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Epoxy ketones as versatile building blocks in organic synthesis

Christelle Lauret*

Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Crown Street, Liverpool L7 7DB, UK

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Abstract—The major advances made in the functionalisation of racemic and optically active epoxy ketones where one or several stereogenic centres are either preserved or modified are reviewed. Some relevant applications to the synthesis of natural products and biologically active compounds are also described.

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*Fax: 0151 794 3588; e-mail: chlauret@hotmail.com

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1. Introduction

Racemic and optically active epoxy ketones are among the most versatile building blocks in organic synthesis. Indeed, both the ketone and epoxide moieties can be further functionalised to provide interesting intermediates, useful for the synthesis of natural products or biologically active compounds (Fig. 1).

For example, stereoselective addition of various nucleophiles (hydride, organometallic reagents) to the ketone affords secondary or tertiary epoxy alcohols, which would be more difficult to obtain using other methodologies. Further manipulations can then furnish interesting polyhydroxyl compounds bearing several stereogenic centres. Many more transformations can be achieved on the ketone moiety, such as reductive amination, Baeyer–Villiger oxidation, Wittig olefination and Meerwein–Pondorf–Verley reduction–alkylation.

On the other hand, the epoxide can also be opened by nucleophiles in a *syn*- or *anti*-stereoselective manner and both at the α- or the β-position depending on the conditions used. Reductive cleavage or reductive alkylation of the epoxide also provide useful synthetic intermediates.

This report covers the major advances made in such functionalisations of α,β-epoxy ketones where one or several stereogenic centres are either preserved or modified. Some relevant synthetic applications are described in the last part of the report. The chemistry of epoxy ketones where elimination follows functionalisation of the epoxy ketone, such as transformations leading to functionalised unsaturated ketones, diketones or related substrates are not within the scope of this report.

2. Ketone transformation

2.1. Synthesis of α,β-epoxy alcohols

The stereoselective synthesis of α,β-epoxy alcohols has been the subject of extensive study. They can be obtained via diastereoselective epoxidation of the corresponding allylic alcohols.[1–8] Alternatively, diastereoselective reduction or organometallic addition to the ketone moiety of an epoxy ketone provides the corresponding secondary (Section 2.1.1) or tertiary epoxy alcohols (Section 2.1.2), respectively.

2.1.1. Ketone reduction

2.1.1.1. *anti*-Epoxy alcohols

2.1.1.1.1. Borohydride reagents. A wide range of methods for the *erythro*-selective reduction of α,β-epoxy ketones has been developed in the last twenty

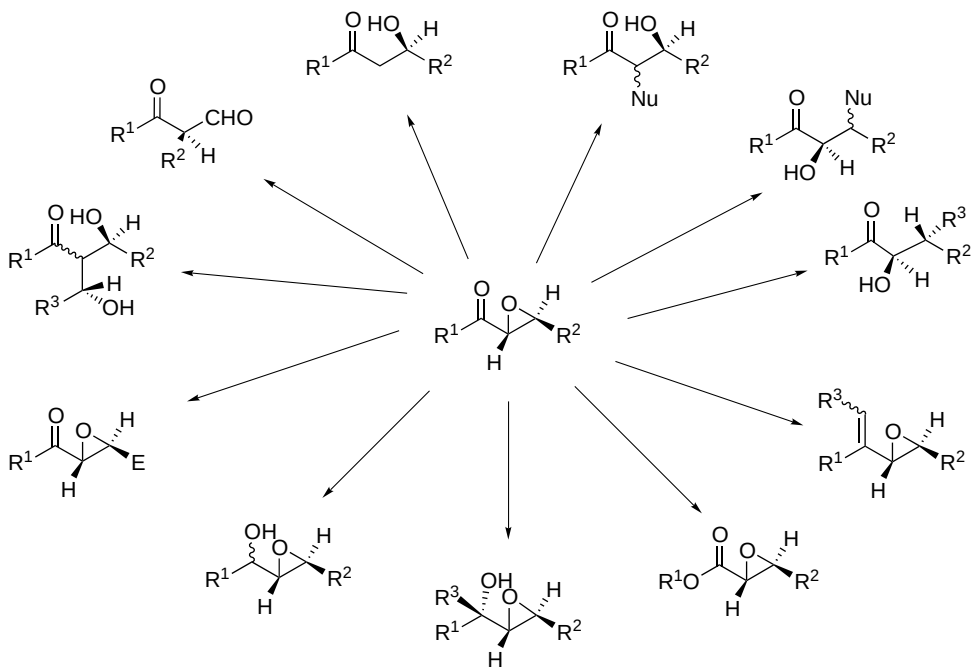


Figure 1. General picture of the transformations of α,β-epoxy ketones featured in this report.

years, most of which involve the use of borohydride reagents. Chautemps et al. showed that the stereoselectivity of sodium borohydride reductions was very much substrate dependant.[9,10] Most notably any bulky substituent at the α-position dramatically reduces the selectivity of the reduction (Table 1). This problem was solved by carrying out the reduction with zinc borohydride.[11,12] It was shown that very high diastereoselectivities are obtained irrespective of the substitution pattern of the epoxide (Table 1). This methodology was subsequently applied to optically active epoxy ketones that had been obtained using the polyleucine-mediated epoxidation of α,β-unsaturated enones.[13]

Several other borohydride reagents have been developed as alternatives to zinc borohydride. Rücker et al. showed, for example, that the Luche reduction conditions[14] (consisting of cerium trichloride heptahydrate and sodium borohydride) also provide excellent diastereoselectivities in favour of the *anti*- (or *erythro*-)-epoxy alcohol.[15] Indeed, some substrates showed even better selectivities under Luche conditions than when using $Zn(BH_4)_2$.[16] Use of sodium borohydride with either calcium chloride or lanthanum chloride gave analogous results to those obtained with zinc borohydride (Table 1).[17,18]

Recently, diisopropoxytitanium(III) tetrahydroborate has been employed for similar chemo- and stereoselective reductions of epoxy ketones.[19] High yields and stereoselectivities were obtained for cyclic epoxy ketones providing the corresponding *anti*-epoxy alcohols. However, lower diastereoselectivities were observed for acyclic ketones.

2.1.1.1.2. Miscellaneous reagents. Halodibutyltin hydrides have proved to be powerful reducing agents for epoxy ketones.[20] When Bu_2SnClH is used, only reductive cleavage of the epoxide is observed. However, by using Bu_2SnFH in THF along with HMPA, high *anti*-stereoselective reduction of the epoxy ketone is obtained furnishing the desired epoxy alcohol in good yield under mild conditions.[21] The formation of the HMPA–Bu_2SnFH complex (Fig. 2) as the active reducing agent was confirmed by NMR spectroscopy.[22] It was found that despite the highly coordinative effect of HMPA, the Lewis acidity of the tin atom was preserved due to the presence of the electronegative fluoride. Chelation of the tin atom to the epoxide oxygen explains the *anti*-selectivity observed (see Section 2.1.1.1.3).[22]

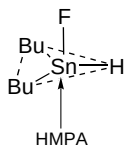
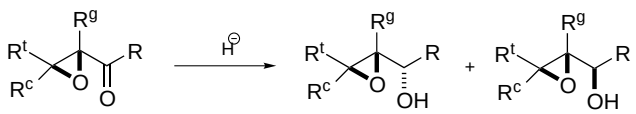


Figure 2. HMPA–Bu_2SnFH complex.

Another approach utilises trimethoxysilanes in the presence of a catalytic amount of lithium methoxide.[23] Using this reagent, epoxy ketones are converted either to *anti*- or *syn*-epoxy alcohols, depending on the solvent used. Employment of a non-polar solvent such as Et_2O results in high *anti*-stereoselectivity, whereas the opposite selectivity is observed using very polar solvents such as HMPA or DMPU.

Table 1. Reduction of α,β-epoxy ketones with borohydride reagents



1 *anti*-**2** *syn*-**3**

Entry	R	R^{gem}	R^{trans}	R^{cis}	$NaBH_4$[9,10] **2**:**3**	$Zn(BH_4)_2$[11,12] **2**:**3**	$NaBH_4$–$CeCl_3$[16] **2**:**3**	$NaBH_4$–$CaCl_2$[17,18] **2**:**3**
1	Me	H	H	H	100:1	98:2	81:19	–
2	*t*-Bu	H	H	H	≥95:≤5	–	–	–
3	Me	Me	H	H	55:45	90:10	91:9	–
4	Me	H	H	Me	≥95:≤5	–	–	–
5	Me	H	H	Me	90:10	–	–	–
6	Me	H	Me	Me	86:14	>99:<1	>99:<1	97:3
7	Me	Me	Me	H	65:35	84:16	93:7	98:2
8	Me	Me	Me	Me	46:54	>99:<1	>99:<1	–
9	*t*-Bu	H	Me	H	≥95:≤5	–	–	–
10	Me	H	*t*-Bu	H	85:15	–	–	–
11	Me	H	H	*t*-Bu	100:0	–	–	–
12	Et	Me	H	H	–	99:1	99:1	–
13	Et	Me	Et	H	–	99:1	–	–
14	*n*-Bu	Me	H	H	–	97:3	–	19:1
15	*n*-Bu	H	H	H	–	–	–	85:15
16	*n*-Bu	H	H	Me	–	–	–	49:1
17	*n*-Bu	H	Me	H	–	–	–	88:12
18	Ph	H	Me	H	–	–	–	91:9

2.1.1.1.3. Mechanistic considerations. The diastereoselective outcome of all of these reduction reactions can be explained using the Cram chelation model.[24,25] Indeed, all of these methods involve the chelation of a metal to the oxygen of both the epoxide and ketone functions, thereby forming a rigid five-membered ring. Hydride then attacks the ketone from the less hindered face (Fig. 3).

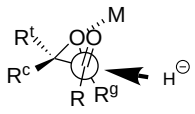


Figure 3. Cram's chelation model.

Some evidence for a chelation controlled reduction model was obtained by study of the $CaCl_2$–$NaBH_4$ reduction of epoxy ketones.[17] Upon addition of $CaCl_2$ to a MeOD solution of an α,β-epoxy ketone, a deshielding of both the epoxide α-methine proton and the methyl protons on the methyl ketone in the ^1H NMR spectrum was observed. These chemical shift changes clearly indicate the coordination of the metal to both oxygens.

2.1.1.2. *syn*-Epoxy alcohols. In contrast to the *anti*-selective carbonyl reduction of epoxy ketones, inventing methods for the *syn*-selectivity reduction has proved a lot more challenging due to the difficulty in overcoming the coordinative effect of the epoxide oxygen. Indeed, only a few such methods have been developed.

Fujita et al. studied the fluoride ion-catalysed reduction of carbonyl groups with hydrosilanes.[26,27] A wide range of silanes and solvents were screened and it was found that $PhMe_2SiH$ and TBAF in polar solvents such as HMPA or DMPU provide the best yields of the corresponding alcohols.[26] Furthermore, when the ketone is functionalised at the α-position, a highly *threo*-selective reduction is observed. Thus, α-alkoxy, α-amino ketones or α-substituted β-keto amides are reduced with *syn*:*anti* ratios typically greater than 9:1. However, only moderate results are obtained for α,β-epoxy ketones with *syn*:*anti* ratios ranging from 65:35 to 71:29.

Higher diastereoselectivities are obtained by employing a novel organotin hydride reagent.[20,28,29] Although Bu_3SnH itself does not show any reduction activity, the addition of tetrabutyl ammonium salts provides high yields and stereoselectivities of the corresponding *syn*-epoxy alcohols.[29] Bu_4NF and Bu_4NCN give the best results with *syn*:*anti* ratios varying from 78:22 to 100:0. The diastereoselective outcome of the reaction is explained in terms of the Felkin–Ahn model (Fig. 4).[30]

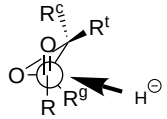


Figure 4. Felkin–Ahn model.

The anion (F^- or CN^-) tightly coordinates to the tin atom (Fig. 5) decreasing its Lewis acidity and therefore preventing its chelation to the epoxide oxygen.

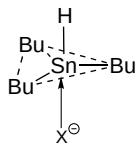


Figure 5. Bu_3SnH–TBAX complex (X = CN, F).

Another example of *syn*-selective carbonyl reduction of epoxy ketones was described in the previous paragraph using hydridosilicates in the presence of a very polar solvent such as HMPA and a catalytic amount of lithium methoxide.[23] Although it was not confirmed which metal (silicon or lithium) participates in the chelation model, it is believed that this chelation is broken by the highly polar solvent. The stereoselectivity is therefore explained using the Felkin–Ahn model.

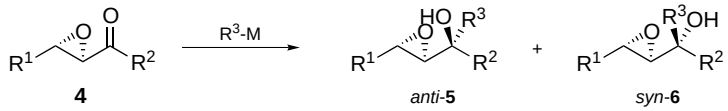
2.1.2. Organometallic addition reactions

2.1.2.1. Alkyl lithium, organocerium and Grignard reagents. Stereoselective organometallic addition to optically active epoxy ketones provides an efficient approach for the synthesis of tertiary epoxy alcohols. Various alkyl metal reagents such as alkyl lithium, organocerium and Grignard reagents have been investigated, and it was found that the diastereoselectivity of the reaction was very much dependant on both the nature of the alkyl metal and the solvent used.[31–33]

The first study of such additions featured β-trimethylsilyl-α,β-epoxy ketones.[31] Although alkyl lithium reagents showed poor selectivity, Grignard reagents provided excellent yields of the corresponding tertiary epoxy alcohol with the *anti*-isomer as the major product. It was also shown that the addition of HMPA could increase the selectivity to over 99:1 (*anti*:*syn*) in most cases; however, methyl ketones gave poor product ratios (Table 2). The diastereoselectivity of the reaction can be explained in terms of the Cram chelate model. Both the epoxide and the ketone oxygen atoms coordinate to the metal and the alkyl metal species then attacks from the less encumbered face. The lower selectivity observed for the methyl ketone derivative can also be explained by the decreased steric demand of the methyl group. This methodology was then further extended to the synthesis of chiral 2,3-epoxy-1,4-butanediols.[32]

Roberts et al. also investigated such transformations comparing the use of organocerium and Grignard reagents.[33,34] The latter were found to give better results and similar observations to those of Sato[31] were made. Indeed, only in the case of a methyl ketone was the diastereoselectivity moderate, other substrates giving excellent diastereomeric ratios.

Table 2. Addition of organometallic reagents to epoxy ketones



Entry	R^1	R^2	Alkyl–metal	Ratio **5**:**6**	Yield (%)	Ref.
1	-$SiMe_3$	*n*-Bu	MeLi–THF	2:1	98	31
2	-$SiMe_3$	*n*-Bu	MeMgI–THF	4:1	99	31
3	-$SiMe_3$	*n*-Bu	MeMgI–THF–HMPA	>99:1	91	31
4	-$SiMe_3$	*n*-Bu	EtMgBr–THF	>99:1	89	31
5	-$SiMe_3$	*n*-Bu	PhMgI–THF	>99:1	98	31
6	-$SiMe_3$	Me	*n*-BuMgBr–THF–HMPA	5:1	90	31
7	-$SiMe_3$	Et	*n*-BuMgBr–THF	>99:1	94	31
8	-$SiMe_3$	C_5H_{11}	MeMgI–THF–HMPA	>99:1	90	31
9	-CH_2OTBS	*n*-Bu	MeMgI–THF–HMPA	49:1	72	32
10	-CH_2OTBS	Me	BuMgCl–THF–HMPA	3:1	n.d.	32
11	-CH_2OTBS	Ph	MeMgI–THF–HMPA	49:1	92	32
12	-CH_2OTBS	Me	PhMgBr–THF–HMPA	99:1	87	32
13	Ph	Ph	MeLi–CeI_3	4:1	91	33
14	Ph	Ph	*n*-BuLi–CeI_3	9:1	80	33
15	Ph	Ph	MeMgI	>99:1	89	33
16	Ph	Ph	BuMgBr	>99:1	60	33
17	Ph	Me	PhMgBr	6:1	70	33

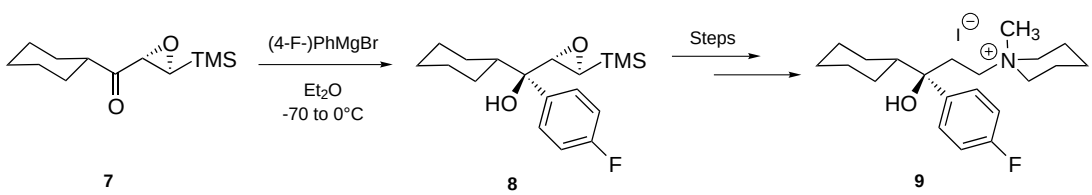
Chelation-controlled addition of a Grignard reagent to an optically active epoxy ketone has been employed for the synthesis of anticholinergic agents.[35] Thus, epoxy ketone **7** was arylated with 4-fluorophenylmagnesium bromide to generate the corresponding *anti*-epoxy alcohol **8** in 83% yield with complete diastereoselectivity. Both enantiomers of the epoxy ketone were arylated, and their corresponding epoxy alcohols could be further functionalised to give both (*R*)-**9** and (*S*)-**9** target compounds (Scheme 1).

2.1.2.2. Organotin reagents. Only one example of chemoselective carbonyl alkylation of epoxy ketones using organostannanes has been reported. This is probably due to the relatively low reactivity of such stannanes towards ketone alkylation; preliminary activation with Lewis acids such as $BF_3{\cdot}Et_2O$, titanium chlorides, or Sn(IV) chlorides is generally required. However, such conditions would be incompatible with the epoxide moiety and side reactions such as epoxide opening could occur. Hence, when chalcone oxide **10** ($R^1=R^2=$ Ph) was treated with allyltri-*n*-butyltin in the presence of $BF_3{\cdot}Et_2O$, a complex mixture was obtained and none of the desired allylated ketone was detected.[36] However, a combination of lead(II) iodide and HMPA proved to be an efficient catalytic system for such a transformation. Catalytic quantities of both PbI_2 and HMPA were necessary for the reaction to occur (10 mol% for PbI_2, 20 mol% for HMPA).[36] Thus, various epoxy ketones were selectively allylated at the carbonyl moiety in moderate to high yields (cf. Table 3). The use of diallyldi-*n*-butyltin instead of allyltri-*n*-butyltin improved the yield in some cases. Another important characteristic of this reaction is the high diastereoselectivity observed, providing the *anti*-epoxy alcohol as the major or sole product in all cases. Although the mechanism has not yet been proved, it is assumed that the reaction proceeds in accordance with Cram's chelation model.

Notably these α,β-epoxy alcohols are versatile intermediates which can undergo further manipulations such as Payne rearrangement, epoxide opening, reductive cleavage and semi-pinacol rearrangements.

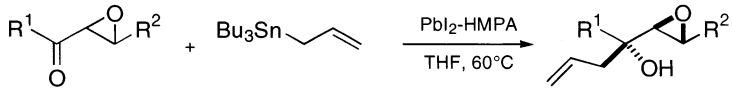
2.2. Miscellaneous ketone transformations

2.2.1. Reductive amination. There are few reports of the preparation of amino epoxides via reductive amination of α,β-epoxy ketones, probably because of the propensity for epoxides to undergo ring-opening in the presence of amines.

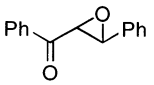
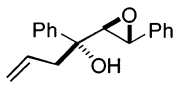
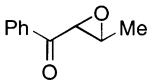
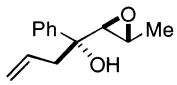
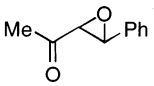
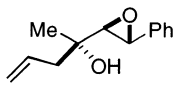
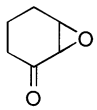
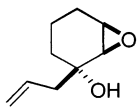
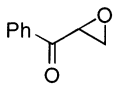
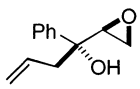


Scheme 1.

Table 3. Reaction of organostannanes with α,β-epoxy ketones



10 **11**

Entry	Substrate	Allylic Tin	Product	Yield
1		**ATT**		100 [a), c)]
2		**ATT**		99 [a), c)]
3		**ATT**		32 [a)]
4		**DTT**		77 [b), d)]
5		**ATT**		18 [a)]
6		**DTT**		73 [b), c)]
7		**DTT**		56 [b), c)]

[a] Conditions: epoxy ketone **10** (1 mmol), allyltributyltin (ATT) (1 mmol), PbI_2 (0.1 mmol), HMPA (0.2 mmol), THF (1 mL), 60°C, 24h. [b] Conditions: epoxy ketone **10** (1 mmol), diallyldibutyltin (DTT) (1 mmol), PbI_2 (0.1 mmol), HMPA (0.2 mmol), THF (1 mL), rt, 24 h. [c] Diastereomer ratio = >99:<1. [d] Diastereomer ratio = 87:13.

The first method was developed in 1994.[37] Treatment of epoxy ketone **12** (R = ^{i}Bu) with benzylamine and sodium triacetoxyborohydride, gave a 9:1 mixture of diastereomers in favour of the *anti*-epoxy amine **13**. However, the yield was very poor (29%), due to competitive aza-Payne rearrangement; consequently, the use of a milder reducing agent was investigated. Using tetramethylammonium triacetoxyborohydride, the reductive amination of several epoxy ketones to the corresponding epoxy amines was achieved with yields ranging from 30 to 69%, and *anti*:*syn* ratios from 72:28 to 19:1 (Table 4).

The stereoselective outcome of the reaction can be explained by the formation of an intermediate bearing an internal hydrogen bond between the epoxide oxygen and the hydrogen of the imminium salt. Hydride then attacks from the less hindered face to give the *anti*-stereoisomer as the major product (Fig. 6).

The same methodology has been applied to the synthesis of *syn*- and *anti*-*N*-protected 3-amino-2-hydroxy alkanoic esters[38] and to the *N*-protected Abbott aminodihydroxyethylene dipeptide isostere subunit **17** (Scheme 2).[39]

As part of a study into the synthetic applications of organotin reagents, Shibata et al. showed that Bu_2SnClH could also be used for the reductive amination of carbonyl compounds.[40] Several functionalised aldehydes and ketones were studied, and one example of an epoxy ketone was examined. Although it had been reported that this reagent could reductively cleave the epoxide moiety (cf. Section 2.1.1.1.2), they found that, in the presence of an amine, the imine moiety was reduced in almost quantitative yield without affecting the epoxide ring. However, the diastereoselectivity of the reaction was not specified.

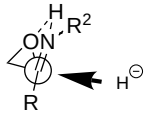
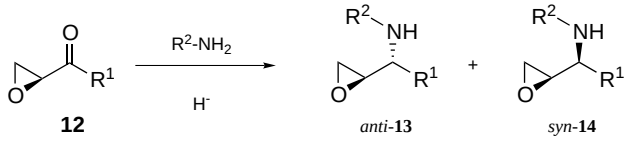


Figure 6.

Table 4. Reductive amination of α,β-epoxy ketones to the corresponding epoxy amines using Me_4NBH_4 as the hydride donor



Entry	Epoxy ketone **12** (R^1)	Amine (R^2)	Ratio[b] **13**:**14** (% yield[c])
1	Me	Bn	72:28 (69)
2	*i*-Pr	Bn	93:7 (33)
3	*i*-Pr[a]	Allyl	91:9 (30)
4	*i*-Bu	Bn	92:8 (68)
5	*i*-Bu[a]	Allyl	93:7 (55)
6	Ph-CH_2	Bn	94:6 (57)
7	C_6H_{11}-CH_2	Bn	19:1 (56)

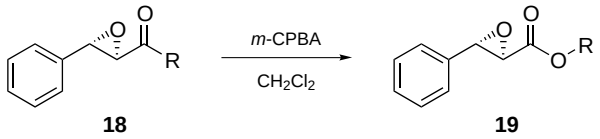
[a] Racemic substrate.
[b] Determined by HPLC and 250 MHz ^{1}H NMR spectroscopy.
[c] Combined, isolated yields of **13** and **14**. Typical procedure: to a mixture of epoxy ketone **12** (1 mmol), amine (1.3 mmol) and acetic acid (1.3 mmol) in 1,2-dichloroethane was added tetramethylammonium triacetoxyborohydride and 4 Å molecular sieves (0.5 g). After stirring for 8 h at rt, the mixture was hydrolysed (K_2CO_3, 1 mol dm^{-3}) and purified.

2.2.2. Baeyer–Villiger oxidation. Baeyer–Villiger oxidation of optically active α,β-epoxy ketones provides an efficient approach to the synthesis of chiral α,β-epoxy esters. Thus, treatment of a number of optically active epoxy ketones **18** with *m*-CPBA in dichloromethane afforded the corresponding epoxy esters **19** in 57–80% yield with no apparent loss of diastereomeric purity (cf. Table 5).[41] As expected, migration of the aryl substituent is favoured; however, one case showed migration of the epoxide moiety lowering the yield of the desired epoxy ester.

The methodology was further extended to *tert*-butyl ketones for the synthesis of Diltiazem and C(13) side-chain of Taxol (cf. Section 5).[42]

2.2.3. Wittig olefination. The carbonyl moiety of an epoxy ketone can be transformed into an alkene via a Wittig reaction. The resulting epoxy alkenes are then prone to various transformations. This strategy was applied in the stereoselective synthesis of some natural plant growth promoting steroids, as shown in Scheme 3.[43] Epoxy ketone **20** was converted to the olefin under Horner–Wadsworth–Emmons conditions, using dimethylphosphonoacetate, furnishing a 10:1 mixture of (*Z*)- and (*E*)-α,β-unsaturated-γ,δ,α-epoxy acid esters **21**

Table 5. Baeyer–Villiger oxidation of α,β-epoxy ketones



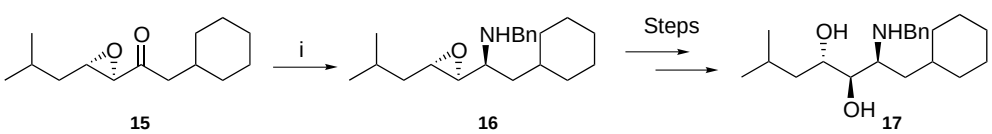
Entry	R	Yield (%)[a]	E.e. (%)[b]
1	Phenyl	74	>99
2	*p*-Cl-Phenyl	88	>99
3	*p*-OMe	57	90
4	*p*-Me-Phenyl	80	>99
5	2-Naphthyl	59	>99

[a] Yields based on recrystallised material.
[b] % e.e. of recrystallised material.

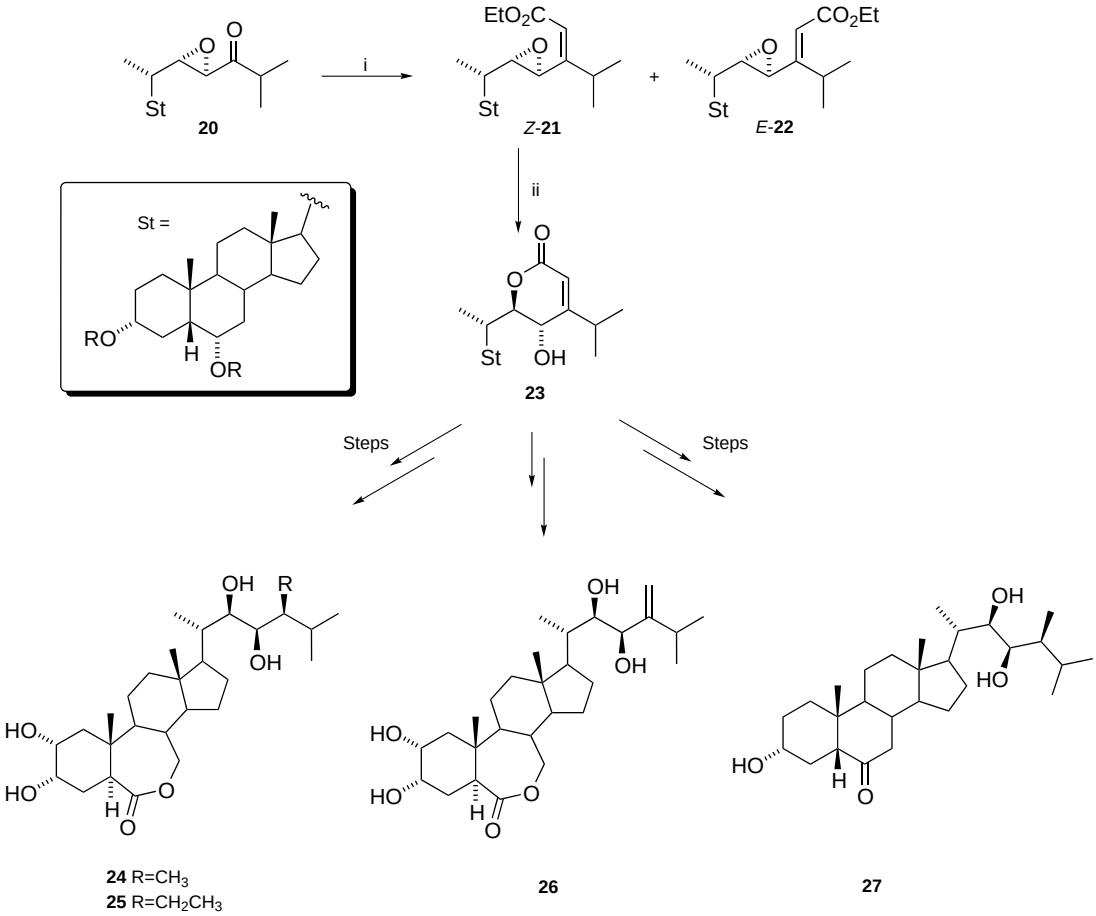
and **22**. The (*Z*)-isomer could be separated by flash chromatography, and subsequently lactonised under acidic conditions to provide the α,β-unsaturated-δ-lactone **23** in quantitative yield. The epoxide was opened with complete inversion of configuration. Further transformations then led to the stereoselective synthesis of brassinolide **24**, homobrassinolide **25**, the side-chain of dolicholide **26** and typhaserol **27**. The same methodology was applied to the synthesis of 26,27-dinorbrassinolide.[44]

Another example of Wittig olefination of epoxy ketones was reported in a study on the hydrozirconation of alkenyloxirane derivatives.[45] Several alkenyloxiranes, including one example derived from α,β-epoxy ketone **28** (Scheme 4), were synthesised and subjected to chemoselective hydrozirconation using the Schwartz reagent (Cp_2ZrHCl, Scheme 4).

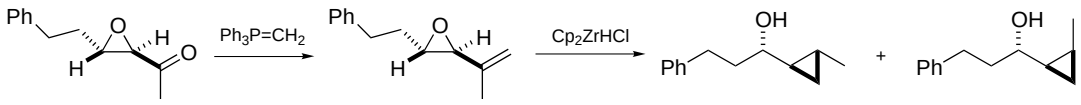
2.2.4. Meerwein–Pondorf–Verley reaction. Enolisable epoxy ketones such as **32** have been shown to be prone to Meerwein–Pondorf–Verley hydride-transfer reduction by Thebtaranonth et al.[46]. Thus, treatment of **32** with lithium diisopropylamide (LDA) leads to epoxy alcohol **33** as a single undefined diastereoisomer in 18–23% yield together with recovered starting material (50–62%). However, when using lithium tetramethylpiperidide (LTMP) as the base, the epoxide enolate **34** obtained readily reacts with electrophiles. Surprisingly, reaction of the enolate **34** with an excess of benzaldehyde resulted in the formation of a single isomer of the epoxy-1,3-diol monoester **35** in 63% yield along with recovered starting material **32**. It was suggested that this transformation proceeds via addition of the enolate **34** to two molecules of benzaldehyde and hydride transfer, in a concerted fashion, through a cyclic transition state (Scheme 5). This transformation



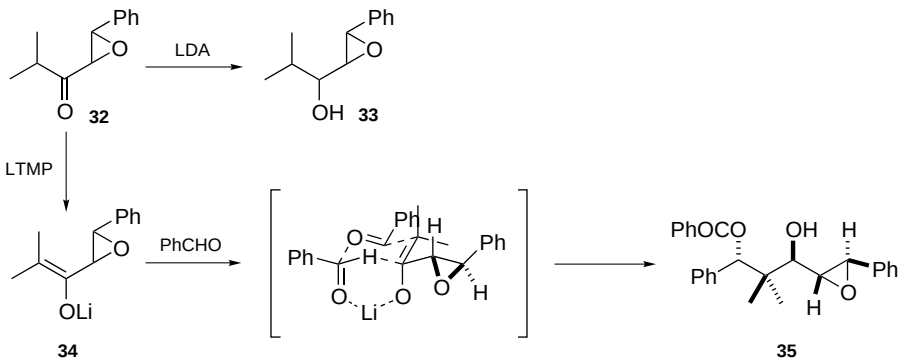
Scheme 2. Synthesis of the Abbott amino dihydroxyethylene dipeptide isostere subunit. *Reagents and conditions*: (i) $PhCH_2NH_2$, AcOH, $Me_4NBH(OAc)_3$, CH_2Cl_2, 4 Å molecular sieves, 8 h.



Scheme 3. Stereoselective synthesis of Brassinolide and its derivatives. *Reagents and conditions*: (i) (a) NaH/$(MeO)_2P(O)CH_2CO_2Et$, (b) Ac_2O/Py; (ii) 30% $HClO_4$/MeOH.



Scheme 4. Wittig olefination of epoxy ketone.



Scheme 5. Meerwein–Pondorf–Verley reaction of α,β-epoxy ketones with benzaldehyde.

was applied to several other epoxy ketones, all giving a single diastereomer of product (yields ranging from 46 to 74%), thus providing an efficient method for the synthesis of epoxy-1,3-diol monoesters.

A similar strategy was later applied to chalcone epoxides leading to the synthesis of epoxy aldol and epoxy tetrahydrofuran derivatives.[47]

3. Epoxide transformation

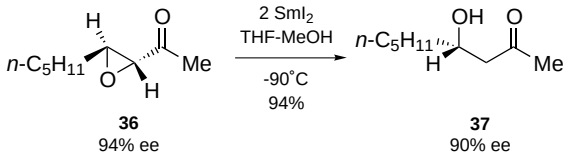
3.1. Functionalisation at the α-position

3.1.1. Reductive cleavage. α,β-Epoxy ketones can be chemo- and regioselectively reduced to β-hydroxy ketones (aldol adducts). This methodology has received particular interest since it provides a mild alternative method to the traditional aldol condensation and allows access to acyclic (intermolecular) as well as cyclic (intramolecular) aldol adducts. It has also been shown that the strategy can be applied to polyfunctional systems en route to natural products.

The first few methods developed, using chromium(II) salts,[48–57] zinc/acetic acid[58,59] or electrochemical methods,[60] often showed undesirable side reactions such as dehydration of the aldols to give the corresponding unsaturated ketones. Later, more efficient methods involving the use of Al/Hg,[55–57,61] NaI/NaOAc[62] or NaTeH[63] were reported.

In 1986, the samarium(II) iodide procedure was discovered which has become one of the most widely used methods for the reductive cleavage of epoxy ketones in organic synthesis. Various acyclic as well as cyclic epoxy ketones can be reduced by this method generally affording the corresponding aldols in good yields.[64] It was shown that the stereochemistry is retained at the β-position but not at the α-position. This observation has been explained mechanistically by the formation of an enol intermediate during the reductive cleavage.

This approach was applied to the chiral epoxy ketone **36** leading to the corresponding chiral, non-racemic aldol product **37** with almost no loss of enantiomeric purity at the β-carbon (Scheme 6).



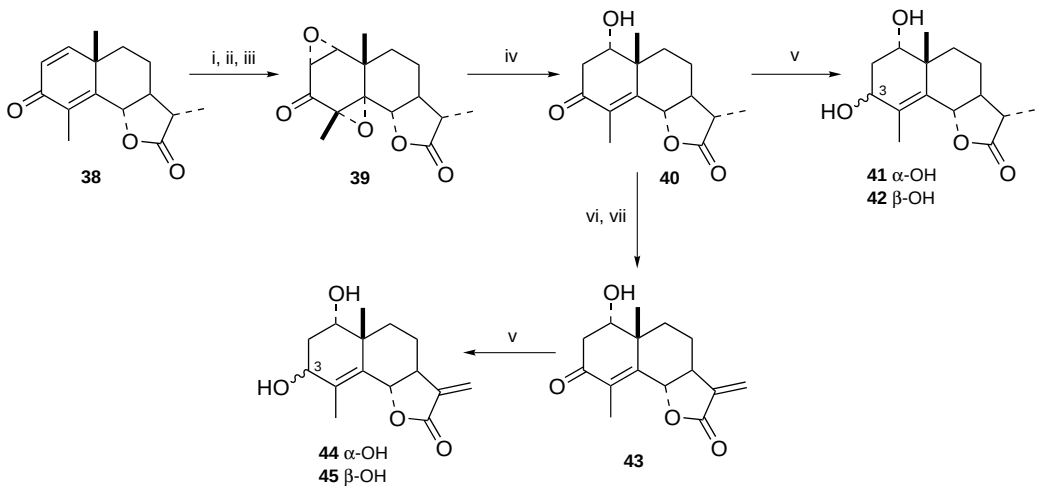
36 94% ee **37** 90% ee

Scheme 6.

A diastereoselective SmI_2-mediated reduction of a trisubstituted epoxy ketone featured as a key step in a synthesis of the C(1)–C(12) segment of epothilone A and B.[65]

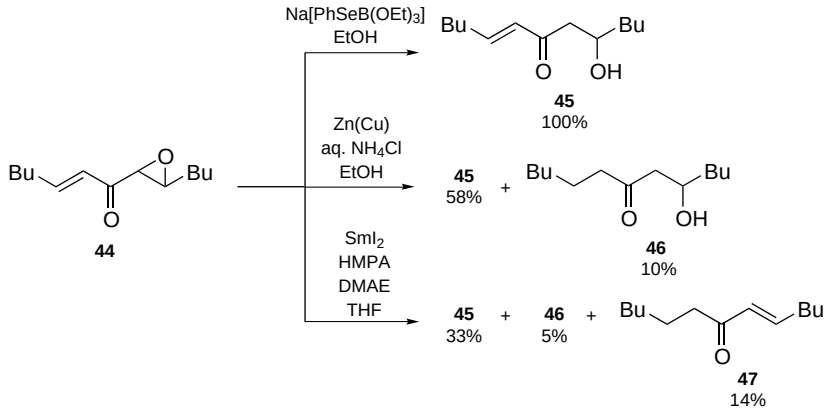
Alternatively a wide range of epoxy ketones may be reduced to aldol adducts by a selenium–borane complex $Na^+[PhSeB(OEt)_3]^-$, generated by $NaBH_4$ reduction of $(PhSe)_2$ in EtOH; typically, very short reaction times and excellent yields were reported.[66] The latter methodology has been applied to the synthesis of eudesmane sesquiterpene lactones[67] (Scheme 7) and naturally occurring diarylheptanoids.[68] To gain access to the eudesmane lactones the epoxy ketone intermediate **39** was obtained from α-santonin **38**. This epoxy ketone was then reductively cleaved to give dehydroisoerivanin **40** as the sole product in 80% yield. Although the presence of the diol was detected during the reduction, it was found that dehydration of the axial tertiary alcohol occurred under the reaction conditions. The other natural products **41**, **43** and **44** were then obtained either by reduction of ketone **40** or by selenium-mediated olefination and reduction at the 3-position.

The mechanism of this reductive cleavage most likely involves a substitution process, differing from the electron-transfer reduction systems previously described (such as SmI_2, zinc, chromium(III) salts, etc.) It is believed that an α-phenylseleno ketone intermediate is formed by selenium substitution at the α-position of the epoxy ketone. A second equivalent of the selenium borate



38 **39** **40** **41** α-OH **42** β-OH **43** **44** α-OH **45** β-OH

Scheme 7. Synthesis of eudesmane sesquiterpene lactones. *Reagents and conditions*: (i) DIBAH, toluene–THF; (ii) *m*-CPBA, CH_2Cl_2; (iii) CrO_3–2Py, CH_2Cl_2; (iv) $Na^+[PhSeB(OEt)_3]^-$, AcOH, EtOH; (v) $NaBH_4$, $CeCl_3$, MeOH; (vi) LDA, $(PhSe)_2$, THF; (vii) H_2O_2, AcOH, THF.



Scheme 8.

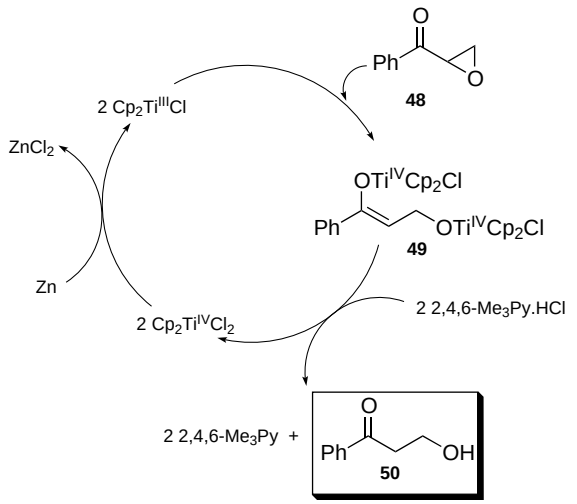
complex then attacks the selenium atom of this first intermediate to give a borane enolate along with diphenyl selenide. Subsequent protonation of the enolate provides the corresponding β-hydroxy ketone.

Significantly, this approach allows the chemoselective reduction of epoxy ketones in the presence of an enone moiety; generally, this discrimination is not possible with the electron-transfer reagents described. Indeed, a comparative study between $Na^+[PhSeB(OEt)_3]^-$, SmI_2, and Zn(Cu) has been made using the epoxy ketone **44** and analysing for reduction products **45**–**47**, thus confirming the ineffectiveness of the last two reagents for this transformation (Scheme 8).[69]

Although this process proved very versatile it suffers from the use of an excess of the phenyl selenolate complex. An alternative, catalytic method for the generation of the phenyl selenolate ion utilises a thiol/diselenide exchange reaction,[70] in which diphenyl diselenide is reduced in situ in the presence of *N*-acetylcysteine sodium salt. Thus, 5% of diphenyl diselenide proved sufficient to promote the reductive cleavage of chiral non-racemic epoxy ketones to the corresponding hydroxy ketones in high yields.

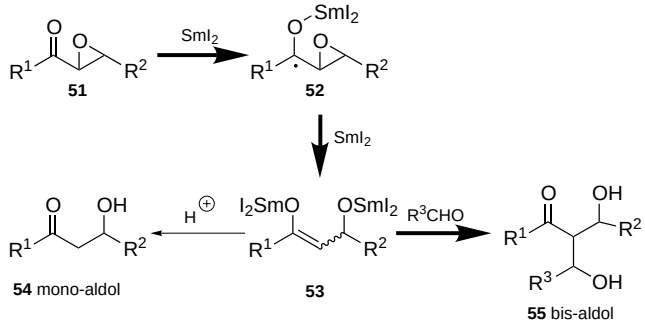
Recently, another approach using Cp_2TiCl has been reported by two groups.[71,72] A catalytic system consisting of Cp_2TiCl_2 (20 mol%), is reduced in situ to Cp_2TiCl, in the presence of powdered Zn (5 equiv.) and collidine hydrochloride (3 equiv.).[72] Epoxy ketone **48** reacts with the low-valent titanium(III) complex to give a titanium enolate β-alcoholate **49**. Subsequent protonation and regeneration of the titanocene(IV) dichloride by collidine hydrochloride provides hydroxy ketone **50**. The catalytic cycle is then completed by zinc reduction of Cp_2TiCl_2 to regenerate the active Cp_2TiCl (Scheme 9). Various epoxy ketones, including chiral, non-racemic epoxides, are reduced under these conditions, in moderate to high yields and short reaction times.

Other methodologies that have been employed sporadically include Pd-mediated hydrogenolysis (Pd(0)/HCOOH/Et_3N and H_2/Pd/C),[73] (H_2/Pd–$BaSO_4$, giving α-hydroxy ketone)[74,75] radical-induced epoxide cleavage using TBTH/AIBN,[76–79] TBTH/*hv*,[76,77] TBTH/amine/*hv*[80–82] or Al-Hg/ultrasound.[83]



Scheme 9. Proposed mechanism of the Cp_2TiCl-mediated catalytic reductive cleavage of epoxy ketones.

3.1.2. SmI_2-mediated aldol reactions. As described in the previous section, α,β-epoxy ketones can be reductively cleaved to β-hydroxy ketones using SmI_2 in the presence of a protic solvent. Modifications of this method in which the samarium enolate intermediate **53** generated during the reaction is trapped with an electrophile, such as an aldehyde, affords the corresponding bis-aldol products **55** (Scheme 10).[84]



Scheme 10.

It was found that bis-aldol adducts obtained from benzaldehyde were very prone to either dehydration at the 2-position or retro-aldol reactions. Consequently, their relative configuration could not be determined. However, in the case of aliphatic aldehydes, the bis-aldol adducts obtained proved stable enough to be converted to their corresponding acetonides. Their configurations were determined by ^{1}H NMR and only two of the four possible diastereomers were detected. It was suggested that a mixture of two isomeric samarium enolate intermediates **53** is generated, whereupon the reaction proceeds via Zimmermann-type transition states. Therefore, *syn*,*syn*-**55** is generated via transition state (A) while *anti*,*anti*-**55** is generated via transition state (D) as shown in Scheme 11 and Table 6.

Table 6. SmI_2-mediated aldol condensation of aldehydes with epoxy ketones

Entry	R^1	R^2	R^3	% Yield (A/B/C/D)[a]
1	Ph	Me	Ph	70 (n.d.)
2	Ph	Me	Et	75 (67/0/0/33)
3	Ph	Me	$Ph(CH_2)_2$	83 (61/0/0/39)
4	Ph	Me	*i*-Pr	88 (4/0/0/6)
5	Ph	*n*-Pr	$Ph(CH_2)_2$	90 (35/0/0/65)
6	Ph	*n*-Pr	*i*-Pr	84 (1/0/0/1)
7	Me	*i*-Pr	Et	85 (88/0/0/12)
8	Me	*i*-Pr	$Ph(CH_2)_2$	95 (3/0/0/1)
9	Me	Ph	$Ph(CH_2)_2$	84 (6/0/0/4)

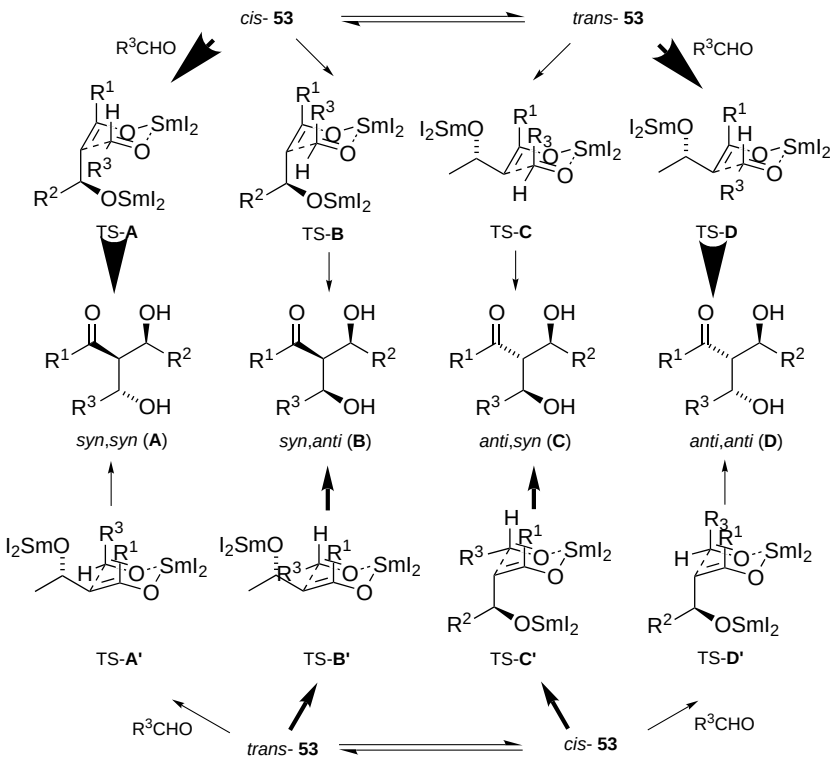
[a] The ratio of the four possible isomers was determined by integration of ^{1}H NMR signals from a mixture of the corresponding acetonide derivatives.

The reaction was also applied to the optically active epoxy ketone **51** (92% e.e., Table 6 entry 5) and no loss of optical purity was observed (both diastereomeric bis-aldol adducts were obtained with 92% e.e.).

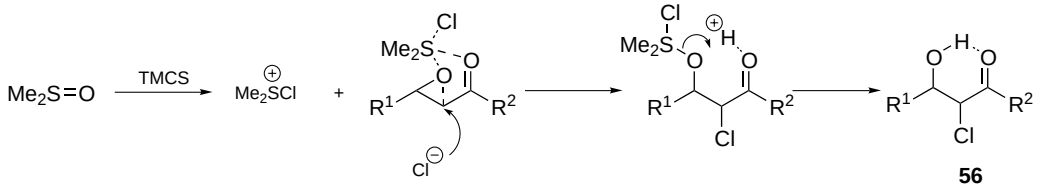
Another example of samarium iodide-mediated aldol condensation of an α,β-epoxy ketone has been used for the synthesis of spiro ketones.[85] The same strategy as that of Mukaiyama was employed but in an intramolecular fashion.

3.1.3. Synthesis of chlorohydrins. Generally epoxide ring opening of α,β-epoxy ketones with nucleophiles occurs at the β-position. This is due to the presence of the electron-withdrawing ketone moiety, which destabilises the developing charge as opening occurs at the α-position. It is not surprising therefore to find a paucity of examples of ring-opening at the α-position in the literature.

However, Grandi et al. have described an efficient stereo- and regiospecific transformation of α,β-epoxy ketones into 2-chloro-3-hydroxy ketones using trimethylchlorosilane–dimethyl sulfoxide (TCMS–DMSO).[86] It was found that a range of epoxy ketones afforded the corresponding 2,3-chlorohydrins **56** in high yields (72–97%). Only when the epoxide was substituted with a phenyl group did the cleavage of the C–O bond occur at the benzylic position. The stereochemistry of two substrates was determined to be *anti*. The chlorodimethylsulfonium species (Me_2SCl), formed in situ from TCMS and DMSO is thought to coordinate to both the epoxide and the ketone oxygens, S_N2 substitution of the chloride ion on the α-carbon then affords a six-membered hydrogen-bonded product (Scheme 12).



Scheme 11. Proposed reaction pathway for SmI_2-mediated aldol condensation of aldehydes with epoxy ketones.



Scheme 12. Formation of 2,3-chlorohydrins from the reaction of epoxy ketones with TMCS and DMSO.

3.1.4. Epoxide opening by sulfur nucleophiles. Selective cleavage of the α-C–O bond of epoxy ketones by sulfur nucleophiles is not very common, and a remote directing group is generally needed. Warren et al. utilised this approach as a key step in the synthesis of β-hydroxyallylic sulfides.[87] Thus, attack of thiol **57** on epoxy ketone **58** occurred preferentially at the less hindered site, distant from the Ph_2PO moiety to give a 5:2 mixture of diastereomers **59**. Stereoselective ketone reduction then provided a pair of separable diols which could be subjected to *syn*-elimination of $Ph_2PO_2^-$ to yield the desired *Z*-allyl sulfide **62** (Scheme 13).

Another example of α-substitution with sulfur nucleophiles was recently described by Wipf et al. as part of their study on the alkylating properties of epoxy ketone natural products.[88] Thus, epoxy ketone **64** was reacted with either thiophenol or glutathione to give a mixture of products which upon treatment with sodium carbonate afforded **66** in 71% yield. The latter was believed to arise from intermediate **65** resulting from opening of both rings of the epoxy ketone (Scheme 14).

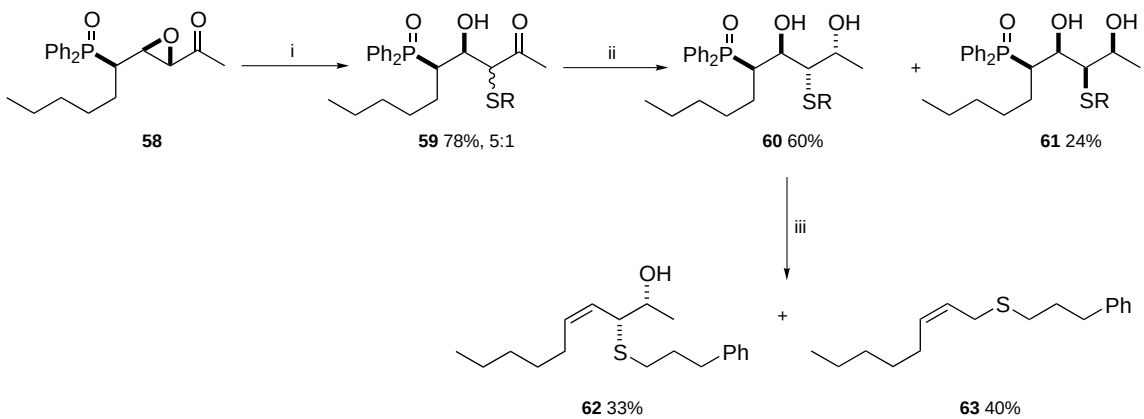
3.2. Functionalisation at the β-position

3.2.1. Intermolecular opening

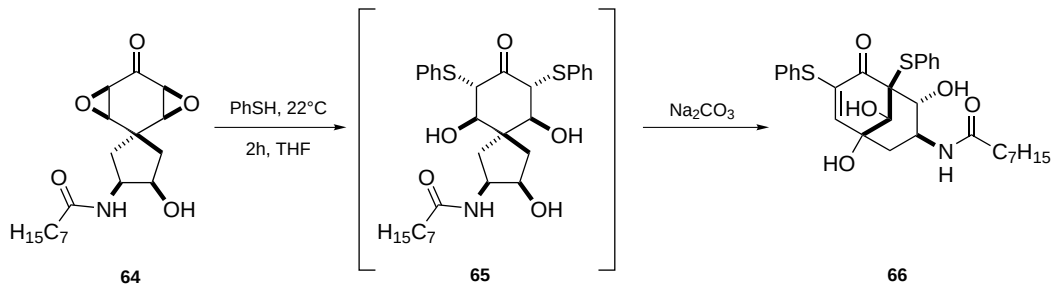
3.2.1.1. Halohydrin synthesis. The synthesis of halohydrins by cleavage of epoxides with halides has been extensively studied and has been reviewed;[89] however, only a few examples relating to epoxy ketones have been reported, enlisting the use of $(CH_3)_2CHO–TiCl_2$,[90] KI/acetic acid,[91] $SnCl_2$,[92] or $SnBr_4$.[93]

One of the most widely used methods involves the employment of HCl.[94] A mixture of *erythro*- and *threo*-chlorohydrins is generally obtained in a ratio depending on the solvent used.[95] Thus, when using a non-polar solvent such as benzene or CH_2Cl_2, an S_Ni ion-pair mechanism is generally involved and retention of configuration is observed leading to the *threo*-isomer (e.g. **68**) preferentially. The latter compound can be cyclised under basic conditions to yield the corresponding *cis*-epoxides (Scheme 15).[96,97]

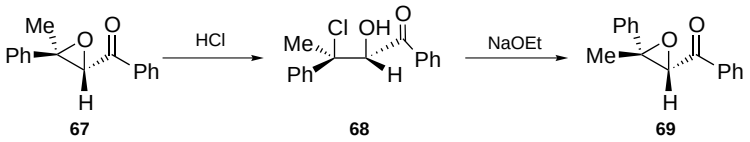
3.2.1.2. Sulfur nucleophiles. During their study on the synthesis of dihydroflavonols via intramolecular open-



Scheme 13. *Reagents and conditions*: (i) $Ph(CH_2)_3SH$ **57**, Et_3N, MeOH, rt, 6 h; (ii) $NaBH_4$; (iii) NaH, DMF.



Scheme 14.



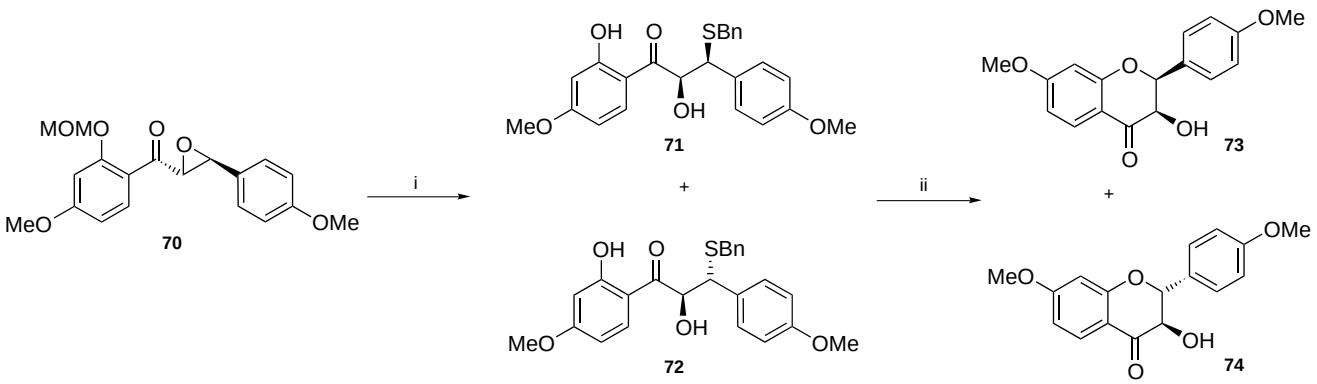
Scheme 15.

ing of 2′-MOM-protected hydroxy chalcone epoxides, Ferreira et al. observed two major limitations; partial epimerisation/racemisation in addition to migration of the aryl group led to low yields and diastereomeric excesses of the desired product (cf. intramolecular opening, Section 3.2.2.1). In order to prevent the racemisation process, the South African team investigated a two-step approach involving tin(IV) chloride-mediated epoxide opening with sulfur nucleophiles prior to deprotection of the MOM group, followed by cyclisation.[98] For example, treatment of epoxy ketone **70** with benzylthiol (BnSH) and $SnCl_4$ at −20°C opened the epoxide moiety; subsequent deprotection at 0°C afforded a mixture of *syn*- and *anti*-α,2′-dihydroxy-β-benzylsulfanyldihydrochalcones **71** and **72** (*syn*:*anti* ca. 2.3:1) in 93% yield. Cyclisation of the mixture using silver tetrafluoroborate ($AgBF_4$) in CH_2Cl_2 at 0°C, gave the desired flavonols **73** and **74** in 71% yield, as a 79:21 mixture of separable *cis*- and *trans*-diastereoisomers (Scheme 16).

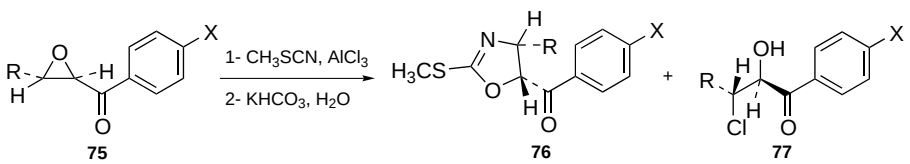
3.2.1.3. Reaction with methyl thiocyanate. *cis*-Oxazolines **76** have been synthesised by treatment of various epoxy ketones of the type **75** with methyl thiocyanate in the presence of aluminium trichloride.[99] It was suggested that opening of the epoxide at the benzylic centre occurs through a highly polar S_N2 type transition state, and inversion of configuration at the reaction centre was observed. The presence of electron-donating moieties on the aryl moiety decreased the yield of oxazoline due to competitive formation of chlorohydrin **77** (Scheme 17).

3.2.1.4. R_3Al reagents. Alkylation at the β-position of α,β-epoxy ketones using trialkylaluminium reagents was reported by Carde et al. in 1999.[100,101] It was found that slow addition of trimethylaluminium (10 equiv.) to a solution of epoxy chalcone **79** and water (6 equiv.) in 1,2-dichloroethane at −30°C afforded a mixture of *anti*- and *syn*-alcohols **80** and **81** in a ratio of 3:1 and 66% combined yield. Both the yield and diastereomeric ratio of the reaction could be improved to 83% and 10:1, respectively, by using only two equivalents of trimethylaluminium and 1.2 equivalents of water. The alcohol **83** was then used as a key intermediate in the synthesis of (*S*)-Naproxen **84**, a powerful anti-inflammatory agent (Scheme 18). Alkylation could also be performed using triethylaluminium affording the corresponding ethyl-substituted hydroxy ketones.

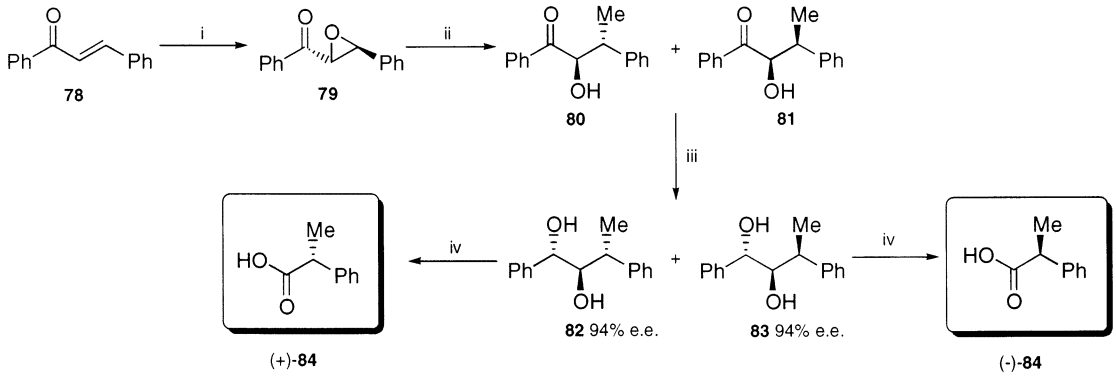
3.2.1.5. Miscellaneous. α,β-Epoxy ketones have been shown to react with electrophiles in the presence of tin halide complexes. Thus epoxy ketones **85** were reacted with benzoyl chloride in the presence of a catalytic amount of tin halide and PPh_3. The regioselectivity of the ring opening proved to be dependent on the complex used. Thus, Bu_2SnCl_2–PPh_3 provided compound **86** preferentially, whereas $SnCl_2$ yielded **87** as the major product (Table 7).[102]



Scheme 16. *Reagents and conditions*: (i) BnSH, $SnCl_4$, DCM, −20 to 0°C, 93%; (ii) $AgBF_4$, DCM, 71%.

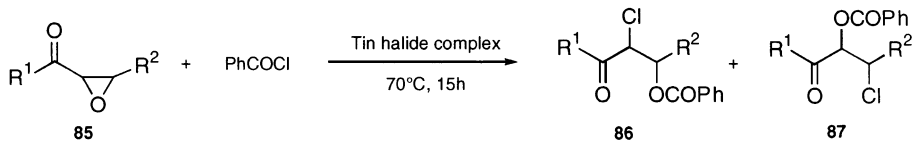


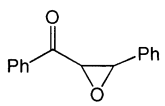
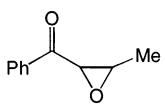
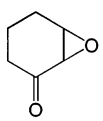
Scheme 17.



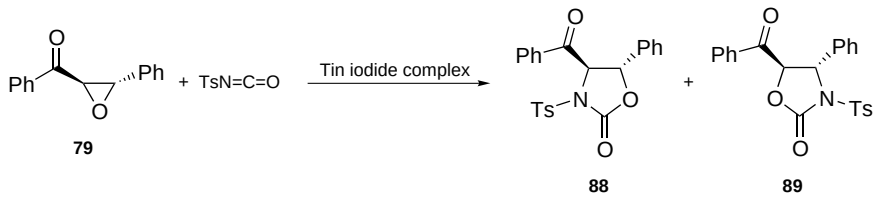
Scheme 18. Alkylation of epoxy ketones using trimethylaluminium. *Reagents and conditions*: (i) poly-L-leucine–SiO_2, urea–H_2O_2, DBU, 30 min, 90%; (ii) Me_3Al (2 equiv.), H_2O (1.2 equiv.), CH_2Cl_2, −78°C, 3 h, 88%; (iii) $Zn(BH_4)_2$ (0.3 equiv.), Et_2O, 0°C, 2 h, 95%; (iv) $NaIO_4$–SiO_2 (1.2 mmol/g, 3 equiv.), CH_2Cl_2, then Jones oxidation, 71%.

Table 7. Reaction of α,β-epoxy ketones with benzoyl chloride and tin halides



Entry	Epoxy ketone **85**	Tin chloride complex	Conditions[a]	Yield (%)	**86** : **87**[b]
1		Bu_2SnCl_2-PPh_3	70°C, 15 h.	80	87 : 13
2		$SnCl_2$-PPh_3	70°C, 15 h.	58	1 : 99
3		Bu_2SnCl_2-PPh_3	70°C, 15 h.	93	79 : 21
4		$SnCl_2$-PPh_3	70°C, 15 h.	30	3 : 97
5		Bu_2SnCl_2-PPh_3	40°C, 15 h.	90	73 : 27
6		$SnCl_2$-PPh_3	25°C, 15 h.	40	1 : 99

[a] Reaction conditions: α,β-epoxy ketone **85** (3 mmol), PhCOCl (3 mmol), tin chloride (0.6 mmol), PPh_3 (0.6 mmol), benzene (3 mL). [b] Determined by ^1H NMR.



Scheme 19.

In the same report, 2-oxazolidones were obtained from epoxy ketone **79** upon reaction with TsN=C=O. Depending on the use of either Bu_2SnI_2–HMPA or SnI_2–PPh_3, compound **88** or **89** was formed predominantly (84:16 and 1:99, respectively) (Scheme 19).

3.2.2. Intramolecular opening

3.2.2.1. Oxygen nucleophiles. The intramolecular cyclisation of **90** was carried out using mercury(II) acetate, followed by treatment with hydroxide and $NaBH_4$. Three main products were isolated (Scheme 20), namely the *trans*-2,5-disubstituted tetrahydrofuran derivative **92**, the organomercurial hydroxide derivative **93** and the hydroxy tetrahydrofuran **94** as a mixture of α- and β-epimers, respectively, in a ratio of 22:5:1:1. The *trans*-stereospecificity was explained in terms of steric effects.[103]

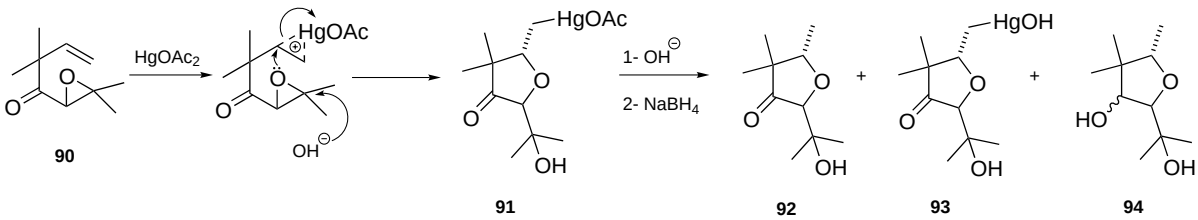
Other examples of oxygen-mediated intramolecular opening of epoxy ketones include the synthesis of flavanols from the corresponding epoxy chalcone precursors. Alkaline hydrogen peroxide oxidation of 2′-hydroxy chalcones, the Algar–Flynn–Oyamada (AFO) reaction,[104–106] has been reported to afford the corresponding flavanol in low yield. However, the initially postulated intermediacy of 2′-hydroxy chalcone epoxides in this process,[106] (as well as in the related Rasoda reaction)[107] was disputed for a long time.[108–112] Since then, epoxy chalcone cyclisation to flavanols has received particular interest,[113–115] and Schlenoff et al. recently re-addressed the question of epoxide intermediacy in the AFO reaction.[116]

One example of such an epoxy chalcone cyclisation features the epoxy ketone **95** which was cyclised to *anti*-flavanol **96** upon acid treatment (Scheme 21).[113,114]

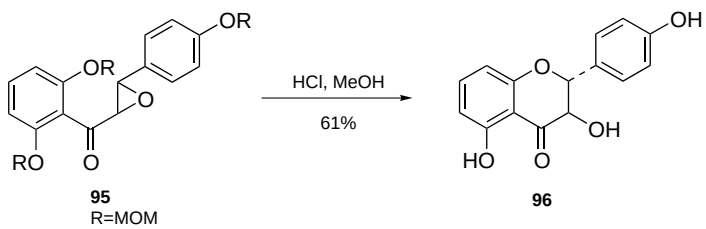
An enantioselective approach was reported later[117] in which a series of MOM-protected polyhydroxylated epoxy chalcones were prepared using the Juliá epoxidation in moderate to good enantioselectivities. Subsequent treatment with acid cleaved the MOM-protecting groups allowing nucleophilic attack of the phenol onto the epoxide ring, thus providing the corresponding flavanoids. However, partial racemisation was observed, which was attributed to a degree of S_N1 character for the cyclisation step; racemisation at the β-position of the cationic intermediate, would lead to the *threo*-intermediate which, under acidic conditions, readily epimerises to the *erythro*-isomer.

Treatment of several epoxy ketones **97** with hydroxylamine hydrochloride in the presence of pyridine generated the corresponding oximes **98** which readily cyclised to the *trans*-isoxazolin-4-ols **99** in 55–84% yield (Scheme 22).[118]

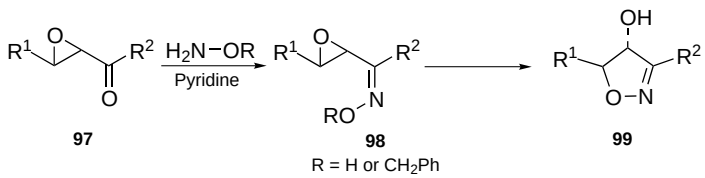
3.2.2.2. Nitrogen nucleophiles. 2′-Aminochalcones have been shown to undergo epoxidation, followed by intramolecular cyclisation to yield 2-aryl-4-quinolones in an analogous manner to 2′-hydroxychalcone (as described in the previous section). For example, in independent studies Donnely et al. and Tökés et al. demonstrated that the 2′-amino-epoxychalcone **100** could be isolated and heated in refluxing acetic acid to



Scheme 20.

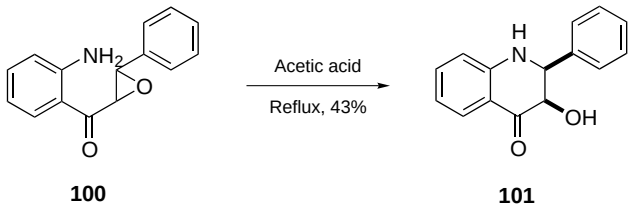


Scheme 21.



Scheme 22.

yield *cis*-1,2,3,4-tetrahydro-3-hydroxy-2-phenyl-4-quinolone **101** (Scheme 23).[119,120]



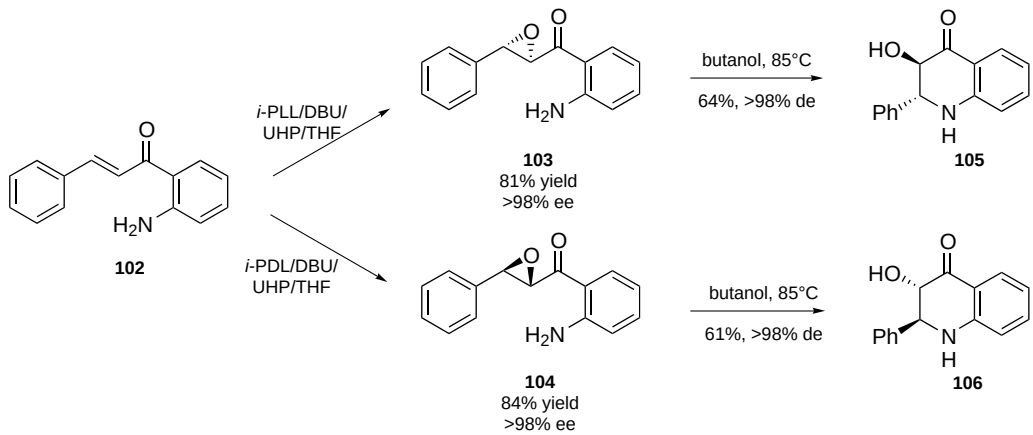
100 **101**

Scheme 23.

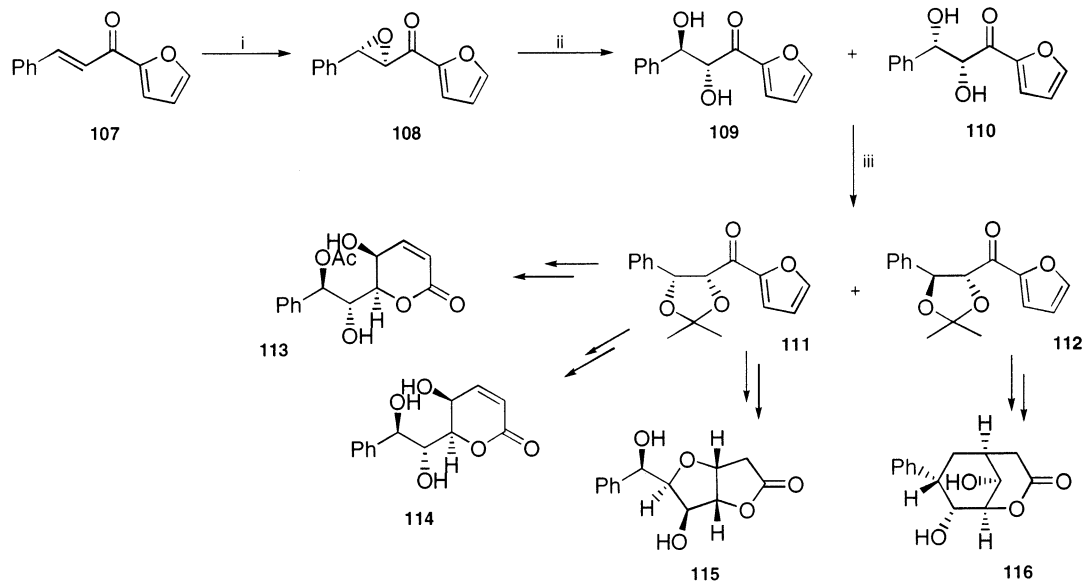
Similarly, treatment of optically active epoxides **103** and **104** (obtained via Juliá epoxidation in very high yield and enantiomeric excesses) with butanol at 85°C yielded the corresponding quinolones **105** and **106** in 64% yield (Scheme 24). Surprisingly the anticipated *threo*-isomer was not obtained, but the *erythro*-isomer was the sole product of the reaction.[121]

3.2.3. Miscellaneous. Other examples of epoxide opening include the Iranpoor hydrolysis of epoxides[122] which has recently been applied to epoxy ketones.[123] Thus, the optically active epoxy ketone **108** was hydrolysed in the presence of iodine in acetonitrile:water at 40°C for 60 h to furnish the *threo*- and *erythro*-diols **109** and **110** (ratio ca. 1:1). The diols were subsequently protected as their acetonides **111** and **112** and separated with overall yields (from the epoxide) of 46 and 38%, respectively. The acetonide **111** was successfully used as a key intermediate for the synthesis of three natural products (+)-8-acetylgonotriol **113**, (+)-gonotriol **114** and (+)-goniofufurone **115**. Moreover, the diastereomeric acetonide **112** was used in a synthesis of goniopypyrone **116** (Scheme 25).

In yeast-mediated hydrolyses of various epoxy ketones **117** it was shown that the epoxide was cleaved to the *syn*-diol, with concomitant reduction of the ketone moiety to give triol **118** as a single diastereoisomer in good to moderate yields (Table 8).[124,125]

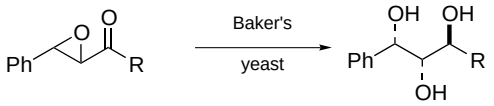


Scheme 24.



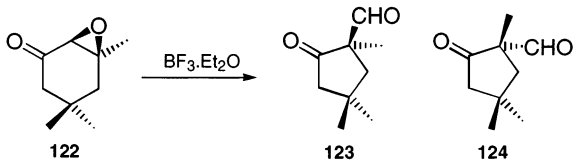
Scheme 25. *Reagent and conditions*: (i) urea–H_2O_2, poly-L-leucine, DBU, THF, rt, 2 h; (ii) I_2 (0.5–1.0 mol%), CH_3CN:H_2O (1:1), 40°C, 60 h; (iii) $Me_2CH(OMe)_2$, toluene-*p*-sulfonic acid, CH_2Cl_2, rt, 5 h.

Table 8. Biotransformation of some epoxy ketones using baker's yeast



117 **118**

R	Yield (%)
Et	51
n-Pr	74
i-Pr	22
n-Bu	74
s-Bu	39
t-Bu	13



122 **123** **124**

Solvent	Ratio **123** : **124**
CH_2Cl_2	73.9 : 26.1
Benzene	56.7 : 43.3

Scheme 27.

4. Miscellaneous transformations

4.1. Epoxy ketone rearrangement

It was found that, in the presence of $BF_3{\cdot}Et_2O$, some chalcone epoxides form fluorohydrins but others rearrange to the corresponding 1,3-dicarbonyl compounds.[126] Inversion of configuration at the carbon where the displacement occurs was observed in most cases for this intramolecular reaction.[127] Mechanistic studies were undertaken in order to find out whether cleavage of the epoxide ring and migration of the acyl group were concerted events.[97,128,129] Thus, the open-chain 1,3-diphenyl-2,3-epoxybutan-1-one **119** was reacted with $BF_3{\cdot}Et_2O$ in an inert solvent such as CH_2Cl_2 to afford **121** in 97% yield, with complete inversion of configuration at the migration terminus and without loss of stereochemistry (Scheme 26).[128] The reaction is thought to be facilitated by neighbouring group participation (NGP) at the carbonyl centre, proceeding via a cyclopropyloxenium ion intermediate **120**.

Later it was reported that when the optically active isophorone oxide **122** was treated with $BF_3{\cdot}Et_2O$ in either benzene or CH_2Cl_2 partial racemisation was observed, suggesting that the reaction mechanism was more complex for cyclic epoxy ketones (Scheme 27).[130]

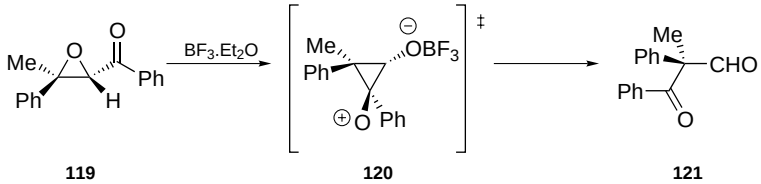
This scenario was subsequently confirmed by Bach and Klix during their study on the synthesis of 8-formyl-1-hyndrindanones and related compounds.[131] It was suggested that for cyclic epoxy ketones, torsional constraints prevented the carbonyl carbon from reaching the necessary alignment for NGP thus precluding a simple concerted acyl migration. It was also stated that a fluorohydrin intermediate (which could suffer from racemisation under the reaction conditions), might be involved in the reaction pathway.

The synthetic applications of this methodology include the synthesis of spirocyclic 1,3-diketones **127** from epoxy ketones **126** (Table 9).[132] Similarly the natural product humulenone **129** was obtained from the key intermediate **128** (Scheme 28),[133] while Asaoka et al. achieved the synthesis of (–)-frontalin **133** and (–)-malyngolide **134** utilising the Lewis acid-catalysed rearrangement of epoxy ketone intermediate **130** as a key step (Scheme 29).[134]

Recently, the construction of a chiral building block such as **136**, possessing a quaternary carbon stereocentre, was reported involving a concerted 1,2-acyl migration of the corresponding acyclic epoxy ketone **135**.[135] This synthon was used in the synthesis of the tricarbonyl compound **137**, a key component in a route to 1-acetyl-aspidospermidine (Scheme 30).[136,137]

4.2. Cross-coupling of α-stannylepoxides

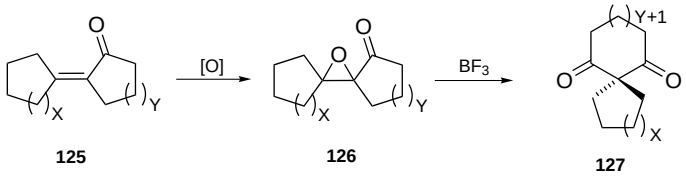
During the last 20 years, there has been considerable interest shown in the area of oxiranyl carbanion chemistry.[138] Epoxy carbanions are able to react with a wide range of electrophiles and provide an attractive approach for the synthesis of functionalised epoxides. However, very low temperatures are generally needed to prevent decomposition, and racemisation is often a problem. One way to form such anions is by transmetallation of α-stannyl epoxides and some exam-



119 **120** **121**

Scheme 26.

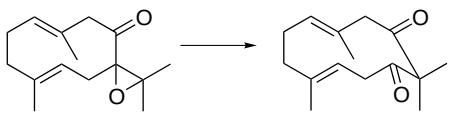
Table 9. Synthesis of spirocyclic 1,3-diketones from epoxy cycloalkanones



125 126 127

Entry	X	Y	Cat. equiv.	Time	Temp. (°C)	Isolated yield of 1,3-dione (%)[a]
1	1	1	0.01	5 min	25	86 (99)
2	1	1	1.0	2 h	−78	(98)
3	2	1	0.1	1 min	25	71 (99)
4	2	1	1.0	5 min	−23	71 (98)
5	3	1	0.1	1 min	25	91 (99)
6	4	1	0.1	1 min	25	83 (99)
7	1	3	0.5	5 min	25	62 (90)
8	2	3	0.5	1 min	35	73 (91)

[a] Purity by GLC in parentheses.



128 129

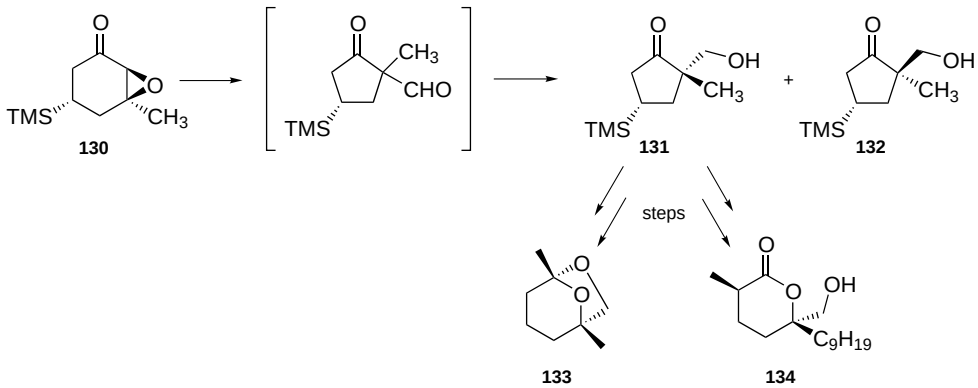
Scheme 28.

ples have been reported.[138] However, application of this methodology to α,β-epoxy ketones is difficult due to the competitive reactivity of the ketone moiety.

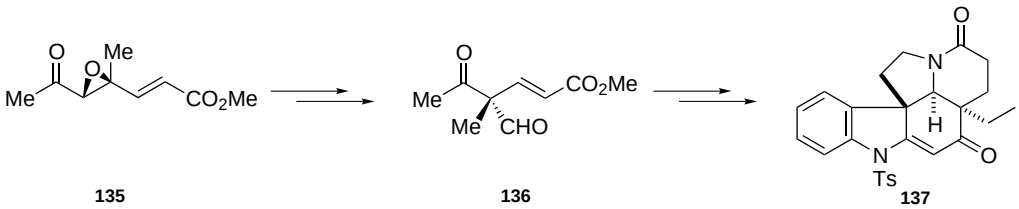
Recently, Falck et al. published an example of transition metal-mediated coupling of α-stannylepoxides with reactive electrophiles.[139] Various functionalised epoxides were treated with Cu_2S and either phenyl chlorothionoformate, allyl bromide or trimethyl silyl bromide to afford cross-coupled products in moderate to good yields. Optically active epoxy ketone **138**, synthesised via Juliá epoxidation of the corresponding unsaturated ketone, gave good yields of the corresponding thionoformate and allyl-substituted epoxy ketones **139** and **140**, respectively, with no loss of diastereomeric excess (Scheme 31).

4.3. Cascade ring-opening/ketyl olefin coupling reaction

cis-1,3-Cyclopentanediols and *cis*-1,3-cyclohexanediols can be synthesised using SmI_2-mediated reaction of α,β-epoxy ketones bearing remote olefin moieties.[140] Slow addition of a THF:methanol (30:1) solution of epoxy ketones **141** to a THF/HMPA (1:4) solution of SmI_2 (6 equiv.) at 0°C provided the desired cyclised product as a mixture of diastereomers (Table 10). An important feature of the reaction is the exclusive formation of *cis*-diols, which was explained by the formation of a samarium(III) chelate intermediate during the reaction. As can be seen from Table 10, the second stereocentre is formed with high diastereoselectivity, a

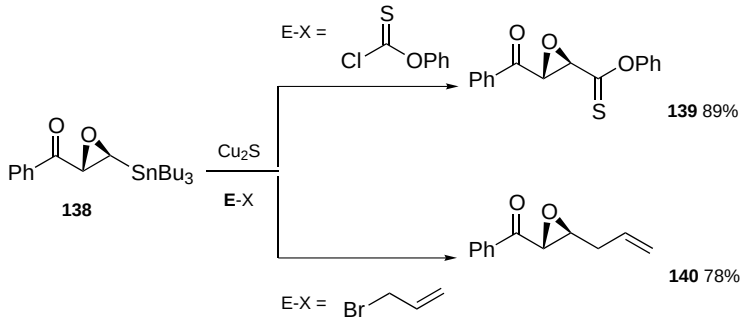


Scheme 29.



135 **136** **137**

Scheme 30.



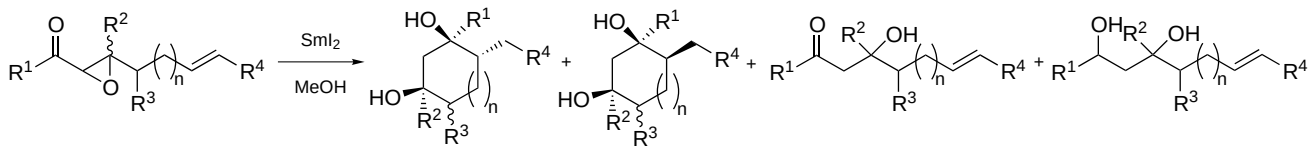
138 **139** 89% **140** 78%

Scheme 31.

favourable result of secondary orbital overlap between the developing methylene radical and the adjacent alkyl substituent in the transition state.[140]

A similar strategy was later employed for the synthesis of bicyclic systems using epoxy ketones bearing two alkene moieties.[141]

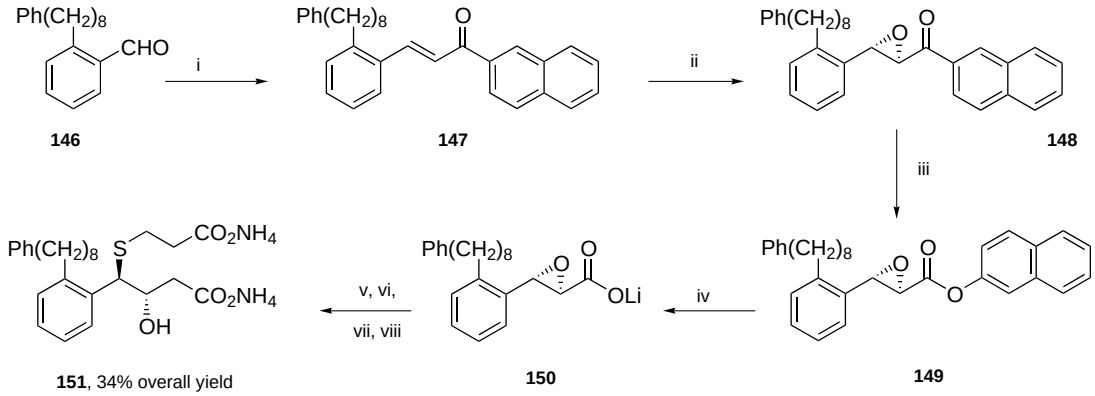
Table 10. Conversion of some epoxy ketones into cycloalkane-1,3-diols



141 **142** **143** **144** **145**

Entry	R^1	R^2	R^3	R^4	n	Yield **142**+**143** (%) (ratio **142**:**143**)[a]	Yield (%) **144**	Yield (%) **145**
1	Me	Me	H	H	1	88 (12:1)	–	–
2	Et	Me	H	H	1	86 (10:1)	–	–
3	*i*-Pr	Me	H	H	1	72 (10:1)	–	–
4	*t*-Bu	Me	H	H	1	10 (7:1)	–	47
5	Ph	Me	H	H	1	–	16[b]	45[b]
6	Me	H	H	H	1	74 (3:1)	–	–
7	Me	*i*-Pr	H	H	1	40 (3:1)	–	26
8	Me	Et	Me	H	1	Mixture[c]	–	[c]
9	Me	Me	H	H	0	61 (>100:1)	–	–
10	Et	Me	H	H	0	65 (100:1)	–	–
11	*i*-Pr	Me	H	H	0	66 (50:1)	–	–
12	*t*-Bu	Me	H	H	0	81 (2:1)	–	–
13	Ph	Me	H	H	0	–	53[b]	24[b]
14	Me	Me	H	Ph	1	82 (2.55:1)	–	–
15	Me	Me	H	CO_2Et	1	85 (>50:1)	–	–
16	*i*-Pr	Me	H	CO_2Et	0	81 (>50:1)	–	–
17	Me	Me	H	Ph	1	79 (1:1.6)[d]	–	–
18	Me	Me	H	Ph	1	79 (1:1)[e]	–	–
19	Me	Me	H	Me	1	78 (1.5:1)[f]	–	–

[a] Ratios of diastereomers were determined by GC analysis of crude reaction mixtures.
[b] The reaction was carried out at −78°C. At 0°C the reaction afforded a mixture of products.
[c] This reaction led to an inseparable mixture.
[d] This reaction was carried out at −78°C.
[e] This reaction was carried out at 0°C.
[f] This reaction was carried out at −20°C.



Scheme 32. *Reagents and conditions*: (i) 2-acetonaphtone, NaOEt, EtOH; (ii) poly-L-leucine, NaOH, H_2O_2, EDTA, *n*-hexane, H_2O; (iii) *m*-CPBA, CH_2Cl_2; (iv) LiOH, MeOH, H_2O; (v) $HS(CH_2)_2CO_2Me$, NaOMe; (vi) NaOH; (vii) HCl; (viii) NH_4OH.

5. Synthetic applications

A wide range of natural products and biologically active compounds have been synthesised using one or more of the previously described transformations of α,β-epoxy ketones.

5.1. Leukotriene precursors

The synthesis of the leukotriene antagonist SK&F 104353 was accomplished using epoxy ketone **148** as the key intermediate.[142] Baeyer–Villiger oxidation of optically active **148** provided the corresponding epoxy ester in 87% yield and >99.5% e.e. Transformation to the lithium carboxylate **150**, followed by stereoselective opening of the epoxide at the benzylic position with the sodium salt of methyl-3-mercaptopropionate furnished the methyl ester of **151**. Subsequent hydrolysis and treatment with ammonium hydroxide then gave the target compound **151** with an overall yield of 35% (Scheme 32).

5.2. Diltiazem and Taxol

Baeyer–Villiger oxidation of epoxy ketones was used as a key step in the total synthesis of several biologically active compounds in single enantiomer form. The potent blood pressure lowering agent Diltiazem **157**, was obtained from KF buffered *m*-CPBA oxidation of the requisite epoxy ketone.[42] Subsequent epoxide opening at the benzylic position with retention of configuration gave intermediate **155** which was cyclised and further alkylated and acylated to yield Diltiazem in ca. 30% overall yield (Scheme 33).

Another example involves the synthesis of the Taxol™ side-chain **165**.[42] Epoxy ketone **159** was oxidised with *m*-CPBA to give epoxy ester **160**. Subsequent epoxide opening using HCl gas followed by base treatment afforded *cis*-epoxy ester **162**. Amino alcohol **164** was then obtained either by direct epoxide opening with methanolic ammonia or by treatment with sodium azide followed by hydrogenation. Benzoylation and acidic ester hydrolysis then furnished the desired target compound **165** (Scheme 34).

5.3. Protected galactonic acid derivative

Very recently, Ray et al. reported the synthesis of a galactonic acid derivative from epoxy ketone **166**.[143] Zinc borohydride reduction of **166** followed by treatment with phenyl isocyanate afforded the urethane **168**. Further functionalisation gave the galactonic acid derivative **170** in ca. 60% overall yield (Scheme 35).

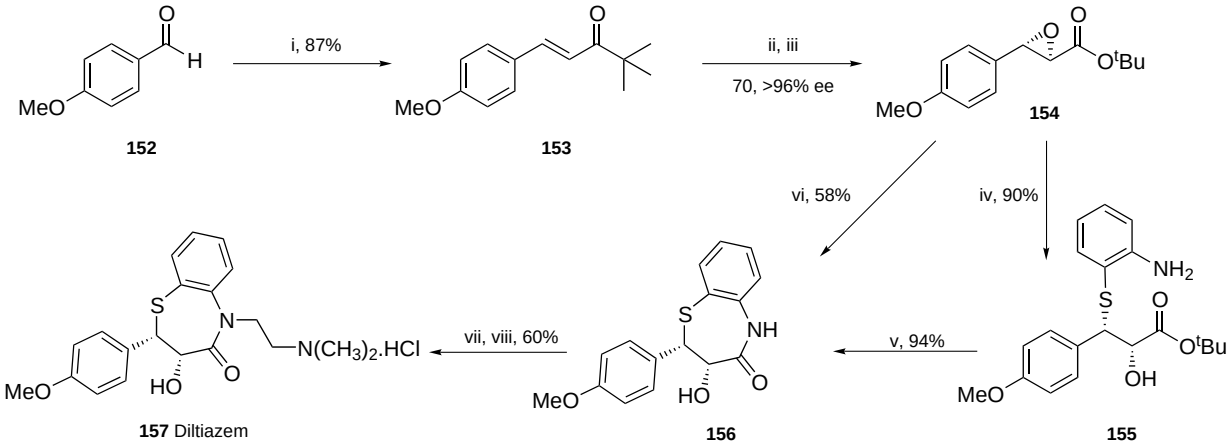
5.4. Novel protein kinase C activators

The catalytic asymmetric total syntheses of (+)-decursin **176** and three related natural products, (+)-decursinol **175**, (−)-prantschimgin **178** and (+)-marmesin **177** were achieved by Shibasaki et al. from epoxy ketone **172**.[144] Thus, Grignard addition to **172** furnished epoxy alcohol **173** which could be reductively cleaved to give **174**. Subsequent transformations then led to the target PKC activators **175**, **176**, **177** and **178** (Scheme 36).

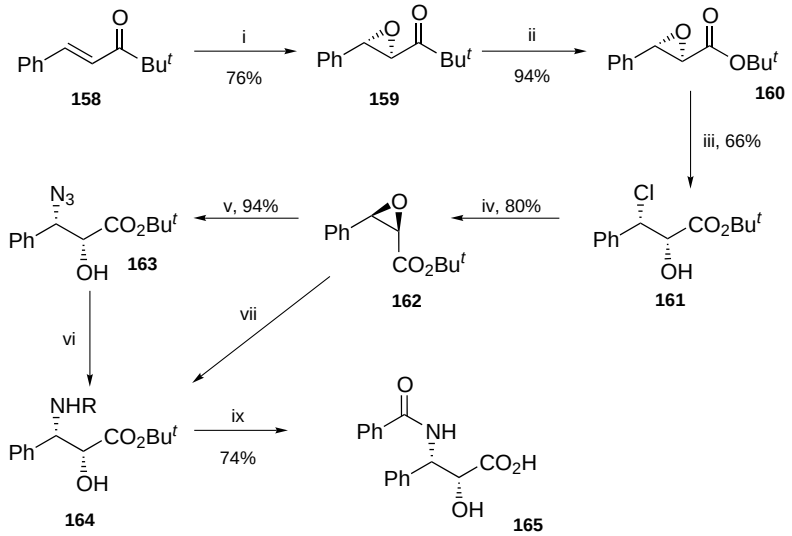
6. Conclusion

The past 50 years have witnessed an ever-growing interest in the chemistry of epoxy ketones. A fascinating range of transformations has been developed and has proven increasingly valuable for the synthesis of natural products and biologically active compounds, such as the leukotriene antagonist SK&F 104353 and the potent blood pressure lowering agent Diltiazem.

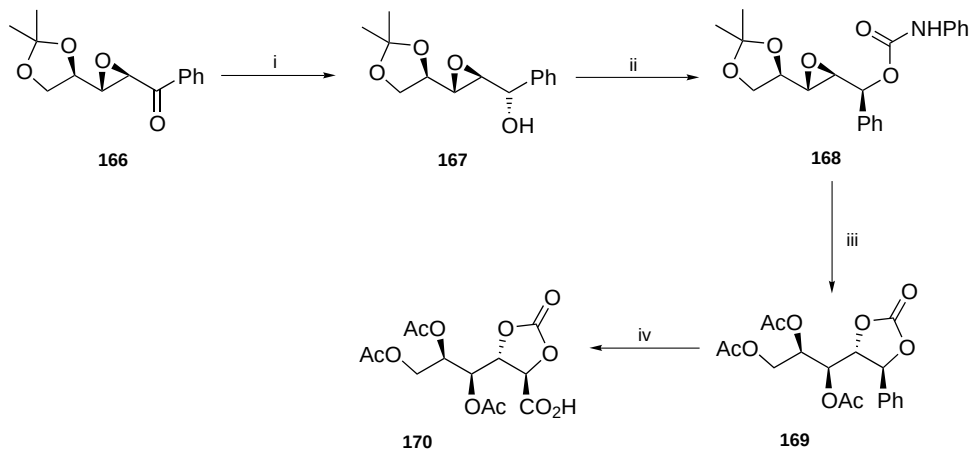
Furthermore, the excellent chemo-, regio- and diastereoselectivities observed in most cases coupled with the recent development of several methods for the synthesis of chiral non-racemic epoxy ketones[145] should further promote the value of such intermediates in asymmetric synthesis.



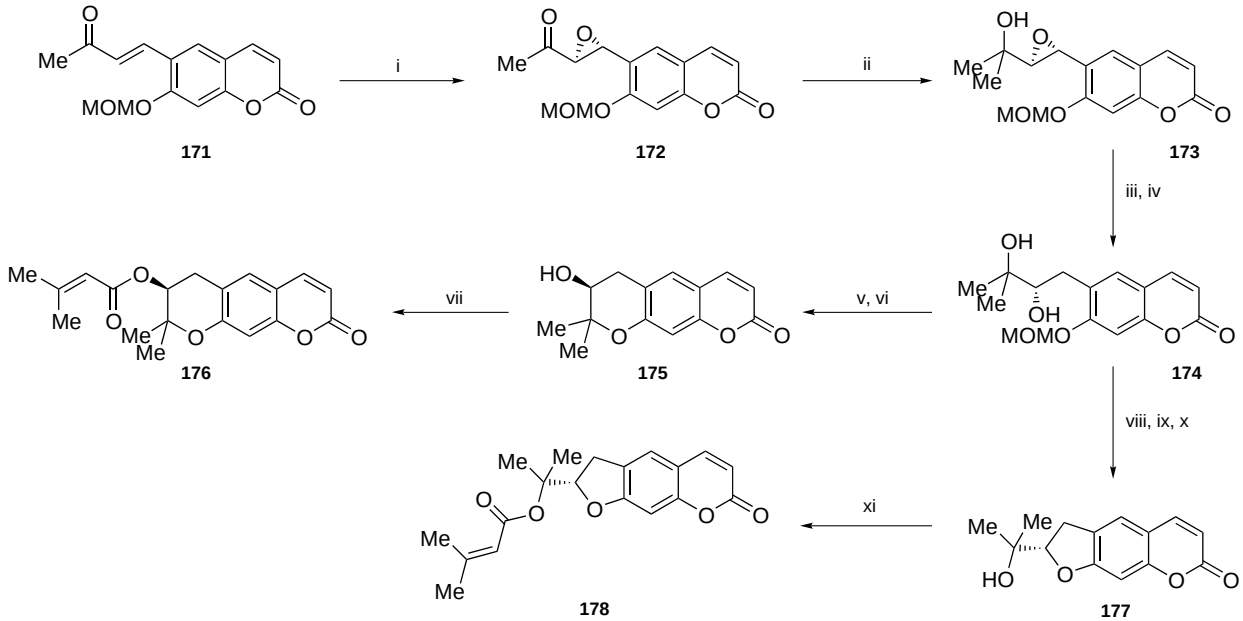
Scheme 33. *Reagents and conditions*: (i) pinacolone, NaOMe, MeOH; (ii) *I*-PLL, UHP, DBU, THF, 20 h; (iii) KF, *m*-CPBA, CH_2Cl_2; (iv) *o*-aminothiophenol, toluene, reflux; (v) xylene, reflux; (vi) *o*-aminothiophenol, mesitylene; (vii) 2-(dimethylamino)ethyl chloride·HCl, K_2CO_3, EtOAc; (viii) acetic anhydride, pyridine, DMAP.



Scheme 34. *Reagents and conditions*: (i) *I*-PLL, UHP, DBU, 12 h; (ii) *m*-CPBA, CH_2Cl_2; (iii) HCl (g), CH_2Cl_2; (iv) Amberlite IRA-420 (OH^-), THF; (v) NaN_3, MeOH, H_2O; (vi) H_2, Pd/C, EtOAc; (vii) NH_3, MeOH; (viii) benzoyl chloride; (ix) trifluoroacetic acid, CH_2Cl_2.



Scheme 35. *Reagents and conditions*: (i) $Zn(BH_4)_2$, Et_2O; (ii) PhNCO, pyridine, CH_2Cl_2; (iii) (a) $BF_3{\cdot}Et_2O$, Et_2O, H_2SO_4, (b) Ac_2O, pyridine, DMAP, CH_2Cl_2; (iv) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O.



Scheme 36. *Reagents and conditions*: (i) La-(*R*)-BINOL, O=AsPPh$_3$, TBHP; (ii) MeMgBr, THF, −78°C, 76%; (iii) NaBH$_4$, BH$_3$·THF, THF, 0°C, 74%; (iv) conc. HCl–H$_2$O–THF (1:3:4), 40°C, 92%; (v) Tf$_2$O, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, 0°C, 92%; (vi) Pd(OAc)$_2$ (10 mol%), DPPF (20 mol%), NaO^{t}Bu, toluene, 90°C, 80%; (vii) Senecioyl chloride, DMAP, LHMDS, THF, −40 to 0°C, 72%; (viii) TESCl, imidazole, CH$_2$Cl$_2$, rt, 92%; (ix) Pd(OAc)$_2$ (10 mol%), (*S*)-tol-BINAP (12 mol%), K$_2$CO$_3$, toluene, 90°C, 91%; (x) TBAF, THF, rt, 95%; (xi) Senecioyl chloride, DMAP, LHMDS, THF, −40 to 0°C, 83%.

Future work in this area might also involve the development of new transformations based on this functional group. For example, the reaction of epoxides with ester, ketone and amide enolates has recently been described.[146] However, no examples involving epoxy ketones have been reported thus far. Such a transformation might offer new possibilities for the synthesis of polyhydroxyl homochiral intermediates.

It can be concluded that this class of compounds certainly holds great prospects, and that further exploration in this field will lead to more challenging and exciting chemistry.

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