *J. Organometal. Chem.*, (1985) **285**, 375.
- [17] Jackson, W. R.; Lovel, C. G.; Perlmutter, P.; Smallridge, A. J., *Aust. J. Chem.*, (1988) **41**, 1099.
- [18] Jackson, W. R.; Perlmutter, P.; Smallridge, A. J., *J. Chem. Soc., Chem. Commun.*, (1985), 1509.
- [19] Jackson, W. R.; Perlmutter, P.; Smallridge, A. J., *Aust. J. Chem.*, (1988) **41**, 251.
- [20] Bulat, A. D.; Antipov, M. A.; Belorusova, L. V.; Passet, B. V., *J. Org. Chem. (USSR)*, (1981), 1923.
- [21] Jackson, W. R.; Perlmutter, P.; Smallridge, A. J., *Tetrahedron Lett.*, (1988) **29**, 1983.
- [22] Jackson, W. R.; Perlmutter, P.; Smallridge, A. J., *Aust. J. Chem.*, (1988) **41**, 1201.
- [23] Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J., *Tetrahedron: Asymmetry*, (2001) **12**, 657.
- [24] Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T., *J. Org. Chem.*, (1988) **53**, 3539.
- [25] Funabiki, T.; Yamazaki, Y.; Sato, Y.; Yoshida, S., *J. Chem. Soc., Perkin Trans. 2*, (1983), 1915.

36.1.4	Synthesis by Addition to Alkynes and Alkenes A. T. Russell	
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36.1.4	Synthesis by Addition to Alkynes and Alkenes	191
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36.1.4 Synthesis by Addition to Alkynes and Alkenes

A. T. Russell

General Introduction

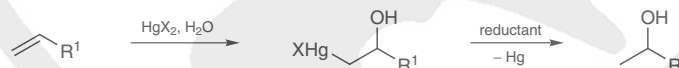
Alcohols are versatile and important compounds in organic chemistry, both as final products and as synthetic intermediates. A number of methods have been discovered for their synthesis from alkenes and alkynes by addition reactions. Methods based on hydroboration are considered in Section 36.1.1.3, and in *Science of Synthesis*, Vol. 6 (Boron Compounds), while hydrozirconation is covered in *Science of Synthesis*, Vol. 2 [Compounds of Groups 7–3, (Mn···, Cr···, V···, Ti···, Sc···, La···, Ac···) (Section 2.11.4.6.1.1)]; these are therefore not mentioned here. In the application of a method during a synthesis, a serious consideration is functional-group compatibility, whilst skeletal rearrangement during a transformation can also be an issue. Thus, in assessing the value of a method a number of aspects of selectivity need to be considered, specifically chemoselectivity, regioselectivity, stereoselectivity and, in the case of double and triple bonds, the effect of the degree of substitution. The sensitivity of a range of protecting groups to the conditions of reaction is a particular concern. In the following sections these issues are discussed wherever possible.

36.1.4.1 Method 1:
Oxymercuration Followed by Reduction

SAFETY: Great care should be taken in the handling of mercury and its compounds. Mercury is toxic by inhalation and is a cumulative toxin. It is very toxic to aquatic organisms. While the specific toxicity of each salt should be established before it is used, mercury(II) salts in general are very toxic by inhalation, in contact with the skin, or if swallowed, and exhibit cumulative effects. Some salts cause burns and again they are very toxic to aquatic organisms.

The oxymercuration of alkenes is a venerable reaction, with the earliest studies being reported by Hofmann and Sand in 1900.^[1] When this process is used in tandem with a reductive demercuration protocol, then a powerful method for the Markovnikov hydration of alkenes is obtained (Scheme 1), the mildness of which makes it an interesting alternative to acid-catalyzed hydration (see Section 36.1.4.2). A wide range of mercury(II) salts has been combined with a diverse set of reductants to effect this overall transformation.

Scheme 1 Prototypical Markovnikov Oxymercuration–Reduction of an Alkene



The substantial body of early work, prior to 1951, in this area has been reviewed by Chatt^[2] and details of the stereochemical aspects of this work were summarized by Zefirov.^[3] Subsequently, a number of reviews have been published, including those by Kitching,^[4,5] Matteson,^[6] Larock,^[7–9] and Seyferth.^[10] Piecing together some key aspects of this work allowed Brown to propose, in 1967, a rapid, mild, and highly effective one-pot experimental procedure that has become widely applied in organic synthesis.^[11] In regiochemical terms it is nicely complementary to the anti-Markovnikov hydroboration–oxi-

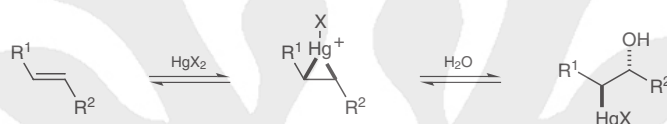
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ation or hydrozirconation–oxidation route from alkenes to alcohols {see, respectively, Section 36.1.1.3 and *Science of Synthesis*, Vol. 2 [Compounds of Groups 7–3, (Mn···, Cr···, V···, Ti···, Sc···, La···, Ac···)] (Section 2.11.4.6.1.1)}. Although the use of a toxic heavy metal must have implications for the applicability of this method on a large scale, the excellent regioselectivity observed makes it a good method for small-scale transformations and high-value synthetic intermediates. The results obtained may be compared and contrasted with the cobalt–oxygen and manganese–oxygen methods that have been advanced in more recent years (see Section 36.1.4.3).

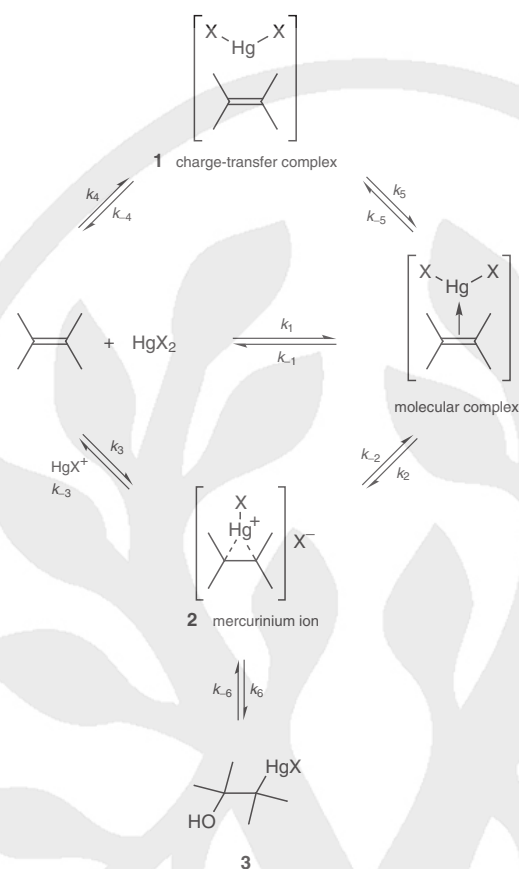
As the mechanism of the reduction step varies widely and is frequently vital to the deployment of this protocol in synthesis, it will be examined in each of the variations that follow. The mechanism of the oxymercuration step is more general across a number of reaction conditions, but has proved controversial and has been the subject of a considerable number of detailed investigations. From these investigations have emerged two distinct cases: the first pertains to acyclic and simple cyclic alkenes and the second to certain strained and bicyclic alkenes.

The first has the widest synthetic significance and is generally, though not exclusively, thought to proceed via reversible formation of a mercurinium ion,^[12] followed by attack of water *anti* to the mercury (Scheme 2).

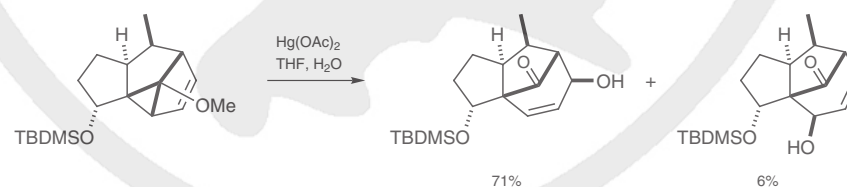
Scheme 2 Mechanism and Stereochemistry for Oxymercuration of a Simple Alkene^[12]



It is in the detail of this mechanism that differences emerge and an outline of some of these positions is given below. A discussion of the kinetics is available^[13] and this range of reaction pathways is illustrated in Scheme 3; the rate expression is stated to be: $\text{rate} = k_3 k_6 [\text{HgX}_2][\text{alkene}]$. For most mercury(II) salts that undergo extensive ionization in the polar solvents generally used in this procedure^[14] the usual pathway proceeds directly to the mercurinium ion **2**, a process thought to involve only a small activation energy, and then undergo slow, rate-limiting attack to give the oxymercury compound **3**. The mercury(II) salts to which this generalization pertains include, *inter alia*, mercury(II) perchlorate, nitrate, trifluoroacetate, and acetate, *i.e.* those that are commonly employed in the synthetic reaction protocol (although it has been observed that the presence of 50% tetrahydrofuran can suppress this ionization^[15]). With more covalent mercury compounds, such as mercury(II) chloride, formation of the mercurinium ion is considered to be rate limiting. The reversal of mercurinium ion formation is also faster with more ionic species.^[16]

Scheme 3 Bach's Mechanism for the Oxymercuration of an Alkene^[13]

Mercury(II) acetate is suggested to be suitable for less reactive alkenes, with a mixture of mercury(II) oxide and 1 equivalent of a strong acid, e.g. perchloric acid, appropriate for less reactive alkenes that do not give stable carbenium ions by loss of an HgX anion (see also **31** to **32** for an example of the use of strong acid in promoting this reaction, Scheme 11, Section 36.1.4.1.1), and mercury(II) oxide or mercury(II) chloride for those prone to such ionizations.^[17] An interesting synthetic use of such ionizations is reported by Wender in his synthesis rudmollin (Scheme 4).^[18] In an analysis of the methoxymercuration reaction of certain styrenes, a rate-limiting formation of a mercurinium ion has been proposed.^[19,20]

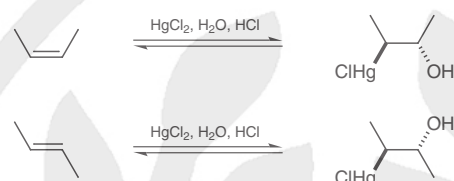
Scheme 4 An Oxymercuration-Mediated Ring Opening in Wender's Rudmollin Synthesis.^[18]

A sophisticated analysis of the oxymercuration reaction led to the conclusion that while it is possible to interpret the available data in terms of a rate-limiting formation of a positively charged intermediate, the more likely explanation is that solvation of that intermediate is the slow step. Whilst a definitive conclusion could not be reached on the na-

for references see p 239

ture of that intermediate, significant carbenium ion character is inferred on the basis of the sizable Hammett-Taft ρ^* value (-3.3), although not sufficient to imply a lack of bridging, an observation that is consistent both with the generally observed Markovnikov regiochemistry of this reaction and the stereospecificity in oxymercuration of (*Z*)- and (*E*)-but-2-ene (Scheme 5) and (*Z*)-stilbene.^[21,22]

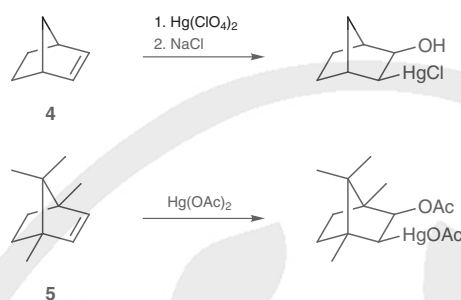
Scheme 5 Stereospecificity of Successive Oxymercuration–Demercuration of (*Z*)- and (*E*)-But-2-ene^[22]



In a comparative analysis of the bromination and oxymercuration of a range of alkenes, the relative rates of addition to variously substituted compounds were studied, in terms of their ionization potentials and a steric term, ϵ , leading to the charge-transfer complex **1** (see Scheme 3). It was concluded that the mechanism of the two reactions are essentially the same, when the steric adjustment is made, and that mercurinium ion formation is the rate-limiting step.^[23] Another similar study allowed a more detailed grouping of reaction rates with substrate structure, emphasizing the sensitivity of the oxymercuration reaction to steric effects.^[24] The situation as it pertains to α -alkylstyrenes has been discussed in some detail.^[25]

Although theoretical treatments had predicted the existence of a mercurinium ion,^[26] definitive evidence that such a species can exist has proved difficult to obtain, with some claims preceding the detection, by Olah, of long-lived examples under superacid conditions.^[27] Such species have also been detected in the gas phase.^[28] Its intermediacy under standard reaction conditions is generally implied, though on good grounds, rather than definitively demonstrated.^[29] However, a further claim to observation of this intermediate using NMR, under normal reaction conditions, has been made.^[30] The stereospecificity encountered in the generation of many oxymercury compounds^[31] is certainly readily interpretable in terms of the existence of a mercurinium ion. Its more ephemeral nature than, say, a bromonium ion may, in part, be traceable to it being a two-electron, three-center bonded species, as opposed to the bromonium ion four-electron, three-center bond.^[32]

The second case involves an unusual *cis* addition, which is exemplified by norbornene (**4**) and 1,4,7,7-tetramethylbicyclo[2.2.1]hept-2-ene (**5**) (Scheme 6),^[33] with *exo* addition to **5**, albeit at a slower rate than **4**, being quite remarkable. Whilst a nonclassical carbenium ion treatment^[34] would appear a simple explanation of this phenomenon, objections to this have been raised on the grounds that none of the characteristic rearrangement products of such a cation is observed (such rearrangements have been observed under superacid conditions, above $-30\text{ }^\circ\text{C}$, but not under standard synthetic oxymercuration conditions^[35]). In addition, the strong preference for other cyclic species, e.g. an episulfonium ion, to form on the *endo* face was considered strong evidence against this proposition.^[36,37] Instead, what amounts to a β -mercurio carbenium ion was proposed, though why this prefers to form on the *exo* face and not exhibit the usual tendency of such cations to rearrange is less clear.

Scheme 6 *cis* Addition to Two Bicyclo[2.2.1]heptanes^[33]

Traylor favored a front-side attack via a four-centered transition state.^[33] A theoretical investigation by Bach concluded that front-side attack on a distorted mercurinium ion represents the lowest-energy pathway, at least for the norbornene case.^[26] Such low-energy distortions from a symmetrical species (cf. Lewis et al.^[19,20]) raises the question as to whether there is in fact a disagreement regarding the nature of this intermediate or rather a range of ion types, with the limiting cases being a β -mercurio carbenium ion at one end and a symmetrical bridged structure at the other extreme. Such a continuum of ions, dependent on the structure of the substrate, reagent, and conditions, has some support.^[27,38] Indeed, in a subsequent ^{199}Hg NMR study, a mercury resonance for the stable mercurinium ion from ethene was not observed, an observation interpreted as a slow (on the NMR timescale) ring opening–ring closing equilibrium.^[35] In a comparison of studies of the methoxymercuration of styrenes and hydroxymercuration of atropic acids, a switch from closed to open ions has been noted, again supporting the idea of a range of ion structures, and the significance of the polarity of the solvent in determining the exact nature of the intermediate ion was identified.^[19,20]

Many other studies have been carried out and these can be found within the references cited above.

36.1.4.1.1

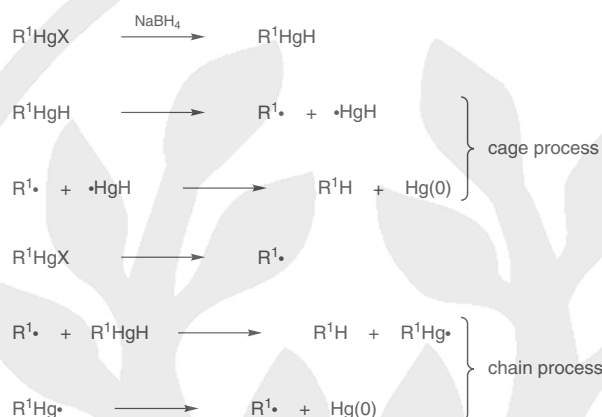
**Variation 1:
Using Mercury(II) Acetate–Sodium Borohydride**

Hydration of an alkene by treatment with mercury(II) acetate and then sodium borohydride has become the most widely applied reagent combination to effect oxymercuration–demercuration. The usual protocol is that introduced by Brown and involves a rapid, one-pot procedure using a mixture of tetrahydrofuran and water as solvent. Whilst mercury(II) acetate is soluble in water, on addition of tetrahydrofuran a yellow precipitate forms [presumably mercury(II) oxide], the dissolution of which, on addition of an alkene, serves as a rough indicator of completion of the oxymercuration step (typically a few minutes). Addition of the borohydride liberates metallic mercury concomitant with reduction of the substrate, again in just a few minutes.^[11,39] An early use of mercury(II) acetate, in diethyl ether, was reported by Sand and Genssler, while the use of borohydride was initially reported by Henbest.^[31,40] The particularly high yields that accompany the Brown procedure seem to be a result of its remarkable rapidity, with longer reaction times frequently being detrimental. In this regard, the observation of the very fast nature of the borohydride reduction in aqueous media was a key part of the development of this method.^[41] This reductant has significantly greater general efficacy than hydrazine (a cancer suspect agent), which reacts much more slowly and frequently generates significant quantities of dialkylmercury compounds. In addition, some β -elimination to regenerate the original alkene can occur with hydrazine. Occasionally, β -elimination can accompany the use of borohydride, but this can be suppressed by use of diethyl ether/water mixtures as solvent.^[42] The definitive study on the mechanism of this reduction was carried out by

for references see p 239

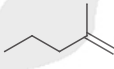
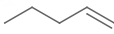
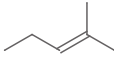

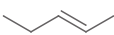
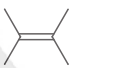
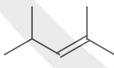
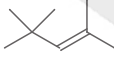
Whitesides^[43] and a radical process was demonstrated;^[29] subsequent work favors a chain over a cage mechanism (Scheme 7).^[44] An invariance of mechanism over a range of hydride (or deuteride) sources has been noted, which suggests significant synthetic scope when balancing functional-group compatibility with demercuration, e.g. tributyltin hydride–hydrido(tributylphosphine)copper(I) might be used in the reduction step.

Scheme 7 Mechanism for the Borohydride Reduction of Organomercury Compounds^[43,44]



A study of the relative reactivity of variously substituted double bonds provides a useful tool in planning the deployment of the process in multifunctional compounds.^[45] The order of reactivity established is shown in Table 1.

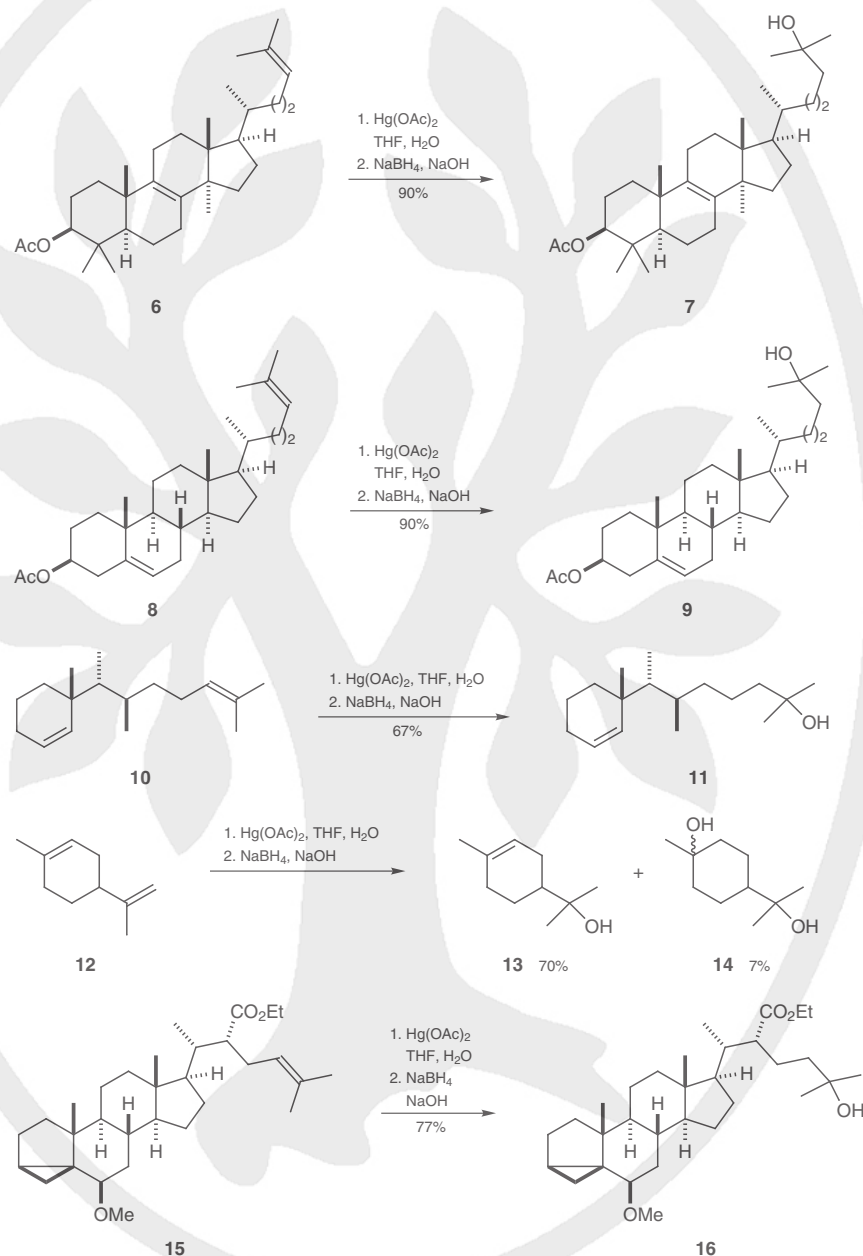
Table 1 Rates of Oxymercuration, with Respect to Cyclohexene, of Variously Substituted Double Bonds^[45]

Alkene	Relative Reactivity	Ref
	48	[45]
	6.6	[45]
	1.24	[45]
	0.56	[45]
	0.17	[45]
	0.061	[45]
	0.056	[45]
	0.02	[45]

Thus, the relationship of rate to steric hindrance is complicated,^[23,24] although generally increased hindrance, for a given substitution pattern on the double bond, reduces the

rate. The presence of electron-withdrawing groups tends to reduce the rate of reaction.^[24] The rate differences in further categories of alkenes are also reported, e.g. cyclohexene > cyclopentene >> cyclooctene.^[45] The differences between some of these rates is sufficient to be exploitable in a synthetic route (Scheme 8). The highly selective oxymercuration of the trisubstituted bond in **6** to afford **7** is thus easily understood, and that in **8** to give **9** is impressive and illustrates the importance of flanking groups.^[46]

Scheme 8 Selectivity between Alkenes on the Basis of Substitution^[46–49]



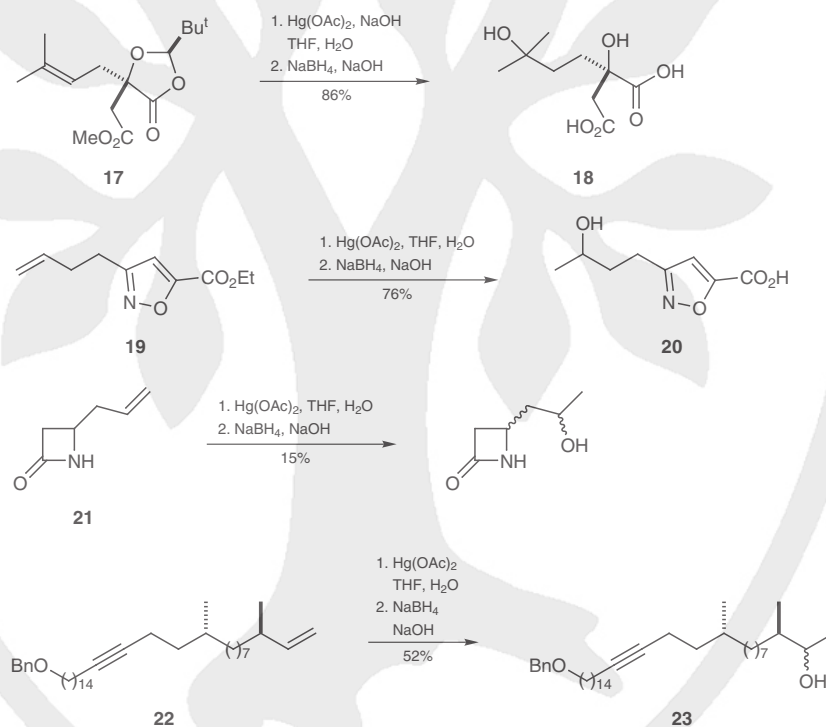
Given the modest rate differences between *Z*-alkenes and trisubstituted alkenes noted in the model systems, the 67% yield achieved by in the transformation of **10** into **11** is respectable.^[47] In a study of the selective hydration of dienes, it was demonstrated that limo-

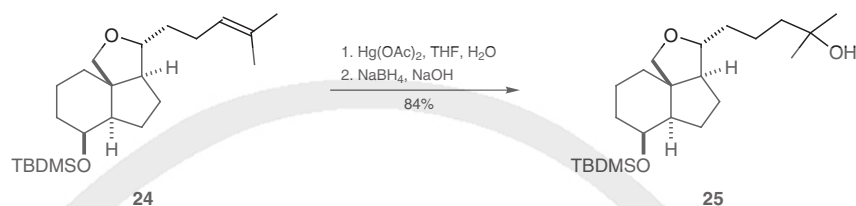
for references see p 239

nene (**12**) shows a clear preference for hydration of the terminal disubstituted double bond, to give **13** rather than **14**.^[48] Indeed, this selectivity has been further optimized (see Sections 36.1.4.1.4 and 36.1.4.1.5). It is instructive to contrast this selectivity with that of the acid-catalyzed hydration of **12** in Section 36.1.4.1.2.1. The final example in Scheme 8, the hydration of steroid derivative **15** to afford **16**, is included as the parallels between cyclopropane and alkene chemistry are always interesting to examine, the high selectivity being in keeping with the relatively slow rates of oxymercuration of cyclopropanes.^[49–51] In addition, the survival of the ester in **15** and the acetates in **6** and **8**, under basic aqueous conditions, is worthy of note. This last point raises the issue of functional-group compatibility: it is found to be generally good.

However, in contrast to the examples above, ester hydrolysis is an issue during reactions of **17** and **19** to give **18** and **20**, respectively (Scheme 9).^[52,53] Groups that are generally stable include acetals, e.g. methoxymethyl ethers,^[54] dioxolanes,^[55] acetonides,^[56] tetrahydropyranyl ethers,^[57] and dimethyl acetals;^[58] ethers, e.g. benzyl,^[59] *tert*-butyldimethylsilyl (see **24** to **25**)^[60]; and amides such as 2,2,2-trifluoroacetamide.^[61] A variety of heterocycles, including monocyclic β -lactams in modest yield,^[62] oxiranes,^[63] and pyridines^[64] are also found to be compatible, for example **19** and **21**. Additionally, the method is found to be selective for alkenes in the presence of alkynes, giving products such as **23** from **22** in reasonable yield.^[65]

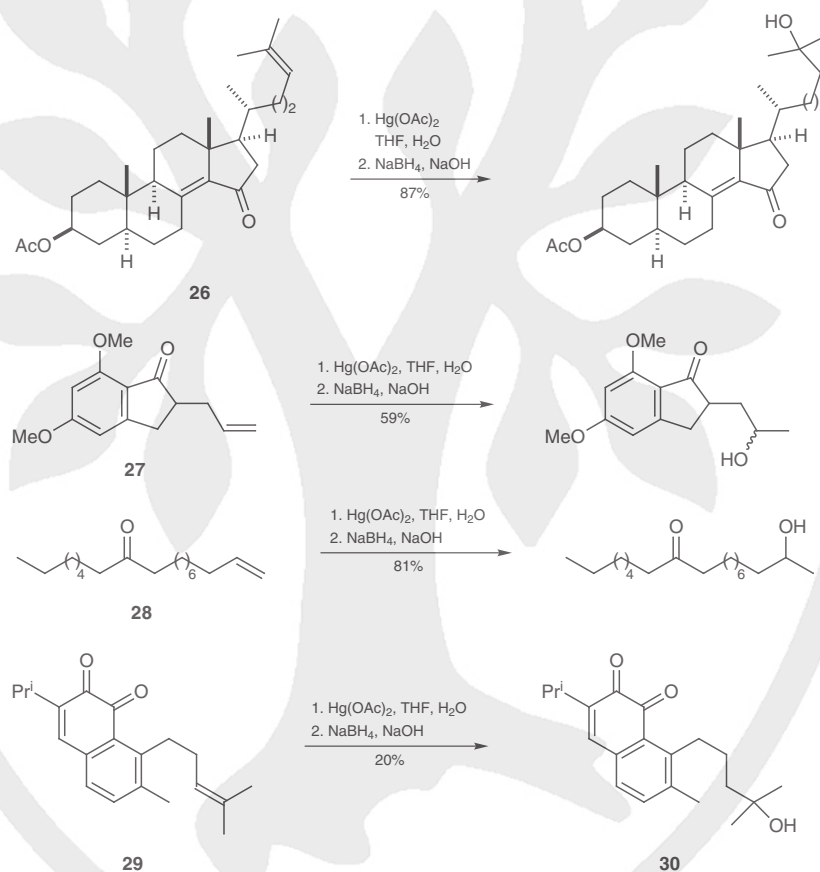
Scheme 9 Functional-Group Compatibility of the Oxymercuration–Demercuration Procedure^[52,53,60,62,65]





Perhaps the least obvious issue of functional-group compatibility is that of ketones, usually readily reducible by sodium borohydride; these have been found to survive in several examples (Scheme 10). Examples of concomitant reduction are also known.^[66] Both α,β -unsaturated and aryl ketones, e.g. **26** and **27**, as well as simple ketones such as **28** deliver surprisingly good yields.^[67–69] Although a 20% yield is modest, given the reactivity of benzo-1,2-quinones, the hydration of **29** to give **30** is still noteworthy and perhaps defines a limit to what might be achieved.^[70]

Scheme 10 Functional-Group Compatibility of Ketones in the Oxymercuration–Demercuration Procedure^[67–70]

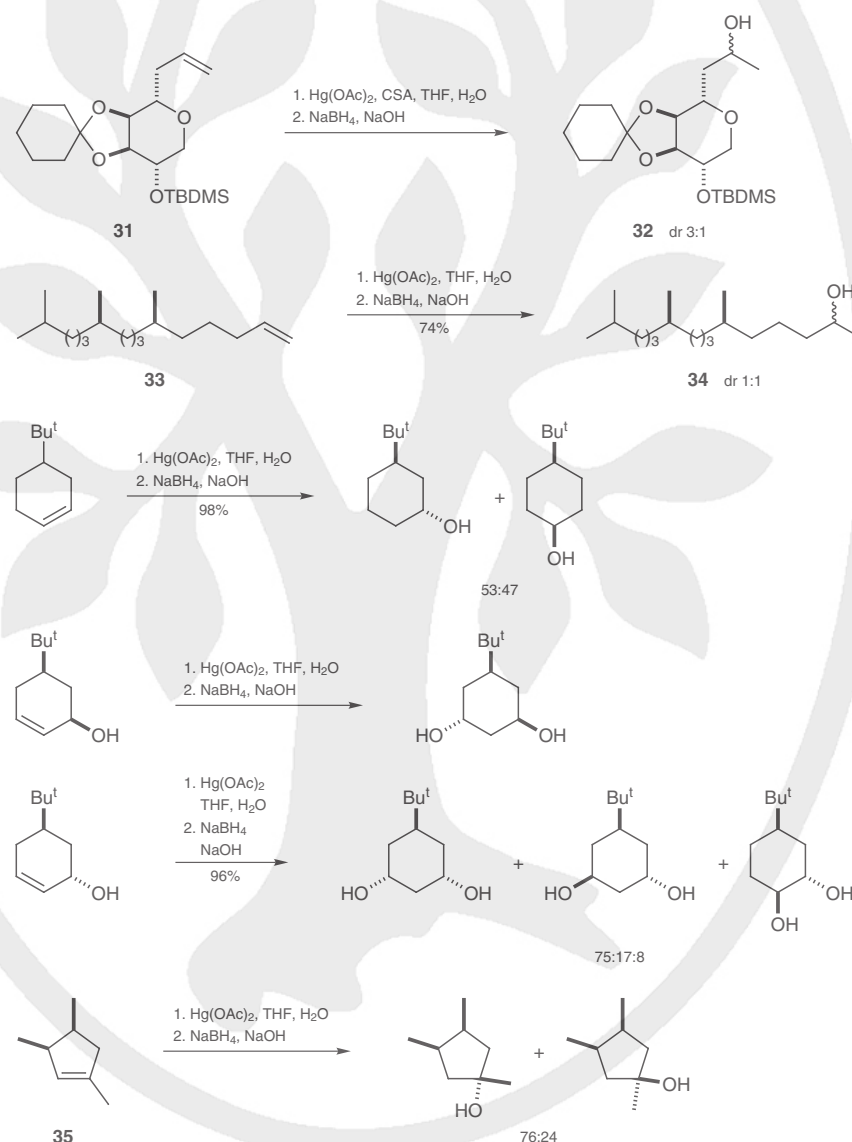


With respect to relative stereochemistry, the level of induction in acyclic cases is usually not high. The two cases **31** and **33** (Scheme 11), as well as **21** and **22** in Scheme 9 and **28** in Scheme 10, serve to illustrate the situation (see also **52** in Scheme 15, Section 36.1.4.1.4).^[71,72] In the case of **32**, a yield of 85% is reported for the process encompassing a prior *tert*-butyldimethylsilyl and subsequent benzyloxymethyl protection. Whilst no stereochemical induction could have been expected in the synthesis of **34**, the two diaste-

for references see p 239

reomers can be subsequently separated by selective enzymatic hydrolysis of the corresponding acetate. In cyclic systems, each molecule must be analyzed individually, but some examples with both high regio- and stereoselectivity are known. In general, for six-membered rings, ring opening of an intermediate mercurinium ion to give diaxial products appears important. The presence of an electron-withdrawing group adjacent to the double bond serves to direct attack γ to itself.^[15] The cyclopentene **35** primarily undergoes hydroxylation *anti* to the methyl groups, suggesting fast, reversible mercurinium ion formation (on the more hindered face), followed by rate-limiting attack from the less hindered face. The regiochemistry is the standard Markovnikov orientation.^[73] Some other examples are given in Scheme 11.

Scheme 11 Stereochemical Induction in the Oxymercuration–Demercuration Procedure^[15,71–73]



Bicyclic alkenes can give rise to highly stereoselective reactions and have been discussed in some depth.^[33,74]

5-[(3*R*,3*aS*,5*aR*,6*S*,9*aS*)-6-(*tert*-Butyldimethylsiloxy)octahydro-3*H*-indeno[1,7*a-c*]furan-3-yl]-2-methylpentan-2-ol (25); Typical Procedure:^[60]

CAUTION: Mercury(II) acetate is highly toxic and may be fatal if ingested or inhaled.

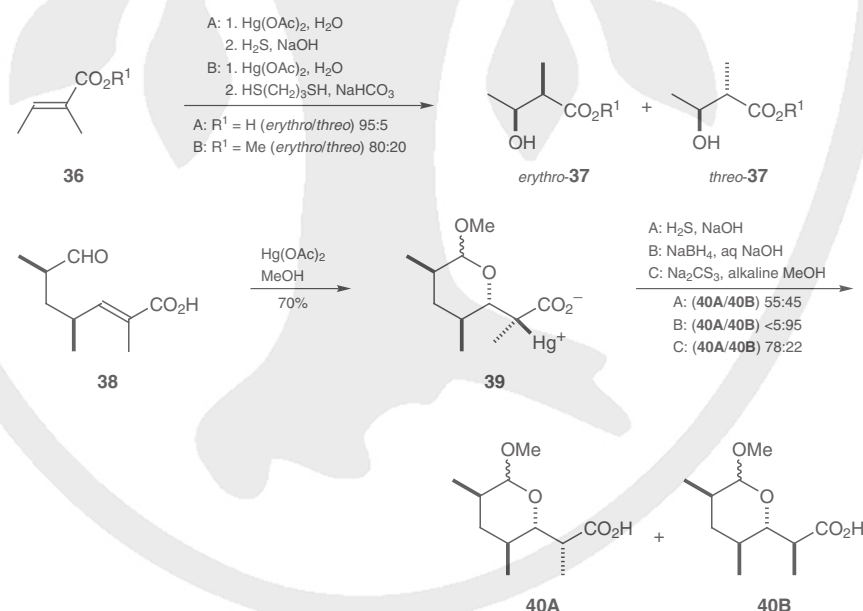
A mixture of alkene **24** (130 mg, 0.34 mmol) and Hg(OAc)₂ (120 mg, 0.37 mmol) in THF/H₂O (1:1; 20 mL) was stirred for 7 d. Then, 3 M NaOH (8 mL) and a 0.5 M soln of NaBH₄ in 3 M NaOH (3.4 mL, 1.7 mmol) were successively added. After the mixture was stirred for 15 min, brine (15 mL) was added; the mixture was then extracted with Et₂O (3 × 15 mL). The combined organic phase was dried, filtered, and concentrated under reduced pressure to afford a yellow residue, which was purified by flash chromatography (EtOAc/hexanes 1:4) to give, after concentration and drying under very low pressure, a colorless oil; yield: 113 mg (84%).

36.1.4.1.2

**Variation 2:
Using Mercury(II) Acetate–Sodium Trithiocarbonate**

Sulfides and thiosulfates react rapidly with organomercury(II) salts but, in general, the products are unstable and tend to lead to retro-oxymercuration with regeneration of the alkene. However, in the case of α,β -unsaturated esters and acids, following mercuration, immediate demercuration to yield the alcohol or alkoxy derivative occurs on treatment with, for example, hydrogen sulfide.^[2] This mild demercuration method is not widely applied but has found application with the two classes of substrate mentioned above and has been found to deliver demercuration with predominantly retention of configuration under certain conditions. For example, highly stereoselective hydration of tiglic acid **36** (R¹ = H) gives *erythro*-**37** (R¹ = H) (*sodium borohydride* mediated demercuration delivers a 1:1 mixture of diastereomers) (Scheme 12).^[75] The regiochemistry of the hydroxylation fits with ring opening of a positively charged intermediate and should be contrasted with the manganese-based protocol in Section 36.1.4.3.

Scheme 12 Use of Sulfides or Trithiocarbonates in the Demercuration Procedure^[75–77]



By contrast, in a study on the synthesis of the Prelog–Djerassi lactone, it was observed that treatment of **39** (prepared from **38**) under the same conditions afforded **40A** and

for references see p 239

40B as a 55:45 mixture of diastereomers (sodium borohydride gave demercuration with >95% formal inversion).^[76] Thus, the stereochemistry of the product appears to be a result of the intrinsic stereochemical preference of a substrate for protonation or hydrogen atom transfer rather than a mechanistic requirement for retention. Sodium trithiocarbonate is one reagent that consistently gives mainly retention of configuration, with selectivities ranging from 2:1 to >95:5. Subsequent work showed that use of propane-1,3-dithiol in ethanol affords good yields and stereoselectivity, with retention of configuration, for alkoxy products, although more moderate stereoselectivity is observed for the hydroxylation of methyl tiglate **36** ($R^1 = \text{Me}$).^[77] Overall, the results are useful but caution must be exercised in their application to new systems.

(2S*,3S*,5R*,6R*S*)-2-[(1S*)-1-Carboxy-1-(hydroxymercurio)ethyl]-6-methoxy-3,5-dimethyl-3,4,5,6-tetrahydro-2H-pyran Inner Salt (39); Typical Procedure:^[76]

CAUTION: Mercury(II) acetate is highly toxic and may be fatal if ingested or inhaled.

A soln of the *E*-aldehyde acid **38** (514 mg, 2.79 mmol) and $\text{Hg}(\text{OAc})_2$ (980 mg, 3.07 mmol) in dry MeOH (6 mL) was stirred at 25 °C for 10 d. The mixture was centrifuged, the supernatant was decanted, and the precipitate was washed with MeOH (5 mL) and Et_2O ($2 \times 5 \text{ mL}$). After drying at 70 °C/1 Torr for 24 h, the analytically pure product was obtained as a mixture of anomers; yield: 815 mg (70%); mp 190 °C (dec).

(2R*)- and (2S*)-2-[(2S*,3S*,5R*)-6-Methoxy-3,5-dimethyltetrahydro-2H-pyran-2-yl]propanoic Acid (40A and 40B); Typical Procedure:^[76]

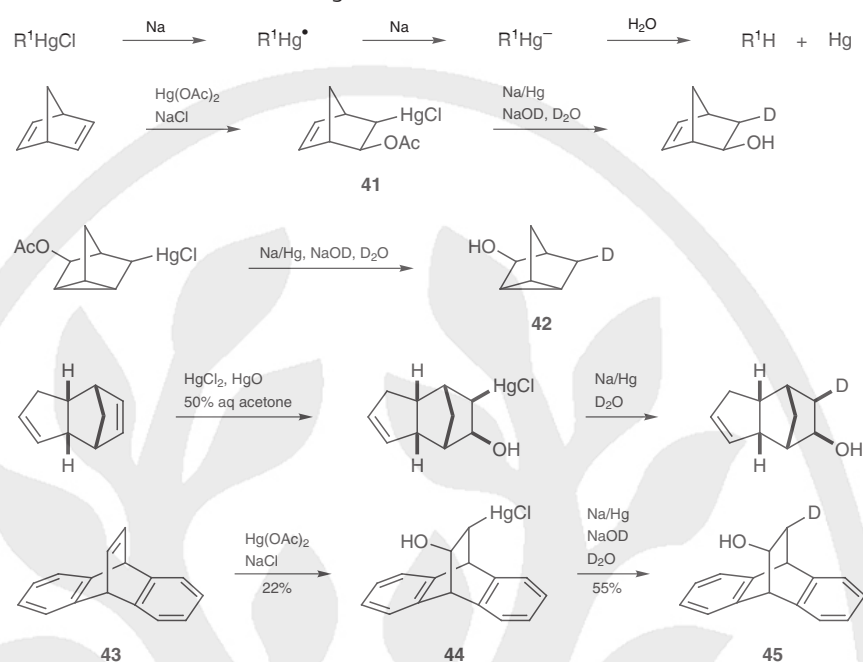
A sample of the crude acetal **39**, prepared from the aldehyde acid **38** (1.14 g, 6.2 mmol), was suspended in MeOH (30 mL), stirred at 25 °C for 3 h, and then cooled in an ice bath. In a separate flask a soln of $\text{Na}_2\text{CS}_3 \cdot 2\text{H}_2\text{O}$ (10.6 g, 60 mmol) in MeOH (50 mL) and 2 M NaOH (2 mL) was stirred at -70 °C. Then, 2 M NaOH (1 mL) was added to the suspension of the acetal, which was then added over 5 min to the vigorously stirred Na_2CS_3 soln. The slush-like mixture was stirred at -50 °C for 1 h, warmed to 25 °C, concentrated at reduced pressure, and brought to pH 7–8 with 2 M HCl. The precipitated HgS was removed by centrifugation and the supernatant was diluted with H_2O , brought to pH 2 with 2 M HCl, and extracted with Et_2O ($2 \times$). Workup of the Et_2O layer provided the acetals **40A** and **40B** in a ratio of 78:22; yield: 1.0 g (75% yield from aldehyde acid **38**).

36.1.4.1.3

Variation 3:

Using Mercury(II) Acetate–Sodium Amalgam

The particular value of this protocol, as with that in Section 36.1.4.1.2, resides in the stereochemistry of the reductive demercuration. In the absence of an obvious mechanism of equilibration, e.g. the presence of an α -carbonyl group,^[76] then retention of stereochemistry is observed. Although it has not yet found wide application in synthesis, there is clear potential for stereospecific deuteration as well as establishing protiated chiral centers. The use of sodium amalgam was first reported by Sand and Singer, with an application to the assignment of the stereochemistry of an organomercury compound by Traylor.^[17,78] A detailed study on this method of demercuration has been reported^[80] and other work utilized ^2H NMR to study its stereochemical outcome.^[81] Some illustrative examples are shown in Scheme 13. The norbornadiene derivative **41** is particularly interesting as the intermediacy of radicals in the reduction process is known to afford tricycloheptane structures of type **42**, but none of these are observed.^[81] The mechanism has been proposed to involve two rapid one-electron transfers to afford a mercury-centered anion which undergoes rapid protonation with retention of stereochemistry.^[80] Unfortunately, as some of these compounds were prepared as part of mechanistic studies, yields are not always available, although the conversion of **43** into **45** via **44** is given in detail.

Scheme 13 Use of Sodium Amalgam in the Demercuration Procedure^[17,80,81]

trans-12-Hydroxy-9,10-dihydro-9,10-ethanoanthracen-11-yl)mercury(II) Chloride (44);
 Typical Procedure:^[80]

CAUTION: Mercury(II) acetate is highly toxic and may be fatal if ingested or inhaled.

CAUTION: Nitromethane is flammable, a shock- and heat-sensitive explosive, and an eye, skin, and respiratory tract irritant.

9,10-Dihydro-9,10-ethanoanthracene (**43**; 4.08 g, 20 mmol) was dissolved in acetone (50 mL), and H₂O (50 mL) containing AcOH (3 mL) was added. To the resulting suspension was added Hg(OAc)₂ (6.88 g, 20 mmol). The mixture was stirred at rt for 1 d as the precipitate dissolved. NaCl (2.36 g, 40 mmol) was added and a precipitate formed. After 3 h of stirring, the suspended precipitate was collected by filtration to give a white powder (4.76 g). [In some analogous preparations, H₂O was added before the precipitate was collected by filtration and the product contained unreacted **43**; the latter was then removed from the product by trituration with Et₂O]. Recrystallization (MeNO₂) gave two crops of product as fine, white crystals; yield: 1.13 g (22%). This material was combined with that from another preparation and the total sample (3.0 g) was recrystallized from nitromethane (250 mL) to give two crops (1.7 g) of small, white crystals; mp 255 °C.

trans-12-Deutero-9,10-dihydro-9,10-ethanoanthracen-11-ol (**45**):^[80]

CAUTION: Mercury vapor is readily absorbed by inhalation and is neurotoxic.

A sample of **44** (229 mg, 0.50 mmol), freshly prepared 2% Na/Hg (7.0 g), and a 1.66 M soln of NaOD in D₂O (2.0 mL, 3.3 mmol) were stirred for 3 d under a CaSO₄ drying tube. CCl₄ (~5 mL) (**CAUTION:** toxic) was added and about 1 h later the mixture was filtered and the residual amalgam and Hg were washed well with CHCl₃. The combined organic layers were separated and washed with H₂O. The soln was dried (MgSO₄) and concentrated to give a white solid (76 mg). Decolorization with activated charcoal in MeOH and recrystal-

for references see p 239

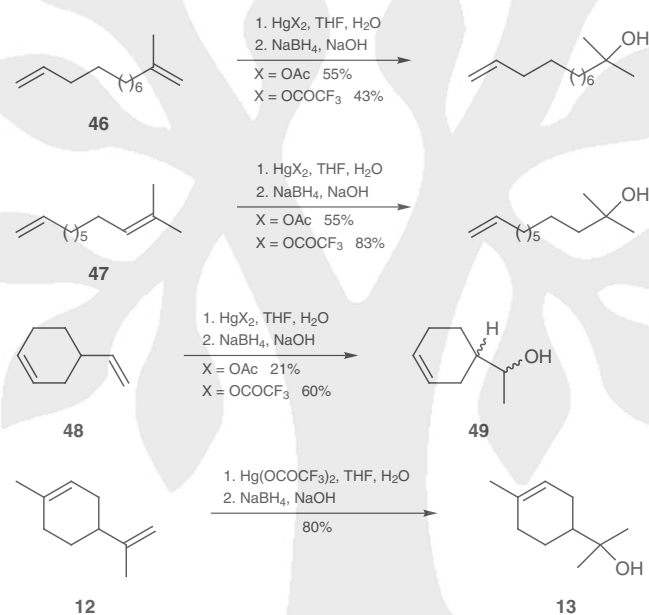
lization (EtOH/H₂O) gave the product; yield: 61 mg (55%); mp 138–140 °C. The data recorded were consistent with alcohol **45** containing 96% D.

36.1.4.1.4

Variation 4:
Using Mercury(II) Trifluoroacetate–Sodium Borohydride

Mercury(II) trifluoroacetate is, by virtue of the strongly electron-withdrawing ligands, more electrophilic and more reactive toward double bonds. While this reagent has not been used as widely as mercury(II) acetate, it has found some use in the selective hydration of certain dienes. Oxymercuration with this salt is fast and reversible, frequently leading to thermodynamic products, whereas kinetic products are more common with mercury(II) acetate.^[16,48] Examination of the reactions in Scheme 14 indicates that the relative success of the two mercury(II) salts is substrate dependent; thus the isomeric dienes **46** and **47** show opposite trends. 4-Vinylcyclohexene (**48**) gives a noticeable improvement in yield of **49** from 21 to 60% on use of the trifluoroacetate,^[48] while a reinvestigation of the oxymercuration limonene (**12**) shows a modest improvement from 70 to 80% (cf. Scheme 8, Section 36.1.4.1.1; see also Section 36.1.4.1.5).^[82] Demercuration is also faster.

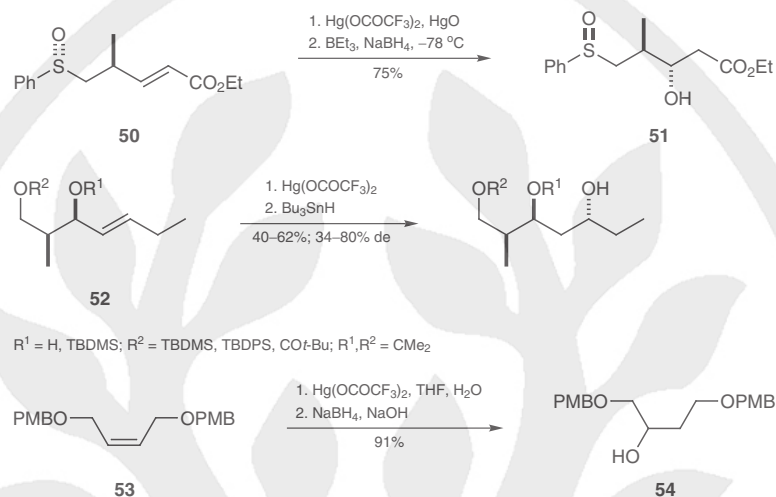
Scheme 14 Site Selection in the Oxymercuration–Demercuration Protocol with Mercury(II) Trifluoroacetate^[48,82]



During a study on the oxymercuration of α,β -unsaturated esters and amides, it was found that the greater rate of reaction of the trifluoroacetate salt is highly advantageous for more substituted cases such as (*E*)-2,4-dimethylpent-2-enoates. Adding an extra equivalent of mercury(II) oxide also buffers the reaction against the 1 equivalent of trifluoroacetic acid generated (see Section 36.1.4.1.5 for an alternative method of addressing this problem).^[77] Similarly, the trifluoroacetate has also been utilized in the hydroxylation of **50** to afford an 18:1 mixture of the diastereomers of **51**; of particular interest in this case is the neighboring-group participation of the sulfoxide and the use of Kang's procedure for low-temperature demercuration (Scheme 15).^[83,84] The stereoselective oxymercuration–demercuration of a series of related alkenes **52**, differing in the protecting groups used, has been examined, resulting in a range of outcomes with yields of 40–62% and diastereomeric excess values of 34–80% (the outcomes of individual cases were not specified). It

should be noted that iodohydroxylation proves superior.^[85] The electron-deficient alkene **53** is hydroxylated to give **54** in high yield, with this reaction forming part of a study on the synthesis and antiviral activity of 9-alkoxyfurines.^[86]

Scheme 15 Use of Mercury(II) Trifluoroacetate in the Oxymercuration–Demercuration Protocol^[83,85,86]



1,4-Bis[(4-methoxybenzyl)oxy]butan-2-ol (54); Typical Procedure:^[86]

CAUTION: Mercury(II) trifluoroacetate is highly toxic and may be fatal if ingested or inhaled.

To a soln of $\text{Hg}(\text{OCOCF}_3)_2$ (17.1 g, 40 mmol) in THF/ H_2O (1:1; 80 mL) was added a soln of alkene **53** (12.8 g, 39 mmol) in THF (10 mL) over 5 min. The resulting two-phase mixture was stirred vigorously at rt for 15 min. To the mixture was added 3 M aq NaOH (40 mL), followed by a 0.5 M soln of NaBH_4 in 3 M NaOH (40 mL), with water-bath cooling. The soln was saturated with NaCl and allowed to stand. The organic layer was collected, dried (MgSO_4), and filtered through Celite. The solvent was removed under reduced pressure to afford an oily solid; yield: 12.27 g (91%).

36.1.4.1.5

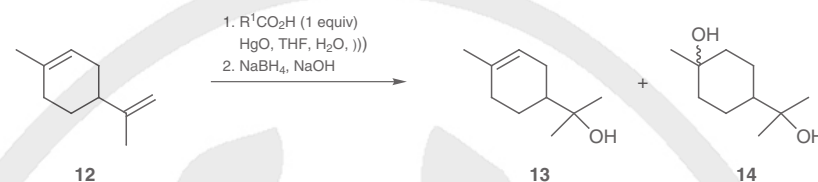
**Variation 5:
Using Mercury(II) Salts–Sodium Borohydride**

A variety of mercury(II) salts have been utilized in the oxymercuration step of this protocol. A study of the relative merits of the acetate, trifluoroacetate, nitrate, and methanesulfonate on simple alkenes reveals the acetate to be generally the best, although all the salts perform well in the cases of monosubstituted and 1,2-disubstituted alkenes.^[87] However, as identified in Section 36.1.4.1.4, in the selective hydroxylation of dienes a change to mercury(II) trifluoroacetate has, on occasion, proved advantageous. In addition, attempts at carrying out asymmetric oxymercuration may require access to other salts. Salts with less nucleophilic counterions, such as mercury(II) nitrate and mercury(II) trifluoroacetate, find a particular use when weak nucleophiles, such as nitriles or *tert*-butyl alcohol, are added to the intermediate mercurinium ion, but these studies fall outside the scope of this article.^[88,89] A facile sonochemical method for the synthesis of a variety of salts with an in situ preparation/reaction has been described. The results for selective hydroxylation of limonene are shown in Scheme 16.^[82] [In this study, a lower yield, 48%, was found for the hydroxylation of **12** to give **13** with commercial mercury(II) acetate than that reported

for references see p 239

previously (see Scheme 8, Section 36.1.4.1.1)] The value of micelles in controlling the oxymercuration selectivity was also noted.^[90]

Scheme 16 Einhorn's Sonochemical Method for In Situ Generation of Mercury(II) Salts^[82]



R ¹	Yield (%) of 13	Yield (%) of 14	Ref
Me	47	18	[82]
CF ₃	80	0	[82]
<i>t</i> -Bu	80	0	[82]
(CF ₂) ₆ CF ₃	80	0	[82]

Attempts at asymmetric hydroxylation began with the use of mercury(II) lactate.^[91] Induction is seen but a diastereomeric excess was not established for the oxymercuration compound generated from cyclohexene. Subsequent work established that modest enantiomeric excess values are achieved by the use of mercury(II) lactate and/or tartrate for some simple alkenes.^[92,93] Enantiomeric excess values of 3–45% have been demonstrated by use of stoichiometric cyclodextrins, while modest enantioselectivity has been achieved in certain allylic amines by using cyclodextrins in a catalytic inverse phase-transfer system, this latter work forming part of a study on the semisynthesis of homopumiliotoxins.^[94,95]

α -Terpineol (13**); General Procedure:**^[82]

The organic acid (1.2 mmol), yellow HgO (1 mmol), and limonene (**12**; 1 mmol) in THF/H₂O (1:1; 5 mL) were sonicated until complete discoloration occurred. The mixture was then reduced with NaBH₄ and worked up as normal (see Section 36.1.4.1.1); yield: 47–80%.

36.1.4.2

Method 2: Acid-Catalyzed Addition of Water

SAFETY: All of the acids mentioned in this section should be individually risk assessed before use. In general, they are toxic, corrosive, and may cause burns. The vapors should not be inhaled, they should not be allowed to come into contact with the skin or eyes, and appropriate safety clothing should be worn at all times. Organic perchlorates are sometimes explosive and perchloric acid can cause fires when mixed with a combustible substance. Therefore, use of perchloric acid requires a particularly careful risk assessment.

This is the simplest and most direct method for the hydration of alkenes and has a long pedigree; for example, Berthelot reported the hydration of propene in 1895.^[96] It avoids the use of toxic heavy metals whilst the employment of inexpensive reagents facilitates scale-up. Around 300000 tons of ethanol are manufactured in the USA per annum by treatment of ethene with sulfuric acid at 250 °C.^[97] Perhaps a barrier to its wider application in synthesis is the preponderance of acid-labile protecting groups that are in common use. Mechanistically, it was first investigated in the 1930s and is thought to proceed via a two-step mechanism that is essentially the reverse of an E1 elimination. Early studies provided data that were consistent with two related mechanisms, differentiated by the

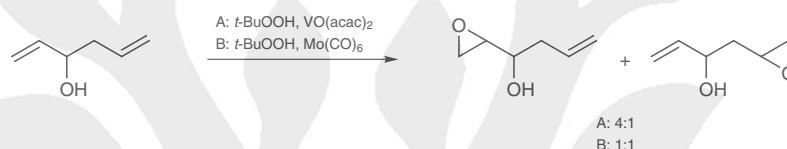
37.2	Product Class 2: Epoxides (Oxiranes)	
<hr/>		
37.2.1	Synthesis from Alkenes by Metal-Mediated Oxidation H. Adolfsson	
<hr/>		
37.2.1.2	Synthesis Mediated by Group 5 Metals	236
37.2.1.2.1	Method 1: Vanadium-Mediated Epoxidation with Alkyl Hydroperoxides	236
37.2.1.2.1.1	Variation 1: With Hydrogen Peroxide	238
37.2.1.2.2	Method 2: Vanadium-Mediated Asymmetric Epoxidation	238

Asymmetric Epoxides 5; General Procedure Using Catalyst 3:^[28]

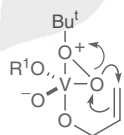
Ti complex **3** (1.8 mg, 1 μmol) and alkene (0.1 mmol) were dissolved in an appropriate solvent (1.0 mL) under N_2 . After addition of 30% aq H_2O_2 (0.101 mmol), the mixture was stirred at rt for the appropriate time (12–48 h). The solvent was removed under reduced pressure and the residue was purified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

37.2.1.2 Synthesis Mediated by Group 5 Metals

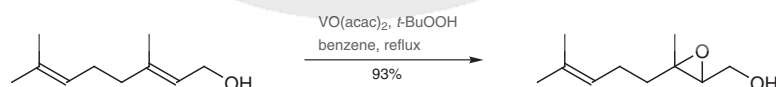
Epoxidation reactions mediated by group 5 metals are dominated by vanadium-based catalysts. In similarity to group 4 metals, the heavier elements (niobium and tantalum) are infrequently employed as catalysts. The discovery that vanadium complexes, in combination with alkyl hydroperoxides, participate 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]

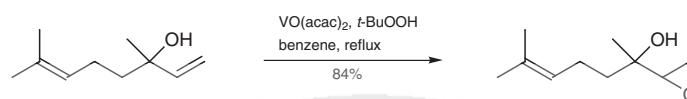
Scheme 8 Vanadium- and Molybdenum-Catalyzed Epoxidation of Allylic Alcohols^[31]

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**

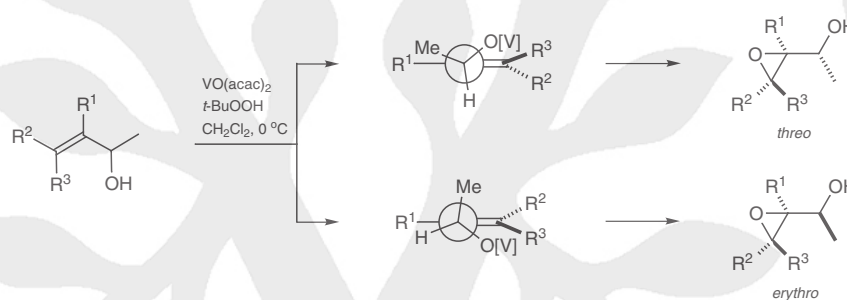
The vanadium-catalyzed epoxidation of allylic alcohols using alkyl hydroperoxides as terminal oxidants proceeds readily at or below room temperature. The epoxidation selectivity for a number of simple alkenes, as well as in more complex diene systems has been systematically investigated. The oxidation 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.

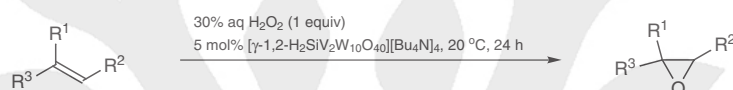
Mimoun and coworkers have demonstrated that stoichiometric amounts of vanadium(V) peroxo complexes containing Schiff-base ligands mediate the epoxidation of unfunctionalized alkenes in moderate to good yields.^[40]

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]

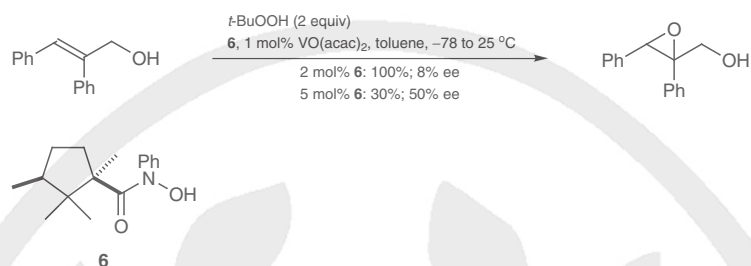
Scheme 12 Polyoxometalate-Catalyzed Epoxidation of Alkenes^[41]



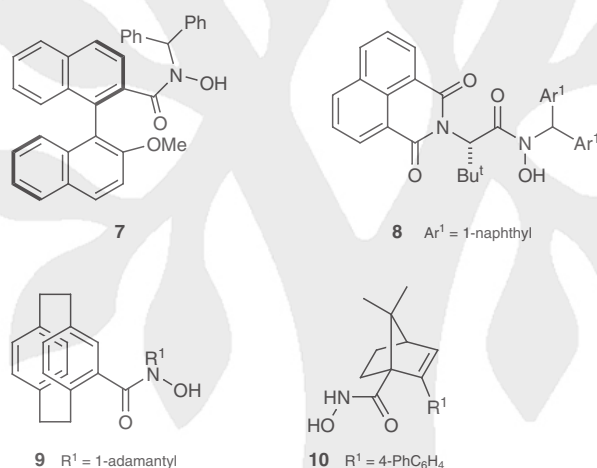
R ¹	R ²	R ³	Selectivity (%)	Ratio (<i>syn</i> / <i>anti</i>)	Yield (%)	Ref
H	H	Bu	99	–	92	[41]
(CH ₂) ₄ Me	Me	H	99	–	90	[41]
Ph	H	H	99	–	88	[41]
CHOH(CH ₂) ₃		H	95	12:88	87	[41]

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.

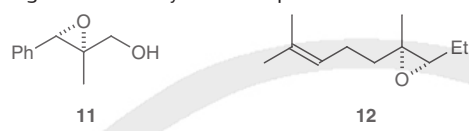
Scheme 13 Vanadium-Catalyzed Asymmetric Epoxidation Using a Hydroxamic Acid Ligand^[33]

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]

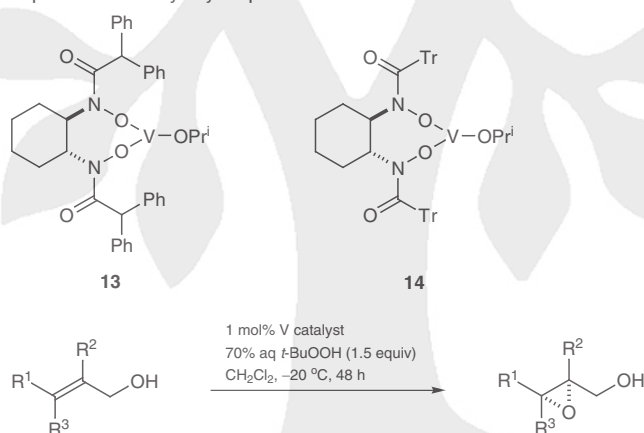
The promising results using hydroxamic acid **7** as a ligand in vanadium-catalyzed asymmetric epoxidations inspired reinvestigation of this epoxidation system.^[46] A number of different chiral hydroxamic acids **8–10** have been prepared (Scheme 14), and vanadium complexes based on these ligands have 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.