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Is osmylation always preferring the richest double bond?

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1. Introduction

1.1. General observations on the osmylation reaction

Osmylation is an excellent method for the transformation of alkenes to 1,2-diols, especially in the presence of tertiary amines like pyridine or quinuclidine as rate accelerators.[1,2] This reaction has gained popularity since a catalytic procedure, which avoids the stoichiometric use of the highly toxic, volatile, and expensive osmium tetroxide has been described.[3] Various reoxidant reagents employed are *N*-methyl-morpholine-*N*-oxide (NMO), potassium ferricyanide (K_3FeCN_6), or *tert*-butyl peroxide (*t*-BuOOH).

Different solvents have also been used such as acetone, acetonitrile, benzene, *t*-BuOH, CH_2Cl_2, dioxane, EtOH, Et_2O, pyridine, or THF (or mixtures of these solvents). Normally, the presence of water is necessary to facilitate the cleavage of the intermediate osmate esters, even if this is not always clearly specified. Numerous additives have been tested in order to activate the overall process, enhancing the cleavage of the osmate intermediate.[4]

For the last decade, AD-mix type reagents have added a stereoselective perspective to this transformation for the creation of chiral 1,2-diols. Figure 1 shows some of the typical reagents such as $(DHQD)_2PHAL$ **1** and $(DHQ)_2PHAL$ **2**,[5a,5b] DHQDCLB **3**,[5c] $(DHQD)_2Pyr$ **4**,[5a,5d] $(DHQD)_2PYDZ$ **5**,[4] $(DHQD)_2AQN$ **6**,[5b] NOE-Lin catalyst **7**,[5e] and a new interesting catalyst **8**.[5f]

In the case of AD-mix β and AD-mix α reagents, the observed enantioselectivities have been rationalized by Sharpless using a convenient model (Fig. 2), where the largest group on the double bond occupies the Southwest corner, and the

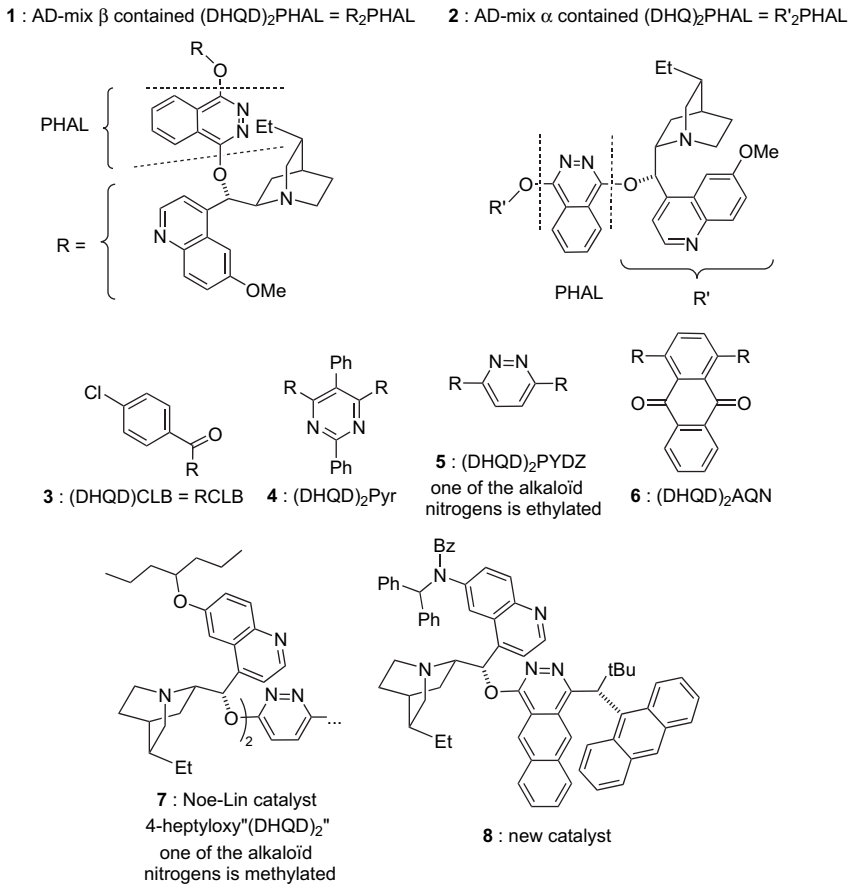


Figure 1. AD-mix type reagents.

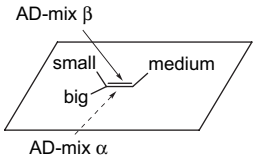
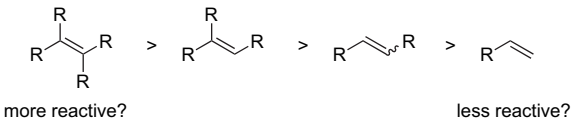


Figure 2.

smallest the Northwest corner.[5a] This model also explains why examples in which the relative steric hindrances of the medium and large groups are similar give no clean results. This additionally corroborates the fact that *Z*-alkenes often afford a very poor enantiomeric excess.

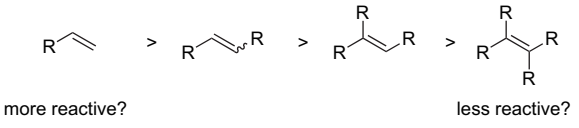
When the general properties of osmylation are discussed, common sense classifies the osmylating reagents as oxidative materials, which consequently prefer the richest alkene functions. As a result, the reactivity order should be that illustrated in Scheme 1. In reality, because OsO_4 is assumed to be so small and reactive, predicting a compound with double bond selectivity with no special additive is very difficult.



Scheme 1. Osmylation preference regarding richness of alkenes.

In a number of reactions, however, both additives and solvents can participate in the chelation of osmium intermediates, thus increasing the size and thereby allowing better selectivities. A crucial question immediately arises: with bulky osmylating reagents, will steric hindrance probably change the reactivity order, as seen in Scheme 2?

Thus, when considering both Schemes 1 and 2, it is not always easy to predict double bond reactivity in any given molecule. A careful literature search was carried out to find non-conventional examples, in which osmylation surprisingly preferred the less-hindered double bond.



Scheme 2. Osmylation preference regarding steric hindrance of alkenes.

The investigation was also extended to identically substituted competitive double bonds (e.g., a terminal alkene versus another terminal alkene). In these cases, steric hindrance is usually the most important aspect to consider and the allylic substitution will preferentially direct osmylation.

Cases where a deactivated alkene was present in the molecule (e.g., α,β-unsaturated esters)[6] have been intentionally avoided.

All of the chosen examples appear in Table 1, and have been subdivided into cases **A**–**N**. The first number indicates how many examples were found and that in parenthesis indicates those with AD-mix type reagents. For case A, where two terminal alkenes are present in the molecule, eight examples were found, five of which using AD-mix type reagents.

A rapid examination of this table shows that even simple osmylation reactions can give regioselectivities in favor of the less-electron-rich alkene.

The goal of this review is to collect all of the interesting cases and to discuss the observed selectivities.

It is interesting to note that, in many examples, the diastereoselectivity was not indicated, because the authors were not interested in the diol itself, but the aldehyde function that could be obtained after a simple sodium periodate oxidative cleavage. In practically all of the cases using only OsO_4 where a regioselective reaction occurred (giving a mixture of diastereoisomers), the affected alkene has been indicated with an arrow, in order to simplify the drawings.

2. Osmylation of monosubstituted alkenes

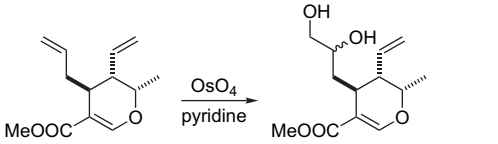
2.1. Monosubstituted alkenes versus monosubstituted alkenes

When molecules with two terminal monosubstituted alkenes are treated with only osmium tetroxide, a regioselective reaction sometimes occurs. In the synthesis of (−)-elenolic acid and (−)-ajmalicine, the most accessible alkene of **9** was preferentially oxidized to **10** in the presence of pyridine (Scheme 3).[7]

In the synthesis of the tetrahydrofuran ring part of the polycavernoside A described by Hayashi, 'symmetrical' di-alkenes

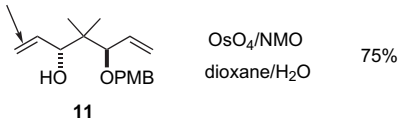
Table 1
Terminologies **A**–**N**—number of references (examples with AD-mix type reagents)

Unaffected alkene ⟹ / Osmylated alkene ⇓					
	A—8 (5)	**B**—4 (2)	**C**—25 (12)	**D**—43 (7)	**E**—8 (0)
		F—1 (1)	**G**—3 (0)	**H**—12 (1)	**I**—9 (1)
			J—33 (14)	**K**—18 (8)	**L**—6 (0)
				M—46 (29)	**N**—3 (1)



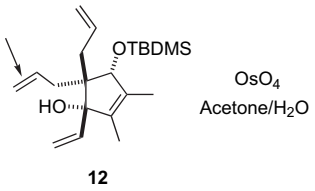
Scheme 3.

were studied (Scheme 4). The moiety closest to the free alcohol function in **11** was preferentially osmylated, presumably due to a 'hydrogen bond'-assisted process.[8]



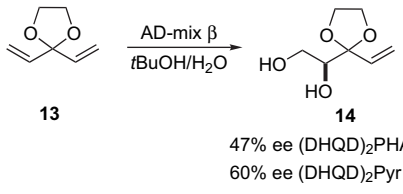
Scheme 4.

An interesting case involving three terminal monosubstituted alkenes and a tetrasubstituted alkene was published by Mehta in the course of the synthesis of the neurotrophic sesquiterpene, merrilactone A (Scheme 5). Only the most accessible alkene bond in **12** was osmylated, where only one α-substitution exists. Interestingly, only the terminal alkene bond positioned on the same face as the free alcohol function is affected.[9]



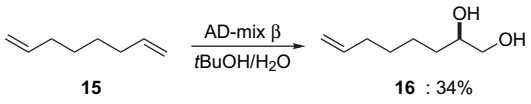
Scheme 5.

This regioselective reaction can also be stereoselective by the use of asymmetric dihydroxylation (AD) reagents, sometimes with excellent inductions. The following example, described by Sharpless, nicely transforms a simple achiral di-alkene compound **13** into an unsymmetrical chiral diol **14** (Scheme 6).[5a]



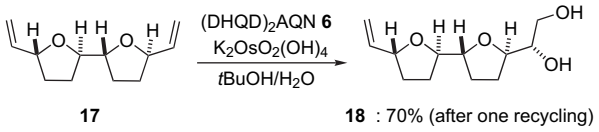
Scheme 6.

To show how interesting this kind of transformation is, it is difficult to find a simpler example than the following (**15**→**16**) described by Sinha in the total synthesis of 34-hydroxyasimicin (Scheme 7).[10]



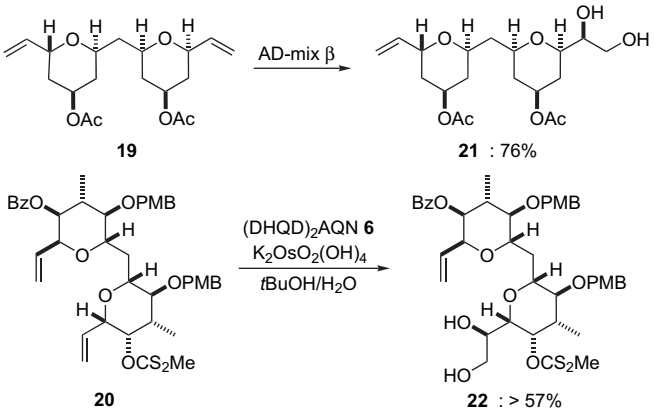
Scheme 7.

In an asymmetric di-alkene **17** described by Burke in the formal synthesis of uvaricin, the use of $(DHQD)_2AQN$ **6** gave a chiral diol **18** (Scheme 8). It is interesting to note that the use of AD-mix β gave only a moderate stereoselectivity.[11]



Scheme 8.

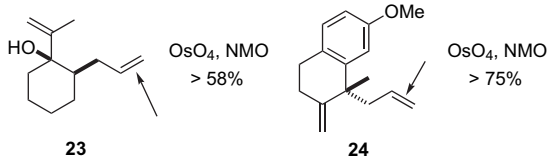
The last two examples in this section concern the chiral starting di-alkenes **19** and **20**, and osmylation cleanly gives a regioselective access to the chiral 1,2-diols **21** and **22**, used in the synthesis of the C1–C17 segment of phorboxazole B and in synthetic efforts toward the C22–C36 subunit of halichondrin B, both published by Burke (Scheme 9).[12,13]



Scheme 9.

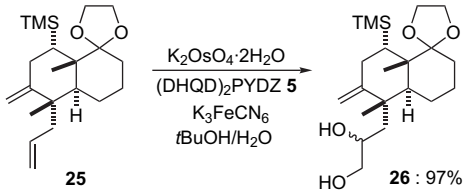
2.2. Monosubstituted alkenes versus 1,1-disubstituted alkenes

Only a few examples exist where a terminal monosubstituted alkene and a 1,1-disubstituted alkene were both present in the molecule to be osmylated. When compounds **23** and **24** were treated with osmium tetroxide and a reoxidant *N*-oxide, it was possible to selectively oxidize the terminal double bond (Scheme 10).[14,15]



Scheme 10.

Only one example **25** with an excellent regioselectivity (forming **26**) was published by Corey in the total synthesis of dysidiolide (Scheme 11).[16]

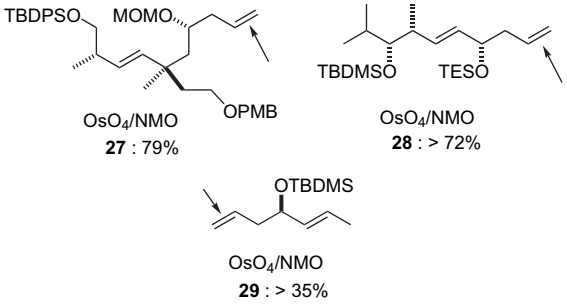


Scheme 11.

2.3. Monosubstituted alkenes versus 1,2-disubstituted alkenes

2.3.1. Achiral osmylation: terminal double bond versus acyclic Z- or E-double bond

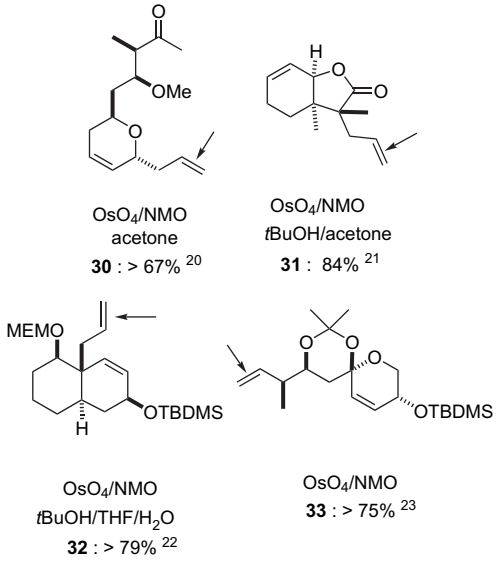
In the three following examples **27**, **28**, and **29** (Scheme 12), described by Williams in the synthesis of the AB-ring system of norzoanthamine,[17] by Rychnovsky in the synthesis of the polyol chain of (−)-roxaticin,[18] and by Paterson in work toward the total synthesis of the marine-derived immunosuppressant, discodermolide,[19] all of the osmylations favored the more-electron-poor double bond. This was presumably because of the steric environment directly around the disubstituted double bonds. In the second example **28**, the authors observed 11% of external double bond osmylation as well as 24% of internal osmylation, if the allylic alcohol was not protected by a TES group.



Scheme 12.

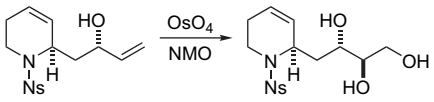
2.3.2. Achiral osmylation: terminal double bond versus cyclic Z-double bond

When a terminal double bond and a cyclic double bond are present in the same molecule, good selectivity is achieved even in cases where steric hindrance is not apparent. In the four following examples **30**–**33**, described by Miyashita in the total synthesis of scytophycin C,[20] by Tadano in the synthetic studies on the trichothecene family,[21] by Ley in the synthesis of a fragment of the insect antifeedant, azadirachtin,[22] and by Ireland in the total synthesis of FK 506,[23] with increasing bulkiness, a net preference for the terminal double bond was observed (Scheme 13).



Scheme 13.

In another example **34**, exclusive external oxidation in the synthesis of azasugar analogs was described by Blechert (Scheme 14), giving **35**. This selectivity may be the result of hydrogen bond chelation of the osmylating reagent with the free alcohol function present in the starting tetrahydropyridine.[24]

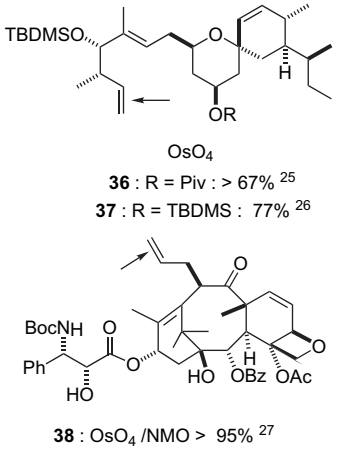


Scheme 14.

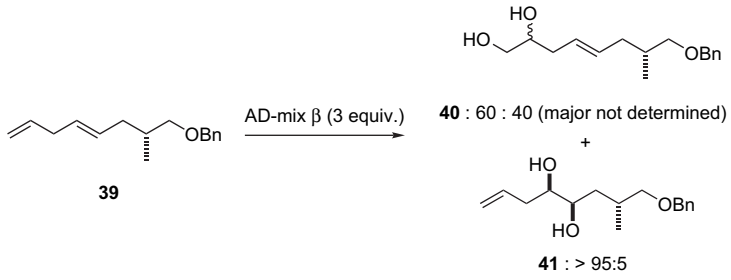
In the final three examples **36**–**38**, oxidation only occurs at the terminal alkene bonds, compared to both disubstituted cyclic alkenes and a trisubstituted alkene (Scheme 15).[25–27]

2.3.3. Chiral osmylation with AD-mix type reagents: terminal bond versus acyclic Z- or E-double bond

Forsyth observed good selectivity for the terminal alkene bond of **39** in the synthesis of substituted tetrahydrofurans.



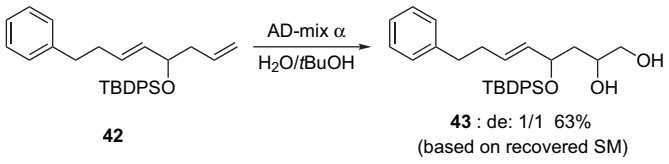
Scheme 15.



Scheme 16.

Only a relative ratio (for **40** and **41**) was given to indicate the regioselectivity of the reaction, with no change occurring when using $(DHQD)_2Pyr$ **4** or $(DHQD)_2AQN$ **6** (Scheme 16).[28]

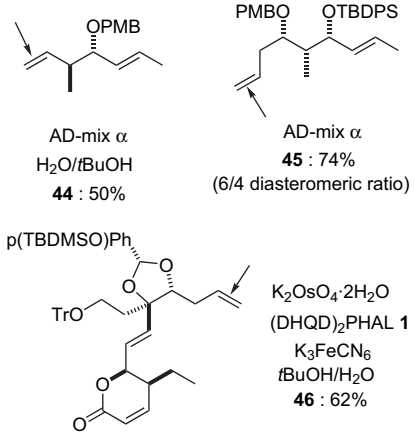
In a specific study of selective dihydroxylation of terminal olefins (**42**→**43**), a preference for the monosubstituted double bond was also observed. Andrus noted that, when the alcohol function is not protected with a TBDPS group, the internal disubstituted double bond is additionally oxidized (Scheme 17).[29]



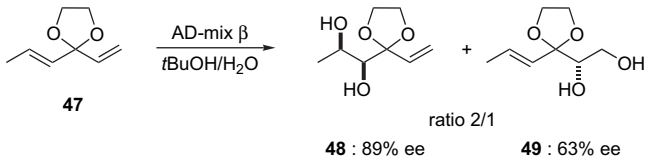
Scheme 17.

The three following examples **44**–**46**, described by Toshima in synthetic studies on concanamycin A,[30] by Williams in the total synthesis of (−)-ratjadone,[31] and by Fukuyama in the total synthesis of leustroducsin B,[32] showed the same selectivity for the terminal double bond (Scheme 18).

Based on the above examples, selectivity in osmylation seems to favor the terminal, less sterically hindered double bond. The very simple cases would not be selective but, unfortunately, the following case example (**47**→**48**+**49**) indicates that the reality is probably more complex to predict (Scheme 19).[5a]



Scheme 18.



Scheme 19.

2.3.4. Chiral osmylation with AD-mix type reagents: terminal double bond versus cyclic Z-double bond

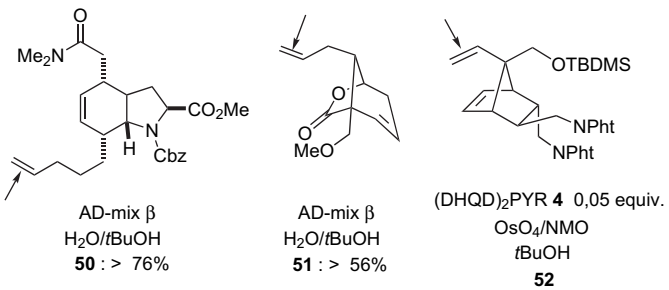
In general, osmylation of a terminal double bond is favored, as opposed to a cyclic disubstituted double bond. Three different examples **50**–**52** (with no indicated diastereoselectivity) have been described by Wipf in the total synthesis of (−)-stenine,[33] by Hart in the synthesis of analogs of the alkaloid, yohimbine,[34] and by Carreira in the enantioselective synthesis of the cyclopentyl core of axinellamin (Scheme 20).[35]

2.4. Monosubstituted alkenes versus trisubstituted alkenes

In this category, many examples were found in which the selectivity was in favor of the terminal double bond, as compared to the trisubstituted double bond (see Section 2.3.2, where three examples **36**–**38** have already been described[25–27]). In the majority of the reactions, the steric hindrance of the trisubstituted double bond is so large that osmylation is practically as difficult as in the extreme case of a tetrasubstituted double bond.

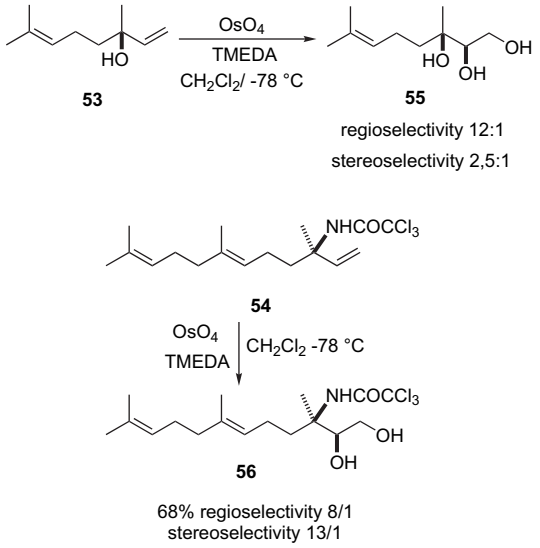
2.4.1. Achiral osmylation: terminal double bond versus acyclic Z- or E-double bond

The first two simplest cases **53** and **54** (giving, respectively, **55** and **56**) are probably controlled by a hydrogen bond



Scheme 20.

interaction between the OsO_4 reagent and an allylic alcohol or a trichloroacetimidate in the α-position, directing the dihydroxylation to the terminal double bond. Both of these examples are part of a general study initiated by Donohoe on the role of TMEDA in the osmylation process (Scheme 21).[36,37]

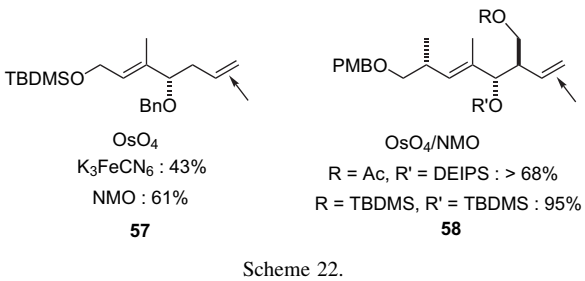


Scheme 21.

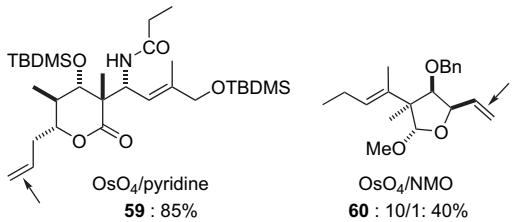
Hydrogen bonding is clearly not responsible for the selectivity in the following examples **57** and **58**, described by Leahy et al. in their synthetic studies on rhizoxin[38] and the closely related examples studied by Smith III and Taylor in their total synthesis of (+)-13-deoxytedanolide[39] and myriaporones (Scheme 22).[40]

The selectivity improves even more when the two double bonds are separated by a cyclic core (**59** and **60**) and when the system is trisubstituted with bulky groups (Scheme 23).[41,42]

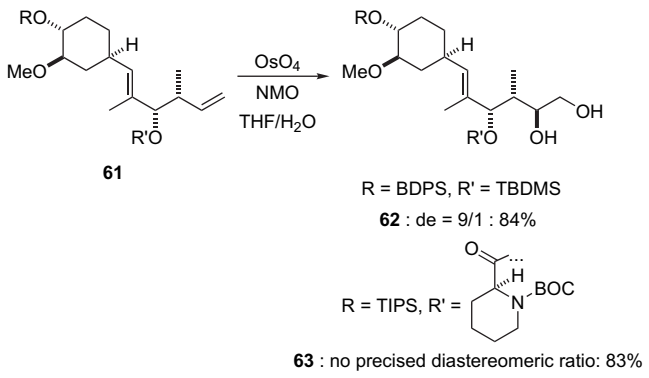
In the independent studies of Ireland on FK 506 and Furber on analogs of SBL 506, both authors observed similar regioselectivities (**61**→**62** and **63**), the reaction being completely selective in the second study (Scheme 24).[23,43]



Scheme 22.

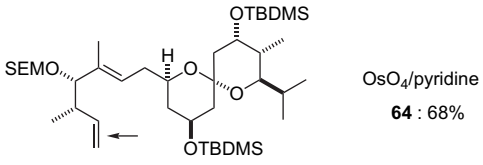


Scheme 23.



Scheme 24.

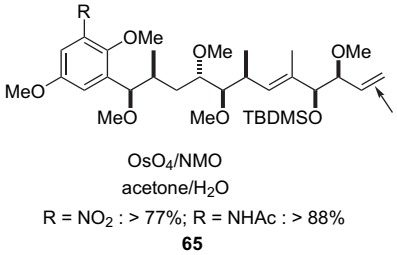
In work closely related to the studies published by Danishefsky and Ley,[25,26] Thomas oxidized only the terminal double bond in the synthesis of the aglycone **64** of avermectin A_{2b} (Scheme 25).[44]



Scheme 25.

The groups of Panek and Nakata chose selective side chain osmylation of **65** as a method to generate an aldehyde function in their approaches to the total synthesis of herbimycin A (Scheme 26).[45,46]

Finally, in more complex molecules (**66** and **67**), a terminal diol function was cleanly obtained by both Nicolaou in the total synthesis of rapamycin and Goulet in the synthesis of derivatives of the immunosuppressant, ascomycin (Scheme 27).[47,48]

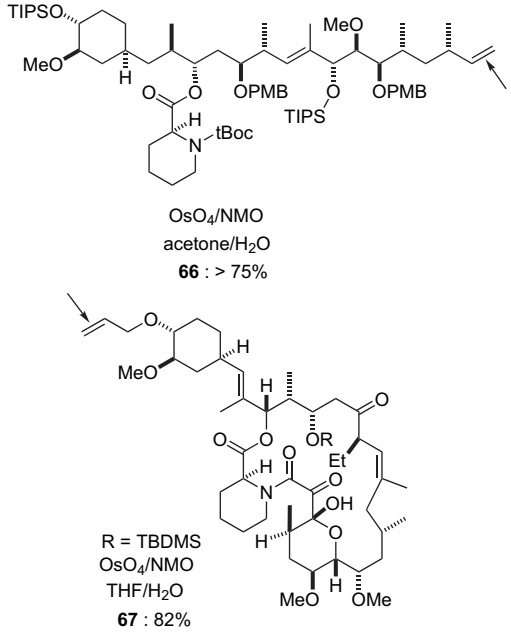


Scheme 26.

2.4.2. Achiral osmylation: terminal double bond versus cyclic double bond

The selective osmylation of an allyl terminal bond in the presence of a cyclic core is a very efficient procedure.

This was largely exemplified in the total synthesis of (+)-dihydrocodeinone and (+)- and (−)-morphine,[49] by Trost in



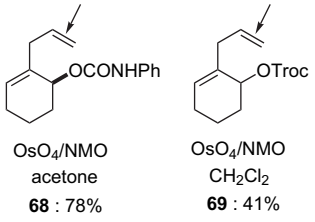
Scheme 27.

the enantioselective synthesis of (−)-galanthamine and (−)-morphine,[50] and in the formal total synthesis of aspidospermidine,[51] and the stereocontrolled synthesis of complex polycycles (e.g., **68**–**74** in Scheme 28 and Table 2).[52,53]

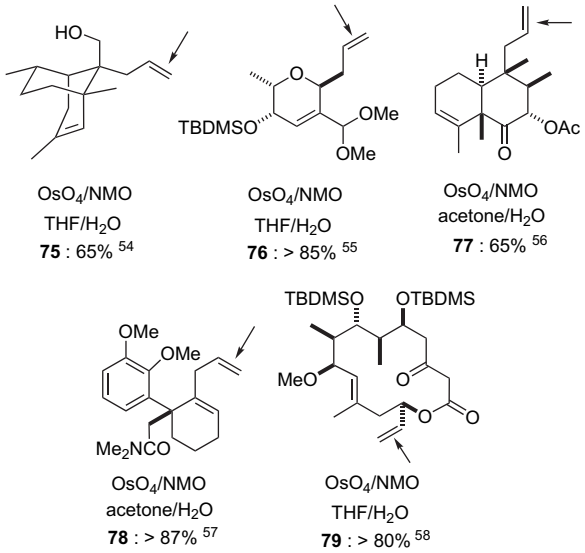
In more elaborate cyclic systems **75**–**79**, the selectivity for osmylation of the terminal double bond proves to be excellent, as illustrated in Scheme 29.[54–58]

The most complex examples are found in the taxoid-related compounds **80**–**83**, described by Soga in the synthesis of docetaxel analogs, where osmylation occurs preferentially at the external alkene function (Scheme 30 and Table 3).[27]

Selective osmylations have frequently been used for a variety of steroids **84**–**94** because a trisubstituted double bond is often encountered in the core skeleton typical of these of compounds (Scheme 31).[59–67]

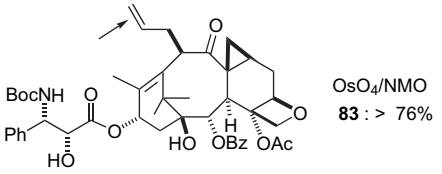


Scheme 28.



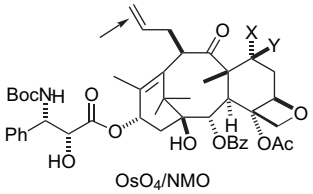
Scheme 29.

The use of different AD-type reagents with an achiral dialkene **95** has opened up the way to the creation of the enriched diol **96** with very good enantioselectivity, as illustrated by Sharpless (Scheme 32 and Table 4).[5b] Interestingly, a non-conventional reagent **97** has been used.



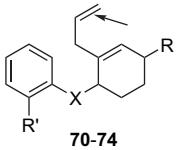
Scheme 30.

Table 3
Synthesis of docetaxel analogs

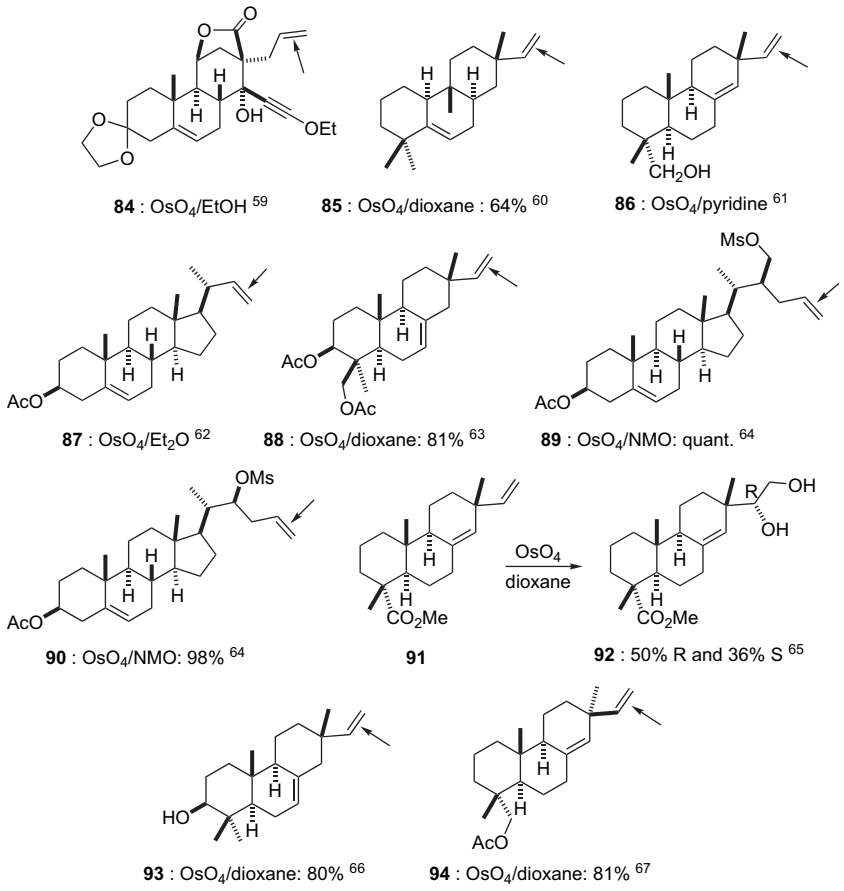
		X	Y	Yield (%)
	**80**	H	H	>63
	81	H	OCH_2F	>68
	82	F	H	>51

80-82

Table 2
Selective osmylation of an allyl terminal bond in the presence of a cyclic core

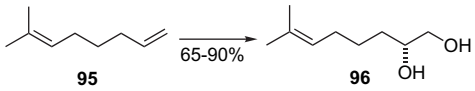
		70	**71**	**72**	**73**	**74**
	R	H	CHMeOMs	H	H	H
	R′	I	I	NO_2	NO_2	NO_2
	X	NMs	NMs	O	NSO_2Ph	NMs
	Yield (%)	58	78	99	72	62

70-74



Scheme 31.

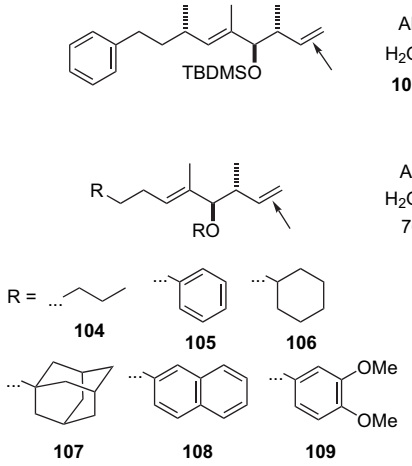
Table 4
A chiral diol from a simple di-alkene

	AD-type reagent	Configuration	ee (%)
	$(DHQD)_2PHAL$ **1**	**96** *R*	99
	$(DHQ)_2PHAL$ **2**	**96** *S*	95
	$(DHQD)_2AQN$ **6**	**96** *R*	99
	$(DHQ)_2AQN$ **97**	**96** *S*	96.5

Scheme 32.

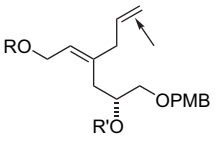
This principle was extended to more elaborated di-alkenes **98–109** (with no induction of diastereoselectivity), as in the synthesis of the C(1)–C(16) fragment of bryostatins,[68] in the total synthesis of stipiamide,[29,69] and in the synthesis of phenalamides.[70,71] In each instance, the neighboring alcohol was protected to avoid any hydrogen bond-assisted chelation, which could disturb the desired selectivity (Schemes 33–35 and Tables 5 and 6).

The last two examples **110** and **111** show that, even with more elaborate structures, such as those studied by Trivedi in the synthesis of potential pregnenolone and progesterone spin probes and by Roush in studies on the synthesis of kijanolide, the use of AD-type reagents permits a selective oxidation of the terminal double bond.[72,73] It should be noted that the example described by Roush is a rare case, where osmylation with OsO_4 'classical conditions' and the AD-reagent procedure were compared (Scheme 36).



Scheme 35.

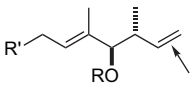
Table 5
Synthesis of the C(1)–C(16) fragment of bryostatins

		R	R′	Yield (%)
	**98**	TBDMS	TBDMS	70
AD-mix β H_2O/*n*BuOH	**99**	TBDPS	TMS	70

98-99

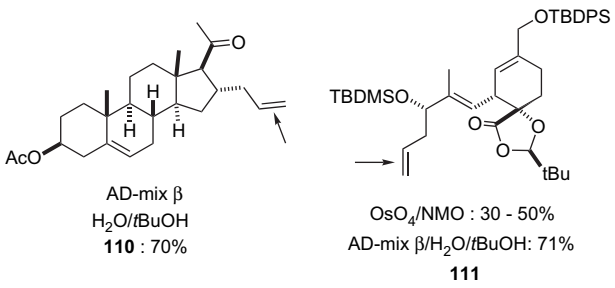
Scheme 33.

Table 6
A key step in the total synthesis of stipiamide

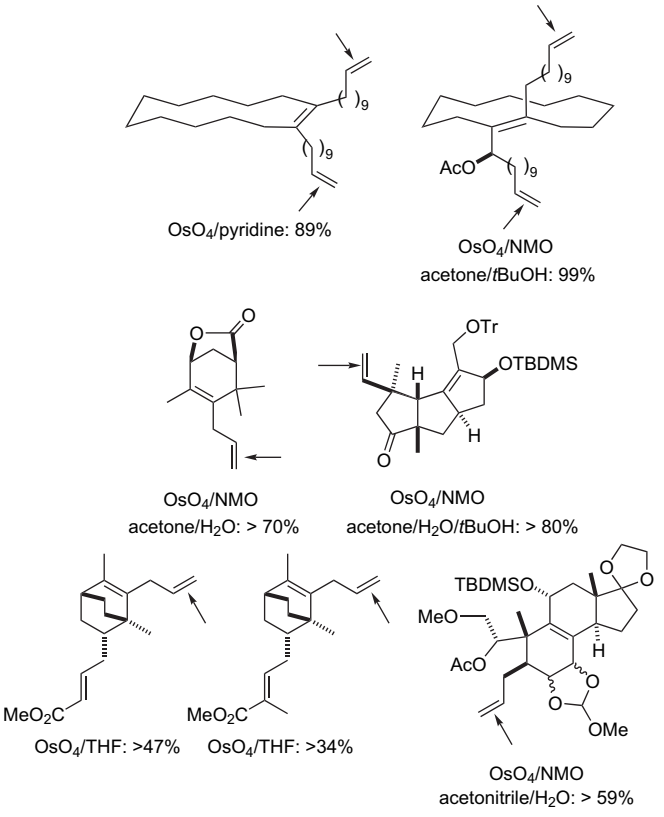
		R	R′	Yield (%)
	**100**	TBDMS	Ph	87 (15/1 regioselectivity)
AD-mix α H_2O/*t*BuOH	**101**	TBDPS	Ph	86
	102	TBDMS	Bn	61 (86% with AD-mix β)

100 - 102

Scheme 34.



Scheme 36.



Scheme 37.

2.5. Monosubstituted alkenes versus tetrasubstituted alkenes

When a compound contains a tetrasubstituted double bond, this moiety is so difficult to osmylate, due to its steric hindrance, only the terminal monosubstituted double bond is oxidized. This selectivity has been amply described by Marshall in the synthesis of betweenanenes,[74,75] by Winkler in the synthesis of a taxinine analog,[76] by Shibasaki in synthetic studies on capnellol and in the synthesis of wortmannin,[77,78] by Houk in work on the taxane skeleton,[79] and by Soga in the synthesis of taxoids from dihydrobaccatin (Schemes 37 and 38 and Table 7).[80]

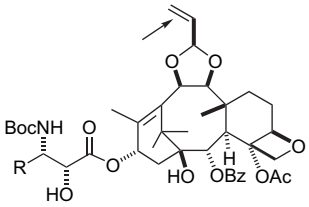
3. Osmylation of 1,1-disubstituted alkenes

There are only a few examples of osmylation of a 1,1-disubstituted alkene in the presence of other alkene bonds.

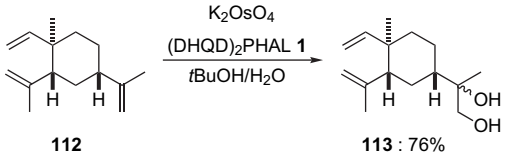
3.1. 1,1-Disubstituted alkenes versus 1,1-disubstituted alkenes

Only one example **112** was published by Corey in the enantioselective total syntheses of β-elemene and fuscol, allowing formation of **113**.[81] One of the two disubstituted double bonds is selectively oxidized, without touching the terminal one. It is interesting, however, to note the observed regioselectivity, presumably due to the steric hindrance of the left-hand part of the molecule (Scheme 39).

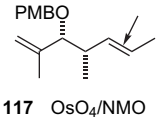
Table 7
Synthesis of taxoids from dihydrobaccatin

	R	2-Pyridyl	*t*-Bu	3-Fluoro-2-pyridyl	2-Thiazolyl	4-Thiazolyl	5-Thiazolyl
	Yield (%)	>82	>96	>78	>70	>88	>54

Scheme 38.



Scheme 39.



Scheme 41.

3.2. 1,1-Disubstituted alkenes versus 1,2-disubstituted alkenes

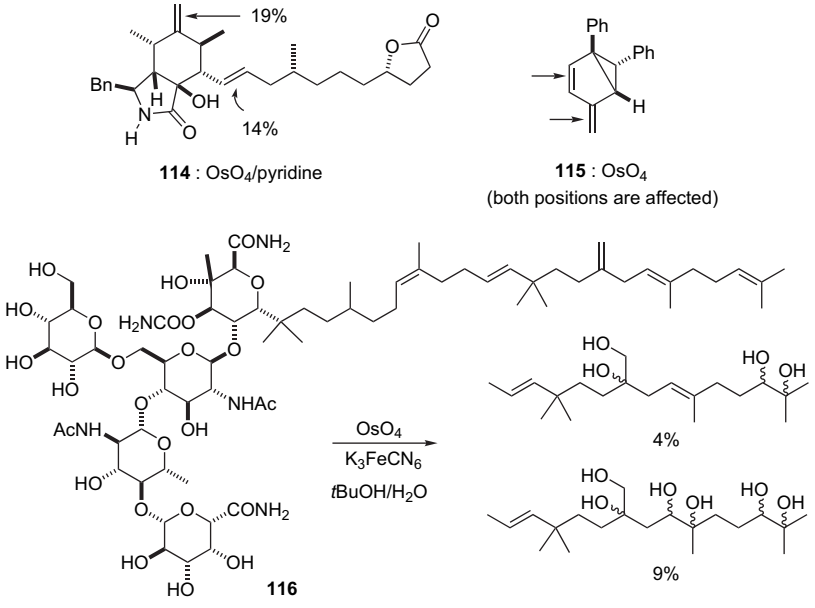
This type of transformation is very rare and, to the best of our knowledge, only three low-yielding examples **114–116** were described in the literature, by Zimmermann in the di-π-methane rearrangement, by Tamm in the synthesis of cytochalasin B, and by Welzel in a study of moenomycin A (Scheme 40).[82–84] In the last example, however, there is no selectivity data and the major product is highly osmylated.

In fact, only one example **117**, in which the 1,2-disubstituted alkene was osmylated preferentially, was published by Hoffmann and Stürmer in their work on the synthesis of erythronolide fragments, but the authors stated that their results were difficult to reproduce (Scheme 41).[85]

3.3. 1,1-Disubstituted alkenes versus trisubstituted alkenes

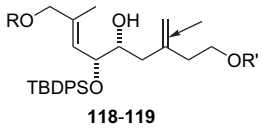
Two examples **118** and **119** with acyclic double bonds have been cited by Williams et al. in their synthetic studies toward phorboxazole A, where good selectivities for the 1,1-disubstituted double bond have been observed (Scheme 42 and Table 8). Interestingly, a free hydroxyl group is present in the studied molecules and the observed selectivity is probably due to the OTBDPS group, which sufficiently hinders the trisubstituted double bond.[86,87]

A particularly interesting example **120**, in which small amounts of a 1,1-disubstituted double bond were osmylated in the presence of a trisubstituted double bond, was published by Tadano in the total syntheses of (+)-cheimonophyllon E and (+)-cheimonophyllal (Scheme 43). It was observed that



Scheme 40.

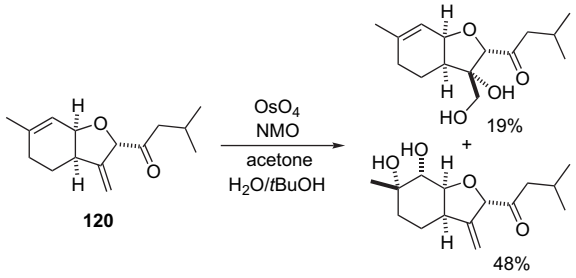
Table 8
Synthetic studies toward phorboxazole A

		R	R′	Yield (%)
				
	118	MOM	Piv	>80
	119	Piv	TBDMS	>95

118-119

Scheme 42.

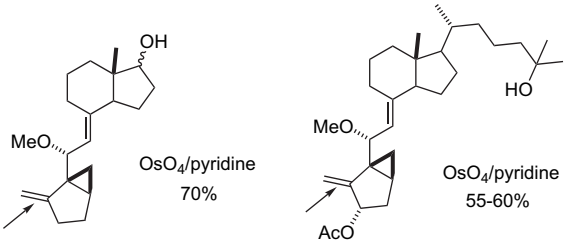
the trisubstituted double bond was oxidized. The stereoselectivity is difficult to explain, because the osmylation seems to occur on the same face as the isobutyl keto side chain. Very probably, the cis-ring junction is responsible for the preferential attack on the back face.[88]



120

Scheme 43.

Schnoes in the synthesis of 25-hydroxycholecalciferol[89] and DeLuca in an approach to the synthesis of derivatives of vitamin D_3 [90] have described analogous examples (Scheme 44).

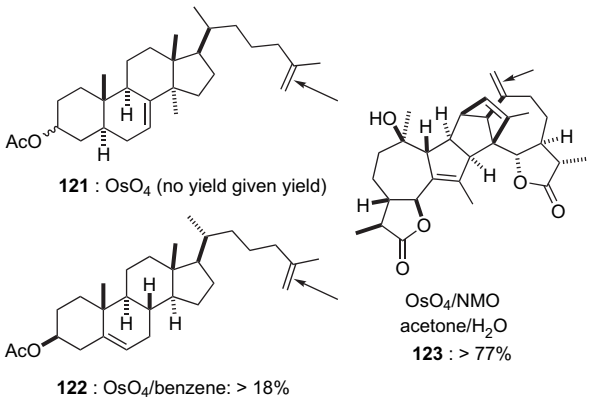


Scheme 44.

The last three examples **121**–**123**, in a polycyclic series, follow the same behavior, as shown by Dawson et al. in their work on sterols, by Makin in the synthesis of isotope-labeled vitamin D, and by Zhai in the total synthesis of absinthin (Scheme 45). It should be noted that, in the third example, a tetrasubstituted alkene bond also remained untouched.[91–93]

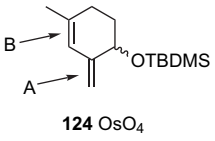
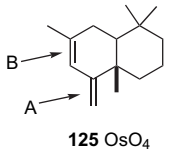
Two conjugated systems **124** and **125** have been studied by Clark in the taxol series and by Urones in the homochiral synthesis of polygodial and warburganal (Scheme 46 and Table 9). An acceptable regioselectivity in favor of the 1,1-disubstituted double bond was possible, but this was highly dependent on the experimental conditions.[94,95]

Only two examples **126** and **127** exist where AD-type reagents have been used to obtain good regioselectivity, as



Scheme 45.

Table 9
Osmylation of conjugated systems

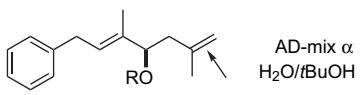
	Reaction conditions	Yield (%)	
		A	*B*
	**124**/*t*-BuOH/acetone/H_2O/NMO	44	19
	125/*t*-BuOH/THF/H_2O/NMO (0.23 mmol SM)	47	12
	125/*t*-BuOH/THF/H_2O/NMO (0.76 mmol SM)	31	29
	**125**/*t*-BuOH/Et_4NOH/*t*-BuOOH (0.34 mmol SM)	13	0
	125/Pyridine stoichiometric (0.14 mmol SM)	0	9

124 OsO_4

125 OsO_4

Scheme 46.

described by Andrus on the selective dihydroxylation of non-conjugated dienes[29] and Kobayashi in the synthesis of terpentecin (Scheme 47).[96] The nature of the protecting group is crucial, because the TBDPS group masks the internal double bond.



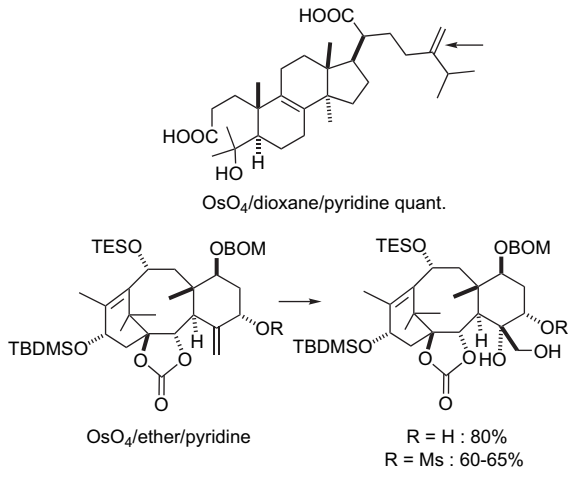
126 : R = TBDPS: 70% de: 1/1

127 : R = Ac: 30% regioselectivity 3/1

Scheme 47.

3.4. 1,1-Disubstituted alkenes versus tetrasubstituted alkenes

The reactions' studies essentially deal with polycyclic systems, with a steroid skeleton (eburicoic acid) or taxoid derivatives (taxol or azetidine-type taxanes), and the selectivities proved to be excellent (Schemes 48 and 49 and Table 10). This is not surprising, as tetrasubstituted alkene bonds are almost impossible to osmylate.[93,97–102]



Scheme 48.

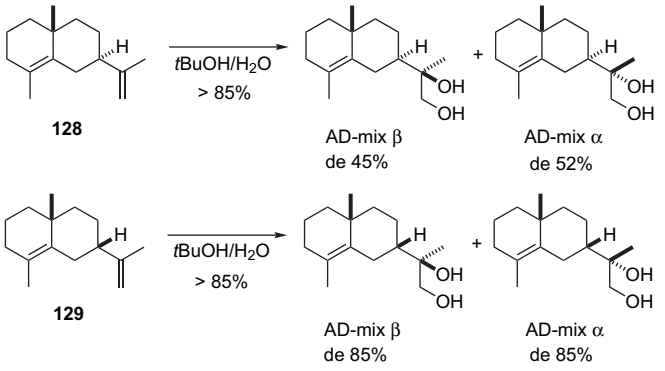
Applying AD-type reactions to this type of di-alkene compounds **128** and **129** gave excellent regioselectivity and modest-to-good diastereoselectivities, depending on the starting material, as described by Li in the enantioselective total synthesis of glutinone (Scheme 50).[103]

4. Osmylation of 1,2-disubstituted alkenes

1,2-Disubstituted alkenes are the source of several studies, with OsO_4 alone as well as with AD-type reactions.

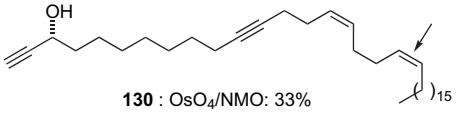
4.1. 1,2-Disubstituted alkenes versus 1,2-disubstituted alkenes

The first examples **130**–**133**, described with OsO_4 without any chiral additives, show that it is possible to osmylate *Z*- or *E*-double bonds, but with a general preference for



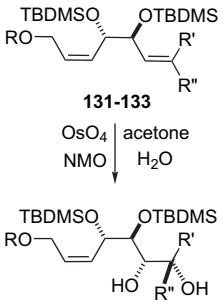
Scheme 50.

the *E*-double bonds, if the surrounding steric hindrance is equivalent. This was illustrated by Kobayashi in a study of lembehyne A[104] and by Saito and Moriwake in their work on differentiation in osmium tetroxide-catalyzed dihydroxylation (Schemes 51 and 52 and Table 11).[105]



Scheme 51.

Table 11

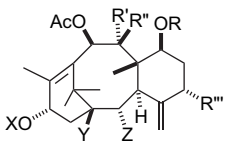


	R	R′	R″	Yield (%)
131	Ac	CH_2OAc	H	79
132	Bn	CH_2OBn	H	72
133	Ac	H	CH_2OAc	68 (regioselectivity 13/1)

Scheme 52.

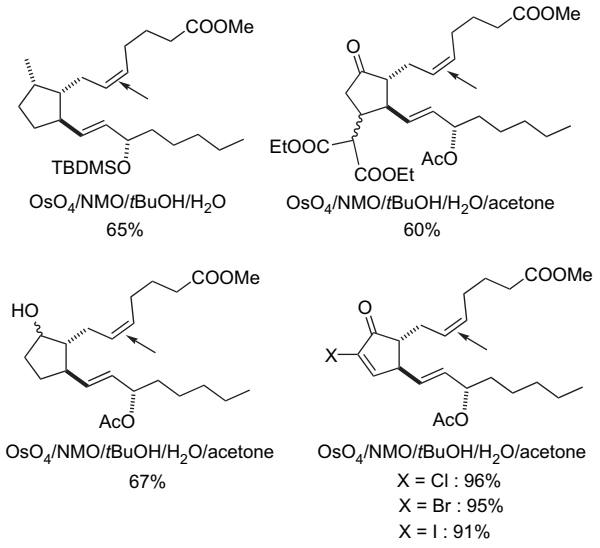
When the *E*-alkene is α-disubstituted, osmylation readily occurs on the most accessible *Z*-alkene bond, as shown by Dominguez in the synthesis of modified prostaglandins (Scheme 53).[106–108]

Table 10
Studies on taxoid derivatives



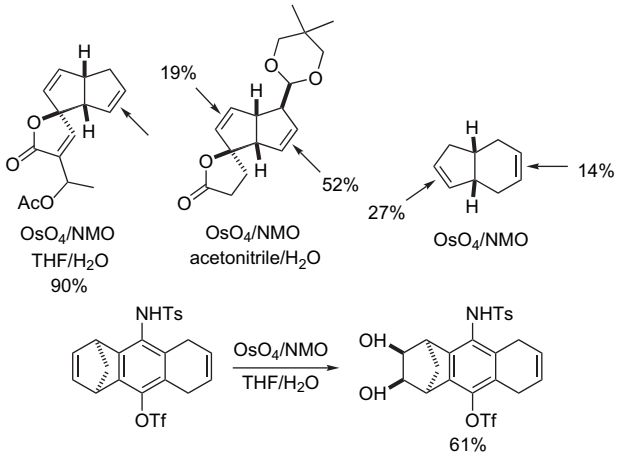
Scheme 49.

Reaction conditions	R	R′	R″	R‴	X	Y	Z	Yield (%)
OsO_4/THF/pyridine	TES	=O		Br	TES			96
OsO_4/NMO/acetone/H_2O	Ac	OAc	H	OH	Ac	H	H	94
OsO_4/THF/pyridine	Troc	=O		Br	TIPS	OH	OBz	76
OsO_4/Et_2O/pyridine	PMB	=O		Cl	TBDMS			86



Scheme 53.

In cyclic systems, it is possible to selectively oxidize one alkene if α-substitution is low, as studied by Trost in the total synthesis of plumericin, allamcin, and allamandin.[109] If there is a choice between a five- and a six-membered ring, the selectivity proves to be quite poor, as shown by Whitesell in the synthesis of diverse bicyclooctanes.[110] A constrained double bond was selectively oxidized in the total syntheses of herbindole B and *cis*-trikentrin B, where steric decompression after osmylation was the driving force of the reaction (Scheme 54).[111]



Scheme 54.

In the steroid family (brassinolides, ergosterol, and its derivatives, bruceantin), clean osmylation always occurs on the *Z*-alkene moiety, as shown in the following examples (Scheme 55).[112–118]

In the case of complex structures with many functional groups, it is possible to direct osmylation by effectively choosing bulky protecting groups, or by considering the α-substitution pattern. This strategy was used by Arseniyadis in the synthesis of an A-seco-taxoid subunit and by Ireland in an approach to the total synthesis of chlorothricolide (Scheme 56).[119–121]

AD-type reagents can nicely introduce asymmetry, as demonstrated by Sharpless first with achiral di-alkenes **134** (giving **135**), **136–140**, and with a further extension to chiral derivatives (Scheme 57 and Tables 12 and 13). In the cases where chiral centers are already present in the substrate, the overall observed induction can result from matched behavior (Scheme 58 and Table 14).[5a,122]

Sinha and Keinan studied the osmylation of two open chain di-alkenes **141** and **142** (giving, respectively, **143** and **144**) in their total syntheses of mucocin and uvaricin. The *E*-alkene is selectively oxidized in the presence of a *Z*-alkene and, sometimes, it is possible to touch only one *E*-alkene, even if the overall characteristics seem very similar (Scheme 59).[123,124]

In the brassinolide steroid family, Anastasia has described a double osmylation of an *E*- and *Z*-alkene, while leaving a *Z*-alkene unaffected (Scheme 60 and Table 15).[125]

Osmylation of a conjugated 1,2-disubstituted di-alkene **145** gave a vicinal triol as the major reaction product (Scheme 61).[34] This regioselectivity resulted from hydrogen bond-assisted oxidation.

AD-type osmylations have also proved to be very efficient in generating chiral compounds starting from simple conjugated di-alkenes **146** and **147**, with a preference for *E*-alkene bond systems, as shown by Sharpless (Scheme 62).[126]

Similar results have been described with more elaborate conjugated dienes. Examples in this area are numerous, by Sharpless with achiral di-alkenes and tertiary allylic alcohols, by Ariza and Garcia in the synthesis of (−)-methylenolactocin, by Kumar in the synthesis of posticlure, by Corey in polyol syntheses, and by Stephenson in the preparation of enantiopure tricarbonyliron complexes. Interestingly, the presence of a free hydroxy group did not disturb the selectivity in favor of the most accessible alkene function (Schemes 63–65, Tables 16 and 17).[122,127–131]

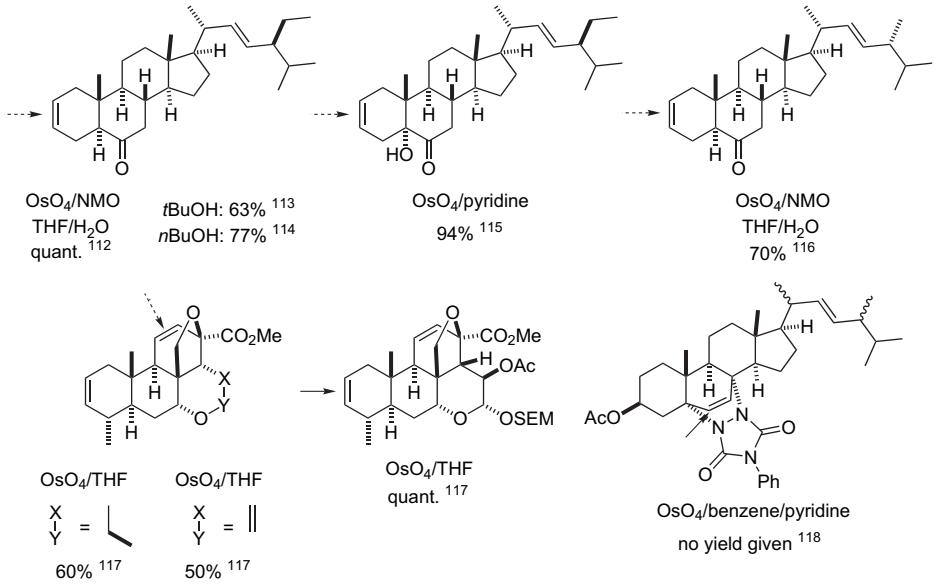
With sensitive functions like an epoxide and a brosylate, in the synthesis of isofurans published by Taber, a small selectivity for the more accessible alkene can be observed (Scheme 66).[132]

When asymmetric dihydroxylation conditions are applied to symmetrical cyclic conjugated di-alkenes **148–154**, interesting chiral structures are formed (Table 18, Scheme 67).[133]

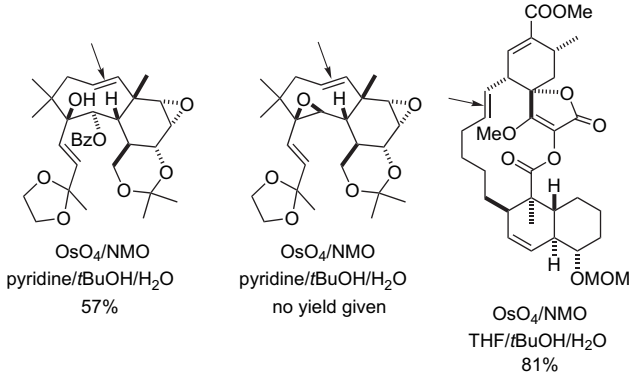
4.2. 1,2-Disubstituted alkenes versus trisubstituted alkenes

4.2.1. Unconjugated achiral osmylation

Selective osmylation of an acyclic 1,2-disubstituted alkene in the presence of a trisubstituted alkene proved to be efficient with simple OsO_4 treatment. This was illustrated by Welzel et al. in their study on moenomycin A,[84] by Panek in the total synthesis of (+)-macbecin I[134] and by Mincione and Bovicelli in their work on vitamin D_2 (Scheme 68).[135]



Scheme 55.



Scheme 56.

Several examples have been described with cyclic steroid compounds, where a good regioselectivity was achieved with non-chiral reagents (Schemes 69–71 and Table 19).[136–139]

4.2.2. Unconjugated chiral osmylation

The selective osmylation of an allyl terminal bond in the presence of a cyclic core is a very efficient procedure.

The use of AD-type reagents improves the observed selectivities. As an example, in the synthesis of fumagillol,[140] AD-mix α was chosen, because it normally prefers to osmylate the rear face of the trisubstituted alkene bond (and thus the most electron-rich). It was thus planned that a mismatch effect would leave unchanged the side chain trisubstituted alkene, considering that, in the model proposed by Sharpless, the very bulky α-quaternary carbon occupied a non-favorable pocket (Scheme 72). As a consequence, access to this alkene was forbidden, and AD-mix α preferred the 1,2-disubstituted cyclic alkene (AD-mix β prefers the top face of the trisubstituted alkene).

An extensive study was published by Hoffmann et al. in the course of their synthesis of bryostatin C-ring. The use of several AD-type reagents with different starting materials gave a large library of results (Schemes 73–76 and Tables 20–23).[141]

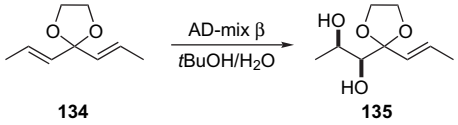
4.2.3. Conjugated achiral osmylation

Two last examples **155** and **156** with more complex structures and conjugated double bonds were described by Kuo in the transformation of mevinolin and by Edmunds in a study on herboxidiene (Scheme 77).[142,143] In each case, osmylation favored the disubstituted double bond.

4.2.4. Conjugated chiral osmylation

In their approaches toward a total synthesis of the immunosuppressant, sanglifehrin A, Metternich, Sedrani, and Wagner

Table 12
Asymmetric dihydroxylation of a simple di-alkene

	AD-type reagent	(DHQD)$_2$PYR **4**	(DHQD)$_2$PHAL **1**
 **134** → **135**	ee	72%	93%

Scheme 57.

Table 13
Asymmetric dihydroxylation of cyclic di-alkenes

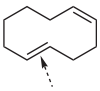
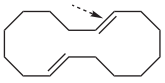
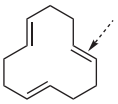
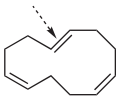
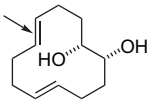
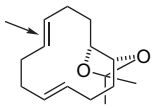
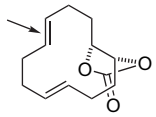
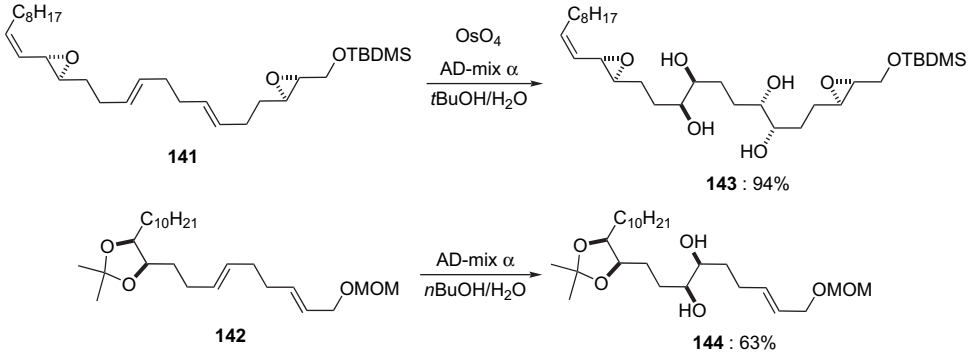
AD-type reagent	$(DHQD)_2PYR$ **4** (ee, %)	$(DHQD)_2PHAL$ **1** (ee, %)	AD-type reagent	$(DHQD)_2PYR$ **4** (ee, %)	$(DHQD)_2PHAL$ **1** (ee, %)
 **136**	94	51	 **137**	92	50
 **138**	95	65	 **139**	89	22
 **140**	88	69			

Table 14
Asymmetric dihydroxylation of cyclic chiral di-alkenes

	AD-type reagent de (yield)	$(DHQD)_2PYR$ **4** 50% (65%)	$(DHQ)_2PYR$ 99.4% (72%); inversed diastereoselectivity	Quinuclidine 94% (61%), inversed diastereoselectivity
	AD-type reagent de (yield)	$(DHQD)_2PYR$ **4** 78% (81%)	$(DHQ)_2PYR$ 98% (85%), inversed diastereoselectivity	Quinuclidine 78% (80%), inversed diastereoselectivity
	AD-type reagent de (yield)	$(DHQD)_2PYR$ **4** 91% (80%)	$(DHQ)_2PYR$ 98% (85%), inversed diastereoselectivity	Quinuclidine 48% (87%), inversed diastereoselectivity

Scheme 58.



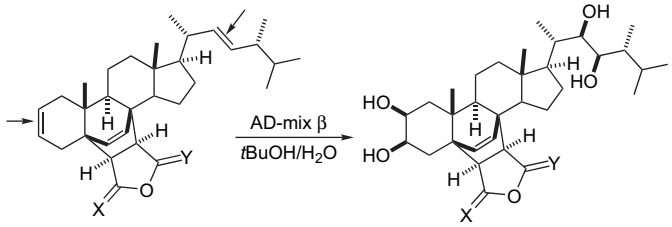
Scheme 59.

selectively osmylated only one of the four possible alkene bonds (Scheme 78).[144,145] No explanation was given, but it seems that the steric environment of the oxidized alkene played a major role.

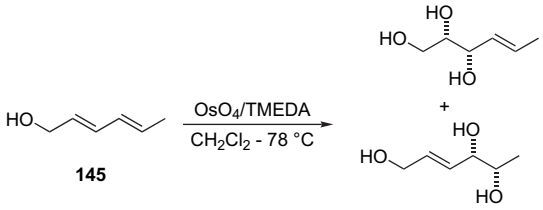
When the disubstituted alkene is cyclic, regio- and stereoselective osmylations produce quite low yields, even with bulky side chains (Schemes 79–81 and Tables 24–26).[132,146]

Excellent regioselectivity was obtained in the synthesis of a quartromicin subunit **157**, where osmylation occurred only at the disubstituted acyclic side chain (Scheme 82).[147]

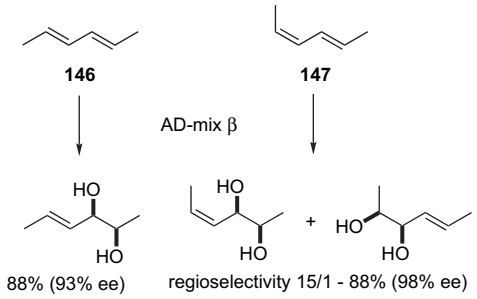
Table 15
Asymmetric dihydroxylation in the brassinolide steroid family

	X	Y	Yield (%)
	H_2	O	78
	O	H_2	76

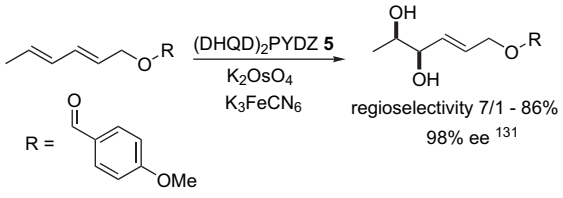
Scheme 60.



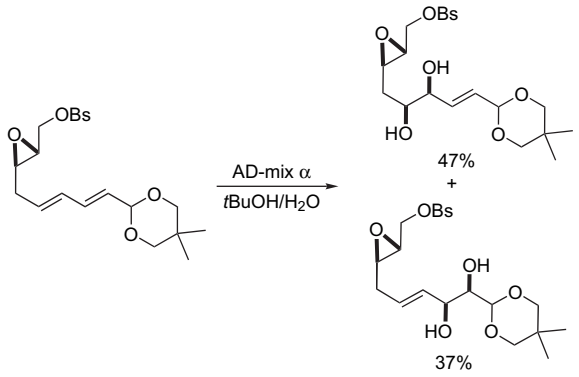
Scheme 61.



Scheme 62.

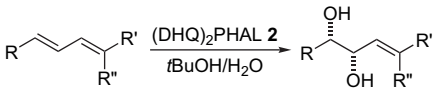


Scheme 65.



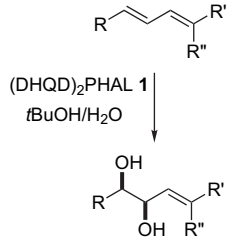
Scheme 66.

Table 16
Asymmetric dihydroxylation of conjugated dienes (**1**)

	R	R′	R″	Yield (%)	ee (%)
	*n*-Pn	*n*-Pn	H	45	100[127]
	n-C_9H_{19}	H		78	100[128]

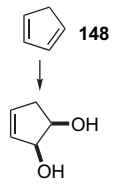
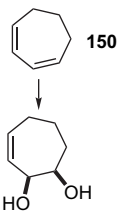
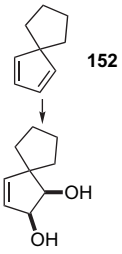
Scheme 63.

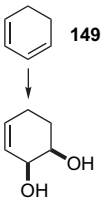
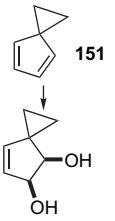
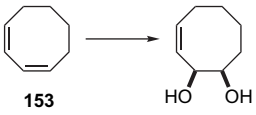
Table 17
Asymmetric dihydroxylation of conjugated dienes (**2**)

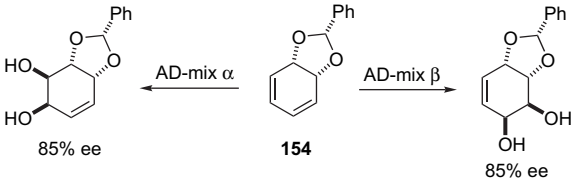
	R	R′	R″	Yield (%)	ee (%)	
	n-C_9H_{19}	H		79	100[128]	
	Me	CMe_2OH	H	74	93[129]	
	Me	CH_2OBz	H	91	>98[122,130]	regio 17/1; minor: 91% ee
	Me	$(CH_2)_7OAc$	H	82	95[122]	regio 2/1; minor: 94% ee

Scheme 64.

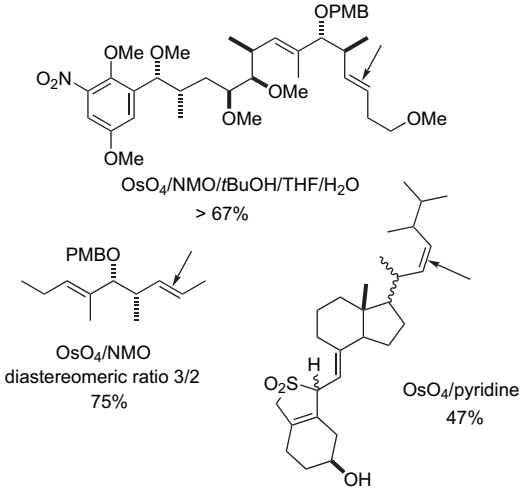
Table 18
Asymmetric dihydroxylation of symmetrical cyclic conjugated di-alkenes

	AD-type reagent	Yield (%)	ee (%)
 **148**			
	$(DHQD)_2PHAL$ **1**	37	38
	$(DHQD)_2Pyr$ **4**	15	7
	DHQDIND	39	29
 **150**			
	AD-type reagent	Yield	ee
	$(DHQD)_2PHAL$ **1**	37	30
	$(DHQD)_2Pyr$ **4**	37	21
	DHQDIND	28	1
 **152**			
	AD-type reagent	Yield	ee
	$(DHQD)_2PHAL$ **1**	71	70
	$(DHQD)_2Pyr$ **4**	Not given	70
	DHQDIND	Not given	73

	AD-type reagent	Yield (%)	ee (%)
 **149**			
	$(DHQD)_2PHAL$ **1**	97	37
	$(DHQD)_2Pyr$ **4**	88	23
	DHQDIND	82	24
 **151**			
	AD-type reagent	Yield	ee
	$(DHQD)_2PHAL$ **1**	38	53
	$(DHQD)_2Pyr$ **4**	34	55
	DHQDIND	36	50
 **153**			
$(DHQD)_2PHAL$ **1** : 5% ee - 29%			

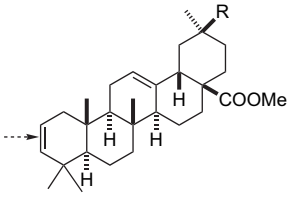


Scheme 67.

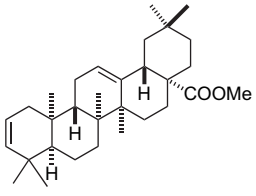


Scheme 68.

Table 19
Osmylation of steroid compounds

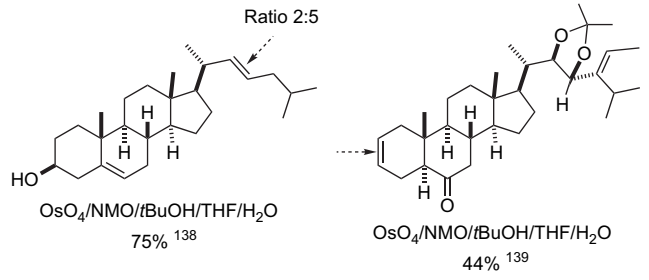
	Reaction conditions[136]	R	Yield in diol α (%)	Yield in diol β (%)
	OsO_4/dioxane	CH_3	37	7
	OsO_4/dioxane	COOMe	Not given	Not given

Scheme 69.

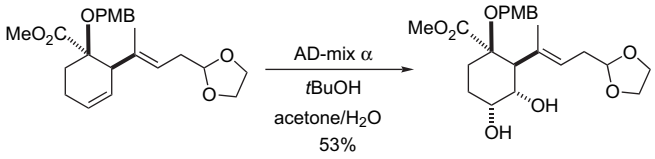


OsO_4/benzene 96% [137]

Scheme 70.



Scheme 71.



Scheme 72.

4.3. 1,2-Disubstituted alkenes versus tetrasubstituted alkenes

It is not surprising to find that the regioselectivities in these cases are excellent, because tetrasubstituted alkenes are very difficult to osmylate under any conditions, as previously mentioned. Except for the first example described by Mincione and Bovicelli in their work on vitamin D_2 (see Section 4.2), all studies concern taxoid-type compounds (taxol and paclitaxel analogs, Schemes 83–85 and Table 27).[134,148–152]

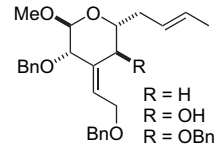
5. Osmylation of trisubstituted alkenes

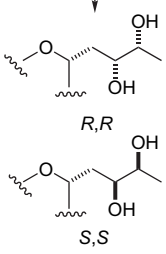
5.1. Trisubstituted alkenes versus trisubstituted alkenes

5.1.1. Achiral osmylation

Most of the examples in this area have been published in the geranyl, farnesyl, squalene, and steroid families (Schemes 86 and 87, Tables 28 and 29). When OsO_4 is used alone with-

Table 20
Asymmetric dihydroxylation in the course of the synthesis of bryostatin C-ring (**1**)

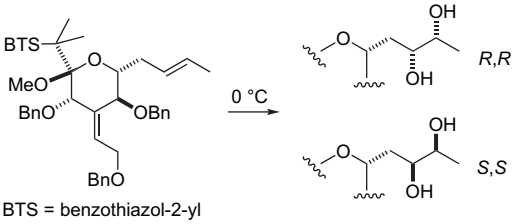
	AD-type reagent	R	*T* (°C)	Ratio *R*,*R*/*S*,*S*	Yield (%)	R	Ratio *R*,*R*/*S*,*S*	Yield (%)	R	Ratio *R*,*R*/*S*,*S*	Yield (%)
											
	OsO_4, NMO; *t*-BuOH, THF, H_2O	H	20	1.3:1	73				OBn	1.2:1	99
	$(DHQD)_2PHAL$ **1**	H	20	2.7:1	70						
	$(DHQD)_2PHAL$ **1**	H	0	3.7:1	64				OBn	3.0:1	75
	DHQDCLB **3**	H	0	2.7:1	80						
	$(DHQD)_2AQN$ **6**	H	0	5.2:1	79	OH	7.8:1	99	OBn	15:1	90
	$(DHQD)_2PYR$ **4** 10%	H	0	8.0:1	77	OH	8.4:1	99	OBn	4.5:1	88
	$(DHQD)_2PYR$ **4** 50%	H	0	8.1:1	97						
	$(DHQD)_2PYR$ **4** 10%; OsO_4 0.01 equiv.	H	0	11.5:1	99						



Scheme 73.

Table 21
Asymmetric dihydroxylation in the course of the synthesis of bryostatin C-ring (**2**)

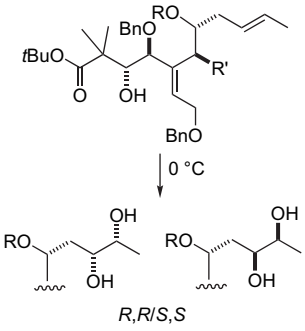
AD-type reagent	Ratio *R*,*R*/*S*,*S*	Yield (%)
$(DHQD)_2PHAL$ **1**	2.1:1	98
DHQDCLB **3**	3.2:1	97
$(DHQD)_2AQN$ **6**	7.2:1	90
$(DHQD)_2PYR$ **4**	3.1:1	89



Scheme 74.

Table 22
Asymmetric dihydroxylation in the course of the synthesis of bryostatin C-ring (**3**)

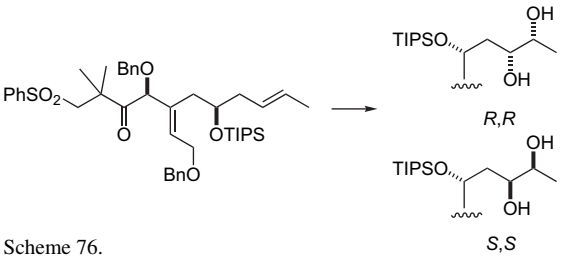
AD-type reagent	R=H; R′=H	R=H; R′=OBn	R=TBDMS; R′=H	R=TIPS; R′=H
$(DHQD)_2PHAL$ **1**	2.7:1 (85%)			
DHQDCLB **3**	2.6:1 (87%)			2.3:1 (96%)
$(DHQD)_2AQN$ **6**	2.9:1 (87%)	10:1 (91%)		
$(DHQD)_2PYR$ **4**	4.9:1 (97%)	3.4:1 (57%)	1.6:1 (81%)	1.3:1 (99%)



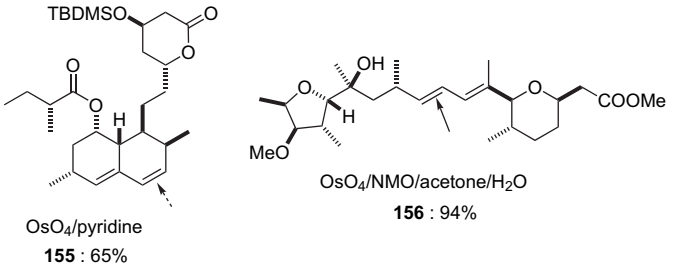
Scheme 75. Ratio *R,R/S,S* (Yield)

Table 23
Asymmetric dihydroxylation in the course of the synthesis of bryostatin C-ring (**4**)

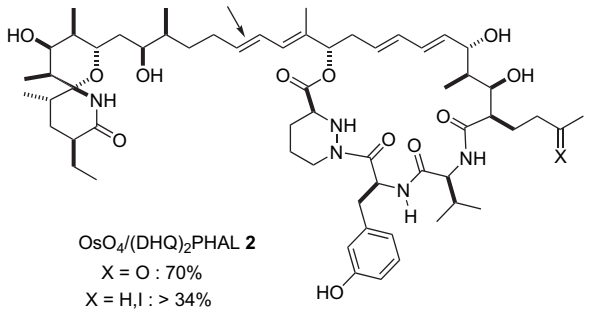
AD-type reagent	*T* (°C)	Ratio *R,R/S,S*	Yield (%)
OsO_4, NMO; *t*-BuOH, THF, H_2O	20	1.1:1	86
$(DHQD)_2PHAL$ **1**	0	1.9:1	92
DHQDCLB **3** 10%	0	2.2:1	74
DHQDCLB **3** 20%	0	2.7:1	97
$(DHQD)_2PYR$ **4**	0	1.4:1	83



Scheme 76.



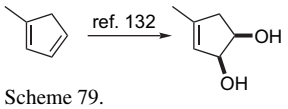
Scheme 77.



Scheme 78.

Table 24
Asymmetric dihydroxylation of cyclic conjugated dienes (**1**)

AD-type reagent	Yield (%)	ee (%)
$(DHQD)_2PHAL$ **1**	14	56
$(DHQD)_2PYR$ **4**	10	8
DHQDIND	8	31



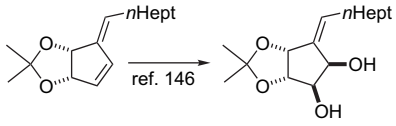
Scheme 79.

out any specific additive, a good regioselectivity in geranyl derivatives is observed. It is interesting to note that, in the last two examples, hydrogen bond-assisted osmylation gave a special induction to the alkene bond closest to the hydroxy group.[36,153–155]

In the farnesyl series (Scheme 88), regioselectivities were observed and, once again, a hydroxy function directed the osmylation to a specific trisubstituted proximal alkene (even if a monosubstituted alkene remained untouched).[156–158]

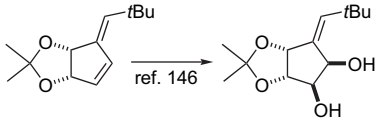
In an approach to the synthesis of (−)-chettaphanins, *ent*-halimic acid, and *ent*-cladocorans, Marcos reported a good regioselectivity with oxidation of the most accessible alkene function (Scheme 89 and Table 30).[159,160] The nature of the R′ group, adding a chelating effect, presumably directs the osmylation on the same alkene.

Table 25
Asymmetric dihydroxylation of cyclic conjugated dienes (**2**)

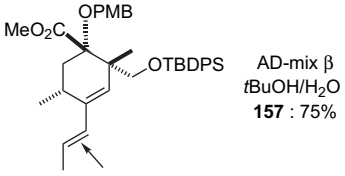
	Reaction conditions	Yield (%)	Regioselectivity (%)	de (%)
	K_3FeCN_6/*t*-BuOH/H_2O; $K_2Os(OH)_4$, quinuclidine	67	48–52	
	OsO_4/$(DHQ)_2PHAL$ **2**	Not given	55–45	78
	OsO_4/$(DHQD)_2PHAL$ **1**	Not given	55–45	78

Scheme 80.

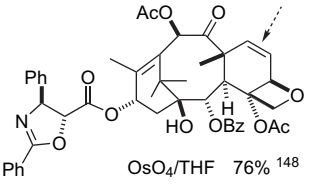
Table 26
Asymmetric dihydroxylation of cyclic conjugated dienes (**3**)

	Reaction conditions	Yield (%)	Regioselectivity (%)	de (%)
	K_3FeCN_6/*t*-BuOH/H_2O; $K_2Os(OH)_4$, quinuclidine	78	55–45	84

Scheme 81.

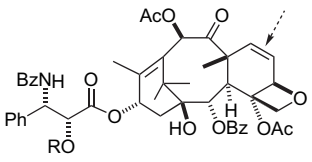


Scheme 82.



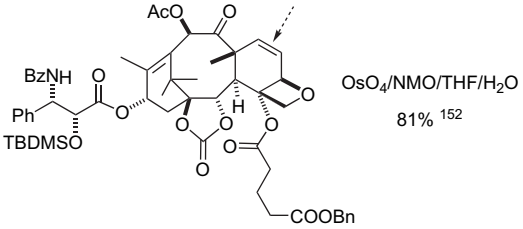
Scheme 83.

Table 27
Osmylation of taxoid-type compounds

	Reaction conditions	R	Yield (%)
	OsO_4/NMO	H	71[149]
	OsO_4/THF	TBDMS	46[148]
	OsO_4/pyridine/THF	TBDMS	85[150]
	OsO_4/NMO/acetone/H_2O	TES	75[151]

Scheme 84.

Lastly, many examples have been studied in the steroid family (16α-hydroxyhydrocortisone, epoxy- and dehydrocholesterols, saponin, OSW-1), often with a good diastereoselectivity for the rear face, as illustrated in Schemes 90–94 and Tables 31–33).[161–167]



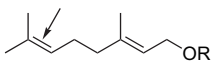
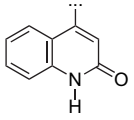
Scheme 85.

5.1.2. Chiral osmylation

With AD-type reagents, three simple compounds **158–160** have shown efficient regio- and/or enantioselectivities, as shown by Sharpless and Krief (Scheme 95).[5a,120,168]

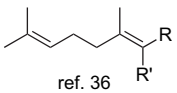
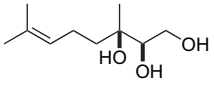
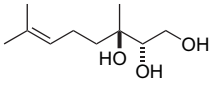
Chiral osmylation of geranyl or farnesyl derivatives, squalene, and steroids offers convenient and non-expensive access to various interesting chiral diols.

Table 28
Osmylation of geranyl derivatives (**1**)

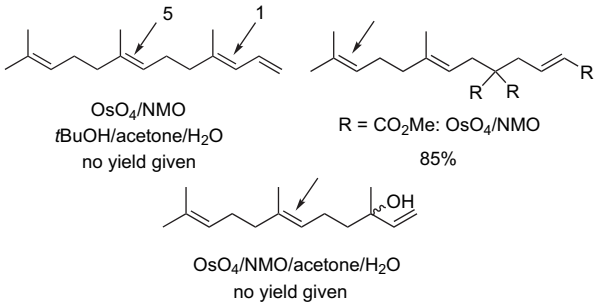
	Reaction conditions	R	Yield (%)
	OsO_4/NMO; *t*-BuOH/acetone/H_2O	Ac	97[153]
	OsO_4	TBDMS	31[154]
	OsO_4; pyridine/Et_2O		45[155]

Scheme 86.

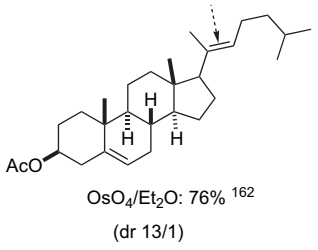
Table 29
Osmylation of geranyl derivatives (2)

	Reaction; conditions	R	R′	Major product (racemic mixture)	Yield (%)	Dr
 ref. 36	OsO_4/TMEDA; CH_2Cl_2, −78 °C	CH_2OH	H		74	>25:1
	OsO_4/TMEDA; CH_2Cl_2, −78 °C	H	CH_2OH		68	4:1

Scheme 87.



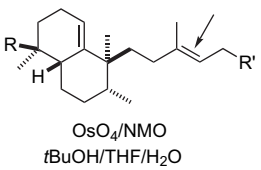
Scheme 88.



Scheme 91.

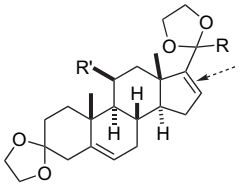
- Geranyl compounds (Schemes 96–100 and Tables 34–37).[5f,169–176]
- Farnesyl compounds (Schemes 101–103 and Tables 38 and 39).[5e,5f,177–183]
- Higher isoprenoids and squalene compounds (Schemes 104–106 and Tables 40 and 41).[5e,5f,184]

Table 30
Selective osmylation on a side chain versus endocyclic alkene

	R	R′	Yield (%)
 OsO_4/NMO $tBuOH/THF/H_2O$	CO_2Me	OH	99
	CH_2OH	OMe	99
	CH_2OH	OH	97

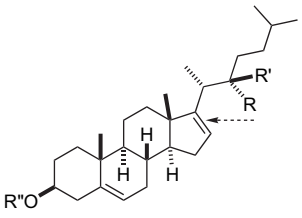
Scheme 89.

Table 31
Osmylation on steroid derivatives (**1**)

	R	R′	Yield (%)
 OsO_4 pyridine/benzene [161]	Me	H	45
	CH_2OAc	H	65
	CH_2OH	OH	44

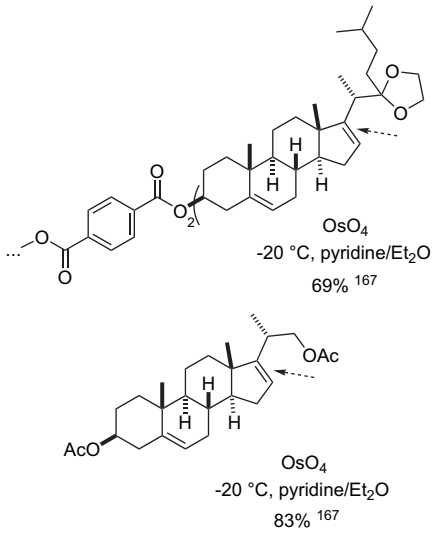
Scheme 90.

Table 32
Osmylation on steroid derivatives (**2**)



Scheme 92.

Reaction conditions	*T* (°C)	R	R′	R″	Yield (%)
OsO_4/pyridine/Et_2O	−50	OH	H	OAc	90[163]
OsO_4/pyridine/Et_2O	−50	OPMB	H	OAc	80 (10 on the other bond)[163]
OsO_4/pyridine/Et_2O	−40	OTMS	H	OAc	50[163]
OsO_4/pyridine/Et_2O	−40	O		OAc	40[163]
OsO_4/pyridine/Et_2O	−30	OCH_2CH_2O		OAc	81 (10 on the other bond)[163]
OsO_4/pyridine/Et_2O	−20	OCH_2CH_2O		OTBDMS	41[64]
OsO_4/pyridine/Et_2O	−78	OCH_2CH_2O		OAc	57[165]
OsO_4/pyridine/THF	−35	H	H	OTBDMS	51[166]
OsO_4/pyridine/THF	−35	OTBDMS	H	OTBDMS	78[166]



Scheme 93.

Table 35
Osmylation of geranyl compounds (**2**)

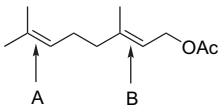
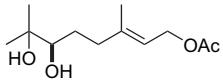
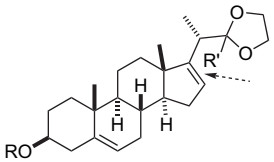
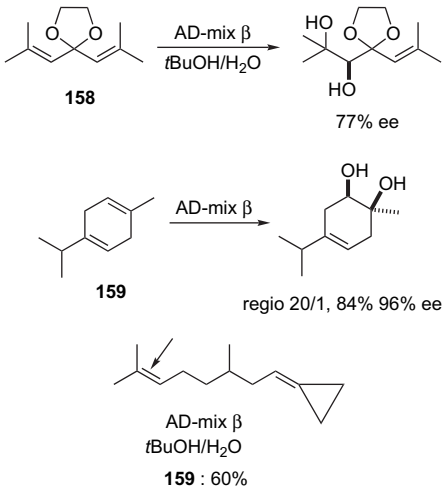
	Reaction conditions	*T* (°C)	*A*/*B*	ee (%)	Yield (%)
	Cat. OsO_4/K_3FeCN_6		>99:1		Not given[169]
	OsO_4/THF/Pyridine/*t*-BuOH/H_2O		5:1		57[170]
	AD-mix β; *t*-BuOH/H_2O	0	95.5:4.5	92–98	80–82[170,171]
	AD-mix α; *t*-BuOH/H_2O	0	92.5:7.5	90 (inversed config.)	78[170]
Scheme 97.	PYDZ K_2OsO_4; *t*-BuOH/H_2O	0	100:0	>95	70–76[172,173]

Table 33
Osmylation on steroid derivatives (**3**)

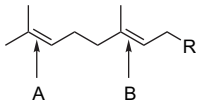
	Reaction conditions	*T* (°C)	R	R′	Yield (%)
	OsO_4/pyridine/Et_2O	−20	TBDMS	H	83[165]
	OsO_4/pyridine/THF	−40	TBDMS	Me	38[165]
	OsO_4/pyridine/THF	−40	TBDMS	*n*-Pr	34[167]

Scheme 94.



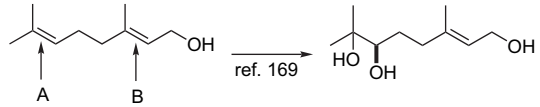
Scheme 95.

Table 36
Osmylation of geranyl compounds (**3**)

	Reaction conditions	R	*A*/*B*
	Cat. OsO_4/K_3FeCN_6	OMe	>98:2
	Stoich. OsO_4	OMe	>98:2
	Stoich. OsO_4	NHMs	67:33
ref. 171	Stoich. OsO_4	NHTs	60:40
	Stoich. OsO_4	NHNs	60:40

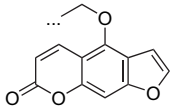
Scheme 98.

Table 34
Osmylation of geranyl compounds (**1**)

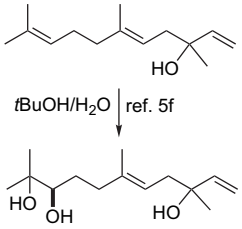
	Reaction conditions	*A*/*B*	ee (%)	Yield (%)
	Cat. OsO_4/K_3FeCN_6	80:20		Not given
	OsO_4 1 equiv 5% quinuclidine	90:10		Not given
	$(DHQD)_2PHAL$ **1**	>98:2	94	89

Scheme 96.

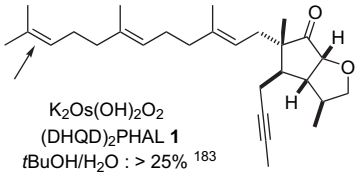
Table 37
Osmylation of geranyl compounds (**4**)

Reaction conditions	R	R′	Yield (%)	ee (%)
AD-mix α; *t*-BuOH/H_2O	$CH_2OCONHPh$	H	Not given	100[174]
AD-mix β; *t*-BuOH/H_2O	$CH_2OCONHPh$	H	Not given	100% (inversed config.)[174]
AD-mix α	H	CH_2OAc	92	92[170]
AD-mix β	H	CH_2OAc	94	97 (inversed config.)[170]
$(DHQ)_2PHAL$ **2**	$CH_2COOtBu$	H	61	97[175]
$(DHQ)_2PHAL$ **2**		H	46	86[176]

Scheme 99.



Scheme 100.



Scheme 103.

Table 38
Osmylation of farnesyl compounds (**1**)

Reaction conditions	*A*/*B*	Yield (%)	ee (%)
AD-mix β	2.2		93[170,177,178]
AD-mix α	Not given	Not given	Inversed config.[170]
NOE-Lin cat. **7**	120	54	96[5e]
K_2OsO_4 NOE-Lin cat. **7** *t*-BuOH/H_2O	Only A	65	96[5e,179]
New cat. **8** *t*-BuOH/H_2O	Only A	72	97[5f]

Scheme 101.

Table 39
Osmylation of farnesyl compounds (**2**)

Reaction conditions	R	R′	Regioselectivity	Yield (%)	ee (%)
$(DHQD)_2PHAL$ **1**	CO_2Me	H	20:1	34	98[180,181]
$(DHQ)_2PHAL$ **2**	CO_2Me	H	9:1	40	92 (inversed config.)[180]
AD-mix β	CO_2Et	F	Total	31	100[182]

Scheme 102.

Table 40

Reaction conditions	*A*/*B*	Yield (%)	ee (%)
4-Heptyloxy‘$(DHQD)_2$’ **7**	50:1	54	95[5e]
$(DHQD)_2$PYDZ **5**	1:1.1	10	Not given[5f]
New cat. **8** *t*-BuOH/H_2O	Only A	59	95[5f]

Scheme 104.

Table 41

Reaction conditions	*A*/*B*/*C*	Yield (%)	ee (%)
AD-mix β	2.4:1.8:1	Not given	32[184]
4-Heptyloxy‘$(DHQD)_2$’ **7** *t*-BuOH/H_2O/Methylcyclohexane	Only A	62	56[5e]
New cat. **8**/*n*-Bu_4NOH *t*-BuOH/H_2O/Methylcyclohexane	Only A	38	90[5f]

Scheme 105.

4-Heptyloxy"$(DHQD)_2$" **7** : 35%-95% ee [5e]

Scheme 106.

In steroids such as epoxycholesterol, cerebrosterol, oxysterols, and squalamine from desmosterol, it is also quite easy to selectively oxidize the side chain alkene, as seen in the following examples (Scheme 107 and Table 42).[5a,185–189]

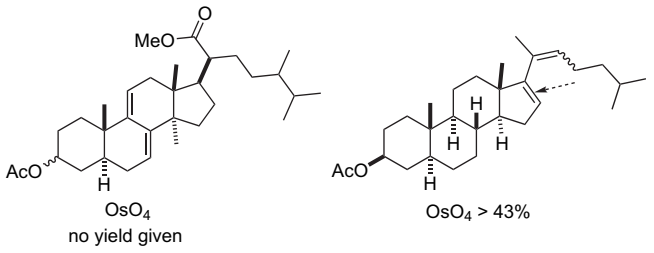
When applied to conjugated di-alkenes (studies of Robertson and Breslow), only two examples of osmylation without any chiral additive were found in the literature, the first

Table 42
Asymmetric dihydroxylation of steroid derivatives

Reaction conditions	R	Yield (%)	de (%)
$(DHQD)_2$PYDZ **5**; *t*-BuOH/H_2O	H	82	92%[185]
$(DHQ)_2$PHAL **2**; *t*-BuOH/H_2O	H	Not given	Only one (inversed config.)[185]
AD-mix β	Ac	87–92	Only one[186–188]
AD-mix α	Ac	>65	Only one (inversed config.)[186]
AD-mix α; *t*-BuOH/H_2O/MTBE	Ac	83	98.6[189]
$(DHQD)_2$PHAL **1**	Bz	Not given	90[5a]
$(DHQ)_2$PHAL **2**	Bz	Not given	88% (inversed config.)[5a]

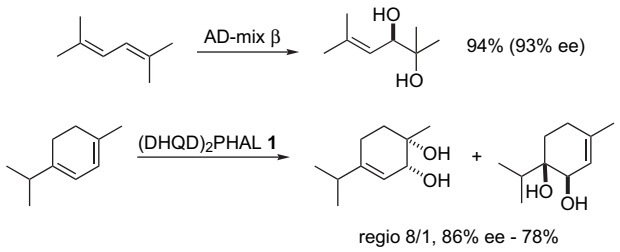
Scheme 107.

example being unclear as to the position of the obtained diol (Scheme 108).[190,191]



Scheme 108.

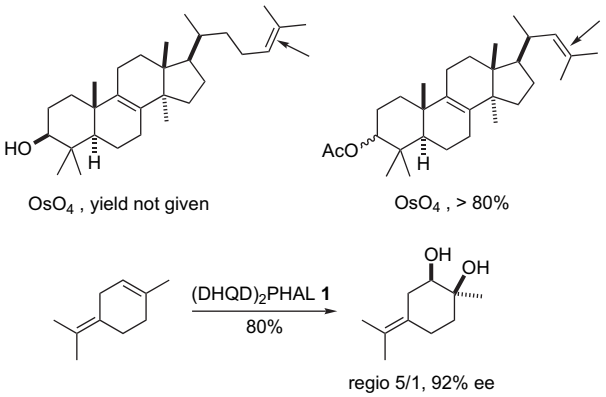
Finally, to the best of our knowledge, only two very simple AD-type reactions with di-trisubstituted conjugated di-alkenes have been published by Sharpless (Scheme 109).[122,126]



Scheme 109.

5.2. Trisubstituted alkenes versus tetrasubstituted alkenes

Only two examples have been described where the trisubstituted alkene moiety is preferentially oxidized in steroid derivatives, and only one asymmetric case was studied in a cyclic structure (lanosterol, agnosterol, pregnenone, Scheme 110).[122,192,193]



Scheme 110.

6. Conclusion

Osmylation is logically seen as a selective process in favor of the richest double bond. We have demonstrated in this review that this is not a generality, as numerous examples are described in the literature where the less-rich double bond is preferentially dihydroxylated. This interesting preference can be amplified using AD-type reagents, adding significant steric hindrance to the overall system. Moreover, an excellent chiral induction can be anticipated, this important fact enriching the scope of this popular procedure.

Acknowledgements

We would like to thank Dr. K. Plé for helpful discussions.

References and notes

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Biographical sketch

Antoine Français was born in Le Mans (07-10-1979). He received his master's degree in organic chemistry in 2004 in Université Paris-Sud 11. During the corresponding training course, he worked on the sequence CIM (Claisen–Ireland rearrangement followed by ring-closing metathesis) and its application under the guidance of Professor Arnaud Haudrechy and Doctor Olivier Bedel. In the same university, he currently continues his education as a Ph.D. student under the direction of Professor Jean-Marie Beau in the Laboratoire de Synthèse de Biomolécules. He is working on a one-pot synthesis of orthogonally and regioselectively protected carbohydrates by tandem catalysis and its application in the synthesis of bioactive molecules.

Olivier Bedel was born in 1976 (February 19th) near Paris. He graduated in 2000 from ESCOM (Ecole Supérieure de Chimie Organique et Minérale) and then started his doctoral period in the Laboratoire de Synthèse des Substances Naturelles directed by Professor Yves Langlois by working on asymmetric [2+3] cycloaddition of azomethine imine ylides. He carried out his thesis work in the same laboratory under the supervision of Professor Arnaud Haudrechy, working on fumagillin and spirotetronic unit synthesis, and he obtained his Ph.D. in 2004. After one year of a post-doctoral contract at Sanofi-Aventis in Toulouse, he is currently a medicinal chemist in the same company in the Vitry-sur-Seine research center.

Arnaud Haudrechy was born in Rouen (09-04-1965). He obtained his Ph.D. degree in 1990 from the Université of Paris VI (with Professor Pierre Sinaÿ) in the field of carbohydrates and transition-metal chemistry (Tebbe's reagent). In 1990, he joined the group of Professor Yoshito Kishi (Harvard University) as a post-doctoral fellow working on preferred conformations of *C*-glycosides and synthesis and conformational analysis of carbon analogs of the blood group determinant H-Type II. In 1992, he joined the University Paris-Sud as a lecturer in organic chemistry, working with Professor Yves Langlois on low-temperature asymmetric Diels–Alder reactions and synthesis of (+)-huperzin A, fumagillin and the spirotetronate subunit of the quartromicins (with a sequential Claisen-Ireland/metathesis concept). He is now a full Professor of Organic Chemistry at the Université de Reims Champagne-Ardenne, and his research program is focused on the use of carbohydrates for the synthesis of biologically active molecules.