Regio- and enantio-selective catalytic epoxidation of conjugated dienes

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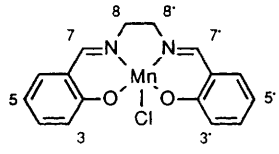
The regio- and enantio-selective catalytic epoxidation of conjugated aliphatic dienes have been studied using a variety of achiral and chiral manganese salen complexes and sodium hypochlorite or iodosylbenzene as the terminal oxidant. The catalysts show a preference for the less substituted alkene in most of the dienes studied, and in some cases a regioselectivity of 100% is found. The regioselectivity is dependent on the terminal oxidant applied. The enantiomeric excess (ee) obtained varies for the different conjugated dienes and the ee is generally highest for internal alkenes, where an ee of up to 71% is observed, whereas 48% is the highest observed ee for the less substituted alkenes. The ee is also dependent on the terminal oxidant applied. The regio- and enantio-selectivity have also been studied for different 1-(*para*-substituted phenyl)buta-1,3-dienes, but no regio- and enantio-selectivity dependence on the different substituents are observed. A competitive epoxidation experiment with styrene and 1-phenylbuta-1,3-diene shows that the latter is the most reactive and the difference in reactivity is discussed on the basis of the frontier orbitals of the two systems. The electronic structure of the oxo–manganese salen intermediate is investigated using INDO/1 calculations and it is found that the triplet state is the most stable state of the intermediate. Based on the electronic structure of the oxo–manganese salen intermediate a mechanism for the oxygen transfer step to the conjugated diene is proposed.

Introduction

One of the challenges in oxidation chemistry is to achieve regio- and enantio-selective reactions. For the epoxidation of dienes having two alkene functionalities placed in different steric and/or electronic environments, the goal is thus to be able to oxidize the desired carbon–carbon double bond in an enantioselective manner, leaving the remaining alkene functionality untouched. Only a few reagents can regioselectively epoxidize one of the alkene functionalities in a substrate containing several carbon–carbon double bonds.

Much more effort has been devoted to the enantioselective epoxidation of alkenes leading to asymmetric epoxides. The Sharpless epoxidation of allylic alcohols was the first breakthrough in this field,[1] and this method led to the preparation of a variety of different allylic epoxides of which many have been used for the synthesis of valuable target molecules.[2] More recently, Jacobsen and co-workers, in particular, have reported the catalytic asymmetric epoxidation of unfunctionalized alkenes using chiral Mn(salen) complexes as the catalyst and sodium hypochlorite or iodosylbenzene as terminal oxidant (t.o.).[3a,4] This procedure is particularly advantageous in the enantioselective epoxidation of *cis*-alkenes,[3b] but very recently the enantioselective epoxidation of tri-substituted alkenes[3d] and enantioselective epoxidation leading to *trans*-epoxides[3c] have also been achieved.

Conjugated dienes possess two alkene functionalities which can be epoxidized in a regioselective, as well as, an enantioselective manner, giving vinyl epoxides which are important building blocks in organic synthesis.[5] The use of transition metal complexes as catalysts for the epoxidation of conjugated dienes has only been described a very few times.[6–10] Epoxidation of simple conjugated dienes such as buta-1,3-diene, penta-1,3-diene, 2-methylbuta-1,3-diene (isoprene), using $Mo(CO)_6$, $OV(acac)_2$ and manganese porphyrins as the catalysts have been performed, but a very low selectivity was obtained;[7] *e.g.* the epoxidation of methylbuta-1,3-diene using $Mo(CO)_6$ as a catalyst and *tert*-butyl hydroperoxide as t.o. gave a mixture of 3,4-epoxy-3-methylbut-1-ene and 3,4-epoxy-2-methylbut-1-ene in a 4:1 molar ratio,[7a] *i.e.* the more substituted double bond was the most reactive. One of the other problems faced in the oxidation of conjugated dienes is that polymerization is often observed.[7a]



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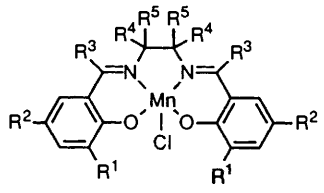
Chiral Mn(salen) complexes have recently been found to catalyse the asymmetric epoxidation of cycloocta-1,3-diene and *tert*-butyl (*E*,*Z*)-hexa-2,4-dienoate-,[8] and we have in a recent communication shown that achiral M(salen), and M(porphyrin) (M = Mn^{III}, Fe^{III}) complexes can catalyse the regioselective epoxidation of primarily the less substituted double bond of 1,3-diene systems[9]—a regioselectivity which is significantly different from the results obtained by epoxidation with *m*-chloroperbenzoic acid (MCPBA). More recently Jacobsen *et al.* have epoxidized the *cis*-alkene in internal *cis*,*trans*-dienes and cyclic dienes in an enantioselective manner.[10]

This paper presents the regio- and enantio-selective epoxidation of simple conjugated dienes (mainly 1,3-dienes), our aim being to develop a catalytic system which has a preference for one of the carbon–carbon double bonds in a conjugated diene. We have mainly focused on the epoxidation of the less substituted double bond of the conjugated diene, as this is the one which is the most difficult to epoxidize by ordinary epoxidation reagents, since these normally react with the most electron rich double bond.[11] For this purpose a series of complexes, based on the Mn(salen) system, **1**, has been prepared, where different substituents are introduced in the



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a: $R^1 = R^2 = R^3 = R^4 = R^5 = H$
b: $R^1 = Bu^t$; $R^2 = Me$; $R^3 = R^4 = R^5 = H$
c: $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Me$
d: $R^1 = R^4 = R^5 = H$; $R^2 = Me$; $R^3 = Ph$
e: $R^1 = R^3 = R^4 = R^5 = H$; $R^2 = NO_2$
f: $R^1 = R^3 = H$; $R^2 = NO_2$; $R^4 = R^5 = Me$
g: $R^1 = R^3 = H$; $R^2 = NO_2$; $R^4 = H$; $R^5 = (CH_2)_4$ (*rac*)
h: $R^1 = Bu^t$; $R^2 = Me$; $R^3 = R^4 = H$; $R^5 = Ph$ (*R,R*), (*S,S*)
i: $R^1 = Bu^t$; $R^2 = Me$; $R^3 = R^4 = H$; $R^5 = Bu^t$ (*R,R*), (*S,S*)

positions: 3, 3′, 5, 5′, 7, 7′, 8 and 8′ in an attempt to improve both the regio- and enantio-selectivity.

The epoxidation of the conjugated dienes has also been studied from a theoretical point of view using INDO/1[12] and MM2[13] calculations in an attempt to account for the regio- and enantio-selectivity in the oxygen transfer step.

Results and discussion

A series of different Mn(salen) complexes substituted in positions 3, 3′, 5, 5′, 7, 7′, 8 and 8′ has been prepared, **1a–i** (see Experimental section for their preparation). The substituents introduced are chosen in an attempt to try to improve both the regio- and enantio-selectivity for the epoxidation of the conjugated dienes.

In order to evaluate the regioselectivity of the epoxidation the definition of the regioselectivity index (ri) given in eqn. (1) has

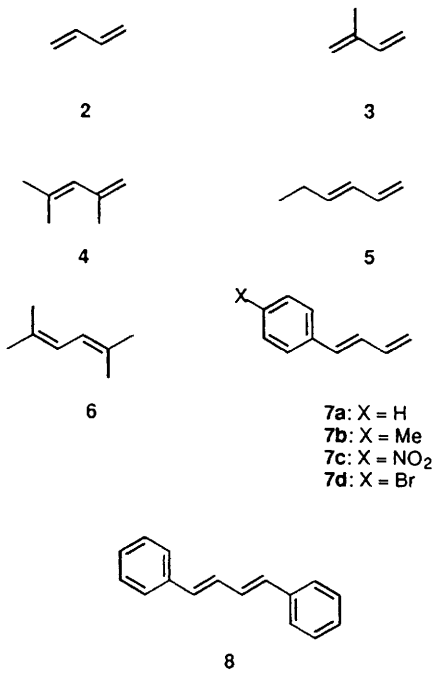
$$ri = \frac{ls - hs}{ls + hs} \times 100\% \qquad (1)$$

been used, where *ls* and *hs* are the amount of the less and highest substituted epoxide of the conjugated diene formed, respectively. An *ri* value of 100 thus represents the regioselective epoxidation of the less substituted alkene of the conjugated diene, while an *ri* value of −100 represents the regioselective epoxidation of the more substituted alkene of the conjugated diene studied.†

The epoxidation of the following conjugated dienes has been studied: buta-1,3-diene, **2**, 2-methylbuta-1,3-diene (isoprene), **3**, 2,4-dimethylpenta-1,3-diene, **4**, (*E*)-hexa-1,3-diene, **5**, 2,5-dimethylhexa-2,4-diene, **6**, (*E*)-1-(*p*-X-phenyl)buta-1,3-dienes, **7a–d**, (*E,E*)-1,4-diphenylbuta-1,3-diene, **8**.

The results for the epoxidation of buta-1,3-diene, **2**, using **1a**, **b**, **h** and **i** and sodium hypochlorite (NaOCl) or iodosylbenzene (PhIO) as the t.o. are presented in Table 1. Buta-1,3-diene **2**, can be monoepoxidized in relatively good yield using **1a** and **b** as the catalysts and, especially, with PhIO as the t.o. (Table 1, entries 1, 2). Using the chiral catalysts **1h** and **i** and NaOCl as the t.o. leads to a relatively low enantiomeric excess (ee) (entries 3, 5), and the presence of pyridine *N*-oxide (pyr-*N*-oxide, entry 4) causes only a slight increase in the ee of the monoepoxide. It is generally observed that applying NaOCl as the t.o. leads to a

† It should be noted that the definition of ri is different from the definition of the ri index in our recent communication (ref. 9).



2 3 4 5 6

7a: X = H
7b: X = Me
7c: X = NO_2
7d: X = Br

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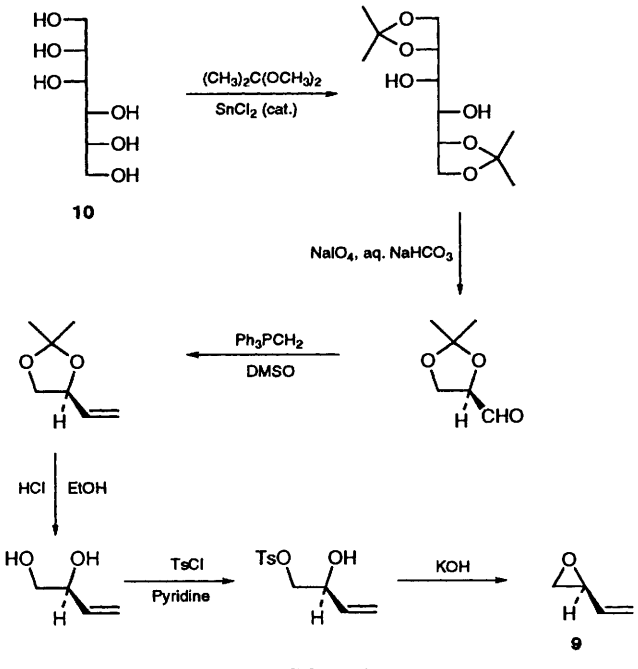
Table 1 Epoxidation of buta-1,3-diene **2** to give 3,4-epoxybut-1-ene using PhIO and NaOCl as terminal oxidants (results for NaOCl are given in parentheses)

Entry	Catalyst	Donor ligand	Yield epoxide (%)	Ee[a]
1	**1a**	—	92 (40)	—
2	**1b**	—	71 (50)	—
3	(*R,R*)-**1h**	—	(66)	(13)(3*S*)[b]
4	(*R,R*)-**1h**	Pyr-*N*-oxide	(72)	(17)(3*S*)[b]
5	(*S,S*)-**1i**	—	(61)	(10)(3*R*)[b]

[a] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$. [b] The assignment is based on an independent synthesis (see text).[14]



Scheme 1

Table 2 Epoxidation of 2-methylbuta-1,3-diene (isoprene) **3** using PhIO and NaOCl as terminal oxidants (results for NaOCl are given in parentheses)

				3,4-Epoxy-2-methylbutene		3,4-Epoxy-3-methylbutene		
Entry	Catalyst	Donor ligand	Yield (%)	Yield (%)	Ee[a]	Yield (%)	Ee[a]	*ri*
1	**1a**	—	100 (34)	29 (0)	—	71 (100)	—	−42 (−100)
2	**1b**	—	92 (89)	26 (37)	—	74 (63)	—	−48 (−26)
3	**1c**	—	70 (40)	32 (0)	—	68 (100)	—	−36 (−100)
4	**1d**	—	56 (38)	30 (29)	—	70 (71)	—	−40 (−42)
5	(*S*,*S*)-**1h**	—	(95)	(41)	(37)	(59)	(33)	(−18)
6	(*S*,*S*)-**1h**	Pyr-*N*-oxide	(95)	(41)	(46)	(59)	(37)	(−18)
7	(*S*,*S*)-**1h**	4-Me-pyr	(68)	(41)	(43)	(59)	(31)	(−18)
8	(*R*,*R*)-**1i**	—	(44)	(34)	(35)	(66)	(30)	(−32)
9	(*R*,*R*)-**1i**	Pyr-*N*-oxide	(52)	(32)	(38)	(68)	(25)	(−36)
10	(*R*,*R*)-**1i**	4-Me-pyr	(50)	(33)	(31)	(67)	(26)	(−34)

[a] Determined by GC using a chiral β-cyclodextrin column.

Table 3 Epoxidation of 2,4-dimethylpenta-1,3-diene **4** using NaOCl and PhIO as terminal oxidants (results for NaOCl are given in parentheses)

				4,5-Epoxy-2,4-dimethylpent-2-ene		3,4-Epoxy-2,4-dimethylpent-1-ene		
Entry	Catalyst	Donor ligand	Yield (%)	Yield (%)	Ee[a]	Yield (%)	Ee[a]	*ri*
1	**1a**	—	64	77	—	23	—	54
2	**1b**	—	76 (100)	92 (88)	—	8 (12)	—	84 (76)
3	**1c**	—	50	93	—	7	—	86
4	**1d**	—	46	94	—	6	—	88
5	(*S*,*S*)-**1h**	—	68	89	31	11	11	78
6	(*S*,*S*)-**1h**	Pyr-*N*-oxide	45	85	31	15	9	70
7	(*S*,*S*)-**1h**	4-Me-pyr	78	86	31	14	33	72
8	(*R*,*R*)-**1i**	—	58	88	17	12	2	76
9	(*R*,*R*)-**1i**	Pyr-*N*-oxide	59	92	17	12	2	84
10	(*R*,*R*)-**1i**	4-Me-pyr	77	92	14	8	2	84

[a] Determined by GC using a chiral β-cyclodextrin column.

lower yield of the monoepoxide, compared with PhIO as the t.o., but in the case of **2** as the substrate no significant difference in ee is observed for the two t.o.s.

In order to assign the stereochemistry of the 3,4-epoxybut-1-ene formed, (+)-(*S*)-3,4-epoxybut-1-ene **9** was prepared by an independent synthesis from **10** as outlined in Scheme 1.[14]

The independent synthesis of **9** (Scheme 1) made it possible to correlate the absolute configuration of the 3,4-epoxybut-1-ene formed in the present reaction by ^{1}H NMR spectroscopy. By using (*R*,*R*)-**1h** as the catalyst (+)-(*S*)-3,4-epoxybut-1-ene, **9**, was formed with 17% ee.

Table 2 presents the results for the epoxidation of 2-methylbuta-1,3-diene (isoprene) **3**. 2-Methylbuta-1,3-diene (isoprene) **3** can be monoepoxidized in good yields with both PhIO and NaOCl as the t.o. (Table 2). The *ri* values for the epoxidation of **3** are an exception, as these are negative, compared with the other conjugated dienes (*vide infra*). Catalysts **1a** and **c** give a regioselective epoxidation (*ri* = −100%) when NaOCl is applied as t.o. (entries 1, 3), whereas only −42% and −36% are obtained with the same catalysts, **1a** and **c**, respectively, using PhIO as t.o. (entries 1, 3). These results, as well as others presented in later tables show that the *ri* is dependent on the t.o. applied. Using the chiral catalysts **1h** and i and NaOCl as the t.o. lead to a small negative *ri* (entries 5, 8: −18% and −32%, respectively). The highest ee (46%) is obtained for the less substituted alkene in **3** using **1h** as the catalyst in the presence of pyridine *N*-oxide (entry 6). The same catalytic system also give the best ee (37%) for the more substituted alkene in **3** (entry 6). Comparing the catalyst **1h** with **1i**, it appears that the highest yields are obtained using the former, but in terms of ee and *ri* only small variations are found. The donor ligands pyridine *N*-oxide and 4-methylpyridine have only a very small influence on the ee.

The results for the epoxidation of 2,4-dimethylpenta-1,3-diene **4** are given in Table 3. The epoxidation of 2,4-dimethylpenta-1,3-diene **4** has mainly been studied with PhIO as t.o., because the use of NaOCl leads to an over-oxidation and the production of cleavage products. The reactions proceed with high *ri*, generally higher than 70%. The best *ri* is obtained using **1d** as the catalyst, but the yield of the monoepoxide is relatively low (Table 3, entry 4), except for **1b** as catalyst (entry 2). The chiral catalyst **1h** gives the highest ee (entries 5–7), but the effect on the ee of the presence of donating ligands is minimal, except for the epoxidation of the highest substituted double bond in **4** with **1h** as the catalyst, as the presence of 4-methylpyridine leads to 33% ee (entry 7), compared with an ee of 11% in the absence of the donor ligand (entry 5). For the epoxidation of the less substituted alkene 31% ee is obtained by applying **1h** as the catalyst, whereas only an ee of 14% is obtained using **1i** as the catalyst.

Monoepoxidation of (*E*)-hexa-1,3-diene **5** catalysed by **1a–d**, **h** and **i** with PhIO and NaOCl as the t.o.s gives the results presented in Table 4. The results for the epoxidation of (*E*)-hexa-1,3-diene **5** show a relatively high *ri*, especially for the chiral catalysts with PhIO as t.o. The chiral catalysts **1h** and **i** gave *ri* > 70% (Table 4, entries 5–10), but it should be noted that the presence of donor ligands reduces the *ri* slightly. The results show that the catalysts **1h** and **i** can, to a large extent, selectively epoxidize the less substituted double bond in **5**. These catalysts also give a relatively high ee of especially the highest substituted double bond in **5**; the highest ee, 71%, is obtained with **1i** as the catalyst and NaOCl as t.o. (entry 9). It should also

Table 4 Epoxidation of (*E*)-hexa-1,3-diene **5** using NaOCl and PhIO as terminal oxidants (results for NaOCl are given in parentheses)

				1,2-Epoxyhex-3-ene		3,4-Epoxyhex-1-ene		
Entry	Catalyst	Donor ligand	Yield (%)	Yield (%)	Ee[a]	Yield (%)	Ee[a]	*ri*
1	**1a**	—	87 (12)	71 (64)	—	29 (38)	—	42 (28)
2	**1b**	—	59 (100)	85 (76)	—	15 (24)	—	70 (52)
3	**1c**	—	67 (20)	89 (60)	—	11 (40)	—	78 (20)
4	**1d**	—	55 (32)	78 (68)	—	22 (32)	—	56 (36)
5	(*R*,*R*)-**1h**	—	85 (38)	94 (93)	13 (20)	6 (7)	35 (41)	88 (86)
6	(*R*,*R*)-**1h**	Pyr-*N*-oxide	(97)	(88)	(22)	(12)	(54)	(76)
7	(*R*,*R*)-**1h**	4-Me-pyr	(95)	(89)	(11)	(11)	(43)	(78)
8	(*R*,*R*)-**1h**	Pyr-*N*-oxide (0 °C)	(95)	(88)	(22)	(12)	(50)	(76)
9	(*S*,*S*)-**1i**	—	75 (95)	90 (87)	1 (14)	10 (13)	40 (71)	80 (74)
10	(*S*,*S*)-**1i**	Pyr-*N*-oxide	(95)	(87)	(3)	(13)	(58)	(74)

[a] Determined by GC using a chiral β-cyclodextrin column.

Table 5 Epoxidation of 2,5-dimethylhexa-2,4-diene **6** to give 4,5-epoxy-2,5-dimethylhex-2-ene using PhIO and NaOCl as terminal oxidants (results for NaOCl are given in parentheses)

Entry	Catalyst	Donor ligand	Yield (%)	Epoxide ee[a]
1	(*R*,*R*)-**1h**	—	80 (68)	3 (13)
2	(*R*,*R*)-**1h**	Pyr-*N*-oxide	(97)	(11)
3	(*R*,*R*)-**1h**	4-Me-pyr	(69)	(23)
4	(*R*,*R*)-**1h**	4-Me-pyr (0 °C)	(74)	(25)
5	(*S*,*S*)-**1i**	—	65 (70)	10 (24)
6	(*S*,*S*)-**1i**	Pyr-*N*-oxide	(77)	(20)

[a] Determined by GC using a chiral β-cyclodextrin column.

be noted that for the epoxidation of the more substituted double bond in **5** using **1i** as the catalyst the ee is very dependent on the t.o. used (entries 5, 9). Addition of donor ligands to this reaction does not increase the ee (entries 6–8, 10), compared with the reaction in the absence of a donor ligand (entries 5). Reducing the reaction temperature from room temperature to 0 °C did not alter the *ri* and ee significantly (entries 6, 8). The ee obtained in entry 9 is, according to our knowledge, one of the highest ee's obtained for the epoxidation of an *E*-alkene. It should also be noted that only a very low (*E*) to (*Z*) isomerization takes place in the reaction as less than 2% of (*Z*)-3,4-epoxyhex-1-ene is formed.

The results for the epoxidation of 2,5-dimethylhexa-2,4-diene **6** are shown in Table 5. The epoxidation of 2,5-dimethylhexa-2,4-diene **6** has only been studied using the chiral catalysts and in most cases with NaOCl as t.o. The monoepoxide is formed in good yield, especially with **1h** as the catalyst and pyridine *N*-oxide as donor ligand (Table 5, entry 2), but the ee obtained with this substrate is relatively low. It is also observed that the ee is dependent on the t.o. used.

In order to study the epoxidation of conjugated aromatic dienes a series of (*E*)-(1)-(*p*-substituted 1-phenyl)buta-1,3-dienes **7a–d** has been prepared. The results for the monoepoxidation of **7a–d** are given in Table 6. The epoxidation of **7a–d** shows a very high *ri*, especially with the chiral catalysts, **1h** and **i**, as *ri* > 95% is obtained; *i.e.* these catalysts show a significant preference for the terminal double bond in **7a–d**. The attachment of a nitro substituent to the phenyl group in the catalysts, **1e–f**, does not alter the yield of the monoepoxide, but to a certain extent the *ri* is altered (entries 1–3), compared with the other catalysts. The different substituents in the *para*-position at the phenyl group of the diene, have no influence on the *ri* and ee (entries 4–8). It is observed that the monoepoxide obtained by epoxidation of **7b**, where an electron donating substituent is present at the *para*-position in the phenyl group, is less stable compared with the other epoxides. The ee obtained with the chiral catalysts is only about 20% (entries 4–8).

To test the influence of the different substituents in the *para* position of the phenyl group in **7a–d** on the epoxidation rate a series of competitive experiments where **7a–c** are epoxidized in the presence of **7d** (the dienes are present in equimolar amounts) has been performed. The results using **1b** as a catalyst and NaOCl as t.o. are shown in Table 7.

The competitive experiments for the epoxidation of **7a–c** in the presence of **7d** show that the former are much more reactive than the latter; *i.e.* an electron withdrawing group in the *para*-position of the phenyl substituent of buta-1,3-diene decreases the reactivity of the terminal carbon–carbon double bond of the conjugated diene. These results indicate that the alkene in the present epoxidation reactions acts as a nucleophilic-like reagent and thus that the oxygen atom which is transferred from the oxo–Mn(salen) intermediate is of electrophilic nature. The electrophilicity of the oxygen atom is similar to the electronic nature of oxygen atom transferred to alkenes from MCPBA [11] and early-transition metal–peroxo complexes.[6]

The epoxidation of (*E*,*E*)-1,4-diphenylbuta-1,3-diene **8** has also been investigated using (*R*,*R*)-**1h** and (*S*,*S*)-**1h** as the catalysts and NaOCl as t.o. The monoepoxide is formed in 90% yield, but a low ee is introduced, as only about 10% is obtained.

The epoxidation of **7a** using (*R*,*R*)-**1h** as the catalyst and NaOCl as the t.o. leads to a remarkable low ee compared with the epoxidation of styrene, **11**, where an ee of 62% is obtained under the same reaction conditions. In an attempt to study the reactivity of **7a** in relation to **11** and to account for this low ee in the epoxidation of **7a** compared with the epoxidation of **11** a series of experimental and theoretical investigations have been performed. Competitive epoxidation of **7a** and **11** (present in equimolar amounts) catalysed by (*R*,*R*)-**1h** and NaOCl as the t.o. leads to a 90% conversion of **7a** into the corresponding epoxide, whereas only 51% of styrene is converted into styrene oxide. This experiment shows that **7a** is much more reactive than **11**. The difference in reactivity is due to electronic effects and in an attempt to account for this the frontier orbitals of **7a** and **11** have been calculated by the INDO/1[12] procedure and are presented in Fig. 1.

The HOMO and LUMO of **7a** and **11** are outlined to the left and right, respectively, in Fig. 1. The HOMOs of **7a** and **11** are calculated to be at −7.68 and −8.26 eV, respectively. The LUMOs for **7a** and **11** are calculated to be at −0.17 and 0.22 eV, respectively. Using a frontier orbital line of reasoning, *i.e.* the energy term from the second-order perturbation theory shown in eqn. (2), and the results shown in Fig. 1 it appears that **7a** should be more reactive than **11**. The increased reactivity of **7a** relative to **11** comes from a decrease in the energy difference

Table 6 Epoxidation of 1-(*p*-X-phenyl)buta-1,3-dienes **7** using NaOCl as the terminal oxidant

				3,4-Epoxy-1-(*p*-X-phenyl)butene		3,4-Epoxy-4-(*p*-X-phenyl)butene	
Entry	X	Catalyst	Yield (%)	Yield (%)	Ee[a]	Yield (%)	*ri*
1	H	**1e**	66	88	—	12	76
2	H	**1f**	85	92	—	8	84
3	H	**1g**	63	91	—	9	82
4	Me	(*R,R*)-**1h**	73	>98	20	<2[b]	>95
5	H	(*R,R*)-**1h**	89	>98	20	<2[b]	>95
6	Br	(*R,R*)-**1h**	81	>98	18	<2[b]	>95
7	NO_2	(*R,R*)-**1h**	66	>98	Nd[c]	<2[b]	>95
8	Br	(*S,S*)-**1i**	88	>98	18	<2[b]	>95

[a] Determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$. [b] Ee not determined. [c] Nd = Not determined.

Table 7 Competitive epoxidation of 1-(*p*-X-phenyl)buta-1,3-dienes **7a–c** relative to *p*-nitrophenylbuta-1,3-diene **7d** using NaOCl as terminal oxidant

			3,4-Epoxy-1-(*p*-X-phenyl)butene	3,4-Epoxy-1-(*p*-nitrophenyl)butene
Entry	X	Catalyst	Yield (%)[a]	Yield (%)[a]
1	Me	**1b**	90	44
2	H	**1b**	85	43
3	Br	**1b**	79	45

[a] Determined by ^{1}H NMR spectroscopy.

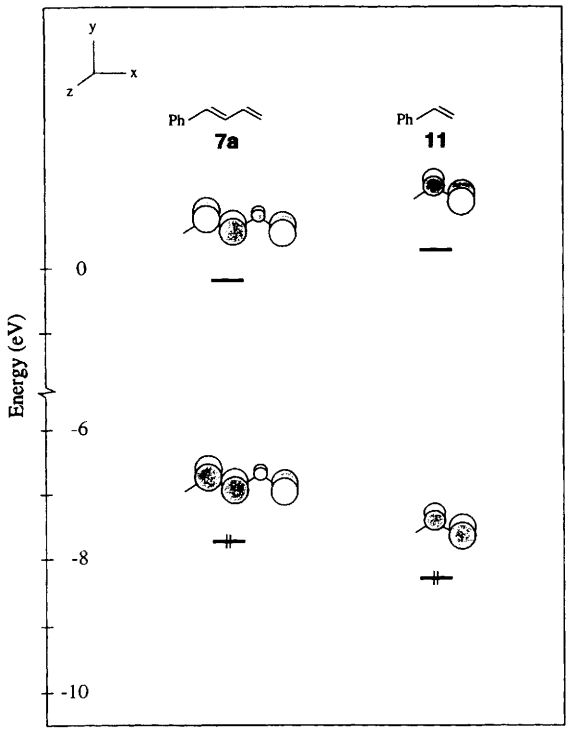


Fig. 1 The frontier orbitals of 1-phenylbuta-1,3-diene **7a** to the left and styrene **11** to the right

in the denominator in eqn. (2) as HOMO(**7a**) is higher in energy

$$\Delta E \propto \frac{|H\mathrm{ij}|}{E\mathrm{i} - E\mathrm{j}} \qquad (2)$$

than HOMO(**11**) and LUMO(**7a**) is lower in energy than LUMO(**11**). Interaction of HOMO(**7a**) with an acceptor orbital and/or LUMO interacting with a donor orbital, of the oxo–Mn(salen) intermediate will thus lead to a better interaction compared with similar interactions of **11**. Inspection of the distribution of the frontier orbitals in **7a** and **11** reveals, that for the former, both the HOMO and LUMO are mainly located at the internal alkene (coefficients about 0.42 each), while the coefficients at the two terminal carbon atoms are 0.2 and 0.4, with the largest coefficient is found at the terminal carbon atom. The coefficients for styrene are for the LUMO 0.33 and 0.48, and for the HOMO 0.32 and 0.49, respectively, where the largest coefficients also are found at the terminal carbon atom.

Before proceeding further let us discuss the electronic structure of the active catalyst. The first step in the epoxidation reaction is generally assumed to be the formation of an oxo–Mn(salen) intermediate from which the oxygen atom is transferred to the conjugated diene. The oxygen transfer from the oxo–Mn(salen) intermediate to an alkene has been the subject of intensive experimental investigations.[15] But, to the best of our knowledge not much effort has been made to understand the electronic structure of the oxo–Mn(salen) intermediate. The electronic structure of this intermediate has now been investigated using INDO/1 calculations[12] not only in an attempt to understand the electronic nature of the intermediate, but also to investigate the oxygen transfer step to the conjugated diene.

The electronic structure of the oxo–Mn(salen) intermediate has been investigated for (*R,R*)-**12** and the calculations are performed for the whole system with a fixed geometry of the ligand. The structural data for the ligand is obtained from the crystal structure of *N,N*-di(3-*tert*-butyl-5-methylsalicylidene) cyclohexanediaminemanganese(III) chloride,[16] but where the cyclohexane part has been exchanged with phenyl substituents. The bond length for the oxo–manganese bond has been taken from a stable low spin d^2 square-pyramidal oxo–manganese complex with a macrocyclic tetramide ligand which has been

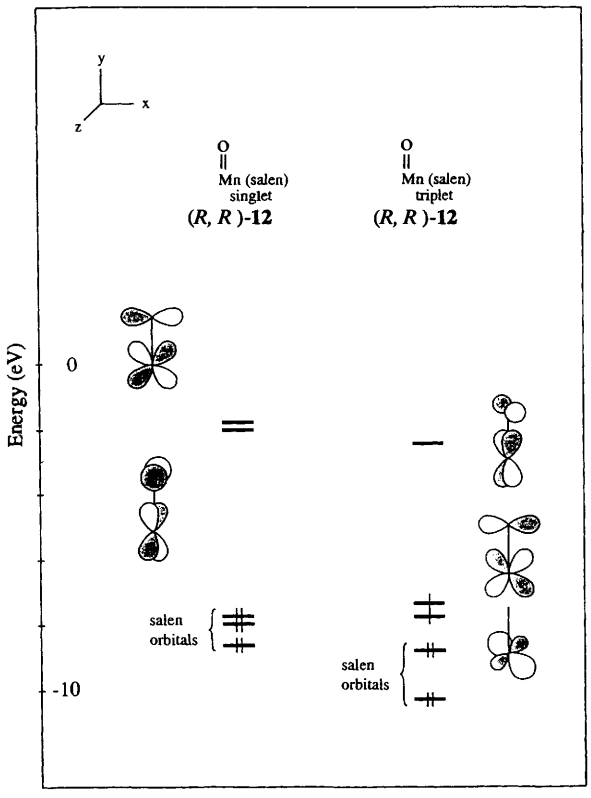
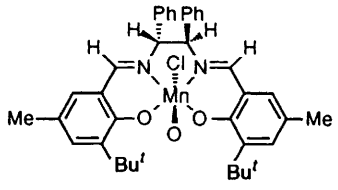


Fig. 2 The frontier orbitals of the oxo–Mn(salen) intermediate (*R*,*R*)-**12**. The singlet state is to the left and the triplet state to the right.

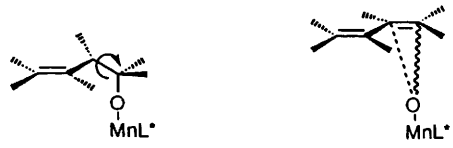


(*R*, *R*)-**12**

characterized by X-ray spectroscopy and has an O=Mn distance of 1.55 Å.[17]

The electronic structure for (*R*,*R*)-**12** is calculated for two different spin states, a singlet, and a triplet state, where the calculation for the latter state is performed using the restricted Hartree-Fock (RHF) procedure. The total energy for the singlets and triplet state of (*R*,*R*)-**12** is calculated to be −328.3354 and −328.3620 au, respectively. It appears thus that the triplet state of (*R*,*R*)-**12** is −17 kcal mol^{-1} ‡ more stable than the singlet state, *i.e.* the most stable electronic configuration of (*R*,*R*)-**12** is an open shell state with two unpaired electrons. Based on the lowest energy state of (*R*,*R*)-**12** one might thus expect that it would show some radical nature in its reactivity, which also has been proposed on the basis of some of the experimental results for the epoxidation of alkenes.[10a,b,15d,18] The frontier orbitals of the singlet and triplet state of (*R*,*R*)-**12** are outlined in Fig. 2.

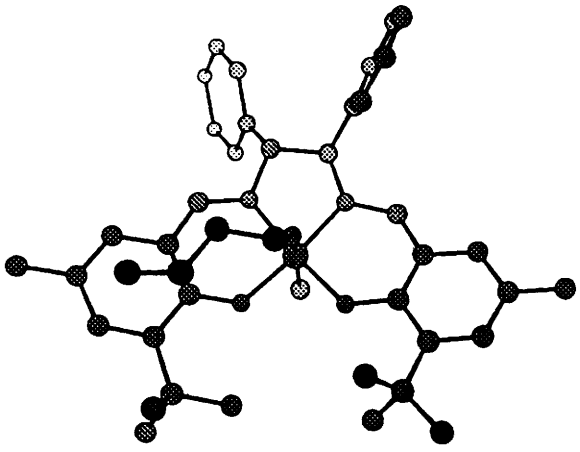
The frontier orbitals for the singlet state of (*R*,*R*)-**12** depicted to the left in Fig. 2 show that the highest occupied MOs are all located at the organic ligand, while the lowest unoccupied MOs are a nearly degenerate set of orbitals at −1.83 and −1.96 eV, located as antibonding O(p_z)–Mn(d_{yz}) and O(p_x)–Mn(d_{xy}) orbitals, respectively. The frontier orbitals of the triplet state of (*R*,*R*)-**12** to the right in Fig. 2 are of more interest in the present study as this is the most stable electronic state of the oxo–Mn(salen) intermediate and probably the one involved in the oxygen transfer reactions. Moving from the singlet to the triplet state of (*R*,*R*)-**12** leads to a change in the frontier orbitals; above the ligand orbitals (all occupied with two electrons) are now two nearly degenerate single occupied MOs (SOMOs). One of the SOMOs is located at −7.76 eV and has antibonding O(p_x)–Mn(d_{xy}) orbital character, while the other, at −7.79 eV, is mainly located at the manganese atom and is a combination of d_z2 and d_{xz}. The LUMO of the triplet state of (*R*,*R*)-**12** is also a combination of antibonding O(p_x–p_z)–Mn($d_{x^2-y^2}$–d_{yz}) orbital character and is calculated to be at −2.29 eV. It is notable that the charge on the oxygen atom for the two different spin states of (*R*,*R*)-**12** is the same (−0.6). The frontier orbitals of the triplet state of (*R*,*R*)-**12** account for the instability of the oxo–Mn(salen) intermediate due to the presence of the antibonding SOMO oxo–manganese orbital. Furthermore, the frontier orbitals of (*R*,*R*)-**12** can also be used to evaluate the electronic properties of the oxygen atom in the oxo–Mn(salen) intermediate. This atom is expected to have mainly electrophilic character due to the LUMO having significant oxygen character. Besides the electrophilic properties of the oxygen atom, radical character should also be expected as the other SOMO also has significant oxygen character. The electrophilic character of the oxygen atom in the oxo–Mn(salen) intermediate is in good agreement with the results presented in Table 7, where the competitive experiments showed that the presence of electron donating substituents increased the yield of the epoxide compared with the presence of substrates with electron withdrawing substituents.



13 **14**

The distribution of the HOMO and LUMO for **7a** indicates that the internal alkene should be the most reactive, but it appears from the present investigations that the terminal alkene is exclusively epoxidized. This is probably due to steric reasons as the approach of the internal alkene of **7a** to the oxygen atom of the oxo–Mn(salen) intermediate leads to steric repulsion between the substituents at the internal alkene and the salen ligand. Furthermore, the reaction of the terminal alkene leads also to the most stable intermediate. The orbital distribution at the terminal alkene in **7a** shows that the terminal carbon atom would be expected to interact much better than the β-carbon atom with the oxygen atom of the oxo–Mn(salen) intermediate as the coefficient at the latter atom is very small compared with the coefficient at the terminal atom. If the orbital coefficients at the alkene in **7a** are compared with the coefficients at the alkene in **11**, it appears that the terminal carbon atom in the latter also has the largest coefficient, but that the coefficient at the β-carbon atom in **11** is significantly larger than the coefficient at the same carbon atom in **7a**. This difference in distribution of the coefficients has an influence of the interaction of carbon atoms of the alkene with the oxo functionality of the oxo–Mn(salen) intermediate. For **11** this interaction might involve mainly the terminal carbon atom, and to a certain extent also the other carbon atom, whereas for **7a** the terminal atom is more or less exclusively involved in the interaction with the oxo-functionality of the oxo–Mn(salen) intermediate, as the coefficient at the β-carbon atom is very small, and therefore is

‡ 1 cal = 4.184 J.



15

not able to overlap with the oxygen atom in the oxo–Mn(salen) intermediate to the same extent as the same carbon atom in **11**.

The difference in the distribution of the HOMO and the LUMO of the substrates could account for the low ee in the epoxidation of **7a** compared with **11**, as the intermediate formed when the terminal alkene interacts with the oxo-functionality of the oxo–Mn(salen) intermediate might have more free rotation around the carbon–carbon bond, see structure **13**, compared with a similar intermediate when **11** is the substrate. In **11**, having a larger orbital amplitude at the β-carbon atom compared with **7a**, a more favourable interaction of this carbon atom with the oxygen atom might be possible, which might favour the former intermediate which has a lower degree of freedom of rotation around the carbon–carbon bond and therefore will lead to a higher ee with this substrate.[15d] The radical nature of (*R*,*R*)-**12** supports an interaction with only one of the carbon atoms of the diene giving an allylic intermediate which also may contribute to a higher degree of rotation around the carbon–carbon bond in this case. Another possible reason for the low ee when **7a** is the substrate is that it is mainly the terminal carbon atom which is involved in the interaction with the oxygen atom of the oxo–Mn(salen) intermediate at the beginning at the reaction course, see structure **14**. However, when **11** is the substrate the β-carbon atom overlaps more with the oxygen atom in the oxo–Mn(salen) complex than with **7a** due to the difference in amplitude at the β-carbon atom for the two substrates and thus loss of ee could occur at this stage of the reaction path. It should also be noted that **14** is in principle a precursor to **13**. We are not at present able to distinguish between these two possibilities for the difference in between simple alkenes and terminal dienes.

In an attempt to account for the stereochemistry of the 3,4-epoxybut-1-ene formed [(+)-(*S*)-3,4-epoxybut-1-ene] from the reaction of buta-1,3-diene with NaOCl in the presence of (*R*,*R*)-**12** as the catalyst, the interaction of the terminal carbon atom in buta-1,3-diene with the oxygen atom of the (*R*,*R*)-**12** has been studied with the following assumptions: the geometry of (*R*,*R*)-**12** and the buta-1,3-diene part are kept fixed and the oxygen–carbon bond length is set to 2.0 Å. The two possible intermediates leading to either (+)-(*S*)- or (−)-(*R*)-3,4-epoxybut-1-ene have thus been investigated using MM2 calculations.[13] The geometrical structure for the most stable of the two possible intermediates is shown in structure **15**. The epoxide formed from this intermediate is (*S*) at the asymmetric carbon atom and this intermediate is calculated to be 3 kcal mol^{-1} more stable than the one leading to (−)-(*R*)-3,4-epoxybut-1-ene and we propose that structure **15** might account for the stereochemical outcome of the reaction.

The present work shows that achiral and chiral Mn(salen) complexes can to a large extent catalyse a regioselective epoxidation of conjugated dienes using sodium hypochlorite or iodosylbenzene as the terminal oxidant. For most of the substrates studied the less substituted diene is epoxidized, but for isoprene the highest substituted alkene is the most reactive. The ee varies, but is generally highest for the internal alkenes, where an ee up to 71% is found, whereas 48% ee is the highest observed for the terminal alkenes. The regio- and enantioselectivity is not affected by variation of electron donating and electron withdrawing substituents, but substrates having electron donating substituents are found to be more reactive than those having electron withdrawing substituents. Furthermore, the conjugated dienes have been found to be more reactive than isolated alkenes, and this can be acounted for by the higher lying HOMO and lower lying LUMO of the conjugated diene compared with the alkene. The lower ee obtained for the the terminal alkene in 1,3-dienes compared with terminal alkenes in these Mn(salen) catalysed reactions can also be accounted for by the frontier orbitals of the substrates as the diene has a small amplitude in both the HOMO and LUMO at the β-carbon atom compared with the terminal carbon atom. This smaller amplitude can cause either a weaker interaction of the β-carbon atom as it approaches the oxygen atom in the oxo–Mn(salen) intermediate and/or a weaker interaction of the β-carbon atom with the oxygen atom in the radical intermediate formed by reaction of the diene with the oxo–Mn(salen) intermediate as semi-empirical theoretical calculations show that an open shell—a radical intermediate—(triplet state) of the oxo–Mn(salen) intermediate is more stable that the closed shell system. The enantioselective outcome of the reaction can be accounted for by energy calculations of an intermediate where the terminal carbon atom of the diene interacts with oxygen atom of the oxo–Mn(salen) intermediate and has a preferred alignment of the diene relative to the chiral salen ligand.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions in a Varian Gemini spectrometer at 300 and 75 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in ppm downfield from tetramethylsilane (TMS). *J* values are given in Hz. Mass spectra were recorded on a Micromass 7070F mass spectrometer and GC–MS on a Trio-2 spectrometer. GC was performed on a HP 5890 using a chiral β-cyclodextrin column (J & W Scientific Cyclodex-B column, 30 m × 0.25 mm id, 0.25 μm film).

Materials

The solvents were purified according to standard methods before use. 1-Phenylbuta-1,3-diene,[19] 1-(*p*-tolyl)buta-1,3-diene,[19] 1-(*p*-bromophenyl)buta-1,3-diene,[19] 1-(*p*-nitrophenyl)-buta-1,3-diene,[20] the manganese(III)(salen) complexes, **1a–d** and **h**[3b] and iodosylbenzene (PhIO)[21] were prepared according to the literature. The manganese(III)(salen) complexes, **1e**, **f** and **g** were received as gifts from Professor Bjørn Åkermark, The Royal Technical Highschool, Stockholm, Sweden. Complex **1i** was prepared in a similar way as **1h**, with the exception of the amine part of the ligand which is prepared according to the procedure given below. 4-Methylpyridine, pyridine *N*-oxide, buta-1,3-diene, 2-methylbuta-1,3-diene (isoprene), 2,4-dimethylpenta-1,3-diene, (*E*)-hexa-1,3-diene, 2,5-dimethylhexa-2,4-diene, (*E*,*E*)-1,4-diphenylbuta-1,3-diene and sodium

hypochlorite (NaOCl) (15%) are commercially available. These compounds were analysed for purity before use.

Preparation of (+)-/(−)-2,2,5,5-tetramethylhexane-3,4-diamine

2,2,5,5-Tetramethylhexane-3,4-diamine was prepared according to the literature procedure.[22] The diamine was isolated as a 1.3:1 mixture [(±):*meso*] of diastereoisomers. Before resolution the diamine (2.00 g) was dissolved in light petroleum (3 cm^3) and kept at −20 °C. The *meso*-diastereoisomer precipitated as clear crystals. The supernatant was concentrated under reduced pressure to give a 10:1 mixture of diastereoisomers. The diamine enriched in the (±)-diastereoisomer (314 mg, 2.0 mmol) was dissolved in isopropyl alcohol (30 cm^3), warmed to 75 °C and then (−)-mandelic acid (609 mg, 4.0 mmol) was added to it. The solution was cooled to ambient temperature. After 5 days crystals appeared and the solution was filtered, the crystals were washed with isopropyl alcohol (3 cm^3) and then recrystallized from isopropyl alcohol (25 cm^3), separated and dried. The optical purity of the resulting mandelate salt was checked by ^1H NMR spectroscopy.[23] The salt was added to aq. NaOH (1.0 mol dm^{-3}; 5 cm^3) at 0 °C. The aqueous phase was washed with CH_2Cl_2(2 × 5 cm^3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure to afford the (+)-diamine (31 mg, 18%). The procedure was not optimized. $[\alpha]_D^{20} = +12$ (*c* 0.13, CH_2Cl_2); δ_H 0.91 (18 H), 1.2–1.6 (4 H, br) and 2.55 (2 H).

General procedure for the regioselective and asymmetric epoxidation of conjugated dienes.

The manganese(III)(salen) complex (6.5 mg, 0.01 mmol) and the diene (0.25 mmol) were dissolved in CH_2Cl_2(2.0 cm^3). An aqueous solution of 15% NaOCl (approx. 0.6 mmol) and Na_2HPO_4(0.05 mol dm^{-3}; 0.80 cm^3) adjusted to pH 11.3 was added and the mixture vigourously stirred at room temperature for 24 h. A portion of the CH_2Cl_2-phase (0.5 cm^3) was added to light petroleum (0.5 cm^3) and then filtered through a layer of Al_2O_3(20 mm). The Al_2O_3 was washed with 50% CH_2Cl_2 in light petroleum (1.0 cm^3) and then the solvent was evaporated. In reactions where donor ligands were present, 0.1 mmol of the ligand was added to the organic phase before mixing with the solution of NaOCl. In the reactions with PhIO, this reagent was added instead of NaOCl. The residue was analysed by ^1H and ^{13}C NMR spectroscopy. The ee was determined by GC or by ^1H NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent. The yields, ri and ee are given in the Tables above.

^1H and ^{13}C NMR data

1,2-Epoxyhex-3-ene. δ_H 1.02 (t, *J* 6.4, 3 H), 2.09 (q, *J* 6.4, 2 H), 2.66 (dd, *J* 2.8, 5.2, 1 H), 2.96 (dd, *J* 4.1, 5.2, 1 H), 3.33 (m, 1 H), 5.13 (dd, *J* 8.2, 15.4, 1 H) and 6.02 (d, *J* 15.4, 1 H); δ_C 13.1, 25.3, 48.8, 52.6, 126.5 and 138.8; *m/z* 98 (M^+).

4,5-Epoxy-2,5-dimethylhex-3-ene. δ_H 1.29 (s, 3 H), 1.36 (s, 3 H), 1.78 (d, *J* 1.5, 3 H), 1.79 (d, *J* 1.5, 3 H), 3.81 (d, *J* 8.1, 1 H) and 5.04 (d, *J* 8.1, 1 H); δ_C 18.4, 24.8, 26.1, 59.7, 60.8, 120.0 and 140.4; *m/z* 126 (M^+).

3,4-Epoxy-1-(*p*-tolyl)but-1-ene. δ_H 2.34 (s, 3 H), 2.78 (dd, *J* 2.5, 5.1, 1 H), 3.06 (dd, *J* 4.1, 5.1, 1 H), 3.52 (m, 1 H), 5.82 (dd, *J* 7.9, 15.9, 1 H), 6.79 (d, *J* 15.9, 1 H), 7.16 (d, *J* 8.1, 2 H) and 7.28 (d, *J* 8.1, 2 H); δ_C 29.3, 49.3, 52.8, 125.8, 129.7, 130.5, 133.2, 134.6 and 138.0; *m/z* 160 (M^+).

3,4-Epoxy-1-Phenylbut-1-ene. δ_H 2.78 (dd, *J* 3.0, 5.2, 1 H), 3.07 (dd, *J* 4.1, 5.2, 1 H), 3.53 (m, 1 H), 5.88 (dd, *J* 8.0, 16.0, 1 H), 6.82 (d, *J* 16.0, 1 H) and 7.20–7.43 (m, 5 H); δ_C 49.3, 52.6, 126.9, 128.1, 128.5, 128.6, 134.6 and 136.1; *m/z* 146 (M^+).

1-(*p*-Bromophenyl)-3,4-epoxybut-1-ene. δ_H 2.78 (dd, *J* 2.7, 5.2, 1 H), 3.07 (dd, *J* 4.2, 5.2, 1 H), 3.51 (m, 1 H), 5.88 (dd, *J* 7.8, 16.0, 1 H), 6.75 (d, *J* 16.0, 1 H), 7.24 (d, *J* 8.5, 2 H) and 7.45 (d, *J* 8.5, 2 H); δ_C 49.2, 52.4, 121.9, 127.8, 127.9, 131.7, 133.3 and 135.0; *m/z* 226 (M^+).

3,4-Epoxy-1-(*p*-Nitrophenyl)but-1-ene. δ_H 2.81 (dd, *J* 2.7, 5.2, 1 H), 3.11 (dd, *J* 4.2, 5.2, 1 H), 3.56 (m, 1 H), 6.09 (dd, *J* 7.6, 16.1, 1 H), 6.87 (d, *J* 16.1, 1 H), 7.52 (d, *J* 8.9, 2 H) and 8.20 (d, *J* 8.9, 2 H); $\delta_C(CDCl_3)$ 49.4, 52.0, 124.1, 126.9, 131.9, 132.0, 142.3 and 147.1; *m/z* 191 (M^+).

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