REVIEW

Alcohols, ethers and phenols

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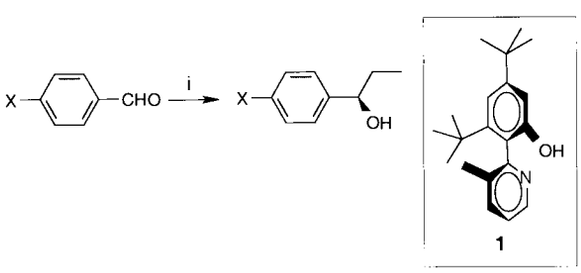
1 Preparation of alcohols

1.1 From carbonyl compounds

1.1.1 Alkylation

In a new slant on the well-known enantioselective addition of diethylzinc to aldehydes, chiral pyridylphenol **1** has been shown to mediate just such a process, but the enantioselectivity of the reaction **increases** with reaction temperature (Scheme 1 and



Scheme 1 *Reagents and conditions*: i, Et_2Zn, **1** (5 mol%), toluene, 0 °C.

Table 1).[1] The enantioselectivity of the reaction follows a linear free-energy relationship, and a higher enantioexcess in the product alcohols is observed for more reactive aldehydes. Using (+)-(*R*)-catalyst, (*R*)-configured alcohols were obtained in all cases.

Diarylated binaphthol **2** mediates highly enantioselective alkylation of aldehydes by diethylzinc.[2] Enantiomeric excesses are uniformly high (≥93%).

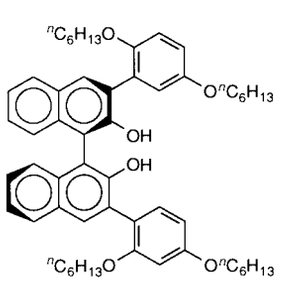
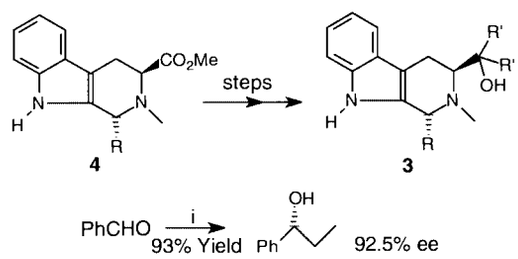


Table 1

X	Yield (%)	Ee (%)
NMe_2	88	40
OMe	96	66
H	92	75
Cl	97	80
CN	92	89

A recent class of aminoalcohols to be studied in asymmetric alkylation of aldehydes by diethylzinc concerns derivatives, **3**, of abrine **4** (Scheme 2).[3]



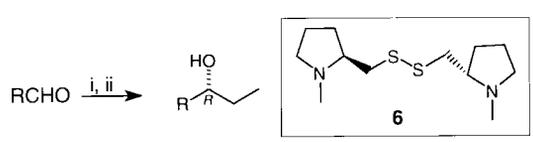
Scheme 2 *Reagents*: i, catalyst **3** (5 mol%), Et_2Zn.

These derivatives catalyse the alkylation, with variable enantioselectivities (24–98% ee), always in favour of (*R*)-alcohols.

Thionorephedrine derivative **5** catalyses the enantioselective addition of diethylzinc to aldehydes.[4] The enantioselectivities of these reactions are uniformly good. In all cases, (*S*)-alcohols are favoured (Scheme 3).

Scheme 3 *Reagents and conditions*: i, 0 to 20 °C, hexane, Et_2Zn.

Another sulfur-containing accelerating ligand useful in asymmetric additions of diethylzinc to aldehydes is disulfide **6**, derived from (*S*)-proline.[5] The enantioselectivity of additions to representative aldehydes are good to mediocre. In all cases, (*R*)-configured alcohols are obtained (Scheme 4 and Table 2).



Scheme 4 *Reagents and conditions*: i, Et_2Zn (2 eq.), **6** (1.25–2.5 mol%), toluene 0 °C, 48 h; ii, HCl.

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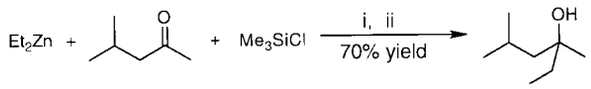
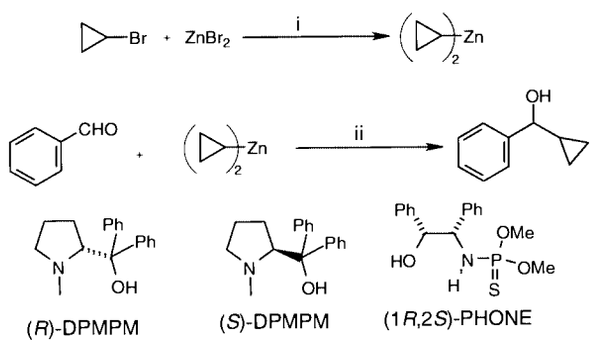
The reaction of a range of dialkylzinc species with ketones is promoted by the presence of silyl chloride or triflates, leading to the formation of silyl ethers of tertiary alcohols in acceptable to good yields.[6] Where aliphatic ketones were used, reduced products (rather than alkylated) were always by-products; aromatic ketones generated these contaminants in generally low yield. Alcohols could be directly obtained from the reaction in one-pot by using an *in situ* acid-catalysed deprotection (Scheme 5).



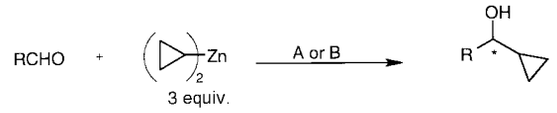
Scheme 5 *Reagents and conditions*: i, $CHCl_2$, −20 °C; ii, $MeOH/H^+$.

Aminoalcohol catalysis of the nucleophilic addition of organozincs to carbonyl compounds has been extended to include cyclopropylzinc reagents.[7] Thus aldehydes react with dicyclopropylzinc and $Ti(O^iPr)_4$ in the presence of a sub-stoichiometric amount of a chiral aminoalcohol to give substituted cyclopropylmethanols in good yield. The enantiocontrol is good (≥90% ee) when aryl aldehydes are used in the presence of the thiophosphoramidate (1*R*,2*S*)-PHONE, but less impressive using aliphatic aldehydes or simple chiral aminoalcohols (Scheme 6, Table 3 and Scheme 7, Table 4).

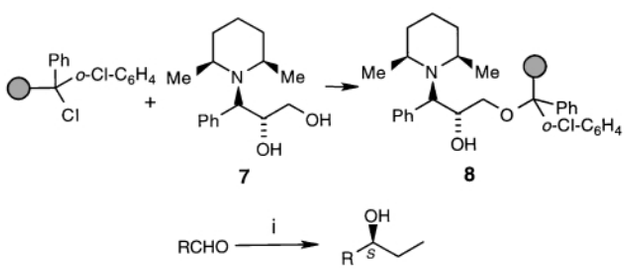


Scheme 6 *Reagents and conditions*: i, Li, ultrasonication, Et_2O, 0 °C; ii, DPMPM or PHONE, $Ti(O^iPr)_4$.

Sanders *et al*. have described in full their use of ^{13}C gel-phase NMR as a powerful analytical tool to study asymmetric additions of diethylzinc to aldehydes.[8] Attachment of enantiomerically pure amino diol **7** to Barlos resin gave solid-supported catalyst **8**, which (at 8% equivalence) catalysed the aforementioned reaction, with good stereoselectivity. The catalyst could easily be regenerated and showed no diminution in activity or selectivity when reused in the asymmetric alkylation reaction (Scheme 8 and Table 5).



Scheme 7 *Reagents and conditions*: Method A: (1*R*,2*S*)-PHONE (0.15 eq.), $Ti(O^iPr)_4$, −30 °C; Method B: (*R*)-DPMPM (0.05 eq.), 0 °C.



Scheme 8 *Reagents and conditions*: i, Et_2Zn, **8** (8 mol%), toluene.

A new ligand class allowing enantioselective addition of vinylzinc reagents to aldehydes has been described by two groups. Thus, ligands **9**–**13** catalyse the addition of these zinc reagents (prepared *in situ via* hydrozirconation and zirconium–zinc exchange) to benzaldehyde enantioselectively, with 95% enantiocontrol in the case of ligand **13**. "Typical" ligands catalysed the process with much lower stereoselectivity (Scheme 9 and Table 6).[9]

Similar work using asymmetric aminothiol ligands has emphasized the influence of nitrogen substituents upon the level of enantioselectivity during such alkylations.[10] Thus, valinol-derived ligands exhibit useful enantiocontrol only when the nitrogen atom is disubstituted (Scheme 10 and Table 7).

Pyrrolidine-2,5-dicarboxylic acid derivatives have been employed as asymmetric mediators of the addition of diethyl-

Table 2

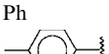
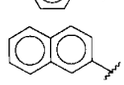
R	Yield (%)	Ee (%)
Ph	76	87
	83	99
	88	90
	96	70
	77	69

Table 4

R	Method	Time/h	Yield (%)	Ee (%)
Ph	A	2	93	96
Ph	B	5	90	86
4-MeO-C_6H_4	A	3	99	97
4-MeO-C_6H_4	B	3	97	96
4-Cl-C_6H_4	A	2	85	91
4-Cl-C_6H_4	B	2	97	94
1-Naphthyl	A	2	89	96
1-Naphthyl	B	2	94	78
PhCH=CH	A	1.5	94	64
PhCH=CH	B	1.5	94	67
$PhCH_2CH_2$	B	1	91	67
Cyclohexyl	B	2	86	71

Table 3

Chiral catalyst (mol%)	Solvent	Temp/°C	Time/h	Yield (%)	Ee (%) (config.)
(*R*)-DPMPM (5)	Hexane–toluene	0	4	90	83 (*S*)
(*R*)-DPMPM (5)	Hexane	0	4	87	77 (*S*)
(*R*)-DPMPM (5)	Hexane–toluene	18	4	87	84 (*S*)
(*S*)-DPMPM (20)	Hexane–toluene	0	5	90	86 (*R*)
(*S*)-DPMPM (20)	Hexane–toluene	0	6	83	85 (*R*)
(1*R*,2*S*)-PHONE (5)	Toluene	−30	2	85	87 (*R*)
(1*R*,2*S*)-PHONE (15)	Toluene	−30	2	93	96 (*R*)

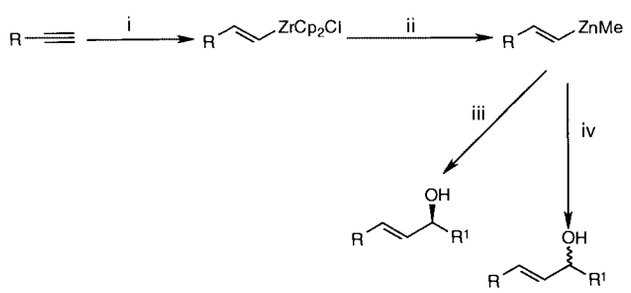
Table 5

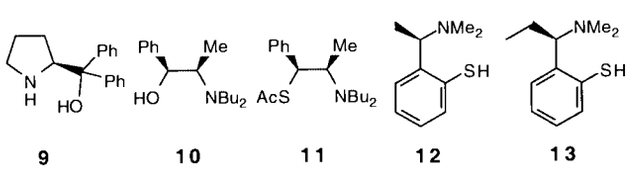
R	Conversion (%)	Selectivity[a] (%)	Ee (%)
Ph	99	98	94
2-F-C_6H_4-	96	96	88
3-F-C_6H_4-	98	96	94
4-F-C_6H_4-	>99	99	95
2-Me-C_6H_4-	91	84	91
3-Me-C_6H_4-	93	94	94
4-Me-C_6H_4-	93	94	94
2-MeO-C_6H_4-	88	92	86
3-MeO-C_6H_4-	>99	98	94
4-MeO-C_6H_4-	86	95	94
1-Naphthyl-	86	84	86
2-Naphthyl-	82	75	90
	86	90	98
^{i}Bu-	99	94	90

[a] Relative preponderance of the desired reaction *versus* side-reactions.

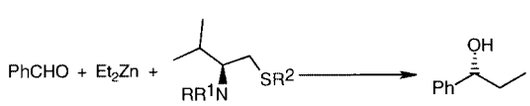
Table 6

R	R′	L* (mol%)	Yield (%)	Ee (%)	Temp./ °C
$C_4H_9CH{=}CH_2$	Ph	**9** (8)	92	38	−30
$C_4H_9CH{=}CH_2$	Ph	**9** (10)	88	81	−30
$C_4H_9CH{=}CH_2$	Ph	**9** (2)	99	19	−30
$C_4H_9CH{=}CH_2$	Ph	**10** (10)	85	1	−30
$C_4H_9CH{=}CH_2$	Ph	**11** (10)	80	70	−30
$C_4H_9CH{=}CH_2$	Ph	**12** (10)	76	89	−30
$C_4H_9CH{=}CH_2$	Ph	**13** (10)	80	95	−30
$C_4H_9CH{=}CH_2$	Ph	**13** (5)	73	90	−30
$C_4H_9CH{=}CH_2$	Ph	**13** (2)	88	78	−30
$C_4H_9CH{=}CH_2$	Ph	**13** (10)	90	83	0





Scheme 9 *Reagents and conditions*: i, Cp_2ZrHCl, CH_2Cl_2, 22 °C; ii, Me_2Zn, −65 °C, toluene; iii, R^1CHO, ligand, −30 °C; iv, R^1CHO, −30 °C.



Scheme 10

zinc to aryl aldehydes. Yields are high and enantioexcesses of the products are moderate to good (61–96% ee). Transition state **14** is postulated to explain the origin of enantioselectivity (Scheme 11 and Table 8).[11]

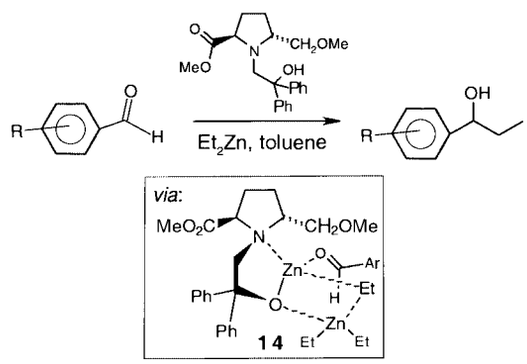
Table 7

R	R^1	R^2	Yield (%)	Ee (%)
Ph	Ph	H	85	75
Bn	Bn	H	91	58
	-$(CH_2)_4$-	H	78	66
Ph	Me	H	80	82
Ph	H	Ph	35[a]	0

[a] Major product benzyl alcohol (38%).

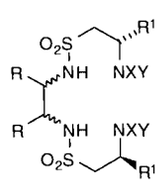
Table 8

R	R^1	Yield (%)	Ee (%)	Configuration
H	H	90	61	(*R*)
H	Me	99	91	(*R*)
p-Me	Me	99	96	(*R*)
o-OMe	Me	85	83	(*R*)
p-OMe	Me	85	73	(*R*)
p-F	Me	96	70	(*R*)
m-F	Me	88	85	(*R*)
p-Cl	Me	92	76	(*R*)
m-Cl	Me	96	90	(*R*)
o-Cl	Me	86	92	(*R*)



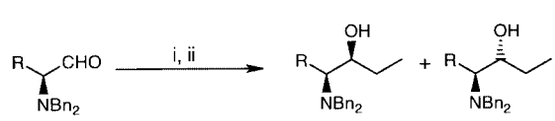
Scheme 11

Chiral diamines react with chiral 2-aminosulfonyl chlorides (obtained from (*S*)-amino acids) to give di(2′-amino)sulfonamides **15**–**19** which mediate asymmetric addition of diethylzinc to aldehydes.[12] Thus, these sulfonamides (prepared as a library) act as co-catalysts in the reaction of aromatic and aliphatic aldehydes with Et_2Zn and tetraisopropyltitanate, yielding (*R*)-alcohols in good yield and with good enantioexcess (≥86% ee).



R = −$(CH_2)_4$−, Ph
15 R^1 = CH_3; X = H; Y = Boc
16 R^1 = $CH(CH_3)_2$; X = H; Y = Boc
17 R^1 = $CH_2CH(CH_3)_2$; X = H; Y = Boc
18 R^1 = CH_2Ph; X = H; Y = Boc
19 R^1, X = -$(CH_2)_3$-; Y = Cbz

Substrate-controlled asymmetric addition of diethylzinc to enantiomerically-pure, chiral pool-derived *N*,*N*-dibenzylamino aldehydes furnishes *syn*-*N*,*N*-dibenzyl-1,2-aminoalcohols of high diastereopurity.[13] The reaction is unusual because the ligand activation required for nucleophilic attack at the carbonyl must be provided by the adjacent amino group, rather than an additional amine as is often the case (Scheme 12 and Table 9).

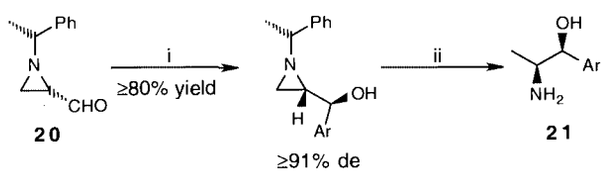


Scheme 12 *Reagents and conditions*: i, Et_2Zn, 0 °C; ii, H_2O, NH_4Cl.

Table 9

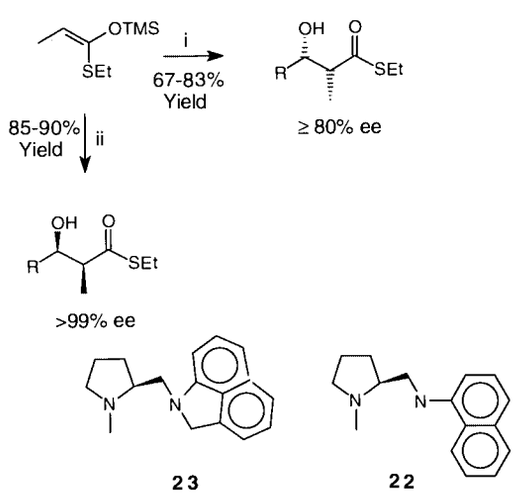
R	Reaction time/h	*syn*:*anti*	Yield (%)
Me	16	88:12	95
^{i}Pr	36	>99:<1	64
^{i}Bu	24	92:8	62
Bn	17	90:10	70
Ph	19	>99:<1	65
CH_2OMEM	24	95:5	70

In a most original approach, a series of analogues of ephedra alkaloids have been prepared by a synthetic sequence involving hydrogenolytic reduction of a monochiral aziridine-2-methanol.[14] The reaction path commences with a diastereoselective nucleophilic attack of an aryllithium upon enantiomerically-pure aziridine-2-carbaldehyde **20**. Use of aryl lithiums in this nucleophilic addition process gave best selectivities (≥91% de, in favour of *threo*-isomer). Reductive ring-cleavage of the aziridine ring and *N*-debenzylation then occurred smoothly using Pearlman's catalyst to give *syn*-1,2-aminoalcohols **21** in good yield. These amino alcohols are analogues of ephedrine; *N*-methylation yields of analogues of norephedrine (Scheme 13).



Scheme 13 *Reagents and conditions*: i, ArLi, THF, −78 °C; ii, $Pd(OH)_2$, H_2, EtOAc, rt.

Interest in aldol reactions and analogous processes continues. Full details of CLAC (Chiral Lewis Acid-Controlled) synthesis of non-racemic chiral 3-hydroxy-2-methyl thioesters have appeared.[15] Both enantiomers may be prepared with good to excellent enantiocontrol (up to >99.5% ee), simply by choice of chiral additive (Scheme 14).

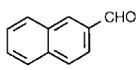
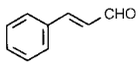
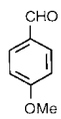
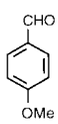
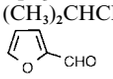
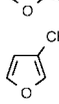
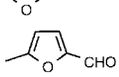
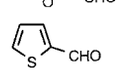
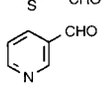
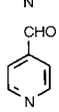


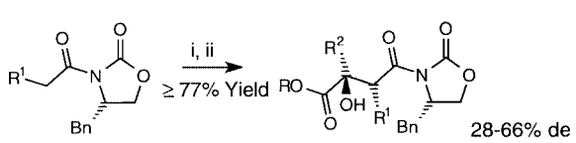
Scheme 14 *Reagents*: i, RCHO, $Sn(OTf)_2$, $Bu_2Sn(OAc)_2$, **22**; ii, RCHO, $Sn(OTf)_2$, $Bu_2Sn(OAc)_2$, **23**.

2,3-Disubstituted-2-hydroxy succinates may be prepared enantioselectively *via* reactions of oxazolidinone enolates with 2-ketoesters.[16] Diastereoselectivities of these aldol reactions are mediocre (≤66% de), although yields are good (Scheme 15).

2′-Hydroxy-1,1′-binaphthyl ester enolates react with aldehydes to give aldol products in good yield and with anti-selectivity. The diastereoselectivity of the process ranges from 27–82% (dr = 63–91:36–9). The authors propose a chelated transition state **24** invoking a *Re–Re* interaction of enolate and

Table 10

RCHO	Solvent	Yield (%)	*anti*:*syn*	Ee *anti* (%)
	THF	97	97:3	76
	THF	95	60:40	70
	THF	98	94:6	68
	THF	91	87:13	82
	THF	94	94:6	64
	THF–toluene (3:1)	85	100:0	70
C_2H_5CHO	THF	71	62:38	—
$(CH_3)_2CHCHO$	THF	58	98:2	70
	THF	99	37:63	30
	THF	95	86:14	72
	THF	99	79:21	34
	THF	97	89:11	60
	THF	91	54:46	48
	THF	90	30:70	27

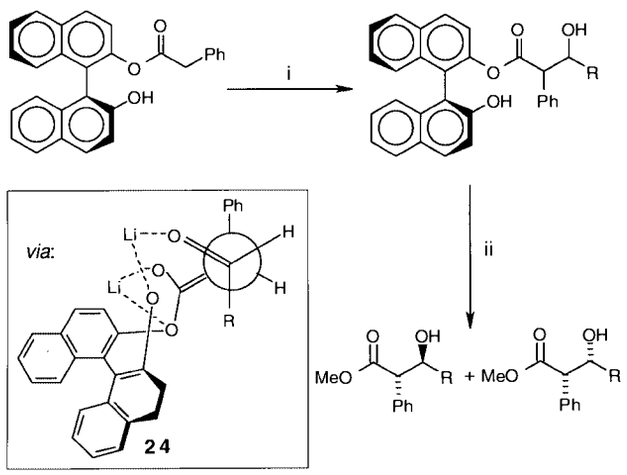


Scheme 15 *Reagents and conditions*: i, LDA, −78 °C, THF; ii, RO_2CCOR^2.

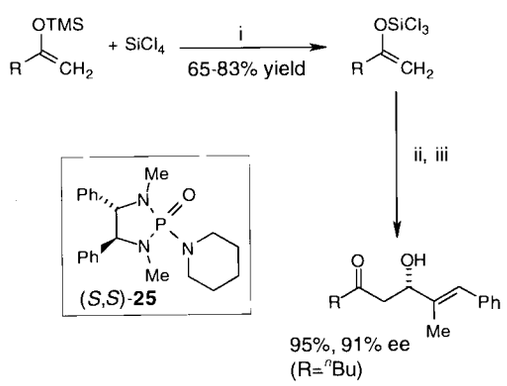
aldehyde to account for the observed preference for (2*S*,3*S*)-configured products (Scheme 16 and Table 10).[17]

Denmark and co-workers have reported further details of the aldol reactions of the trichlorosilyl enol ethers of methyl ketones, with emphasis upon catalytic asymmetric aldol processes. Thus, chiral non-racemic phosphoramide (*S*,*S*)-**25** catalyses the reaction of these enol ethers with a range of aldehydes to give the corresponding 3-hydroxy ketones in good yield and in high enantiomeric purity.[18] The authors report that trichlorosilyl enol ethers may be prepared routinely by reaction of the analogous trimethylsilyl enol ethers with silicon tetrachloride in the presence of a mercury(II) salt. Overall, the method constitutes a useful solution of the 'acetate aldol' problem (Scheme 17).

Other researchers also continue to be attracted to solving the "acetate problem" in asymmetric aldol reactions: camphor-derived ketone **26** is one such chiral auxiliary recently proposed.[19] Thus, the lithium enolate derived from **26** underwent

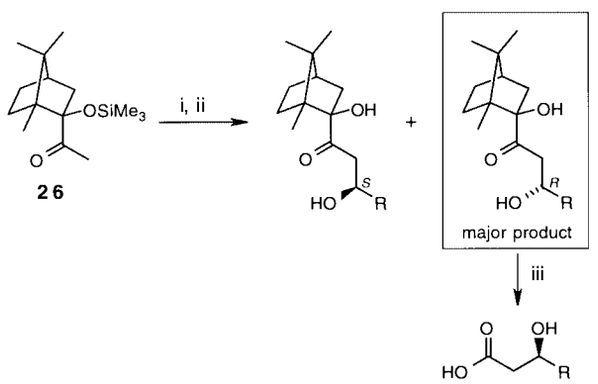


Scheme 16 *Reagents and conditions*: i, base, RCHO, −78 °C, 2 h; ii, LiOMe-MeOH, 0 °C, 1–2 h.



Scheme 17 *Reagents and conditions*: i, $Hg(OAc)_2$, $SiCl_4$ (2.0 equiv.), $Hg(OAc)_2$ (0.01 equiv.), CH_2Cl_2, rt; ii, 5 mol% (*S*,*S*)-**25**, 2-methylcinnamaldehyde, CH_2Cl_2, −78 °C; iii, sat. aq. $NaHCO_3$.

highly diastereoselective reaction with aromatic and aliphatic aldehydes, in good yield, to give aldol products of high enantiopurity (generally ≥92% ee). The auxiliary is cleaved destructively by periodate oxidation, regenerating camphor. The authors propose chelated transition state **27** to rationalize the observed face selectivity (Scheme 18 and Table 11).



Scheme 18 *Reagents and conditions*: i, LDA, THF, −78 °C, RCHO; ii, 1 M HCl, MeOH or TBAF (2 eq.), THF, rt, 5 min; iii, $NaIO_4$, MeOH, H_2O (2:1), rt or reflux, 12–48 h.

Mukaiyama aldol reactions may be carried out in water when scandium tris(dodecyl sulfate) (STDS) is used in the process as a Lewis acid.[20] Indeed, the catalytic activity of STDS is lower when the reaction is carried out in organic solvents. STDS is prepared from $ScCl_3$ and sodium tris(dodecyl sulfate) (Scheme 19, Table 12 and Scheme 20, Table 13).

Table 11

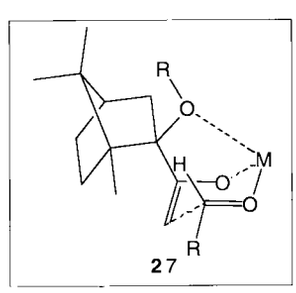
Aldehyde	Time/h	*R*:*S*	Yield (%)
C_6H_5CHO	6	96:4	80
4-$CH_3C_6H_4CHO$	7	96:4	67
$C_6H_5CH{=}CHCHO$	6	92:8	80
$C_6H_5CH_2CH_2CHO$	2	95:5	81
i-C_3H_7CHO	3	97:3	67
$(CH_3)_2CHCH_2CHO$	6	96:4	75
$(CH_3)_3CCHO$	6	>96:<2	70

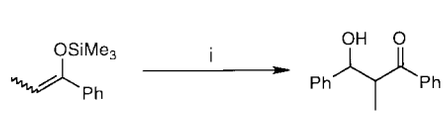
Table 12

Solvent	Yield (%)
H_2O	94
MeOH	4
DMF	14
DMSO	9
CH_3CN	3
CH_2Cl_2	3
THF	Trace
Et_2O	Trace
Toluene	Trace
Toluene	4

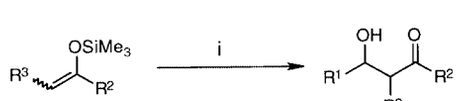
Table 13

R^1	R^2	R^3	Yield (%)	*syn*:*anti*
Ph	Ph	Me	92	49:51
$Ph(CH_2)_2$	Ph	Me	88	44:56
PhCH=CH	Ph	Me	91	40:60
Ph	Et	Me	84	78:22
p-ClC_6H_4	Et	Me	91	79:21
$Ph(CH_2)_2$	Et	Me	82	72:28
PhCH=CH	Et	Me	87	71:29
PhCH=CH	-$(CH_2)_4$-		85	52:48
Ph	Ph	H	94	—
Ph	EtS	Me_2	98	—
C_5H_{11}	EtS	Me_2	91	—
PhCH=CH	EtS	Me_2	92	—
Ph	MeO	Me_2	80	—
2-Pyridyl	Ph	Me	84	24:76
PhCO	Ph	Me	86	66:34



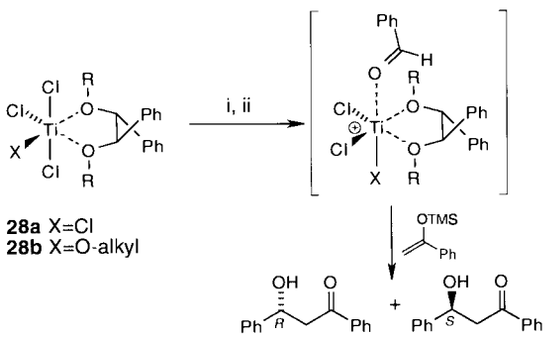


Scheme 19 *Reagents and conditions*: i, PhCHO, STDS (0.1 eq.), solvent, rt, 4 h.



Scheme 20 *Reagents and conditions*: i, RCHO, STDS (0.1 eq.), H_2O, rt, 4 h.

Chiral cationic titanium-based Lewis acids **28** catalyse asymmetric Mukaiyama-like "acetate aldol" reactions. The reactions proceed with mediocre enantiocontrol, but in good yield (Scheme 21 and Table 14).[21]



Scheme 21 *Reagents and conditions*: i, $AgSbF_6$, −20 °C; ii, PhCHO, −78 °C.

Masamune and co-workers have described their observations concerning aldol reaction of boron enolates of esters and amides, species previously considered to be relatively unreactive in such reactions (Scheme 22 and Table 15).[22] Esters of 8-phenylmenthol were shown to react with enantio- and diastereocontrol in such aldol reactions, with the levels of control ranging from mediocre (20% de) to excellent (96% de) (Scheme 23 and Table 16).

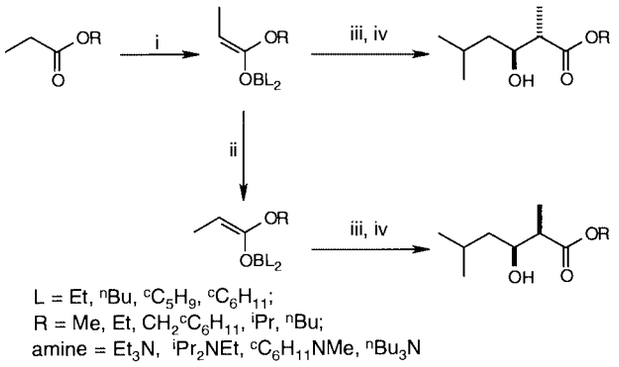
Proceeding *via* an asymmetric aldol-like reaction, chiral ketene dimers may be used to prepare enantiomerically-enriched 2-hydroxymethyl ketones **29** of up to 98% ee.[23] Such dimers are prepared enantioselectively *via* dimerization of

Table 14

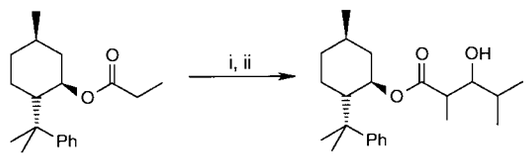
X	R	*R*:*S*	Yield (%)
O-^{i}Pr	Me	58:42	96
O-^{i}Pr	Et	61:39	95
OEt	Et	61:39	93
Cl	^{n}Pr	77:24	76
Cl	Me	77:24	80
Cl	Et	77:23	86
Cl	^{n}Pr	77:23	82

Table 15

R	Reaction time/h	Reaction temp./°C	Yield (%)
^{i}Pr	24	Ambient	98
Ph	48	Ambient	99
^{t}Bu	48	Reflux	75
$(MeO)_2CH$	72	Ambient	97
$(MeO)_2MeC$	48	Reflux	69
^{i}Bu	96	Ambient	94

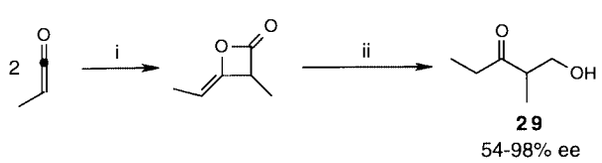


Scheme 22 *Reagents and conditions*: i, L_2BOTf, amine, CH_2Cl_2, −78 °C; ii, −78 to 0 °C; iii, ^{i}PrCHO, −78 °C, 1 h, then 0 °C, 1 h; iv, oxidative work-up.



Scheme 23 *Reagents and conditions*: i, $(^cC_6H_{11})_2BOTf$, Et_3N, CH_2Cl_2, −78 °C, 2 h; ii, ^{i}PrCHO, −78 °C, 1 h; 0 °C, 1 h.

methylketenes, formally a Claisen condensation, mediated by a chiral amine. In all cases, the origins of the enantioselectivity are proposed to lie in the facial bias present in the intermediate ammonium enolates which are formed during the reaction. *Cinchona* alkaloids once again showed their *pseudo*enantiomeric properties, with (*R*)-configured products being obtained when the reaction was catalysed by derivatives of quinidine and the opposite antipode obtained when quinine derivatives were used. The authors speculate that the origin of the enantioselectivity lies in the preference for a single rotameric form of the intermediate ammonium enolate involved, due to an unfavourable steric interaction between the methyl group of the enolate and the quinoline moiety of the amine (Scheme 24 and Table 17).



Scheme 24 *Reagents and conditions*: i, amine (1 mol%), THF, −78 °C; ii, $LiAlH_4$, THF, −78 °C.

The complexes formed between sodium triethylgermanide and a range of lanthanide Lewis acids are strong bases which mediate diastereoselective aldol reactions of ketones with aldehydes.[24] Even when the aldehyde component contains α-protons, only deprotonation of the ketone is observed (Schemes 25 and 26, Tables 18 and 19).

Table 16

Equivalents of $(^cC_6H_{11})_2$-BOTf	Equivalents of Et_3N	Reaction conditions	Yield (%)	*syn*:*anti*	De of major diastereoisomer (%)
1.3	1.5	−78 °C, 3 h	58	2:98	4
1.3	1.5	0 °C, 14 h	59	83:17	96
2.0	3.0	−78 °C, 3 h	87	2:98	4
2.0	3.0	0 °C, 30 min	92	78:22	94
2.0	3.0	−78 °C, 3 h	92	80:20	4
1.3	1.5	−40 °C, 3 h	58	60:40	94

Table 17

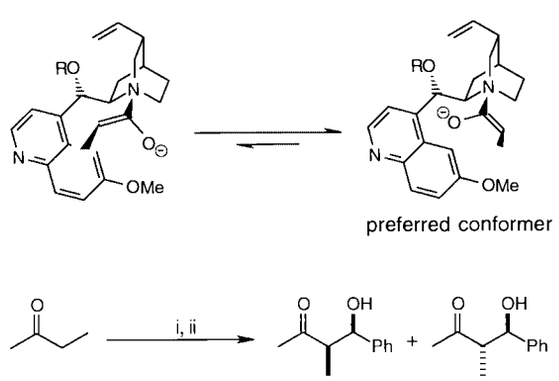
Amine	Absolute configuration of 29 (% ee)
Quinidine	*R* (98)
Propionylquinidine	*R* (97)
Trimethylsilylquinidine	*R* (98)
Quinine	*S* (70)
Propionylquinine	*S* (54)
Trimethylsilylquinine	*S* (93)

Table 18

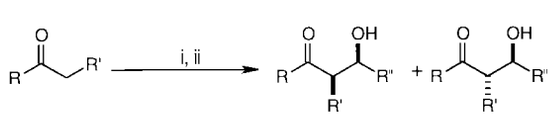
Solvent	$LnCl_3$	Yield (%)	*syn*:*anti*
THF	YCl_3	98	93:7
Et_2O	YCl_3	97	44:56
Toluene	YCl_3	76	44:56
Hexane	YCl_3	50	47:53
THF	$ScCl_3$	98	90:10
THF	$SmCl_3$	98	96:4
THF	$YbCl_3$	98	96:4
THF	None	97	56:44

Table 19

R	R′	R″	Yield (%)	*syn*:*anti*
Ph	H	Ph	97	—
Ph	Me	Ph	97	74:26
Et	Me	$(CH_2)_2Ph$	65	84:16
Et	Me	Pr	97	95:5
^iPr	Me	Ph	97	95:5
^iPr	Me	$(CH_2)_2Ph$	99	94:6
^iPr	Me	Pr	99	92:8
$-(CH_2)_4-$		Ph	96	12:88
$-(CH_2)_4-$		$(CH_2)_2Ph$	93	12:88
Me_2N	Me	Ph	98	97:3
Et_2N	Me	Ph	98	95:5

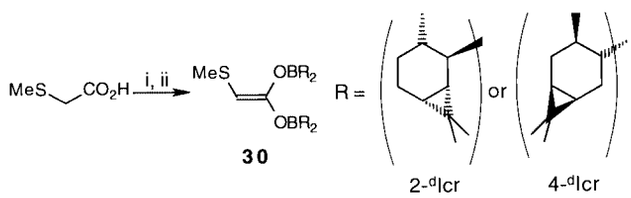


Scheme 25 *Reagents and conditions*: i, Et_3GeNa, $LnCl_3$, HMPA; ii, PhCHO, −78 °C.



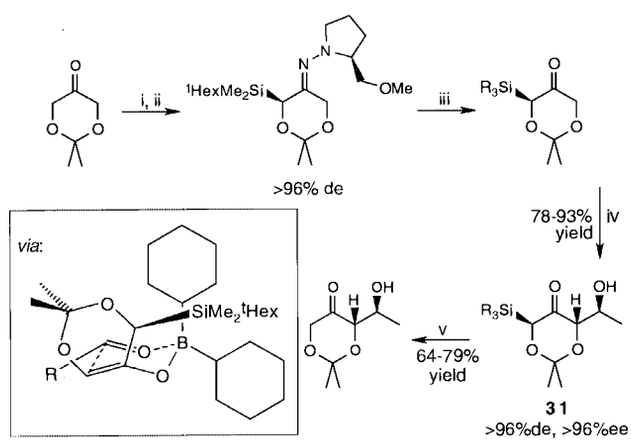
Scheme 26 *Reagents and conditions*: i, Et_3GeNa (1.3 eq.), $SmCl_3$ (0.42 eq.), THF, HMPA, 0 °C, 30 min; ii, R″CHO (1.3 eq.), −78 °C, 30 min.

Caranylboranyl enolates have been used to effect stoichiometric asymmetric aldol reactions of methylthioacetic acid.[25] Thus, methylthioacetic acid reacted with LDA and dicaranylboranyl chlorides to give enolborinates **30**. When (+)-2-isocaranyl ligands were employed, the subsequent aldol reactions of **30** proceeded with variable selectivity for *syn*-products (60–82% de), which were obtained in uniformly high enantioselectivity (≥93% ee); *anti*-products were obtained in poor ee (<12%). When (+)-4-isocaranyl ligands were used, *anti*-products were favoured (84–50% de) and the ees of the favoured diastereoisomer were not as consistently good (≤87% ee) (Scheme 27).



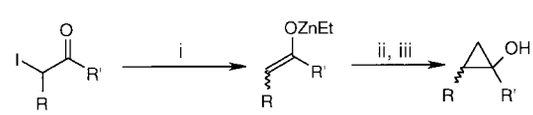
Scheme 27 *Reagents*: i, LDA; ii, R_2BCl.

Enantiomerically-pure silyl-substituted dioxanones have been shown to undergo highly diastereoselective *anti*-aldol reactions.[26] Thus the boron enolate derived from 2,2-dimethyl-4-thexyldimethylsilyl-1,3-dioxan-5-one reacts with a range of aromatic and aliphatic aldehydes with excellent diastereo- and enantioselectivity to give dioxanones **31** in good to excellent yield, *via* the usual Zimmerman–Traxler cyclic transition state. The silyl group may be removed using a HF–triethylamine complex to give 1,3-protected *anti*-1,3,4-trihydroxyketones (Scheme 28).



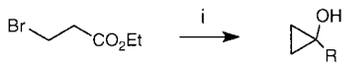
Scheme 28 *Reagents*: i, SAMP, benzene; ii, ^tBuLi, $^tHexMe_2SiOTf$, Et_2O; iii, O_3, CH_2Cl_2; iv, $^cHex_2BCl$, $EtMe_2N$; v, $Et_3N{\cdot}HF$.

Ethylzinc enolates (generated *in situ* from 2-iodoketones) may be cyclopropanated *via* reaction with diiodomethane.[27] A wide range of iodoketones undergo the reaction, in variable yield, and the cyclopropanols formed are obtained as predominantly *cis*-isomers (where applicable) (Scheme 29 and Table 20).



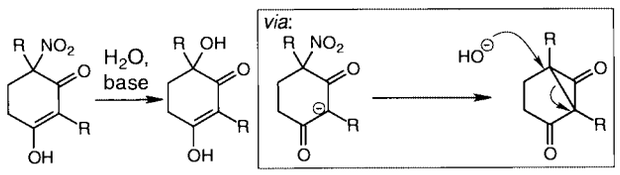
Scheme 29 *Reagents and conditions*: i, Et_2Zn (2.0 eq.), Et_2O, 0 °C; ii, CH_2I_2, 0 °C, 3 h; iii, CH_3OH, −78 °C.

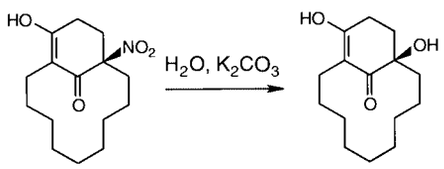
3-Haloesters react with Grignard reagents in the presence of samarium diiodide to give α-substituted cyclopropanols in excellent yield.[28] Cyclopentanols and cyclohexanols may also be prepared under the same reaction conditions using 5- and 6-haloesters, respectively. In the case of 4-haloesters, substituted cyclobutanols are produced in poor yield, the major product of the reaction being 2,2-disubstituted tetrahydrofurans (Scheme 30 and Table 21).



Scheme 30 *Reagents*: i, RMgBr, SmX_2, THF–HMPA.

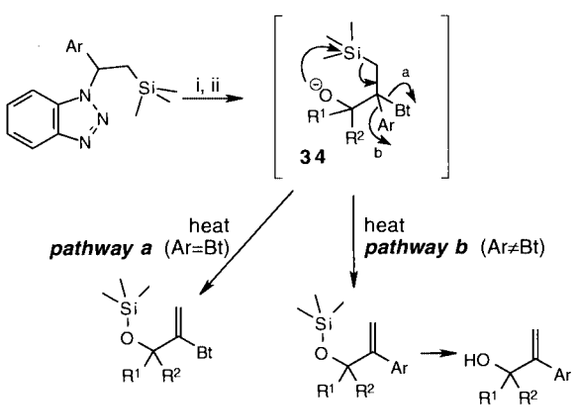
The mechanism of the conversion of α-nitro ketones to the corresponding α-hydroxy ketones under basic aqueous conditions has been studied.[29] The reaction was discovered serendipitously by the authors whilst they were studying ring-expansion reactions of cyclic α-nitroketones; only α-nitro ketones with acidic protons in the α′-position undergo the reaction and the NO_2/OH exchange was shown to proceed *via* retention of configuration (as in the conversion of **32** to **33**). The newly-incorporated oxygen atom (of the OH group) was shown to originate in the solvent. The product formation is explained by a double S_N2 reaction, *via* a Favorskii-like cyclopropane intermediate (Scheme 31).





Scheme 31

The Katritzky group's exploitation of the rich and varied chemistry of benzotriazoles continues unabated. Thus 2-aryl allylic alcohols are produced *via* reaction of 1-(1′-aryl-2′-trimethylsilylethyl)benzotriazolyl anions with carbonyl compounds.[30] These anions react to give alkoxides **34** which immediately undergo Brook rearrangement and elimination of benzotriazole to give silyl ethers of allylic alcohols, in good yield (Scheme 32 and Table 22).



Scheme 32 *Reagents and conditions*: i, ^nBuLi, THF, −78 °C; ii, R^1R^2CO.

The reaction of arylboronic acids with aromatic aldehydes, to give diarylmethanols, is catalysed by rhodium–acac complexes when dppf (1,1′-bis(diphenylphosphanyl)ferrocene) is

Table 20

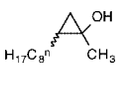
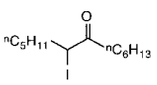
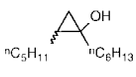
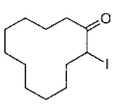
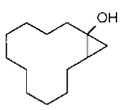
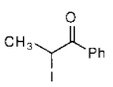
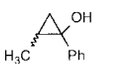
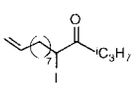
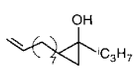
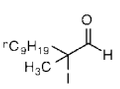
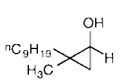
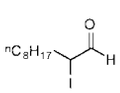
α-Iodocarbonyl	Cyclopropanol	Yield (%)	*cis*:*trans*
		82	93:7
		93	87:13
		58	>99:<1
		34	n.d.
		65	51:49
		92	57:43
		38	—
	Complex mixture	—	—

Table 21

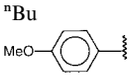
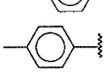
X	R	Yield (%)
I	^nBu	99
I	^iPr	85
I	^cHex	95
I	$TMSCH_2$	95
I	Ph	99
I		95
Cp	^nBu	85
Cp		99
Cp		95

Table 22

Ar	R^1	R^2	Temp (°C)/ time (h)	Additive/eq.	Yield of trimethyl silyl ether (%)	Deprotected yield (%)
$2\text{-}FC_6H_4$	H	$2\text{-}MeOC_6H_4$	90/5	—	22	40
$2\text{-}FC_6H_4$	H	$CH_2CH_2C_6H_5$	rt	—	77	97
$2\text{-}FC_6H_4$	$-(CH_2)_5-$		rt	$CeCl_3$/1	75	100
$2\text{-}FC_6H_4$	H	^iPr	rt	$CeCl_3$/1	67	79
$2\text{-}FC_6H_4$	H	$c\text{-}C_6H_{11}$	115/24	—	67	93
$4\text{-}Me_2NC_6H_4$	H	Ph	105/7	—	52	48
$2\text{-}MeC_6H_4$	H	$2\text{-}MeOC_6H_4$	115/8	—	53	56
$2\text{-}FC_6H_4$	H	CH(Me)Ph	120/1	—	56	97

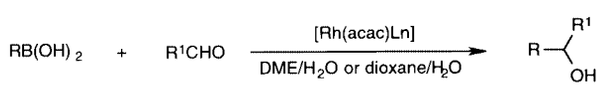
Table 23

$RB(OH)_2$	Aldehyde	Yield (%)
$PhB(OH)_2$	PhCHO	92
$PbB(OH)_2$	$4\text{-}CF_3C_6H_4CHO$	97
$PhB(OH)_2$	$4\text{-}NCC_6H_4CHO$	97
$PhB(OH)_2$	$4\text{-}MeCOC_6H_4CHO$	93
$PhB(OH)_2$	$4\text{-}NO_2C_6H_4CHO$	<1
$PhB(OH)_2$	$4\text{-}BrC_6H_4CHO$	88
$PhB(OH)_2$	$4\text{-}MeC_6H_4CHO$	48
$4\text{-}MeOC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	99
$4\text{-}FC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	52
$4\text{-}MeCOC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	<1
$2\text{-}MeC_6H_4B(OH)_2$	$4\text{-}MeOC_6H_4CHO$	80
$2,4,6\text{-}Me_3C_6H_2B(OH)_2$	$4\text{-}MeOC_6H_4CHO$	31
$PhB(OH)_2$	2-Furaldehyde	78
$PhB(OH)_2$	1-Naphthaldehyde	91
$PhB(OH)_2$	$C_5H_{11}CHO$	69
$PhB(OH)_2$	$C_6H_{13}CHO$	45
$(E)\text{-}C_4H_9CH{=}CHB(OH)_2$	$4\text{-}NCC_6H_4CHO$	76

Table 24

R	Yield (%)	Ee (%)
Ph	75	92
1-Naphthyl	68	88
2-Tolyl	90	98
4-Anisyl	96	97
$4\text{-}BrC_6H_4$	64	89
2-Furyl	65	95
(*E*)-PhCH=CH	62	91
(*E*)-PrCH=CH	96	92
$PhCH_2CH_2$	22	70

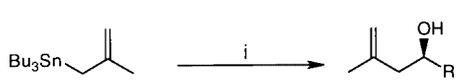
present.[31] The authors suggest that, because the reaction is sensitive to electronic effects, the reaction involves direct nucleophilic addition of the boronate substituent to the aldehyde. The reaction exhibits considerable chemoselectivity, with a wide range of functional groups inert under the reaction conditions (Scheme 33 and Table 23).



Scheme 33

1.1.2 Allylation

Enantioselective allylation of aldehydes by organostannanes mediated by chiral catalysts continues to occupy the attention of workers. Thus, (*R*)-BINAP–silver triflate complex catalyses the nucleophilic attack by methallyl- and crotyltin species to give homoallylic alcohols in generally good yield and with moderate to good enantioselectivity.[32] As is often the case in other allylations, the stereochemistry of the organotin is unimportant, leading in all cases to good regio- and diastereocontrol (Schemes 34 and 35 and Table 24).

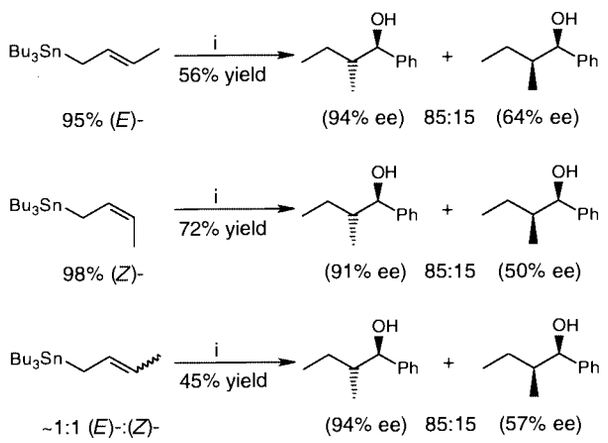


Scheme 34 *Reagents and conditions*: i, (*R*)-BINAP·AgOTf (0.05 eq.), RCHO (1 eq.), −20 °C, 8 h.

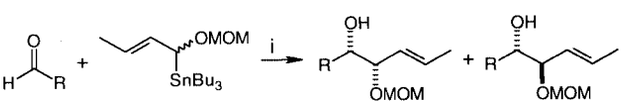
Marshall and co-workers have maintained their keen interest in the allylations of aldehydes by chiral hydroxylated allylstannanes.[33] Thus, the enantiomeric allylstannanes (*S*)- and (*R*)-**35** have been utilized in asymmetric stereoselective S_E2' reactions with *threo* and *erythro*-aldehydes **36** and **37**, respectively, to prepare precursors to differentially-protected L-talose, D-allose, L-glucose and D-mannose. The key mechanistic feature of the reaction is a tin–indium transmetallation; the allylindium species produced by such an exchange react with achiral aldehydes to give predominantly *anti*-1,2-dihydroxypent-4-enes (Scheme 36 and Table 25).

Table 25

R	*anti*:*syn*	Yield 38 (%)
$^nC_6H_{11}$	95:5	99
$^cC_6H_{11}$	98:2	95
(*E*)-BuCH=CH	90:10	85
$^nC_6H_{11}C{\equiv}CH$	90:10	85



Scheme 35 *Reagents and conditions*: i, (*R*)-BINAP·AgOTf (0.2 eq.), PhCHO (1 eq.), −20 °C to rt, 8 h.



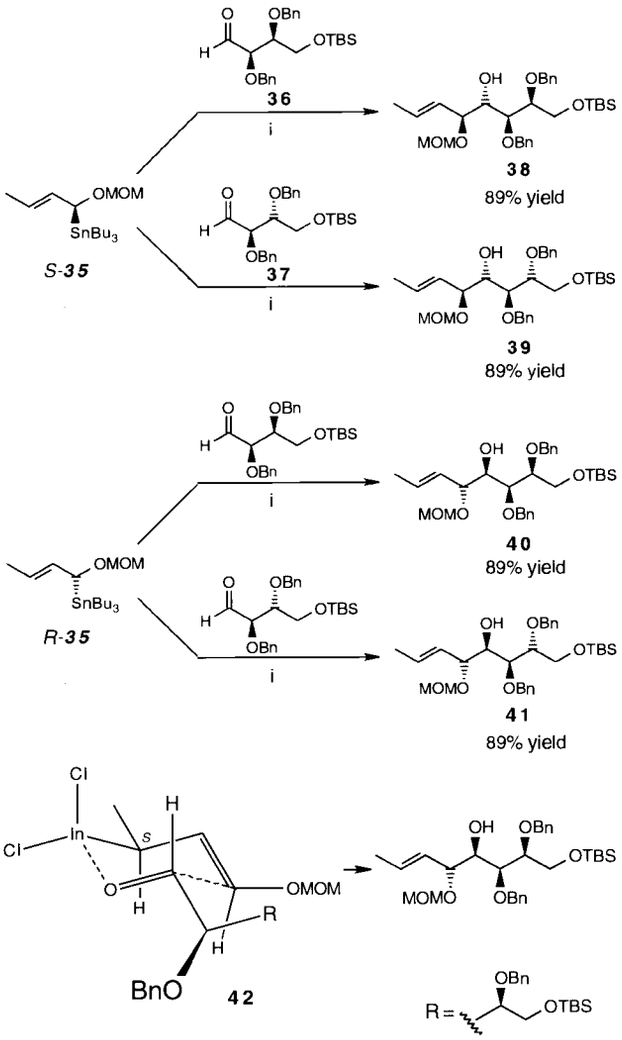
Scheme 36 *Reagents and conditions*: i, $InCl_3$, EtOAc, −78 °C to rt.

When enantiomerically-enriched (*E*)-α-oxy crotylstannane (*S*)-**35** was reacted with aldehydes **36** and **37** in the presence of indium(III) chloride, talose and allose-configured tetrol derivatives **38** and **39**, respectively, were obtained with high diastereo- and enantiocontrol (Scheme 37). Using the antipodal crotylstannane, (*R*)-**35**, gluco- and manno-configured tetrol derivatives **40** and **41** were obtained, again in a highly stereoselective reaction, due to a matched double asymmetric induction. The authors point out that these allylated compounds may be considered to be formal equivalents of differentially-protected L-talose, D-allose, L-glucose and D-mannose. A Zimmerman–Traxler-like cyclic transition state (**42**) which rationalizes the observed stereoselectivity was proposed by the authors.

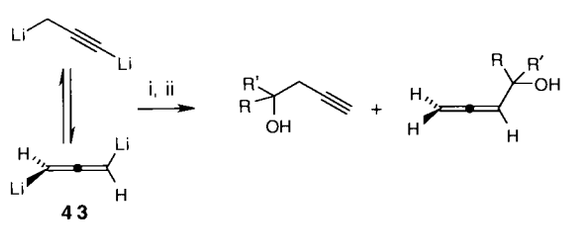
Allene reacts with two equivalents of ^{n}BuLi to give dianion **43** which reacts with aldehydes and ketones primarily *via* the propargyl† anion, to give homopropargyl† alcohols in excellent yield (Scheme 38 and Table 26).[34]

The use of lanthanum(III) triflate enhances both the rate and stereoselectivity of Barbier-type reactions of 4-bromocrotonate esters with arylaldehydes (Scheme 39).[35] In most cases, *anti*-homoallylic alcohols are obtained, although where additional ligation by the aldehyde is possible (for example, in the reaction of pyridine-2-carbaldehyde), this stereoselectivity may be overturned (Scheme 40 and Table 27).

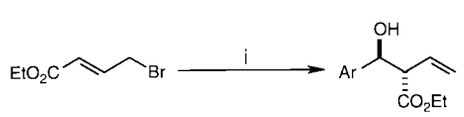
† The IUPAC names for propargyl and homopropargyl are prop-2-ynyl and but-3-ynyl, respectively.



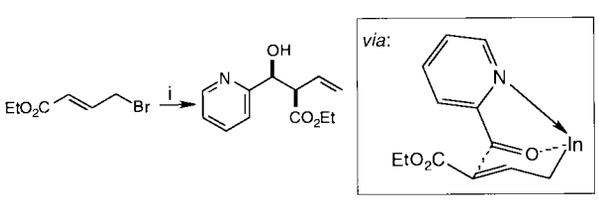
Scheme 37 *Reagents and conditions*: i, $InCl_3$, EtOAc, −78 °C to rt.



Scheme 38 *Reagents*: i, RCOR′; ii, H_3O^+.



Scheme 39 *Reagents*: i, indium, ArCHO, solvent, additive.



Scheme 40 *Reagents*: i, indium, 2-py-CHO, H_2O, $La(OTf)_3$.

(*S*,*S*)-*N*,*N*-Bis(α-methylbenzyl)formamide **44** acts as a Lewis base to catalyse the asymmetric allylation of a range of aryl and aliphatic aldehydes by allyl- and crotylsilanes.[36] The slow process (typically requiring several weeks) requires stoichiometric amounts of HMPA, but gives homoallylic alcohols in up to 98% ee. Contrary to what is frequently observed in asymmetric carbonyl addition reactions, aryl ketones react with poor enantioselectivity (Schemes 41 and 42, Tables 28 and 29).

Table 26

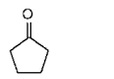
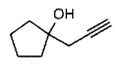
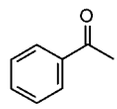
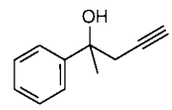
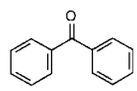
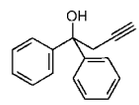
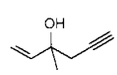
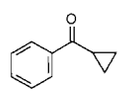
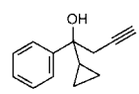
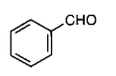
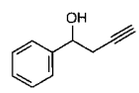
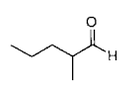
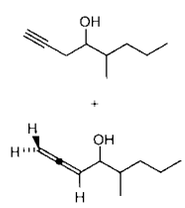
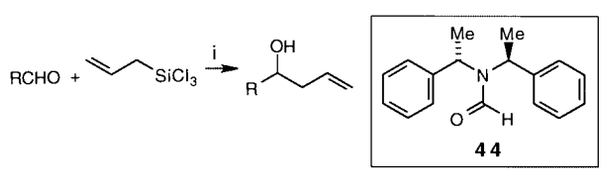
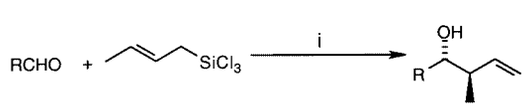
RCOR′	Product(s)	Yield (%)
		90
		93
		90
		80
		90
		93
		84

Table 27

Ar	Solvent	Additive	*anti*:*syn*	Yield (%)
Ph	H_2O	None	86:14	59
Ph	H_2O	$La(OTf)_3$	90:10	99
Ph	DMF	$La(OTf)_3$	99:1	99
2-Furyl	H_2O	$La(OTf)_3$	84:16	51
2-Pyridyl	H_2O	$La(OTf)_3$	5:95	90



Scheme 41 *Reagents and conditions*: i, catalyst **44**, HMPA, C_2H_5CN, −78 °C.



Scheme 42 *Reagents and conditions*: i, catalyst **44**, HMPA, C_2H_5CN, −78 °C.

Allylation of aldehydes using tetraallyltin requires no catalyst when polar solvents are used in the reaction. The reaction is mild and efficient, with homoallylic alcohols being produced in generally good yields (Scheme 43 and Table 30).[37]

Table 28

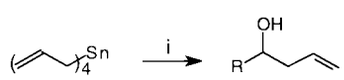
R	**44** (Mol%)	HMPA (mol%)	Time/ weeks	Yield (%)	Ee (%)
Cyclopentyl	20	100	2	72	91
$PhCH_2CH_2$	20	100	3	84	95
$(C_2H_5)_2CH$	20	100	3	74	93
tert-Butyl	40	200	4	61	98
$CH_3(CH_2)_5$	40	200	4	53	68
$CH_2{=}CH(CH_2)_2$	20	100	3	56	86
But-3-ynyl	40	200	3	51	88
Ph	20	100	1	94	8

Table 29

R	Yield (%)	Ee (%)	de
$PhCH_2CH_2$	97	94	>98
$^cC_6H_{11}$	92	98	>98

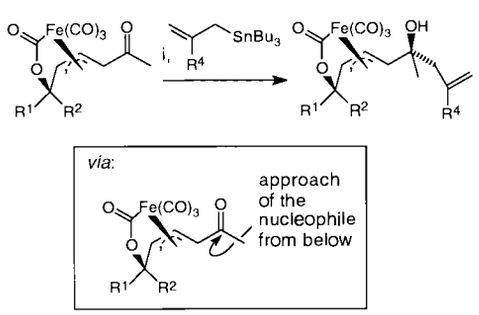
Table 30

R	Solvent	Yield (%)
^{i}Pr	MeOH	69
^{i}Pr	CH_2Cl_2	5
^{c}Hex	MeOH	84
Ph	MeOH	81
Ph	$HCONH_2$	84
Bn	MeOH	98
Bn	Me_2SO	70



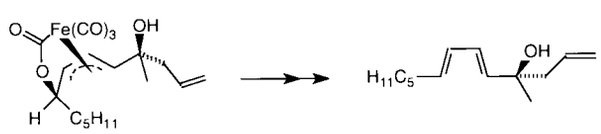
Scheme 43 *Reagents and conditions*: i, RCHO, solvent, rt, <20 hours.

Side-chain acyl groups of π-allyltricarbonyliron lactone complexes react with allylstannanes in the presence of a Lewis acid to give homoallylic tertiary alcohols in good yield and with very high diastereoselectivities.[38] The authors rationalize this selectivity as arising from reaction *via* an s-*cis* configuration (Scheme 44 and Table 31).



Scheme 44 *Reagents and conditions*: i, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C.

The products of the allylation reaction may be converted into stereodefined buta-1,3-dienes (Scheme 45).



Scheme 45

Bis(fluorosulfinyl)imide catalyses the allylation of carbonyl compounds by allyltrimethylsilane.[39] The imide acts as a Brønsted acid catalyst (Scheme 46 and Table 32).

Table 31

R^1	R^2	R^4	Yield (%)	De (%)
H	Me	H	76	>95
H	$^nC_5H_{11}$	H	84	>95
Me	H	H	81	95
$^nC_5H_{11}$	H	H	76	>95
H	Me	CH_2OBn	20	>95

Table 32

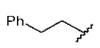
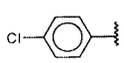
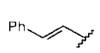
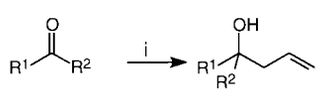
R^1	R^2	Yield (%)
	H	89
$^cC_6H_{11}$	H	91
^{t}Bu	H	86
Ph	H	94
	H	92
	H	50
$-(CH_2)_5-$		86
$-(CH_2)_4-$		No reaction
^{n}Pr	Me	38
Ph	Me	No reaction

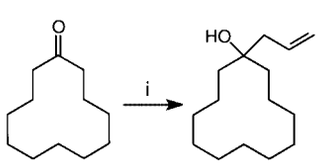
Table 33

Additive	Yield (%)	Reaction time/hours
TMSCl (4 eq.)	43	24
TMSCl (0.4 eq.) $PbCl_2$ (0.2 eq.)	92	0.5
TMSCl (0.4 eq.) $PbCl_2$ (0.1 eq.)	98	0.5
TMSCl (0.4 eq.) $PbCl_2$ (0.01 eq.)	99	0.5
$PbCl_2$ (0.1 eq.)	0	24



Scheme 46 *Reagents*: i, allyltrimethylsilane, $HN(SO_2F)_2$ (5 mol%), CH_2Cl_2.

Manganese metal may be activated by sub-stoichiometric amounts of lead(II) chloride and trimethylsilyl chloride, whereupon Barbier and Reformatsky-like reactions may be carried out (Scheme 47 and Table 33).[40]



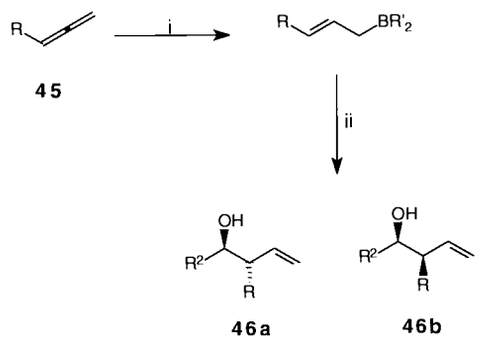
Scheme 47 *Reagents and conditions*: i, Mn (4 eq.), additive, THF, 25 °C.

The hydroboration of monosubstituted allenes provides a general synthetic route to 3-substituted allylboranes and thence to non-racemic homoallylic alcohols.[41] Thus reactions of allenes **45** with either dicyclohexylborane or diisopinocampheylborane give only allylborane products. These boranes give homoallylic alcohols **46**; where appropriate, enantiomeric excesses are moderate to good (Scheme 48 and Table 34).

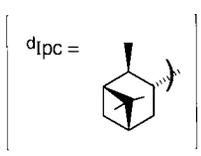
Diisopinocampheylpropargylboranes **47** are obtained upon reaction of metallated 2-alkynes with $^dIpc_2BCl$. **47** reacts at very low temperature with alkyl and aryl aldehydes to give α-allenyl alcohols **48** in good yield as the only product of the reaction.

Table 34

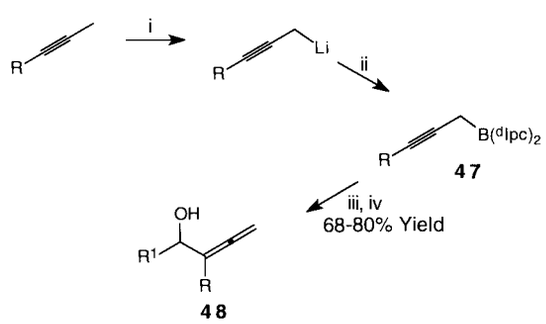
R	R^1	R^2	Yield 46 (%)	*anti*:*syn*	Ee (%) (config.)
^{n}Bu	Cyclohexyl	Ph	81	87:13	—
^{n}Bu	^{d}Ipc	Ph	78	88:12	78 (3*S*,4*R*)
^{n}Hex	Cyclohexyl	Ph	82	88:12	—
^{n}Hex	^{d}Ipc	Ph	81	90:10	74 (3*S*,4*R*)
Ph	Cyclohexyl	Me	82	>99:0	—
Ph	^{d}Ipc	Me	75	>99:0	80 (3*S*,4*R*)



Scheme 48 *Reagents and conditions*: i, R'_2BH, Et_2O, 0 °C to rt; ii, R^2CHO.



The enantioselectivity is generally good, with (*R*)-configured alcohols obtained in all cases.[42] No mechanistic rationalization is presented by the authors to explain the observations (Scheme 49 and Table 35).

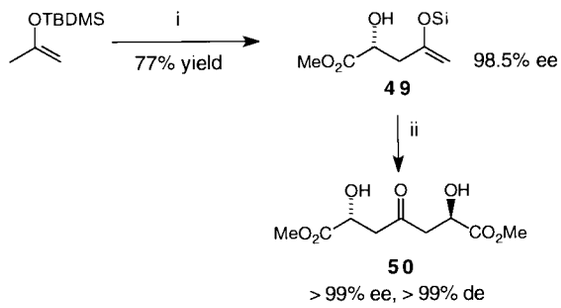


Scheme 49 *Reagents and conditions*: i, ^{n}BuLi; ii, $(^dIpc)_2BCl$, −78 °C to rt; iii, R^1CHO, −100 °C, 2 h; iv, NaO_2H.

Double asymmetric induction in the titanate-catalysed asymmetric aldol reaction of silyl enol ethers with methylglyoxalate allows for a highly enantioselective preparation of C_2-symmetric 2,6-dihydroxy-4-oxoheptanedioates **50**.[43] Thus, reaction of the enol ether of acetone with two equivalents of methylglyoxalate in the presence of a sub-stoichiometric amount of the (*R*)-BINOL-derived Ti(IV) catalyst proceeds to give **50** in good yields and with excellent stereocontrol (>99% ee and >99% de). The authors found that the enantiomeric excess of **50** was enhanced when compared to the intermediate of the reaction, the homoallylic alcohol **49**. Compound **49** was obtained with an ee of only 98.5% (in favour of the (*R*)-isomer) *via* reaction of one equivalent of glyoxalate with enol ether. Thus an asymmetric amplification occurs in the second Mukaiyama reaction: the authors calculate that this second reaction of (*R*)-**49** in the presence of (*R*)-BINOL is approximately 3.4 times faster than that of (*S*)-**49**, thereby allowing a dynamic kinetic resolution (Scheme 50).

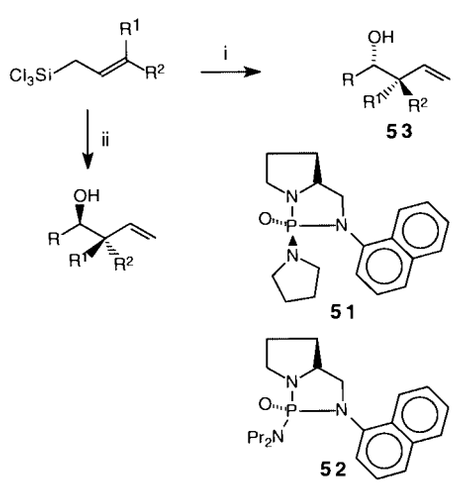
Table 35

R	R^1	Yield (%)	Ee (%)
^{n}Pr	^{i}Pr	80	96
^{n}Pr	Me	74	87
^{n}Pr	Ph	77	87
Me	^{i}Pr	72	96
Me	Me	68	89
Ph	^{i}Pr	70	96



Scheme 50 *Reagents and conditions*: i, $HCOCO_2Me$, (*R*)-BINOL, $Cl_2Ti(O^iPr)_2$ (10 mol%), CH_2Cl_2, 0 °C, 3 h; ii, $HCOCO_2Me$, (*R*)-BINOL, $Cl_2Ti(O^iPr)_2$, CH_2Cl_2, 0 °C, 3 h.

Chiral non-racemic phosphoramides catalyse the asymmetric allylation of aldehydes by allyltrichlorosilanes.[44] In the presence of sub-stoichiometric amounts of (*S*)-proline-derived phosphoramides **51** and **52**, aryl aldehydes are allylated in mediocre to excellent yield and with moderate enantioselectivity to give homoallylic alcohols **53**. Where diastereoisomerism is possible, (*Z*)-arylsilanes exhibit a good selectivity for *syn*-homoallylic alcohols, as predicted by the usual six-membered transition state, whereas (*E*)-silanes favour *anti*-configured products. The most interesting feature of the process is the inversion in enantioselectivity witnessed when the alkylamine sub-unit of the phosphoramide catalyst is changed from pyrrolidine to diisopropylamine; the selectivity changes from being in favour of the (1*R*)-isomer to favouring the (1*S*)-isomer, respectively (Scheme 51).



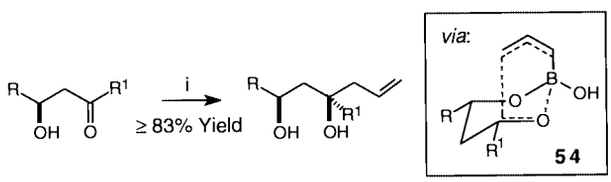
Scheme 51 *Reagents*: i, **51** (10–20 mol%), RCHO (0.1 eq.); ii, **52** (10–20 mol%) RCHO (0.1 eq.).

Kabalka's studies on the use of boron reagents in synthesis continues with the publication of the results of his group's studies of allylation of 3-hydroxyaldehydes and ketones by allylboronic acid. The reaction is diastereoselective (20–84% de), with the highest levels of selectivity being obtained when

Table 36

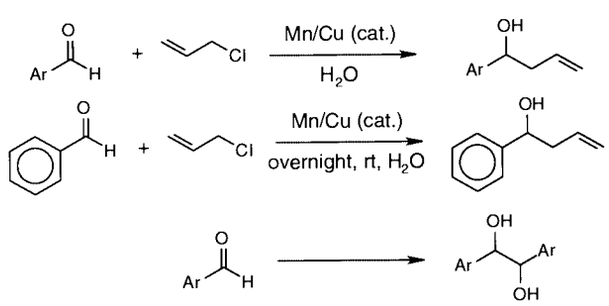
R	R^1	Yield (%)	De (%)
Ph	H	85	44
Bn	H	83	46
^{c}Hex	H	85	34
^{n}Bu	H	84	36
$^n C_{11}H_{23}$	H	88	30
^{t}Bu	H	86	40
Ph	Me	88	78
Ph	Et	84	80
Ph	Ph	93	72
^{i}Pr	Ph	89	84

the carbonyl group bears a phenyl substituent.[45] The stereoselectivity of the reaction (*syn*-1,3-diols always dominate the product distribution) is rationalized by the transition state **54** (Scheme 52 and Table 36).



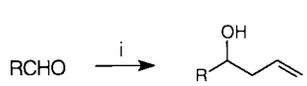
Scheme 52 *Reagents and conditions*: i, allylboronic acid, CH_2Cl_2, rt.

A combination of metallic manganese and copper mediates a Barbier-like reaction of aryl aldehydes with allyl chlorides.[46] The Mn/Cu protocol (no reaction is observed using only one metal) offers greater reactivity than other metal-mediated allylations in aqueous media, the authors claim. Furthermore, the authors report, the presence of acetic acid promotes a pinacol coupling reaction giving dihydrobenzoins in good yield but with poor stereoselectivity (*threo*:*erytho* = 65:35–39:61). Only aromatic aldehydes undergo this coupling process, with ketones being unreactive and aliphatic aldehydes undergoing reduction (Scheme 53, Tables 37 and 38).



Scheme 53

A transition metal salt recently described as catalysing allylation of aldehydes is scandium tritriflate, hailed by Aggarwal and Vennall as a novel mediator of reaction of aldehydes with allyltrimethylsilane (Scheme 54 and Table 39).[47]



Scheme 54 *Reagents*: i, allyltrimethylsilane, $Sc(OTf)_3$ (2–10 mol%), $MeNO_2$.

An intramolecular Barbier-type reaction allows for a simple stereoselective synthesis of fused α-methylene lactones.[48] Thus ω-formylbromomethacrylates **55** react with elemental

Table 37 Pinacol coupling mediated by manganese–HOAc in aqueous medium

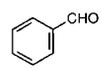
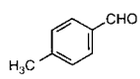
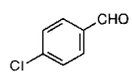
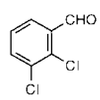
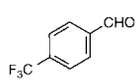
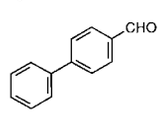
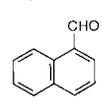
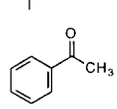
Carbonyl compound	Yield (%)	*threo*:*erythro*
	74	44:56
	70	56:44
	62	56:44
	90	51:49
	85	48:52
	Quantitative	59:41
	92	55:45
	84	56:44
	Reduced	—
	Reduced	—
	No reaction	—
	No reaction	—

Table 38 Pinacol coupling mediated by Mn in NH_4Cl

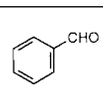
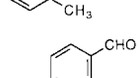
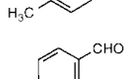
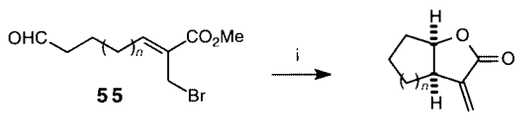
Carbonyl compound	Yield (%)	*threo*:*erythro*
	65	39:61
	81	52:48
	69	65:35
	64	33:67

Table 39

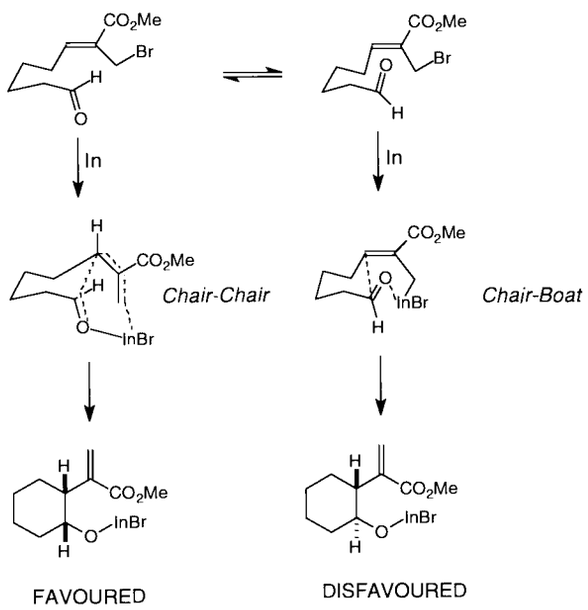
R	Yield (%)
Ph	79
2-Naphthyl	73
p-ClC_6H_4	98
p-$NO_2C_6H_4$	84
Bn	53
^{n}Bu	56
^{c}Hex	62
^{t}Bu	71

indium in water to give *cis*-α-(2′-hydroxy)cyclopentylacrylate which then cyclizes rapidly to the corresponding lactone (Scheme 55).



Scheme 55 *Reagents and conditions*: i, In, H_2O, 12–24 h.

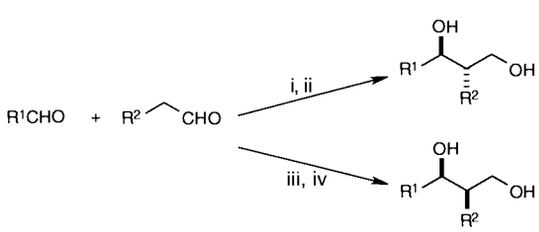
The reaction proceeds, it is postulated, *via* a chair–chair transition state rather than the alternative chair–boat conformer (Scheme 56).



Scheme 56

1.1.3 Reductive addition

A 'one-pot' aldol–carbonyl reduction procedure allows preparation of 2-alkyl-1,3-diols in generally good yield. *syn* or *anti*-Products may be obtained (with variable diastereoselectivity) according to judicious choice of enolization conditions (Scheme 57 and Table 40).[49]



Scheme 57 *Reagents and conditions*: i, $TiCl_4$, CH_2Cl_2, 5 °C; ii, Ti(O-^{i}Pr)$_4$ ('Method A'); iii, $TiCl_4$, base, −78 °C; iv, $LiAlH_4$ ('Method B').

Interest continues in asymmetric carbonyl reduction mediated by enantiomerically-pure oxazaborolidines. For instance, propargyl alcohols may be obtained in high ee by reduction of alkynyl ketones using (*R*)-phenylglycine-derived oxazaborolidine **56**.[50] Intriguingly, it seems that the same alkynylketones may be reduced with the opposite sense of asymmetric induction when their cobalt complexes **57** are employed in the reaction (Scheme 58 and Table 41).

The oxazaborolidine-mediated asymmetric reduction of *ortho*-substituted diaryl ketones reveals an interesting nicety concerning the mechanistic nuances of the process. Thus,

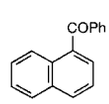
Table 40

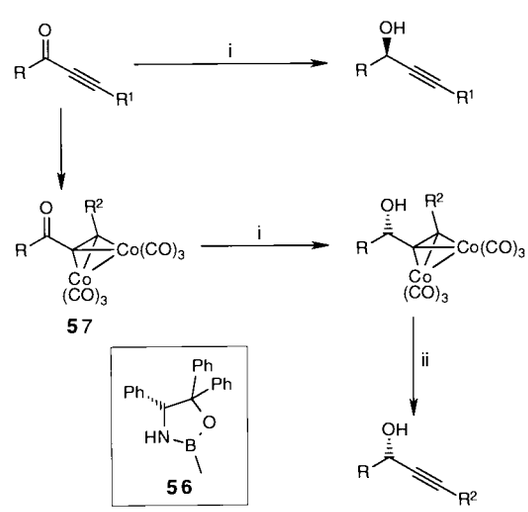
R^1	R^2	Method	Yield (%)	*syn*:*anti*
Ph	Me	A	73	9:91
Ph	Et	A	68	12:88
Et	Me	A	81	13:87
^{i}Pr	Me	A	48	15:85
Ph	Me	B	81	92:8
Ph	Et	B	72	90:10
Et	Me	B	71	86:14
^{i}Pr	Me	B	43	92:8

Table 41

R	R^1	R^2	Yield of alcohol (%)	Configuration (ee (%))
$BnCH_2CH_2$	TMS	—	92	*R* (90)
$BnCH_2CH_2$	H	—	73	*R* (90)
$^cC_6H_{11}$	TMS	—	65	*R* (93)
$^cC_6H_{11}$	H	—	60	*R* (90)
1-Adamantyl	TMS	—	80	*R* (95)
1-Adamantyl	H	—	70	*R* (97)
$BnCH_2CH_2$	—	H	65	*S* (92)

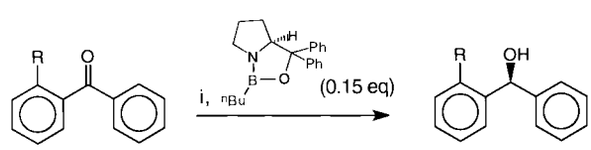
Table 42

R	Yield (%)	Ee (%)
Me	99	97
Br	90	97
	99	97



Scheme 58 *Reagents*: i, BH_3SMe_2, **56**; ii, CAN.

mono-*ortho*-substituted benzophenones give (*S*)-configured alcohols when reduced in the presence of (*S*)-catalyst. This observation suggests that the substituted phenyl group is the less sterically-demanding group, which is contrary to expectations (Scheme 59 and Table 42).

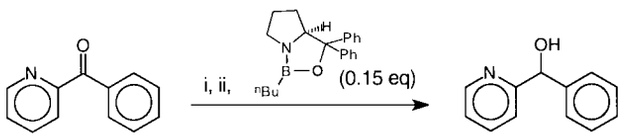


Scheme 59 *Reagents and conditions*: catechol borane (2 eq.), toluene, −40 °C, 17 h.

Table 43

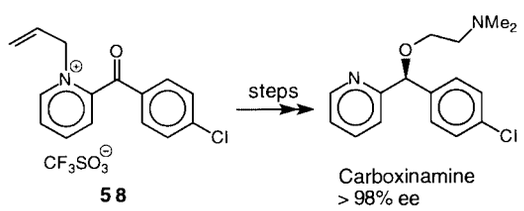
Lewis Acid	Solvent	Temperature/ °C	Time/h	Yield (%)	Ee (%)
None	Toluene	−40	15	89	0
BF_3	CH_2Cl_2	−78	72	30	2
BBr_3	CH_2Cl_2	−78	72	19	11

The authors suggest that this observation is due to a disfavoured steric clash between the *ortho*- and the carbonyl lone pair. In the same report,[51] a preparation of (*S*)-Barbinoxamine (a histamine H_1 antagonist) is described. The key feature of the synthesis is the rather elegant solution to the low selectivity shown during the reduction of pyridylphenones. Thus 2-pyridyl aryl ketones are reduced to alcohols with poor enantioselectivity under typical CBS conditions (Scheme 60 and Table 43).



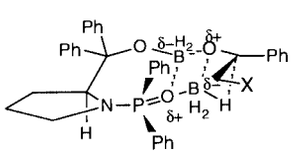
Scheme 60 *Reagents and conditions*: i, Lewis Acid; ii, catechol borane (2 eq.), solvent, temperature.

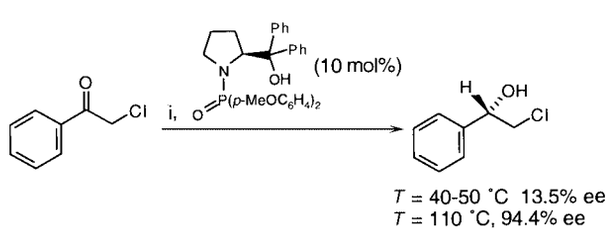
2-Benzoylpyridinium species **58** are, however, reduced with much greater enantioselectivity (≥90% ee), as demonstrated in Scheme 61.



Scheme 61

Diphenylprolinol-derived phosphinamides catalyse an asymmetric reduction of ketones.[52] Best results were obtained when the reaction was performed on haloalkyl aryl ketones and higher levels of enantioselectivity were observed when these asymmetric transformations were carried out at *higher* temperature. The authors suggest a transition state resembling **59** to rationalize their observations (Scheme 62).





Scheme 62 *Reagents*: i, 1.05 eq. $BH_3{\cdot}SMe_2$, toluene.

Mukaiyama and co-workers have examined the effects of ligand structure and alcohol additives upon the enantiocontrol of asymmetric reduction of prochiral aryl ketones by sodium borohydride–aldiminate cobalt complexes.[53] The authors reported that sterically-undemanding substrates were

Table 44

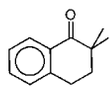
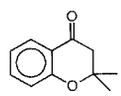
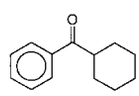
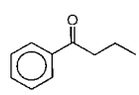
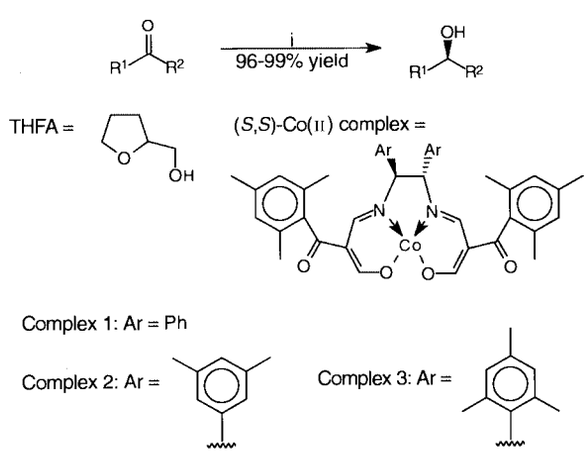
Ketone	Catalyst	Ee (%)
	1	91
	2	75
	1	65
	2	90
	3	60
	1	88
	2	92
	3	74
	1	62
	2	65
	3	95
	1	63
	2	87
	3	97

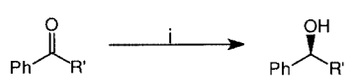
Table 45

R^1	ROH	Ee (%)
^{n}Pr	MeOH	90
^{n}Pr	EtOH	97
^{c}Pr	MeOH	76
^{c}Pr	EtOH	90
^{i}Pr	MeOH	95
^{i}Pr	EtOH	77
^{c}Hex	MeOH	95
^{c}Hex	EtOH	78

reduced with greatest stereocontrol when ethanol was present, while use of methanol was efficacious for ketones of higher steric demand. Variation in the structure of the aldimine ligand had a pronounced effect: less sterically-demanding ketones were reduced most selectively by the cobalt complex whose diamine core bore mesitoyl rather than phenyl substituents. The authors present a mechanistic argument to rationalize these data, based upon an X-ray analysis of one of the cobalt complexes (Schemes 63 and 64, Tables 44 and 45).

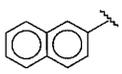
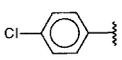
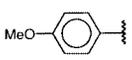
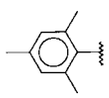


Scheme 63 *Reagents*: i, $NaBH_4$ (1.5 eq.), EtOH (4.5 eq.), THFA (20.6 eq.), (*S*,*S*)-Co(II) complex (0.01 eq.), $CHCl_3$.

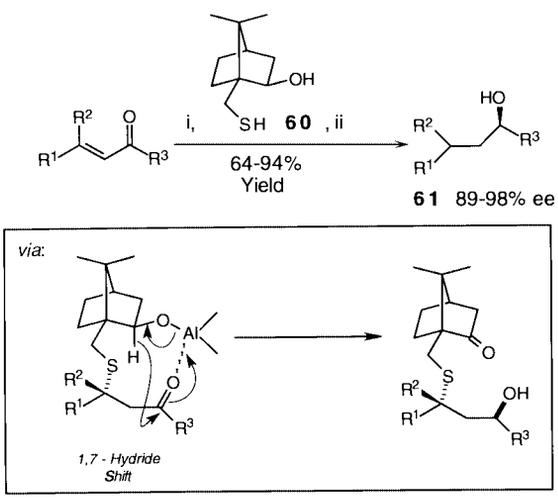


Scheme 64 *Reagents*: i, Co(II) complex 3, $NaBH_4$, THFA, ROH.

Table 46

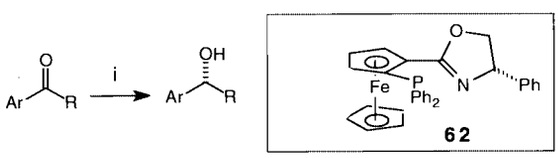
Ar	R	Yield (%)	Ee (%)
Ph	Me	80	94
Ph	Et	85	96
Ph	^{i}Pr	87	88
	Me	92	91
	Me	82	95
	Me	83	93
	Me	83	93
	Me	75	84
	Me	81	95

Asymmetric Meerwein–Varley–Ponndorf reduction of α,β-unsaturated ketones is mediated by dimethylaluminium chloride using hydroxy sulfide **60** as an asymmetric hydride source. Enones may thus be converted by a two-step process into secondary alcohols of high enantioexcess (generally ≥95% ee). The reaction sequence involves asymmetric 1,4-nucleophilic addition of the thiol moiety of **60** to the unsaturated ketone (mediated by the Lewis acid) followed by an asymmetric 1,7-hydride shift to generate the alcohol group. Desulfurization using Raney nickel yields alcohols **61** (Scheme 65).[54]



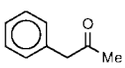
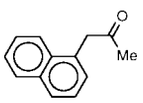
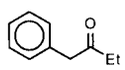
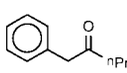
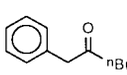
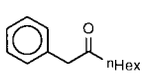
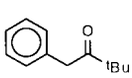
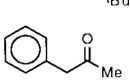
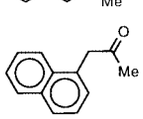
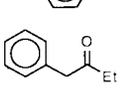
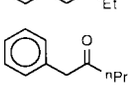
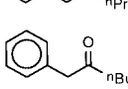
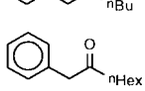
Scheme 65 *Reagents*: i, Me_2AlCl; ii, Raney Ni, $NaPH_2O_2$ buffer.

Hybrid phosphinylferrocenooxazolines **62** have been used to effect asymmetric MVP (Meerwein–Verley–Ponndorf) reduction of prochiral ketones.[55] The reduction of aryl alkyl ketones proceeds in good yield and with good enantiocontrol. In all cases, (*R*)-configured secondary alcohols were obtained from the reaction (Scheme 66 and Table 46).

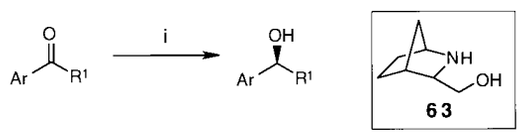


Scheme 66 *Reagents*: i, **62** (0.26 mol%), $RuCl_2(PPh_3)_3$, (0.2 mol%), ^{i}PrOH, ^{i}PrOK.

Table 47

Ketone	Arene	Time/h	Yield (%)	Ee (%)	Configuration
	$C_6(CH_3)_6$	5	92	95	*S*
	$C_6(CH_3)_6$	3	100	94	*S*
	$C_6(CH_3)_6$	5	81	83	*S*
	$C_6(CH_3)_6$	5	81	90	*S*
	$C_6(CH_3)_6$	5	70	89	*S*
	$C_6(CH_3)_6$	5	17	83	*S*
	$C_6(CH_3)_6$	5	<5	—	—
	*p*-Cymene	1.5	91	94	*S*
	*p*-Cymene	1.5	92	97	*S*
	*p*-Cymene	1.5	81	93	*S*
	*p*-Cymene	1.5	60	92	*S*
	*p*-Cymene	1.5	78	95	*S*
	*p*-Cymene	1.5	53	95	*S*

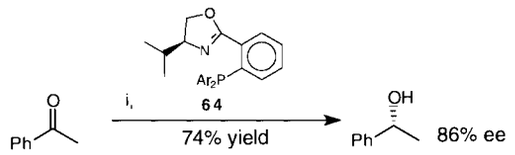
Chiral ruthenium complexes incorporating non-racemic 2-azanorbornene-3-methanol **63** mediate an asymmetric Meerwein–Verley–Ponndorf reduction.[56] Thus, ketones are reduced to the corresponding benzyl alcohols with generally high enantiocontrol when reacted with KO^{i}Pr in the presence of sub-stoichiometric amounts of $\{RuCl_2(C_6[CH_3]_6)\}_2$ or $[RuCl_2(p\text{-cymene})_2]_2$ and **63** (Scheme 67 and Table 47).



Scheme 67 *Reagents*: i, 0.25 mol% $[RuCl_2(arene)]_2$, **63** (2 mol%), ^{i}PrOH/2.5 mol%, ^{i}PrOK.

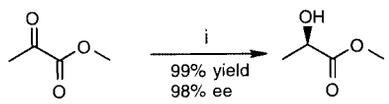
Langer and Helmchen have described the results of enantioselective Meerwein–Verley–Ponndorf reduction of ketones. Thus, asymmetric bidentate ligands **64** mediate the stereoselective preparation of secondary alcohols in variable yield and with variable enantiocontrol (58–94% ee). As is often the case, best results are obtained when aryl ketones are the substrates in the reaction (Scheme 68).[57]

Methyl and ethyl pyruvate are reduced enantioselectively by hydrogen in the presence of cinchonidine-treated PVP



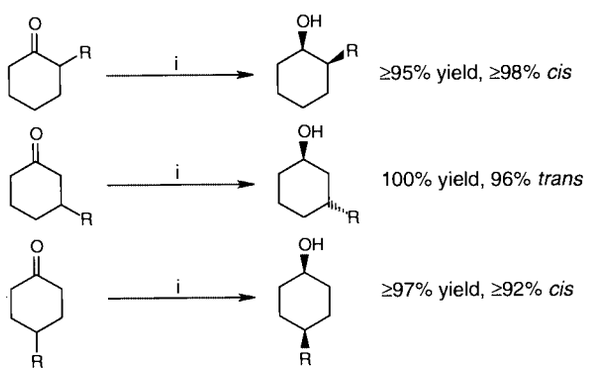
Scheme 68 *Reagents and conditions*: i, ^{i}PrOH, $RuCl_2(PPh_3)_3$, 82 °C.

("polyvinylpyrrolidone") stabilized platinum species (Scheme 69).[58]



Scheme 69 *Reagents*: i, H_2, PVP-Pt, cinchonidine.

Noyori and his co-workers enthusiasm for synthetic methodology directed towards carbonyl reduction shows no sign of abating. A recent output from their laboratories concerns the diastereoselective reduction of simple ketones using elemental hydrogen, mediated by ruthenium(II) complexes in the presence of 1,2-diamines.[59] Thus, substituted cyclohexanones are reduced by a ruthenium hydride species which behaves essentially as a bulky hydride, effecting reduction *via* equatorial attack upon the double bond (Scheme 70).



Scheme 70 *Reagents*: i, H_2, $RuCl_2(PPh_3)$, $H_2NCH_2CH_2NH_2$, KOH.

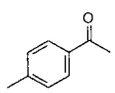
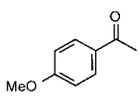
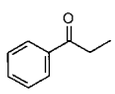
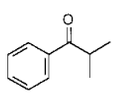
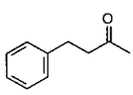
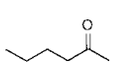
Aromatic ketones and aldehydes are reduced to the corresponding alcohols by hydrogenation in the presence of substoichiometric amounts of a Pd/C–ethylenediamine complex.[60] Yields are generally greater than 90%, and the process is operationally simple, requiring only a balloon of hydrogen gas to proceed (Scheme 71).

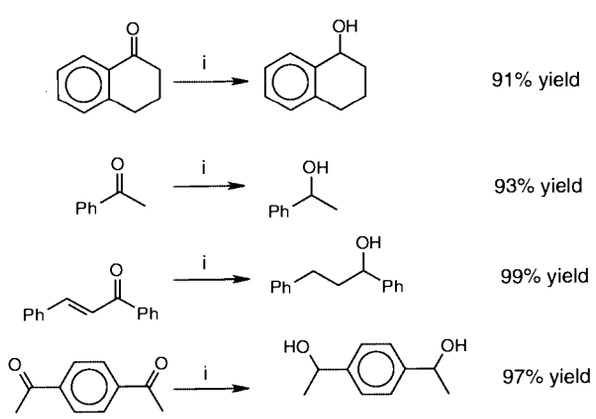
Aromatic methyl ketones are asymmetrically hydrogenated with high levels of enantioselectivity using cationic rhodium complexes and bisphosphane ligands **65**.[61] For the reaction to exhibit good enantioselectivity, 2,6-lutidine and KBr must be present in the reaction mixture (Scheme 72 and Table 48).

Diphosphinyl[2.2]paracyclophane (*S*)-PHANEPHOS **66** mediates asymmetric hydrogenation of 3-ketoesters using Ru(II) complexes.[62] The enantioselectivity of the reaction is high, with (*R*)-enantiomers usually being the main product (Scheme 73 and Table 49).

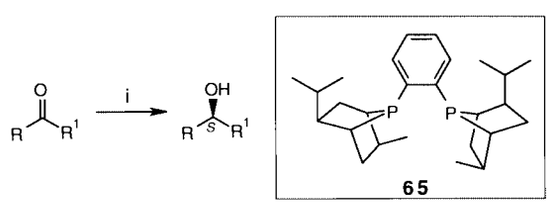
Enaminoketoesters **67** may be converted in good yield and with excellent enantiocontrol into Statine analogues *via* a double asymmetric reduction.[63] Thus **67** is transformed directly into aminohydroxyester **68** upon reaction with H_2 in the presence of chiral Rh(I) or Ru(II) catalysts in virtually quantitative yield and with excellent enantiocontrol (ee >95%). The (3*R*,4*R*)-isomer is the favoured product. The reaction has as its first step hydrogenation of the enamine moiety, as shown by the

Table 48

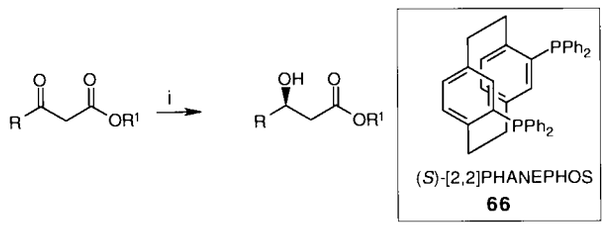
Ketone	Eq. of lutidine	Eq. KBr	Time/h	Yield (%)	Ee (%)
	0.4	—	24	97	95
	0.4	—	53	94	95
	0.8	—	108	56	91
	0.8	1.0	48	83	94
	0.8	—	108	71	89
	0.8	1.0	88	95	93
	0.8	1.0	94	20	72
	0.8	1.0	100	99	96
	0.8	1.0	56	99	73
	0.8	1.0	75	66	85
	0.8	1.0	94	99	84
	0.8	1.0	106	90	92
	0.8	1.0	96	51	94
	0.8	1.0	48	96	75



Scheme 71 *Reagents and conditions*: i, 10% Pd/C-ethylenediamine, H_2, MeOH, <24 h.

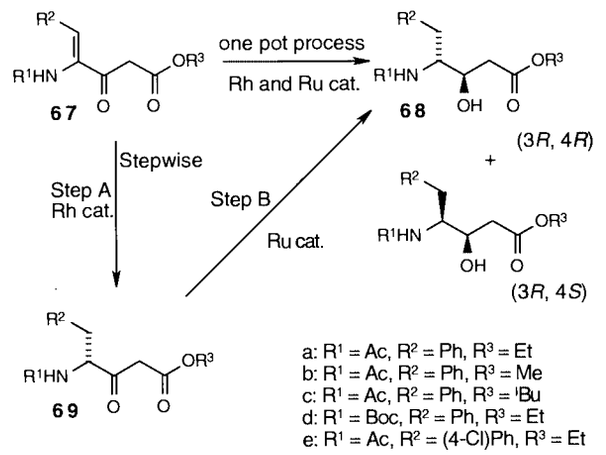


Scheme 72 *Reagents*: i, H_2, $[Rh(cod)Cl]_2$, **65**, 2,6-lutidine, MeOH, KBr.



Scheme 73 *Reagents and conditions*: i, **66**-Ru(II), MeOH–H_2O, H_2/50 psi.

isolation of aminoketoester **69** when lower pressures of hydrogen were employed in the transformation (Schemes 74 and 75, Table 50).



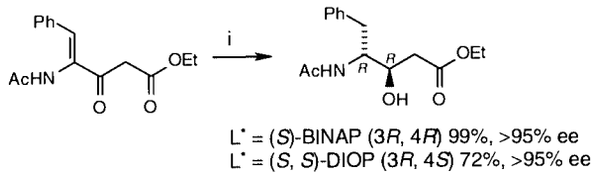
Scheme 74

A polymer-bound Noyori catalyst reduces benzophenone in good yield and with high enantioselectivity.[64] Repeated use of the catalyst is feasible (Scheme 76 and Table 51).

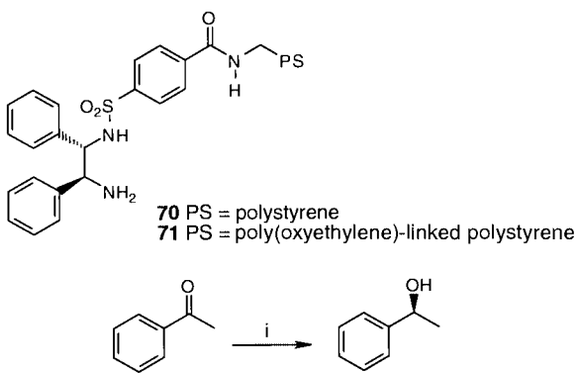
DIPOF, an asymmetric hybrid ferrocene–phosphine/oxazolinyl ligand, is an effective asymmetric mediator in the iridium(I)-catalysed asymmetric hydrosilylation of ketones.[65] Thus, reduction of ketones by diphenylsilane furnishes (after acid hydrolysis of the first-formed silyl ether) secondary

Table 49

R	R^1	Ee (%)	Configuration
Me	Me	96	*R*
Me	^{t}Bu	95	*R*
Me	Et	96	*R*
Et	Me	96	*R*
^{i}Pr	Et	95	*S*



Scheme 75 *Reagents and conditions*: i, $[Rh(COD)L^*]^+ClO_4^-$, $RuBr_2$-[(*S*)-BINAP], EtOH, NEt_3, 40 °C, H_2 10 atm for 24 h, then 90 atm for 24 h.



Scheme 76 *Reagents and conditions*: i, ligand, $[RuCl_2(p\text{-cymene})_2]_2$ (1 mol%), 30 °C, S/C 100, ^{i}PrOH or $HCO_2H{\cdot}Et_3N$.

alcohols in generally moderate ee (9–96%) (Scheme 77 and Table 52).

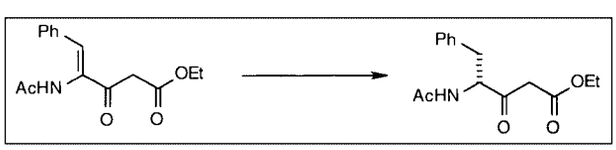
Vanadium-mediated diastereoselective pinacol-type couplings continue to occupy the attention of researchers. Thus, a mixture containing TMSCl, Zn metal and a sub-stoichiometric amount of cyclopentadienylvanadium dichloride mediates the reductive dimerization of a range of aryl and aliphatic

Table 51

Ligand	Solvent	Time/h	Conversion	Ee (%)
70	Neat[a]	28	21	91
71	Neat[a]	28	95	97
70 (2nd use)	Neat[a]	72	96	97
71	Neat[a]	16 (60 °C)	100	92
70	DCM[b]	18	71	>99
70 (2nd use)	DCM[b]	21	52	96
70 (3rd use)	DCM[b]	69	65	91
70	DMF[b]	18	61	95
70 (2nd use)	DMF[b]	21	52	98
70 (3rd use)	DMF[b]	69	80	95
71	DCM[b]	18	42	51
71	DMF[b]	18	46	88

[a] Reaction was run at 1.0 M concentration. [b] Reaction was run at 0.5 M concentration with a HCO_2H–Et_3N to solvent ratio of 1 : 4.

Table 50



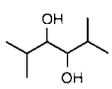
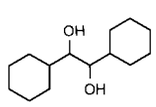
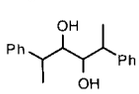
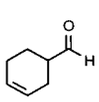
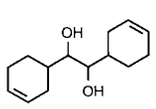
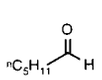
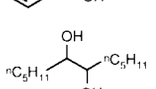
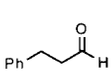
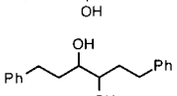
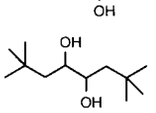
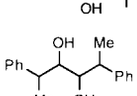
Catalyst	H_2/atm	Additive	Yield (%)	Ee (%)
$[Rh(COD)(S)\text{-BINAP}]^+ClO_4^-$	10	NEt_3	100	>99(*R*)
$[Rh(COD)(S)\text{-BINAP}]^+ClO_4^-$	30	None	100	50(*R*)
$[Rh(COD)(S,S)\text{-DIOP}]^+ClO_4^-$	10	NEt_3	100	50(*S*)
$[Rh(COD)(S,S)\text{-DIOP}]^+ClO_4^-$	30	None	100	33(*S*)
$[Rh(COD)(R,R)\text{-Me-DuPHOS}]^+ClO_4^-$	10	NEt_3	100	>99(*R*)

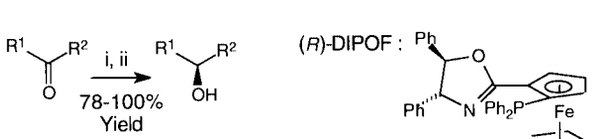
Reaction carried out using 1 mol% of Rh(I) catalyst in ethanol at 40 °C for 24 h.

Table 52

	R^1	R^2	Ee (%)
	Ph	Me	96
	Ph	Et	92
	Ph	^{n}Pr	91
	Ph	^{i}Pr	9
	p-ClC_6H_4	Me	88
		Me	83
		Me	84

Table 53

Aldehyde	Coupling product	Yield (%)	*syn*:*anti*
		89	91:9
		71	90:10
		67	94:6
		100	85:15
		97	50:50
		97	64:36
		100	56:44
		91	57:43



Scheme 77 *Reagents and conditions*: i, $[Ir(COD)Cl]_2$/(*R*)-DIPOF (0.5 mol%), Ph_2SiH_2, Et_2O, 0 °C; ii, H^+.

aldehydes, in generally excellent yields.[66] The 1,2-diols produced are predominantly of *syn*-configuration, but the level of stereoselectivity is crucially dependent on the solvent, with a more strongly-coordinating solvent (DME) leading to poorer diastereoselectivity than a solvent (THF) of weaker donicity (Scheme 78 and Table 53).

Hydrobenzoins are prepared with very high diastereocontrol by low-valent titanium-mediated pinacol coupling of aromatic aldehydes (Scheme 79 and Table 54).[67]

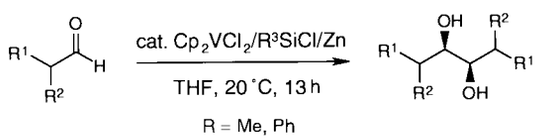
The selectivity of the reaction is rationalized by the intermediacy of bridged Ti(IV) ketyls. Pinacols are also prepared (albeit with lower selectivity) by reaction of ytterbium(II) phenylthiolate (formed *in situ*) with aromatic aldehydes.[68]

Table 54

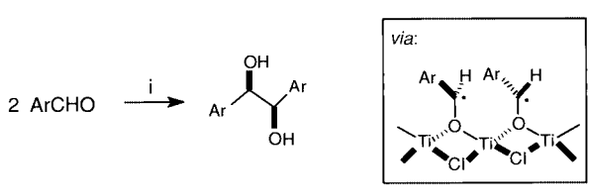
Ar	Yield (%)	De (%)
Ph	65	99
p-Tol	35	>98
p-ClC_6H_4	90	>98
p-BrC_6H_4	96	>98
p-$N{\equiv}CC_6H_4$	95	>98
p-$HO_2CC_4H_4$	90	>98

Table 55

Ar	Yield (%)	De (%)
p-Tol	66	50
p-Anisyl	69	60
Ph	41	60
p-Cl	47	50
p-CN	61	60

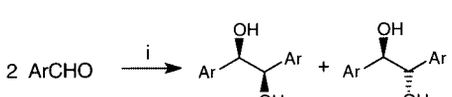


Scheme 78



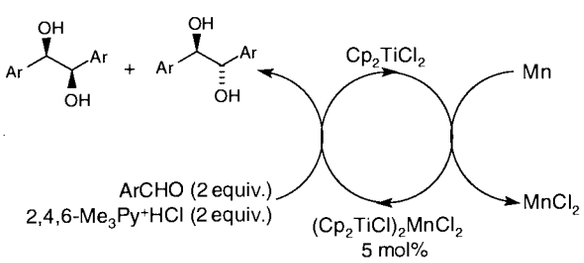
Scheme 79 *Reagents and conditions*: i, $TiCl_3$, CH_2Cl_2, rt, 30 min.

Although the thiolate is acting as a reducing agent, when it was used in attempted reductions of aldehydes and ketones, complex mixtures of products were obtained (Scheme 80 and Table 55).



Scheme 80 *Reagents*: i, Yb, $PhSSiMe_3$ (2 eq.), CH_3CH_2CN.

Aryl aldehydes undergo a titanocene-catalysed pinacol-like coupling reaction to give primarily *syn*-1,2-diols in good yields.[69] Thus, two equivalents of an aldehyde react with a substoichiometric amount of Cp_2TiCl_2 and elemental manganese under buffered conditions to give *syn*-diols (≥96 : ≤ 4 dr) *via* (the authors state) the first example of a catalytic turn-over achieved by protonation of a metal–oxygen bond. The authors justify this claim by describing the influence of the buffer upon the diastereoselectivity of the reaction: a range of pyridinium salts were used and the highest selectivities were observed using the buffer derived from the most basic pyridine (Scheme 81 and Table 56).

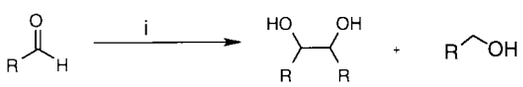


Scheme 81

Table 56

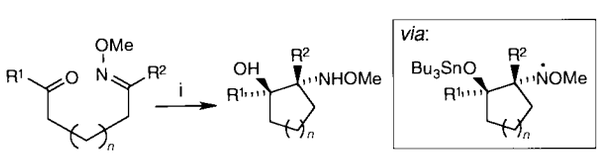
Substrate	Yield (%)	*syn*:*anti*
2-MeC_6H_4CHO	90	97:3
3-MeC_6H_4CHO	85	97:3
4-MeC_6H_4CHO	84	97:3
4-ClC_6H_4CHO	89	97:3
4-BrC_6H_4CHO	82	98:2
4-$MeOC_6H_4CHO$	91	99:1
4-$AcOC_6H_4CHO$	85	99:1
4-PhC_6H_4CHO	87	97:3
4-CH_2=CHC_6H_4CHO	85	96:4
4-(2′-thienyl)-CHO	82	95:5

A variety of aromatic aldehydes undergo pinacol coupling reaction when reacted with magnesium in aqueous solution containing a sub-stoichiometric amount of ammonium chloride.[70] Aliphatic aldehydes are inert to the reaction conditions. The 1,2-diols produced by this reaction are often accompanied by reduced products which, in certain circumstances, dominate the reaction mixture. The diol products are obtained as a *syn*–*anti* mixture in which there is a small excess of the *syn*-isomer (Scheme 82 and Table 57).



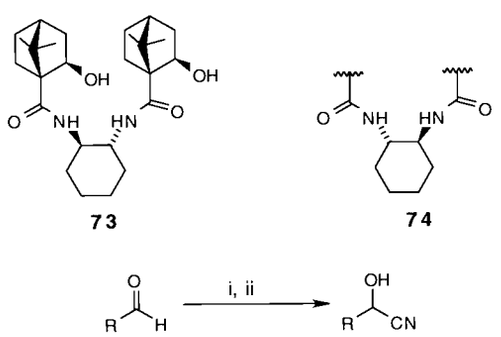
Scheme 82 *Reagents and conditions*: i, Mg, H_2O, rt, 12–24 h.

N-Methoxy *trans*-1-amino-2-hydroxycycloalkanes are obtained upon reaction of oximinoaldehydes and ketones with tributylstannane in refluxing benzene,[71] *via* 5- or 6-*exo-trig* cyclization. All the products are obtained as predominantly *trans*-isomers, with a greater selectivity shown in the formation of five-membered rings (*trans*:*cis* = 2–180:1) when compared to six-membered rings (*trans*:*cis* = 2–7:1) (Scheme 83 and Table 58).



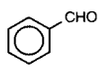
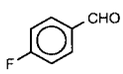
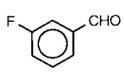
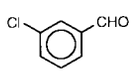
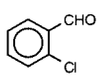
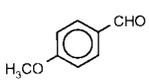
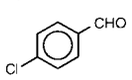
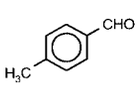
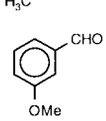
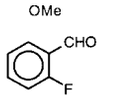
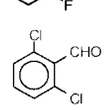
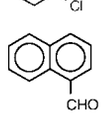
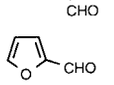
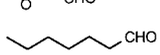
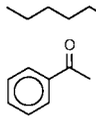
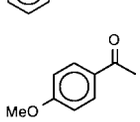
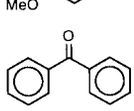
Scheme 83 *Reagents and conditions*: i, Bu_3SnH, AIBN, benzene, heat.

Cyclohexane-1,2-diamine-derived bis-amides **73** mediate the asymmetric silylcyanation of aldehydes by TMSCN in the presence of tetraisopropyltitanate.[72] Using an optimized procedure, the presence of sub-stoichiometric amounts of (*R*,*R*)-bisamide and titanate in the reaction leads (after acidic cleavage of the silyl ether) to (*S*)-cyanohydrins exhibiting generally high enantioexcess. As is often the case, best stereoselectivity was usually observed when aromatic aldehydes were employed in the reaction (Scheme 84 and Tables 59 and 60).



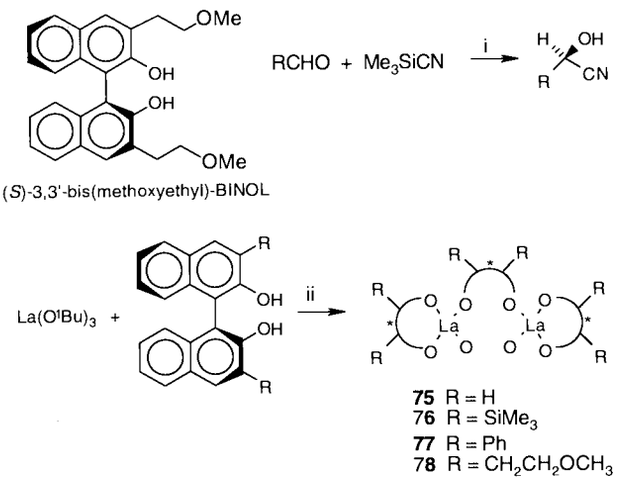
Scheme 84 *Reagents and conditions*: i, TMSCN, $Ti(O^iPr)_4$, **73** or **74**, 4 Å molecular sieves, CH_2Cl_2; ii, 1 M HCl.

Table 57

Substrate	Yield pinacol (%)	Yield reduced product (%)	*syn*:*anti*
	80	1	59:41
	87	0	80:20
	83	6	54:46
	42	11	54:46
	50	27	52:48
	89	0	61:39
	90	7	50:50
	65	8	61:39
	78	0	54:46
	73	10	51:49
	0	74	N/A
	62	30	30:70
	92	0	64:36
	0	0	—
	66	8	53:47
	41	—	53:47
	0	0	N/A

A range of chiral binaphthol-based ligands have also been shown to mediate an asymmetric trimethylsilylcyanation of aldehydes.[73] Thus, reaction of aryl aldehydes with TMSCN in the presence of pre-formed chiral lanthanum "binaphthoxides" proceeds to give 2-hydroxy nitriles in good yield, but with (at best) moderate enantiocontrol (ee = 7–73%). (*S*)-Configured binaphthols led to (*S*)-hydroxy nitriles (Scheme 85 and Table 61).

(*S*)-Cyanohydrins of high enantiomeric purity are obtained from the reaction of a range of aldehydes with HCN, catalysed by the hydroxy nitrile lyase (HNL) from *H. brasiliensis*.[74] Methyl ketones also undergo the reaction, but with inferior levels of enantiocontrol (75–89% ee) (Table 62).



Scheme 85 *Reagents and conditions*: i, 10% mol catalyst, CH_2Cl_2, −78 °C, 10 h; ii, CH_2Cl_2, rt, 12 h.

N-Acetyl enamines derived from α-hydroxyacetophenones are hydrogenated in an enantioselective manner using cationic rhodium complexes based upon chiral ligands (*R*,*R*)-BICP **79** and (*R*,*R*)-DuPhos **80**.[75] Thus, MON-protected hydroxyenamides (prepared in an innovative fashion by reaction of oximes with Fe in acetic anhydride) are converted to deprotected hydroxyamines in quantitative yield and with excellent enantioselectivity (Scheme 86 and Table 63).

Table 58

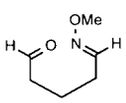
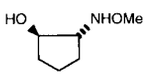
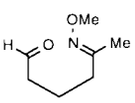
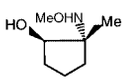
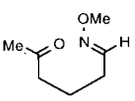
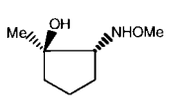
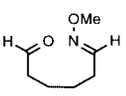
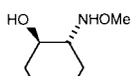
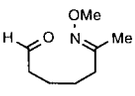
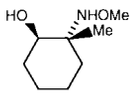
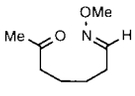
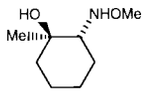
Substrate	Major product	Yield (%)	*trans*:*cis*
		73	18:1
		68	>180:1
		84	7:1
		67	3:1
		44	7:1
		70	2:1

Table 60

Aldehyde	Time/h	Yield (%)	Ee (%)	Configuration
3-Phenoxybenzaldehyde	120	57	97	(*S*)
4-Methoxybenzaldehyde	120	53	97	(*S*)
2-Naphthaldehyde	120	76	96	(*S*)
(*E*)-Cinnamaldehyde	120	51	95	(*S*)
3-Phenylpropionaldehyde	120	62	98	(*S*)
2-Methylbenzaldehyde	120	68	97	(*S*)
Cyclohexanecarboxaldehyde	60	94	87	(*S*)
Valeraldehyde	36	96	89	(*S*)

Table 61

R	Catalyst	Yield (%)	Ee (%)	Configuration
Ph	**75**	81	49	(*S*)
Ph	**76**	86	36	(*S*)
Ph	**77**	84	32	(*S*)
Ph	**78**	77	71	(*S*)
p-$CH_3C_6H_4$	**75**	79	58	(*S*)
p-$CH_3C_6H_4$	**76**	83	40	(*S*)
p-$CH_3C_6H_4$	**77**	82	34	(*S*)
p-$CH_3C_6H_4$	**78**	80	73	(*S*)
p-$CH_3OC_6H_4$	**78**	56	63	(*S*)
$PhCH_2CH_2$	**75**	82	52	(*S*)
$PhCH_2CH_2$	**76**	85	27	(*S*)
$PhCH_2CH_2$	**77**	87	19	(*S*)
$PhCH_2CH_2$	**78**	80	66	(*S*)
p-ClC_6H_4	**75**	93	23	(*S*)
p-ClC_6H_4	**76**	92	7	(*S*)
p-ClC_6H_4	**77**	85	11	(*S*)
p-ClC_6H_4	**78**	82	48	(*S*)
$^cC_6H_{11}$	**78**	76	54	(*S*)

Table 62

RCHO + HCN (molar excess) —HNL→ (*S*)-RCH(OH)CN

	Aqueous citrate buffer pH 4.5		Two-phase reaction system (buffer–tBuOMe) pH 5.5	
R	Conversion (%)	Ee (%)	Conversion (%)	Ee (%)
Ph	67	99	97	99
(*E*)-PhCH=CH	0	0	93	98
3-PhO-C_6H_4	9	99	99	99
$PhCH_2OCH_2$	N.d.	0	92	12
c-C_6H_{11}	94	99	95	99
2-furyl	55	98	95	98
3-furyl	61	99	98	98
3-thienyl	67	98	98	99
$CH_3(CH_2)_4$	N.d.	84	97	98
CH_2=CH	38	94	92	98
(*E*)-$CH_3(CH_2)_4CH$=CH	62	99	96	99
$CH_3(CH_2)_2C\equiv C$	43	80	62	98

Table 59

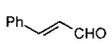
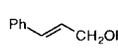
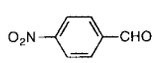
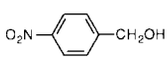
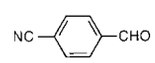
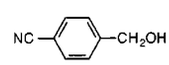
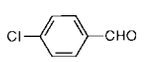
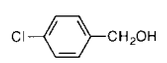
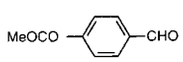
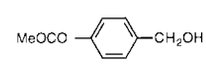
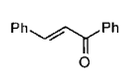
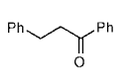
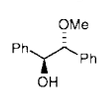
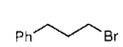
Ligand (mol%)	Ti(O^iPr)$_4$(mol%)	Temp/°C	Time/h	Yield (%)[a]	Ee (%)	Configuration
73 (22)	20	0	10	78	20	(*S*)
73 (22)	20	−30	24	0	—	—
73 (11)	10	30	6	78	48	(*S*)
73 (11)	10	−30	24	74	55	(*S*)
73 (22)	20	−30	18	75	71	(*S*)
73 (16.5)	15	−78	48	79	94	(*S*)
74 (16.5)	15	−78	48	77	4	(*R*)

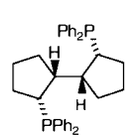
[a] R = Ph.

Table 63

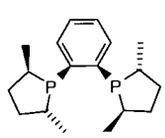
Ar	Ligand	Ee (%)
C_6H_5	**79**	94
p-CH_3-C_6H_4	**79**	94
p-MeO-C_6H_4	**79**	90
p-C_6H_5-C_6H_4	**79**	99
p-Cl-C_6H_4	**79**	97
p-F-C_6H_4	**79**	97
2,4-$F_2C_6H_3$	**79**	98
2-Naphthyl	**79**	95
C_6H_5	**80**	97
p-CH_3-C_6H_4	**80**	96
p-MeO-C_6H_4	**80**	95
p-C_6H_5-C_6H_4	**80**	97
p-Cl-C_6H_4	**80**	98
p-F-C_6H_4	**80**	98
2,4-$F_2C_6H_3$	**80**	95
2-Naphthyl	**80**	98

Table 64

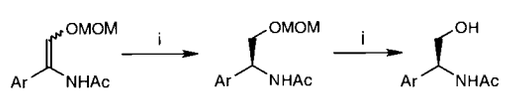
Substrate	Temp/ °C	Product	Yield (%)
PhCHO	25	$PhCH_2OH$	93
n-$C_5H_{11}CHO$	0	n-$C_5H_{11}CH_2OH$	78
^{t}BuCHO	25	^{t}BuCH_2OH	84
	0		99
	0		75
	0		76
	25		93
	25		96
	25		93
	0		82 (>99% de)
	25	PhMe	99
	25		77



(*R*,*R*)-BICP (**79**)



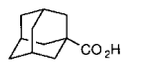
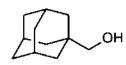
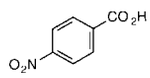
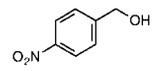
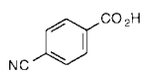
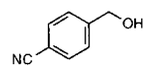
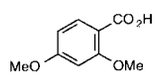
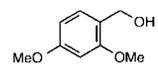
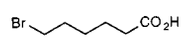
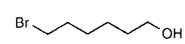
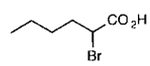
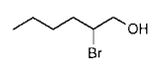
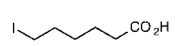
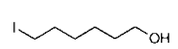
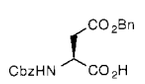
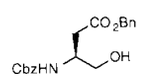
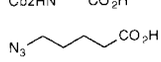
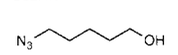
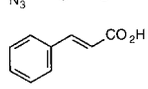
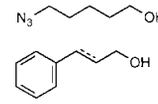
(*R*,*R*)-DuPhos (**80**)



Scheme 86 *Reagents and conditions*: i, [(BICP)-Rh]$^+$ or [(Me-DuPhos)-Rh]$^+$, 10 atm H_2; ii, H^+.

Indium trichloride reacts with tributylstannane at low temperature to give dichloroindium hydride **81**; this reducing agent reacts at room temperature with a range of electrophiles to give hydrogenated or hydrogenolysed products in good yield.[76] The reductant exhibits some chemoselectivity: aromatic acetates, nitriles and nitro compounds are unaffected by the process and chalcone is reduced at the alkene only (Scheme 87 and Table 64).

Table 65

Carboxylic acid	Alcohol	Yield (%)
$CH_3(CH_2)_{16}CO_2H$	$CH_3(CH_2)_{17}OH$	99
		91
		99
		90
		96
		93
		87
		80
		97
		93
		90

Scheme 87

Carboxylic acids may be reduced directly to the corresponding primary alcohols by sodium borohydride *via* acylhydroxybenzotriazoles.[77] Thus, acids are sequentially treated with BOP, Hünig's base (^{i}Pr$_2$NEt) and borohydride to give excellent yields of alcohols. A wide range of functional groups are unaffected under the reaction conditions (although cinnamic acid suffered some reduction at the alkene), thus demonstrating the mildness of the method (Scheme 88 and Table 65).

Scheme 88 *Reagents and conditions*: i, BOP, Hünig's Base, THF, 5 min, rt; ii, $NaBH_4$, 20 min, rt.

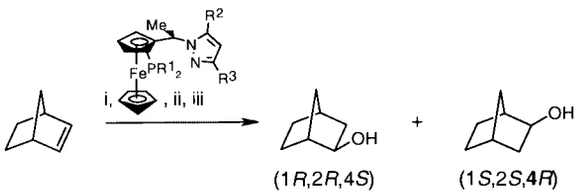
1.2 From alkenes

The asymmetric hydrosilylation of norbornene by trichlorosilane is catalysed by pyrazolyl ferrocenyl ligands.[78] The enantioselectivity of the reaction is improved by judicious choice of ligand substituents (Scheme 89 and Table 66).

Microencapsulation has recently been described as an extrapolation of the uses of polymer supports in osmium tetroxide dihydroxylation of alkenes.[79] Thus, polymer immobilization of OsO_4 using a documented microencapsulation technique[80] gave so-called "MC-OsO_4", which neatly circumvents the infamous volatility problems of the free reagent. Furthermore, the reagent is re-oxidized by NMO under typical reaction

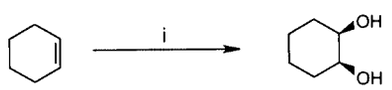
Table 66

R^1	R^2	R^3	T/°C	Ee (%)	Yield (%)
Ph	Me	Me	70	10	54
Ph	Me	Ph	50	39	47
Ph	H	9-Anthracenyl	25	81	54
Ph	H	2,4,6-$(OMe)_3C_6H_2$	0	82	30
Ph	H	2,4,6-$(Me)_3C_6H_2$	0	91	56
3,5-$(F_3C)_2C_6H_4$	H	2,4,6-$(Me)_3C_6H_2$	0	>99.5	59

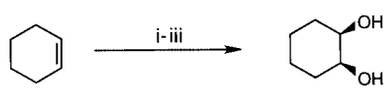


Scheme 89 *Reagents and conditions*: i, $Pd(COD)Cl_2$, $HSiCl_3$/benzene; ii, KF/MeOH; iii, H_2O_2/DMF.

conditions (enabling sub-stoichiometricity in MC-OsO_4) and can be recovered from dihydroxylation reactions and reused. The recovered MC-OsO_4 possesses very similar, if not identical, reactivity to the fresh reagent (Schemes 90 and 91, Table 67 and 68).

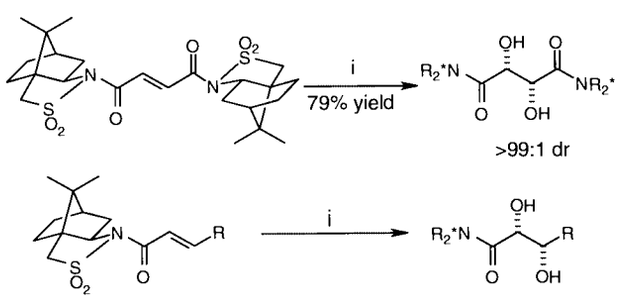


Scheme 90 *Reagents and conditions*: i, MC-OsO_4 (5 mol%), H_2O–acetone–CH_3CN, NMO, rt, 12 h.



Scheme 91 *Reagents and conditions*: i, MC-OsO_4 (5 mol%), H_2O–acetone–CH_3CN, NMO, rt 12 h; ii, Filter; iii, repeat.

In a variation on the usually-employed catalytic asymmetric dihydroxylation protocols, a chiral auxiliary mediated process has been reported to allow an efficient entry into *syn*-2,3-dihydroxyacrylates.[81] Thus, β-substituted *N*-acryloyl derivatives are dihydroxylated in the presence of sub-stoichiometric amounts of osmium tetroxide with good to excellent diastereoselectivity. The best diastereomer ratios (>99 : 1, in favour of the (2′*R*,3′*S*)-configured diols) were obtained using fumaroyl bis-sultam (Scheme 92 and Table 69).



Scheme 92 *Reagents and conditions*: i, NMO, ᵗBuOH, DMF, OsO_4 (0.3 mol%), 20 °C.

1.3 Using biotransformations

4-Substituted 3-alkoxycarbonylpentan-2-ols of high diastereo- and enantiomeric purity may be obtained *via* bioreduction of 2-substituted ketoesters.[82] The reaction involves a dynamic kinetic resolution, whereby only (2*R*)-**82** undergoes reduction by YKER-1 (*Y*east *K*etoester *R*eductase), a reductase from Bakers' Yeast (Scheme 93 and Table 70).

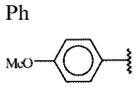
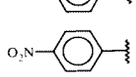
Table 67

Olefin	Product	Yield (%)
		84
		81
		89
		68
		83
		84
		78
		74
		76
		63
		83

Table 68

Run	1	2	3	4	5
Yield of diol (%)	84	84	83	84	83
Recovery of catalyst (%)	Quant.	Quant.	Quant.	Quant.	Quant.

Table 69

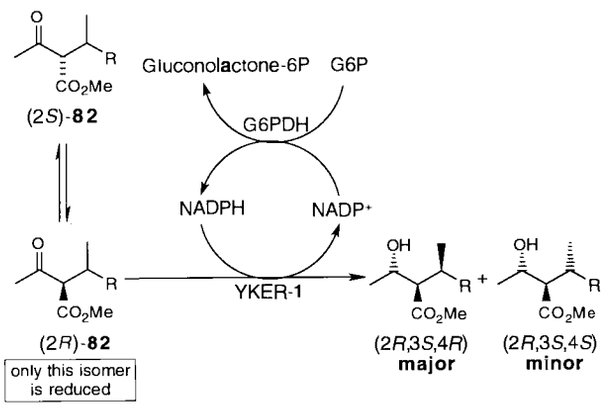
R	Reaction Temp/°C	Yield (%)	Dr
Me	−20	80	95 : 5
CO_2Me	−20	83	85 : 15[a]
CO_2Me	0	78	80 : 20[a]
CO_2Me	20	84	79 : 21[a]
Ph	−20	86	96 : 4
Ph	0	89	95 : 5
	−20	78	95 : 5
	−20	88	85 : 15

[a] (2′*R*,3′*R*) isomer obtained.

Deoxysugars may conveniently be prepared by aldolase-catalysed reaction of phosphatyl 2-thioketones.[83] Thus, reaction of 2-(formylmethyl)-1,3-dioxane with thiophosphate **83** in the presence of FDP-aldolase gave (it was inferred) the 3,4-*syn*

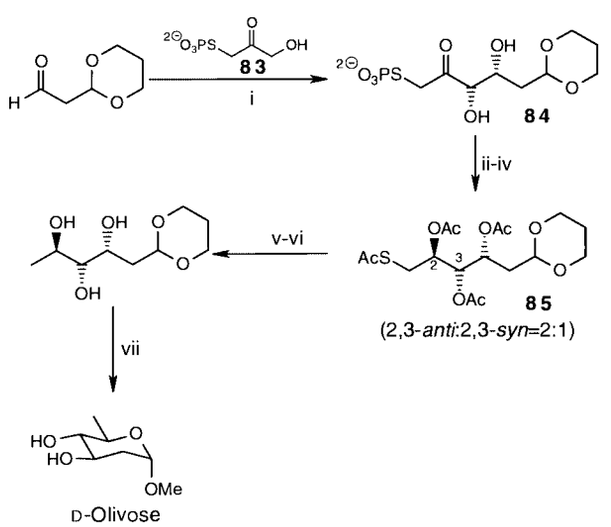
Table 70

R	Conversion (%)	Ratio of products (% ee)	
		Major	Minor
Et	36	71 (>99)	29 (>99)
Ph	46	55 (>99)	45 (>99)
4-MePh	28	51 (>99)	49 (>99)
4-BrPh	22	70 (>99)	30 (>99)
CH_2CO_2Me	30	99 (>99)	1 (—)



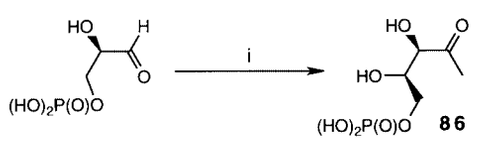
Scheme 93

diol aldol product **84** which was not isolated but was reduced, dephosphorylated and acetylated to give thiosugar **85**. Upon desulfurization and ketal hydrolysis, **85** was converted to D-olivose (Scheme 94).



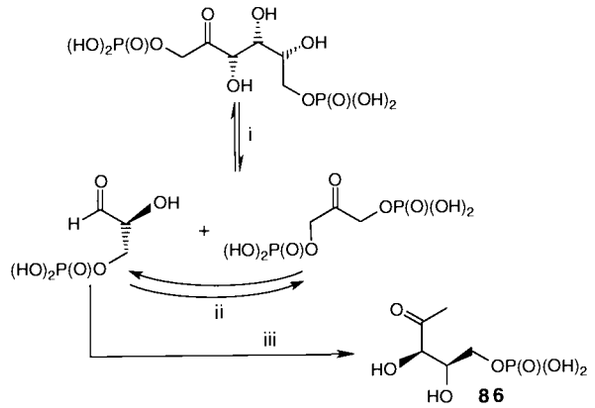
Scheme 94 *Reagents and conditions*: i, FDP-aldolase; ii, $NaBH_4$; iii, PH_3, 4 h; iv, Ac_2O, pyridine; v, RaNi; vi, NaOMe, HOMe; vii, HCl, MeOH.

An improved preparation of 1-deoxy-D-xylulose-5-phosphate **86** utilizing an enzyme-catalysed aldol reaction has been reported.[84] The phosphate **86**, an intermediate in three major biosynthetic pathways, is obtained when glyceraldehyde-3-phosphate is condensed with pyruvate in the presence of *E. coli* 1-deoxy-D-xylulose-5-phosphate synthase (Scheme 95).



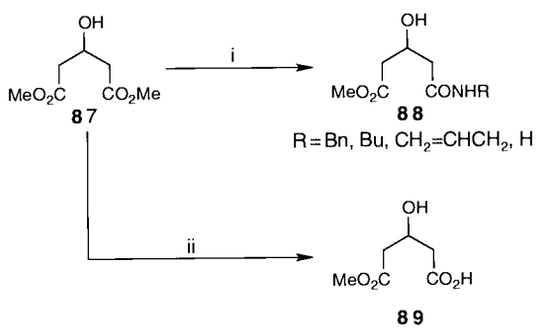
Scheme 95 *Reagents*: i, 1-deoxy-D-xylulose-5-phosphate synthase, pyruvic acid.

Alternatively, a synthesis of **86** may be effected by treating fructose-1,6-diphosphate and pyruvate with rabbit-muscle aldolase, triose phosphate isomerase and partially-purified synthase. Under this protocol **86** was obtained as its barium salt in 47% yield (Scheme 96).



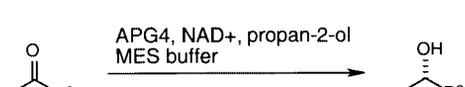
Scheme 96 *Reagents*: i, rabbit muscle aldolase; ii, triose phosphate isomerase; iii, 1-deoxy-D-xylulose-5-phosphate synthase, pyruvic acid.

Candida antarctica catalyses enantioselective desymmetrizing reactions of dimethyl 3-hydroxyglutarate.[85] Thus, in the presence of an amine, glutarate **87** is converted enantioselectively into amidoester **88**. When no amine is present, ester carboxylate **89** is the product of the process (Scheme 97).



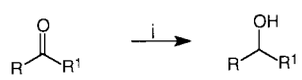
Scheme 97 *Reagents*: i, CAL, RNH_2; ii, CAL.

A wide range of methyl ketones is reduced enantioselectively to the corresponding (*S*)-alcohols using the well-known asymmetric reducing capabilities of *G. candidum*.[86] Although the study reported upon mainly the use of aromatic ketones, β-keto esters and certain aliphatic ketones are also reduced in good yield and with excellent enantioselectivity (Scheme 98 and Table 71).



Scheme 98

A range of ketones are reduced enantioselectively using the acetone powder of *Geotrichum candidum*.[87] Using ketoesters, aryl, alkyl and dialkyl ketones, (*S*)-configured secondary alcohols are obtained in good yields and with excellent enantiocontrol. The experimental procedure is simple and seems amenable to large scale reactions. It is noteworthy that the enantioselectivity of the reduction is vastly superior using the acetone powder rather than the resting cell (>99% ee compared with 39% ee) (Scheme 99 and Table 72).



Scheme 99 *Reagents and conditions*: i, acetone powder of APG4 (10 mg), NAD^+, (0.02 eq.), buffer, 130 rpm, 30 °C, 24 h.

Table 71

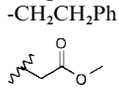
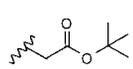
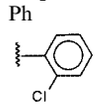
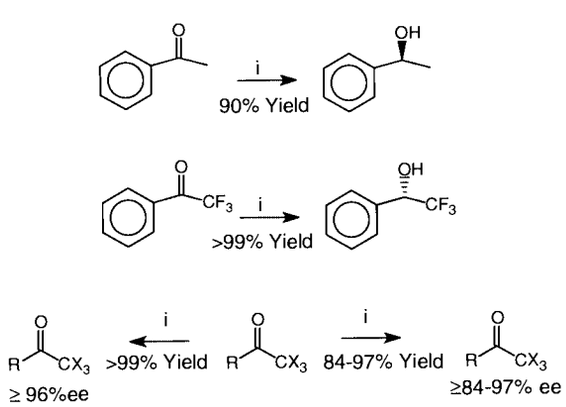
R^2	Yield (%)	Ee (%)	Configuration
H	89	>99	(*S*)
o-F-C_6H_4	>99	>99	(*S*)
m-F-C_6H_4	95	>99	(*S*)
p-F-C_6H_4	74	>99	(*S*)
o-Cl-C_6H_4	>99	>99	(*S*)
m-Cl-C_6H_4	95	99	(*S*)
p-Cl-C_6H_4	62	>99	(*S*)
o-Br-C_6H_4	97	>99	(*S*)
m-Br-C_6H_4	92	>99	(*S*)
p-Br-C_6H_4	95	>99	(*S*)
o-Me-C_6H_4	96	>99	(*S*)
m-Me-C_6H_4	86	>99	(*S*)
p-Me-C_6H_4	78	>99	(*S*)
o-MeO-C_6H_4	84	>99	(*S*)
m-MeO-C_6H_4	90	>99	(*S*)
p-MeO-C_6H_4	29	>99	(*S*)
o-CF_3-C_6H_4	6	97	(*S*)
m-CF_3-C_6H_4	96	>99	(*S*)
p-CF_3-C_6H_4	73	>99	(*S*)
C_6F_5	62	>99	(*S*)
-CH_2Ph	96	>99	(*S*)
-CH_2CH_2Ph	93	>99	(*S*)
	>99	>99	(*S*)
	>99	>99	(*S*)
^{n}Hexane	87	>99	(*S*)

Table 72

R	R^1	Ee (%)
Et	CO_2Me	>99
Et	CO_2Et	>99
Me	Ph	99
Me		>99

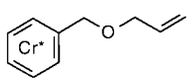
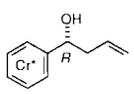
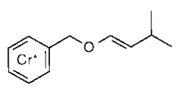
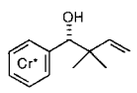
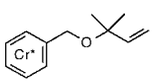
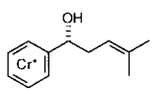
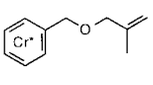
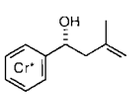
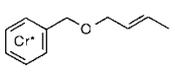
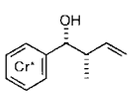
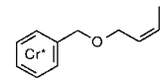
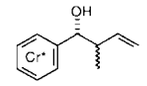


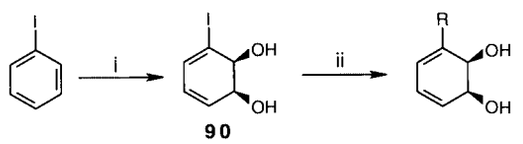
Scheme 100 *Reagents*: i, APG4, NAD^+.

The same dehydrogenase, again used in the form of an acetone powder, reduces methyl ketones with opposite selectivity to that shown in the reduction of the corresponding trifluoromethyl ketones. Both reductions proceed with excellent enantioselectivity and in good yield. The reaction is applicable to aryl, alkyl and dialkyl ketones (Scheme 100).

Boyd *et al.* have used *cis*-(1*S*,2*S*)-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **90** in Stille-like couplings, thereby providing a chemoenzymatic route to a range of enantiomerically-pure dihydrobenzenediols which would not be available directly (Scheme 101).[88]

Table 73

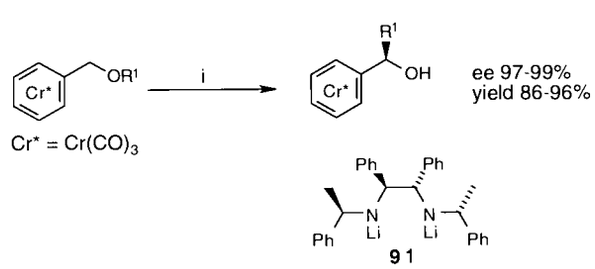
Substrate	Product	Ee (%)	Yield (%)
		96	80
		84	82
		94	25
		91	33
		96	82 *syn*:*anti* 95:5
		*syn* ≥ 90% *anti* ≥ 90%	24 *syn*:*anti* 1:1



Scheme 101 *Reagents*: i, *P. putida* UV4, O_2; ii, $(Bu)_3SnR$, $[(C_6H_5)_3P]_4Pd$.

1.4 Miscellaneous methods

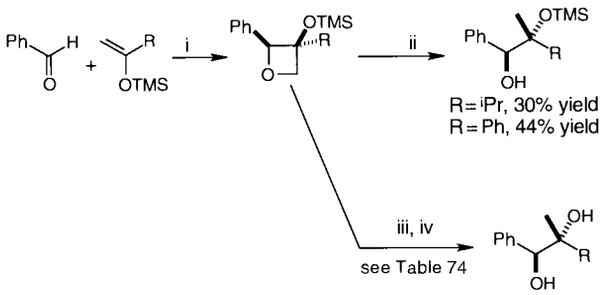
Asymmetric Wittig rearrangement of chromium tricarbonyl complexes of allyl benzyl ethers is mediated by chiral amide base **91**.[89] The enantioselectivity of the process is good to excellent; where possible, diastereoselection is good (Scheme 102 and Table 73).



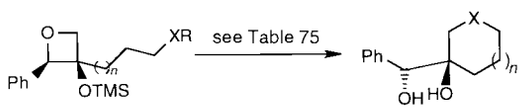
Scheme 102 *Reagents*: i, chiral base **91**.

Silyl ethers of oxetan-3-ols (prepared by photocycloaddition of aromatic aldehydes and silyl enol ethers) undergo cleavage upon reaction with hydride sources to give 2-hydroxy silyl ethers or 1,2-diols, both of which are obtained with high levels of diastereomeric purity.[90] The reaction is highly *umpoled* and could, formally, be considered to be equivalent to nucleophilic addition of either an α-silyloxy carbanion or an α-aryl-α-hydroxy anion to an aldehyde or ketone (Scheme 103 and Table 74).

The same reaction type has been exploited *via* intramolecular nucleophilic substitution to give a variety of heterocyclic structures (Scheme 104 and Table 75).[91] The reaction shows some structural requirements, for example six-*exo* ring-closure is not favoured when the heteronucleophile is oxygen, but proceeds in acceptable yield when sulfur is the nucleophile. In certain

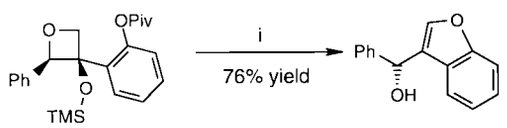


Scheme 103 *Reagents and conditions*: i, *hv*, PhH; ii, $Li(O^tBu)_3AlH$, THF; iii, K_2CO_3, MeOH; iv, $LiAlH_4$, THF.



Scheme 104

cases, dehydration occurs spontaneously, particularly when the heteronucleophile is a phenolic oxygen. In this case, the reaction offers a preparation of 3-substituted benzofurans (Scheme 105).



Scheme 105 *Reagents and conditions*: i, MeMgBr, 25 to 85 °C, DME.

Tebbe-like methylenation of β-lactones gives 2-methyleneoxetanes which undergo an alkylative cleavage in the presence of base to give homopropargylic alcohols in moderate to good yields (Scheme 106 and Table 76).[92]

Table 74

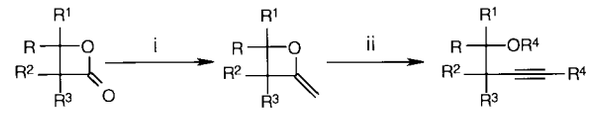
R	Reaction time/h	Reaction temp./°C	Yield (%)
^{i}Pr	24	Ambient	98
Ph	48	Ambient	99
^{t}Bu	48	Reflux	75
$(MeO)_2CH$	72	Ambient	97
$(MeO)_2MeC$	48	Reflux	69
^{i}Bu	96	Ambient	94

Table 75

n	X	R	Reagents	Yield (%)
1	O	Pivaloyl	MeLi	54
2	O	Pivaloyl	MeLi	0
1	S	Ac	MeLi	91
2	S	Ac	MeMgBr	54
1	NTs	H	MeMgBr	52

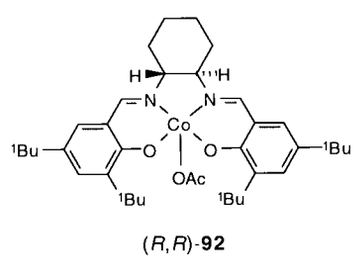
Table 76

R	R^1	R^2	R^3	Yield oxetane (%)	R^4	Yield alcohol (%)
H	H	Ph	CH_2CHCH_2	74	H	85
CH_3	CH_3	H	$(CH_2)_3OSi^tBuPh_2$	60	H	48
$(CH_3)_5$	$(CH_2)_5$	H	CH_3	60	H	86
H	H	Ph	CH_3	76	H	88
H	H	Ph	CH_3	76	$(CH_3)_3Si$	87
H	H	Ph	CH_3	76	CH_3	74

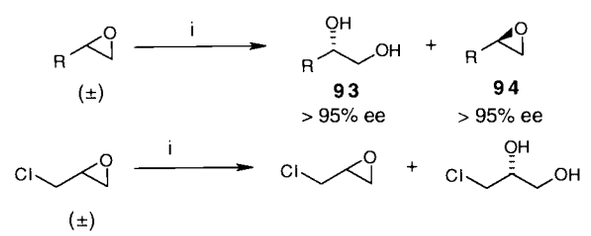


Scheme 106 *Reagents*: i, $Cp_2Ti(CH_3)_2$, toluene; ii, LDA, electrophile.

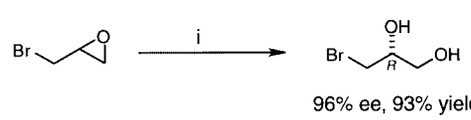
Jacobsen *et al.*'s HKR (hydrolytic kinetic resolution) process has been extrapolated and shown to be adept in the preparation of *epi*halohydrins of high enantiomeric purity.[93] Ring-opening of racemic halohydrins by water in the presence of the familiar Co–salen complex (*R*,*R*)-**92** gives (2*S*)-diol **93** and (2*R*)-epoxide **94**, both in excellent yield and both of high stereochemical purity (Scheme 107). The process which furnished epoxide **94** in highest enantiomeric purity (> 99% ee) did not, however, lead to diol of similar enantioexcess (89% ee). It is notable that the latter reaction furnished a higher-than-theoretical yield of diol, indicating an *in situ* racemization process. Indeed, *epi*bromohydrin was found to racemize rapidly under the HKR conditions and the racemic epoxide gave a nearly quantitative yield of bromo diol with very high enantiomer discrimination (Scheme 108 and Table 77).



(*R*,*R*)-**92**



Scheme 107 *Reagents*: i, (*R*,*R*)-**92**, (0.2–2 mol%), 0.5 eq. H_2O.

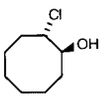
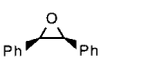
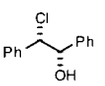
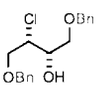


Scheme 108 *Reagents*: i, (*R*,*R*)-**92**, (0.2–2 mol%), 1.5 eq. H_2O.

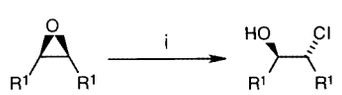
Table 77

Conditions	Epoxide	Diol
0.50 equiv. H_2O, 4 °C:	96% ee, 44% yield	96% ee, 50% yield
0.55 equiv. H_2O, 4 °C:	>99% ee, 42% yield	89% ee, 52% yield
0.30 equiv. H_2O, −10 °C	63% ee	98.7% ee, 27% yield

Table 78

Epoxide	Product	Time/h	Yield (%)	ee (%) (configuration)
		0.3	87	8
		0.3	90	32 (*S*,*S*)
		132	95	2
		3	94	87 (*S*,*S*)
		4	95	72 (*S*,*S*)

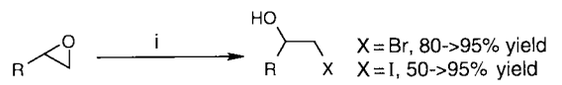
Denmark and co-workers have extrapolated their recent observations using silicon tetrachloride to embrace desymmetrizing halogenative ring-opening of *meso*-epoxides.[94] Thus, symmetrical epoxides react with chlorosilane and a sub-stoichiometric amount of chiral HMPA analogue **95** at low temperature to give 1,2-hydroxy chlorides in generally excellent yields and with moderate to good enantioselectivity (Scheme 109). The reaction, it is postulated, proceeds *via* formation of a



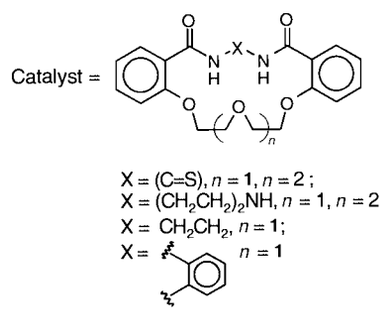
Scheme 109 *Reagents and conditions*: i, $SiCl_4$, **95** (10 mol%), CH_2Cl_2, −78 °C.

chiral phosphoramide-stabilized silenium ion **96**, although the authors defer allocation of the factors underlying the enantioselectivity of the process (Scheme 110 and Table 78).

Macrocyclic diamides mediate the ring-opening of epoxides using elemental iodine or bromine, to give 1,2-hydroxyhalides.[95] In all cases, epoxides were attacked at the least-hindered carbon atom. The authors proposed a macrocycle-mediated *in situ* formation of Br_3^- or I_3^- to rationalize the observations (Scheme 111).

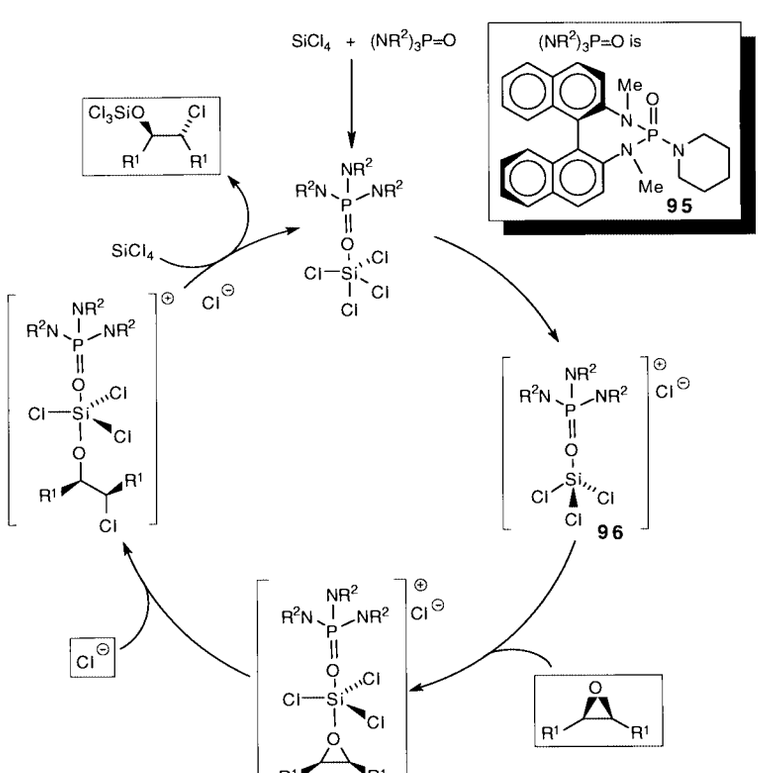


Scheme 111 *Reagents*: i, X_2, catalyst (R = Ph, $PhOCH_2$, $^iPrOCH_2$ and n-C_6H_{13}).



The oxazaborolidinone **97** derived from β-methyltryptophan has recently been reported as a chiral species able to catalyse the asymmetric cleavage of 1,3-dioxolanes by silyl enol ethers.[96] Best results were obtained when a *para*-chlorophenyl substituent was present on boron (Scheme 112 and Table 79).

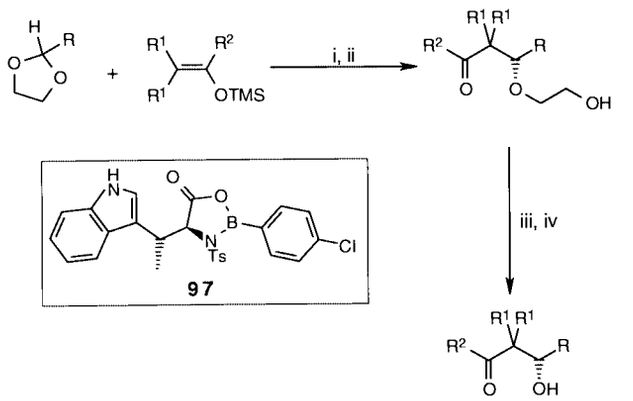
1,6-Diynes are converted to bicyclic hydroxycyclopentadienes upon reaction with methyl(pentacarbonyl)manganese, pentacarbonyl, in variable yield.[97] The reaction proceeds *via* manganated enones **98**, which may often be isolated (Scheme 113 and Table 80).



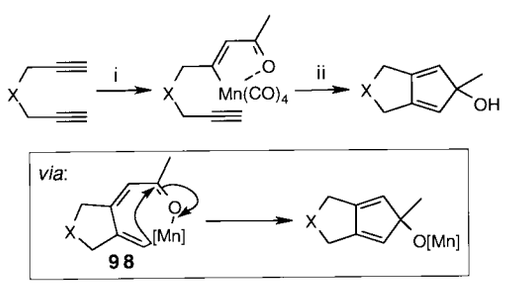
Scheme 110

Table 79

R	R^1	R^2	Yield (%)	Ee (%)
Ph	Me	OEt	88	86
p-$MeOC_6H_4$	H	OEt	86	91
p-$MeOC_6H_4$	H	OEt	82	92
p-$MeOC_6H_4$	H	S^{t}Bu	80	85
p-$MeOC_6H_4$	H	Ph	62	89
2-Furyl	H	Ph	73	93
PhCH=CH	H	Ph	89	88

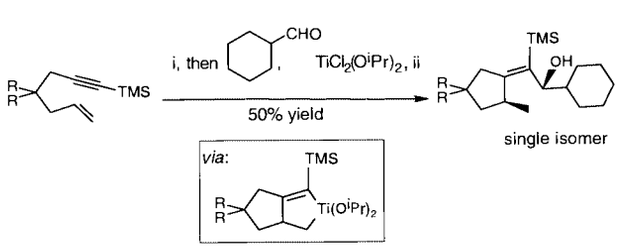


Scheme 112 *Reagents and conditions*: i, **97** (10 mol%), CH_2Cl_2, −20 °C; ii, TBAF; iii, I_2, PPh_3; iv, Zn.



Scheme 113 *Reagents*: i, $CH_3Mn(CO)_5$; ii, Me_3NO, H_2O.

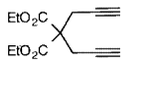
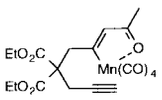
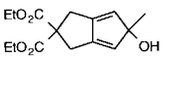
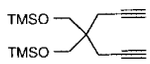
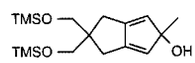
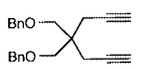
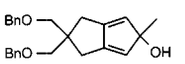
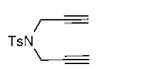
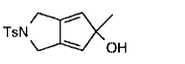
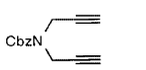
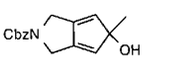
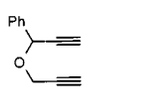
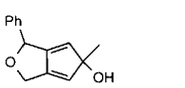
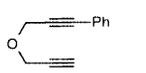
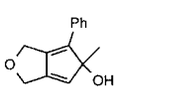
Titanacyclopentenes may be produced by reaction of 1,6- or 1,7-doubly-unsaturated precursors and reacted *in situ* with aldehydes in the presence of Lewis acids to give highly functionalized 1-silylalkylidenecyclopentenes in acceptable yields (Scheme 114).[98] When aromatic aldehydes were employed in the reaction, $TiCl(O^iPr)_3$ was used as Lewis acid, whereas the reaction of aliphatic aldehydes required $TiCl_2(O^iPr)_2$. Where possible, the 1,4-diastereoselectivity of the process was high (usually >95 : <5 in favour of the stereochemistry shown). The reaction comprises a useful addition to the synthetic arsenal because, in all cases, the alkenyl–titanium bond was more reactive than the alkyl–titanium bond, which is in direct contrast to the reactions of analogous zirconacycles (Scheme 114).

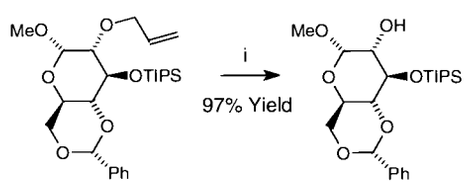


Scheme 114 *Reagents*: i, (η^2-propene)$Ti(O^iPr)_2$; ii, aqueous HCl.

Allylic ethers may be cleaved to give alcohols by treatment with titanates and a Grignard Reagent. The reaction proceeds *via* titanacyclopropane intermediates (Scheme 115).[99]

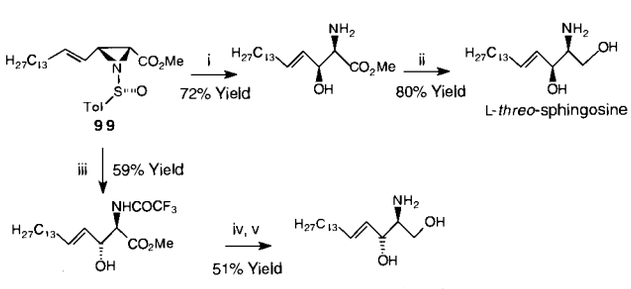
Table 80

Diyne	Yield of **98** (%)	Yield of alcohol (%)
	 55	 90
	50	 83
	41	 71
	72	 52
	Not isolated	 20
	92	 56
	88	 64



Scheme 115 *Reagents*: i, $Ti(O^iPr)_4$, ^{n}BuMgCl (3–4.5 eq.).

The recent studies of Davis *et al.* into the preparation and reactions of enantiomerically-enriched *N*-sulfinylaziridines have been extrapolated with the report of the use of these compounds to prepare sphingosines.[100] Thus, vinylaziridine **99** reacts along a bifurcated synthetic sequence involving regioselective hydrolytic ring-cleavage to give both L- and D-sphingosine (Scheme 116).



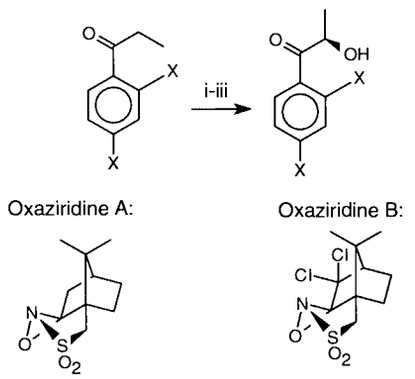
Scheme 116 *Reagents and conditions*: i, 50% aq. TFA/acetone, 0 °C; ii, $LiBH_4$, MeOH, 30 min; iii, TFAA, CH_2Cl_2, 35 °C; iv, $LiBH_4$, MeOH; v, K_2CO_3, EtOH, 50 °C.

The enantioselective hydroxylation of ketones pioneered by Davis *et al.* has been used to good advantage in the synthesis of antifungal azoles, *via* hydroxylation of aryl alkyl ketones (Scheme 117 and Table 81).[101]

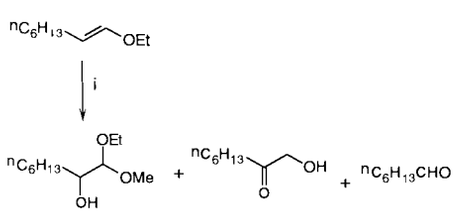
The little-studied reaction of enol ethers with aqueous H_2O_2 has been examined in depth by Yamamoto *et al.*[102] Thus, a range of alkyl vinyl ethers reacted with 35% H_2O_2 and cetylpyridinium peroxotungstophosphate (PCWP) to give mainly α-hydroxy acetals, accompanied by hydroxy ketone and oxidatively-cleaved products (Scheme 118 and Table 82).

Table 81

X	Oxaziridine	Yield (%)	Ee (%) (configuration)
F	A	80	44 (*R*)
F	B	85	80 (*R*)
H	A	88	66 (*R*)
H	B	80	92 (*R*)

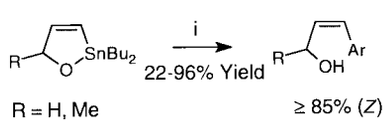


Scheme 117 *Reagents and conditions*: i, THF, −78 °C; ii, NaHMDS, THF; iii, oxaziridine A or B.



Scheme 118 *Reagents*: i, $[C_5H_5N^+(CH_2)_{15}CH_2]_3$ $\{PO_4[W(O)(O_2)_2]_4\}$, CH_3OH–CH_2Cl_2 (1 : 4 v/v).

(*Z*)-3-Arylallyl alcohols are prepared in good to excellent yield by palladium-catalysed cross-coupling of cyclic stannoxanes with aryl iodide.[103] Such stannoxanes may be prepared by intramolecular hydrostannylation of propargyl alcohols by dibutyltin dihydride (Scheme 119). In certain cases the use of LiCl was essential for good yields to be obtained.



Scheme 119 *Reagents*: i, ArI, solvent, temperature catalyst (catalyst: Pd(0), $PdCl_2(PhCN)_2$, Pd(0)/$ZnCl_2$).

A tandem reaction involving Grob fragmentation followed by reductive cyclization occurs when iodomethylhexose derivatives are treated with samarium diiodide. The first reaction,

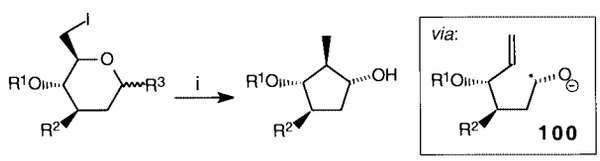
Table 83

R^1	R^2	R^3	Yield (%)
Ac	OAc	OAc	70
Piv	OPiv	OAc	72
Bn	OBn	OAc	76
Piv	H	OPh	72
Bn	H	OPh	71

Table 84

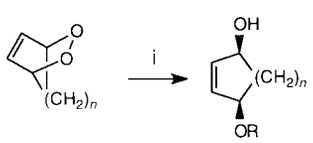
R-Metal	*n*	Yield (%)
	2	93
	2	94
	2	45
^{n}BuLi	2	96
$(^n Bu)_3Zr$	2	50
PhMgBr	2	98
$^c C_6H_{11}MgBr$	2	69
	1	83

reductive ring-cleavage liberates an unsaturated aldehyde which reacts further with SmI_2 *via* the well documented radical cyclization of ketal **100**. This report[104] describes the improved yield of the primary fragmentation reaction gained when a better leaving group (OAc *vs*. OMe) is present at the aromatic centre (Scheme 120 and Table 83).



Scheme 120 *Reagent*: i, SmI_2.

A systematic study of the ring opening reactions undergone by endoperoxides has been reported by Little and Schwaebe. Thus, a range of organometallic nucleophiles react with bicyclic endoperoxides to give monoethers of cycloalkene-1,4-diols in good yield (Scheme 121 and Table 84).[105]



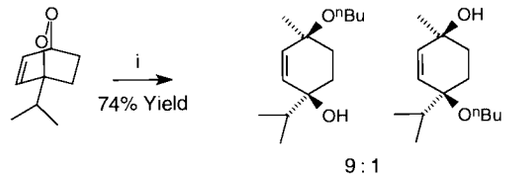
Scheme 121 *Reagents*: i, R-Metal, THF.

When a non-symmetrical endoperoxide, Ascaridole, underwent the reaction, the least hindered oxygen of the peroxide was attacked selectively (Scheme 122).

Table 82

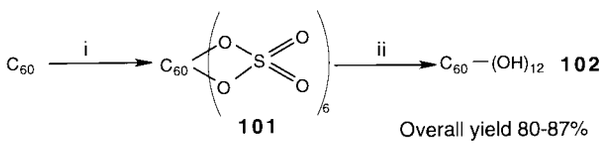
Solvent	Temp/°C	Time/h	Conversion (%)	Yield (%) Acetal	Ketone	Aldehyde
CH_3OH–CH_2Cl_2 (1 : 4)	20	1	53	76	17	6
CH_3OH	20	1	11	<1	<1	<1
CH_3OH–CH_2Cl_2 (1 : 1)	20	1	67	66	7	2
CH_3OH–CH_2Cl_2 (1 : 4)	Reflux	1	59	76	15	8
CH_3OH–CH_2Cl_2 (1 : 4)	Reflux	16	>98	70	16	8
C_2H_5OH–CH_2Cl_2 (1 : 4)	Reflux	1	>98	42[a]	12	12
H_2O–CH_2Cl_2 (1 : 4)	Reflux	1	>98	—	39	23

[a] Diethylacetal obtained.



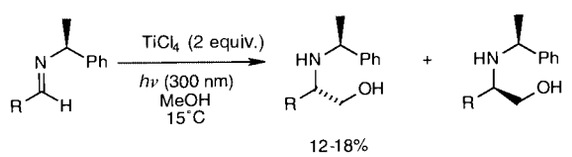
Scheme 122 *Reagents*: i, ^{n}BuLi, THF.

Buckminsterfullerene is converted in good yield by a two-step process into dodecahydroxy-C_{60} *via* sequential reaction with H_2SO_4–SO_3 and water.[106] Thus, in the presence of phosphorus pentoxide, C_{60} is first sulfated to give the hexacyclosulfated fullerene **101** which is hydrolysed upon heating in water to the hydroxylated product **102**. The authors do not comment upon the regioselectivity of the process (Scheme 123).



Scheme 123 *Reagents and conditions*: i, H_2SO_4–SO_3 (28–30%), P_2O_5 (13.0 eq.), 60 °C, 1 h; ii, H_2O, 85 °C, 10 h.

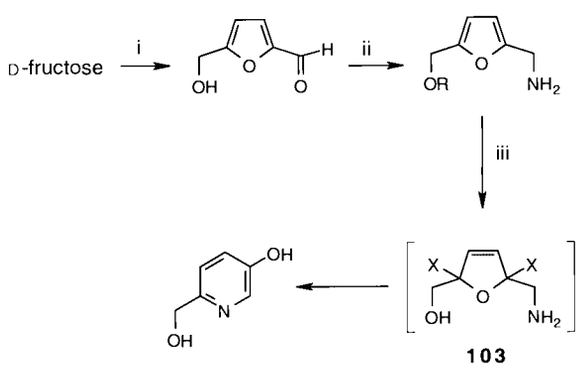
Chiral 1-(hydroxymethyl)alkylamines may be prepared (albeit with poor selectivity and in low yield) by Lewis acid-catalysed photolysis of methanolic solutions of aldimines derived from (*S*)-β-phenylethylamine (Scheme 124).[107]



R	(*S*,*S*:*S*,*R*)
Me	50:50
Ph	80:20
^{t}Bu	73:27

Scheme 124

Furfurylamines react with elemental bromine to give the corresponding 3-hydroxypyridines.[108] The reaction proceeds through the well-known addition compounds **103** (Schemes 125 and 126).



Scheme 125 *Reagents and conditions*: i, H^+; ii, RNH_2, Ni–H_2; iii, Br_2–H_2O, 0 °C.

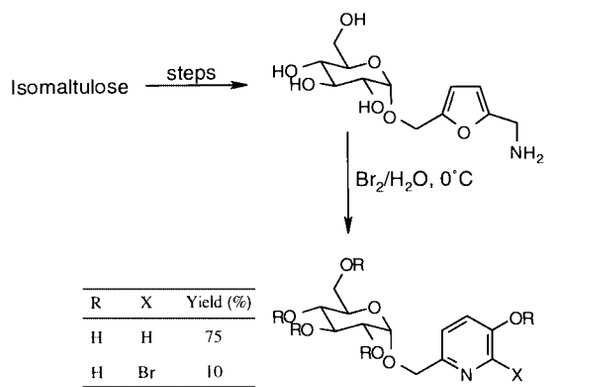
Water-soluble fullerenols may be prepared in "one-pot" *via* addition of nitrogen dioxide radicals to C_{60} itself.[109] Polynitrofullerene $C_{60}(NO_2)_n$ is produced by the reaction and this species may be hydrolysed *in situ* to polyhydroxyfullerenes in mediocre overall yield.

Table 85

Temp/°C	Yield (%)	Ee (%)	Time/days	Solvent
25	27	37	3	MeCN
4	21	42	3	MeCN
−10	57	30	3	MeCN
−20	50	47	2	MeCN
−30	53	31	2	MeCN
−40	93	26	2	MeCN
−75	9	21	3	EtCN

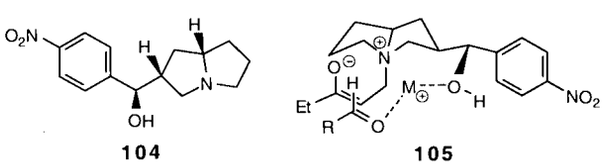
Table 86

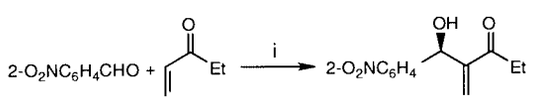
R^1	R^2	Yield (%)	Ee (%)	Time/h
2-$O_2NC_6H_4$	Et	71	67	18
2-$O_2NC_6H_4$	Me	71	53	18
2-FC_6H_4	Et	31	63	48
2-ClC_6H_4	Et	58	72	14
2-BrC_6H_4	Et	63	71	72
3-$O_2NC_6H_4$	Et	51	37	18
2-Pyridyl	Et	83	21	14
3-Pyridyl	Et	93	49	12
4-Quinolinyl	Et	63	70	18
4-$O_2NC_6H_4$	Et	17	39	48



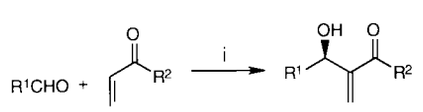
Scheme 126

An asymmetric Baylis–Hillman reaction of alkyl vinyl ketones with electron-deficient aromatic aldehydes is catalysed by proline-derived pyrrolizidin-2-yl‡ alcohol **104**.[110] The reaction (which, it is suggested, has a transition state resembling structure **105**) proceeds in variable (but generally good) yield but with mediocre enantioselectivity (≤72% ee) (Schemes 127 and 128, Tables 85 and 86).





Scheme 127 *Reagents*: i, **104**, 10 mol%.



Scheme 128 *Reagents and conditions*: i, **104** (10 mol%), $NaBF_4$, MeCN, −40 °C.

‡ The IUPAC name for pyrrolizidine is hexahydro-1*H*-pyrrolizine.

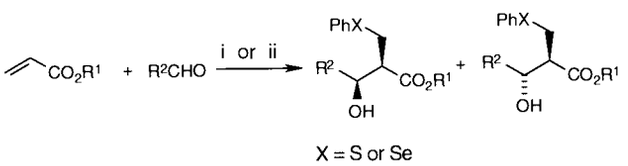
Table 87

R^1	R^2	X	Yield (%)	*syn*:*anti*
Me	Ph	S	62	71:29
Et	Ph	S	64	66:34
^{t}Bu	Ph	S	80	92:8
^{t}Bu	*p*-ClC_6H_4	S	71	89:11
^{t}Bu	1-Naphthyl	S	92	88:12
^{t}Bu	PhCH=CH	S	52	81:19
^{t}Bu	$^nC_5H_{11}$	S	65	73:27
^{t}Bu	Ph	Se	63	85:15
^{t}Bu	*p*-ClC_6H_4	Se	52	81:19
^{t}Bu	2-Naphthyl	Se	64	84:16
^{t}Bu	C_6H_{11}	Se	23	Not determined
^{t}Bu	Ph	O	0	—

Table 88

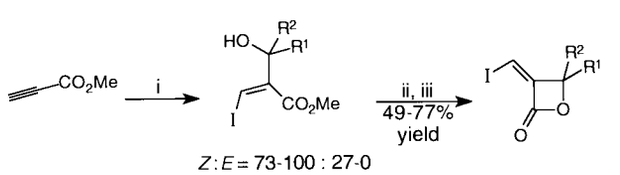
R^1	R^2	Yield (%)
$^nC_5H_{11}$	H	84
^{n}Pr	H	79
^{i}Pr	H	83
Ph	H	87
^{t}Bu	H	90
Me	Ph	60
-$(CH_2)_3$-		32
-$(CH_2)_4$-		32

A Baylis–Hillman-like three-component reaction gives 3-hydroxy-2-(phenylthio)methyl esters in good yield and with moderate diastereocontrol.[111] Thus, reaction of acrylates with lithium thiophenolate in the presence of a range of aldehydes gave primarily *syn*-hydroxy esters. The process was also found to be productive when selenolates were employed rather than thiolates (Scheme 129 and Table 87).



Scheme 129 *Reagents and conditions*: i, PhSLi, CH_2Cl_2, −78–50 °C; ii, $(PhSe)_2$, MeLi·LiBr, −78 °C to rt.

Highly-functionalized 2-hydroxymethyl acrylates may be prepared by the reaction of methyl propiolate with ketones or aldehydes in the presence of tetrabutylammonium iodide and a zirconium(IV) catalyst.[112] In effect, the reaction is, therefore, analogous to the Baylis–Hillman reaction. The products of the reaction may be converted to α-methylene-β-lactones (Scheme 130 and Table 88).



Scheme 130 *Reagents and conditions*: i, R^1R^2C=O, Bu_4NI, $ZrCl_4$, CH_2Cl_2, 0 °C; ii, hydrolysis; iii, $MeSO_2Cl$, Na_2CO_3.

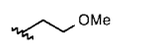
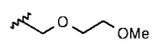
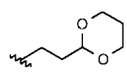
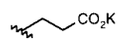
A photolytic process allows conversion of *N*-alkylpyridinium halides into *trans*-2,3-epimino-1-hydroxycyclopent-4-enes in moderate to good yields. Thus, photolysis of **106** in alkaline aqueous solution gives hydroxy aziridine **107** (Scheme 131 and Table 89).

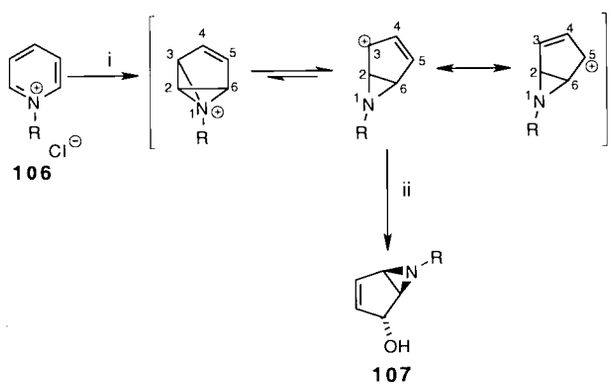
The methodology was used to prepare **108**, an analogue of Mannostatin A.[113]

2 Preparation of ethers

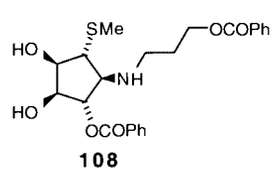
Alkenes are enantioselectively 1-methoxy-2-selenylated upon

Table 89

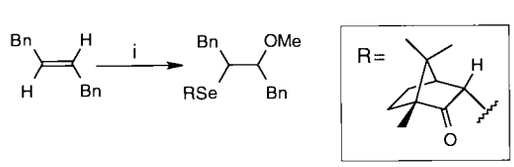
R	Yield (%)
	57
	60
	55
	82
	40



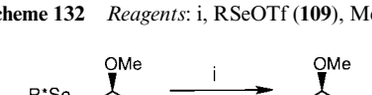
Scheme 131 *Reagents and conditions*: i, *hν*; ii, HO^-.



reaction with chiral camphor-derived selenenyl triflates (Scheme 132).[114] Thus **109** (available from camphor itself in two steps) reacts with a range of alkenes to give methoxy selenides in good yield but with moderate diastereocontrol (dr = ≤94:≥6). When non-symmetrical alkenes were used as substrates. Markovnikoff addition was observed. The authors confirmed the configuration of the product derived from reaction of **109** with styrene as *R* by chemical correlation, but did not confirm the absolute stereochemistry of the other products (Scheme 133 and Table 90).



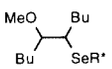
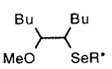
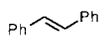
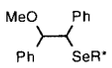
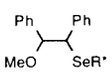
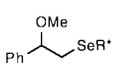
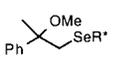
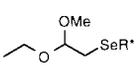
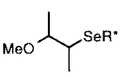
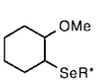
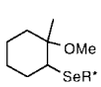
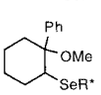
Scheme 132 *Reagents*: i, RSeOTf (**109**), MeOH.

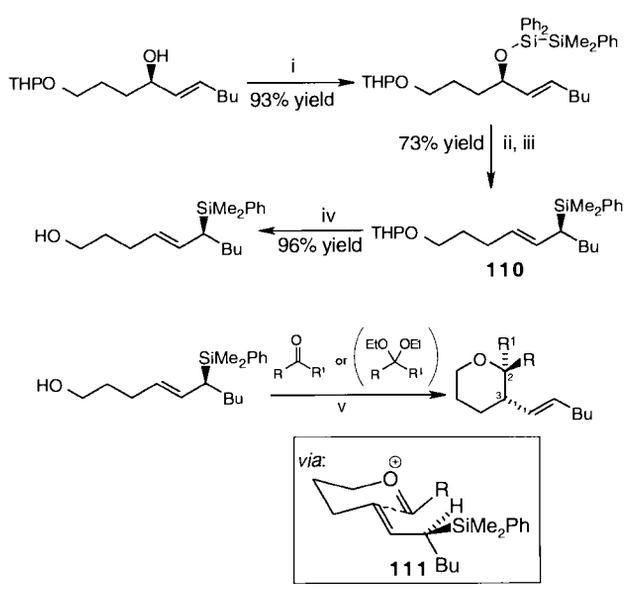


Scheme 133 *Reagents and conditions*: i, Ph_3SnH, AIBN, toluene, Δ.

3-Alkenyl-substituted tetrahydropyrans of high enantiopurity can be prepared by the reaction of non-racemic chiral amino- and hydroxyallylsilanes **110** with carbonyl compounds (or their equivalents).[115] Thus, **110** (prepared *via* an elegant, palladium(0)-catalysed rearrangement of alkoxy- or amino-disilanes) react with aldehydes or acetals at low temperature in the presence of TMSOTf to give primarily *trans*-2-alkyl-3-vinyltetrahydropyrans or -piperidines in generally excellent yield and with good enantiocontrol. The authors propose an A-strain-controlled cyclic transition state **111** to rationalize the

Table 90

Substrate	Product	Isolated yield (%)	Ee (%)
		88	88
		88	50
		65	68
		66	38
		77	48
		88	56
		71	62
		69	74
		71	50
		90	68
		73	72



Scheme 134 *Reagents and conditions*: i, $ClPh_2SiSiMe_2Ph$, Et_3N, THF, rt; ii, $Pd(acac)_2$ (0.02 equiv.), ^{t}OcNC (0.15 equiv.), toluene, reflux; iii, nBuLi, 0 °C; iv, PPTS (0.2 equiv.), EtOH, 55 °C; v, TMSOTf, CH_2Cl_2, −78 °C.

observed stereochemical preference of the reaction (Scheme 134 and Table 91).

Enol ethers may be synthesized with high stereoisomeric purity by the silver(I)-catalysed addition of alcohols to dimethyl acetylenedicarboxylate or methyl propiolate.[116] Thus, in the presence of sub-stoichiometric amounts of silver(I) triflate, (*Z*)-configured 2-alkoxyfumarates or 3-alkoxyacrylates are obtained, generally in good yields (Scheme 135). Care has to be

Table 91

R	R′	Yield (%)	*trans*:*cis*[a]	Ee (%)
Me	H	89	>10:1	93.4
^{n}Hexane	H	92	>10:1	92.1
^{i}Pr	H	98	99:1	92.8
Cyclohexane	H	99	99:1	92.3
^{t}Bu	H	88	9:1	93.6
Me	Me	95	—	91.5
$CH{=}CMe_2$	H	72	12:1	92.0

[a] Refers to ring stereochemistry.

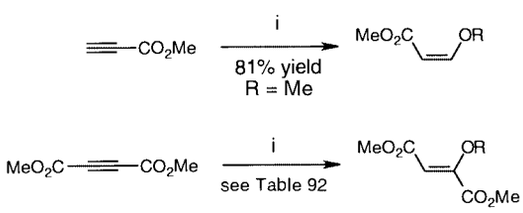
Table 92

ROH	Reaction time/h	Yield fumarate (%)
MeOH	4	87
EtOH	7	87
^{i}PrOH	20	10[a]
^{t}BuOH	20	86
Allyl alcohol	20	0[b]
Propargyl alcohol	20	0

[a] Dimethyl oxaloacetate isolated in 38% yield. [b] Claisen rearrangement occurs (81% yield).

Table 93

R	Yield (%)	**113a**:**113b**
Me	47	12:1
Et	48	19:1
^{i}Pr	40	24:1
Ph	—	—



Scheme 135 *Reagents*: i, ROH, AgOTf (1 mol%).

taken in certain cases to avoid hydrolysis of the enol ether or other side-reactions (Scheme 135 and Table 92).

The balance between 4-*exo*- and 5-*endo*-iodoetherification of asymmetric 2-alkenyl-3-hydroxy acid derivatives is complex, being determined by a variety of structural factors.[117] Thus, aldol reaction products **112** (derived from Evans asymmetric aldol reaction) undergo 4-*exo*-cyclization upon treatment with elemental iodine, yielding only oxetanes **113** as the product of iodoetherification (Scheme 136 and Table 93).

When the 2-alkenyl substituent bears a substituent, the iodoetherification reaction leads to either oxetane or tetrahydrofuran products, depending on the nature of the substitution. Thus, a methyl group on the 'internal' carbon of the alkene leads to a preference for oxetane (Scheme 137 and Table 94).

When the terminal carbon of the alkene bears a methyl group, only tetrahydrofurans are produced and with better diastereoselectivity (Scheme 138 and Table 95).

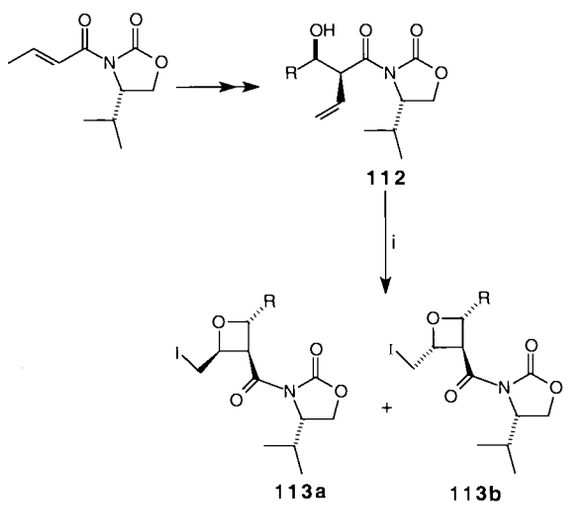
Stannyl enolates of 2-methoxy ketones react in a Michael fashion with a range of enones to give 2-methoxy-1,5-dicarbonyl products in acceptable yield and with variable diastereoselectivity. Thus, exclusively 2,3-*anti*-products are obtained when tributylstannyl enolates are employed in the reaction, whereas 2,3-*syn*-products are favoured when butyldichlorostannyl enolates are used (Scheme 139).[118] The highest level of *anti*-selectivity was observed when an excess of stannylamine **115** was used. The authors deduce that the tri-

Table 94

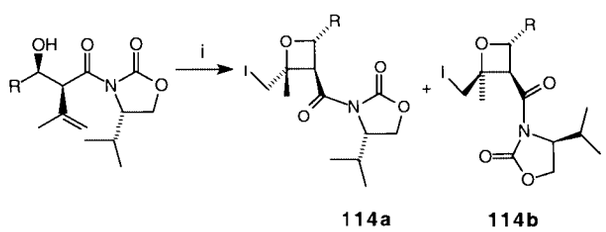
R	Yield (%)	**114a : 114b**
Me	63	>98 : <2
Et	84	82 : 18
^{i}Pr	40	81 : 14
Ph	20	Not determined

Table 95

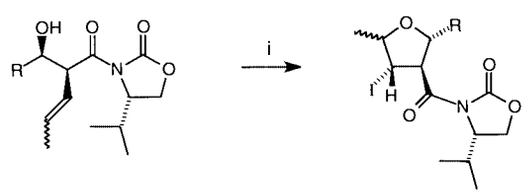
R	Yield (%)
Me	74
Et	77
^{i}Pr	81
Ph	63



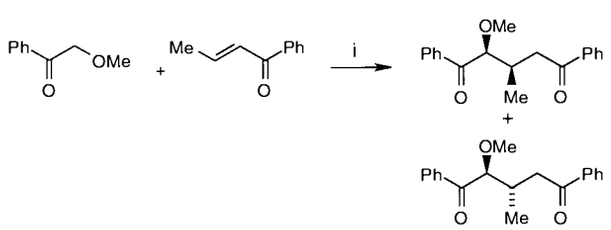
Scheme 136 *Reagents*: i, I_2, $NaHCO_3$.



Scheme 137 *Reagents*: i, I_2, $NaHCO_3$.



Scheme 138 *Reagents*: i, I_2, $NaHCO_3$.

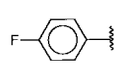


Scheme 139 *Reagents and conditions*: i, $R_3Sn\text{-}N^{i}Pr_2$ (**115**), 0 °C, 2 h.

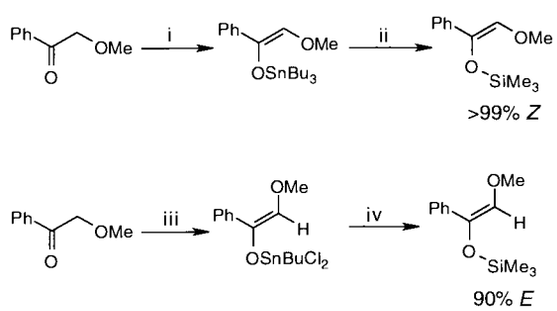
Table 96

Tin amide	Yield (%)	*syn* : *anti*
$Bu_3SnN^{i}Pr_2$	64	0 : 100
$Me_3SnN^{i}Pr_2$	61	9 : 91
$Ph_3SnN^{i}Pr_2$	59	9 : 91
$ClBu_2SnN^{i}Pr_2$	74	50 : 50
$Cl_2BuSnN^{i}Pr_2$	76	79 : 21
$Cl_2BuSnN^{i}Pr_2$ (2 eq.)	84	91 : 9

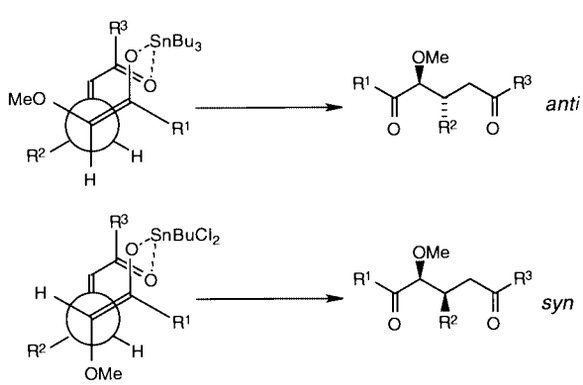
Table 97

Y	*syn* : *anti*
Ph	13 : 87
	12 : 88
	2 : 98
PhS	78 : 22

alkyltin enolates are formed as (*Z*)-diastereomers, whereas the chlorostannyl enolates are of (*E*)-configuration, using NOE experiments (Scheme 140). The authors proposed a closed transition state to rationalise the observed diastereoselectivity (Scheme 141 and Table 96).



Scheme 140 *Reagents and conditions*: i, $Bu_3Sn\text{-}N^{i}Pr_2$, 0 °C, 2 h; ii, Me_3SiBr, rt, 18 h; iii, $Cl_2BuSn\text{-}N^{i}Pr_2$, 0 °C, 2 h; iv, Me_3SiBr, rt, 18 h.

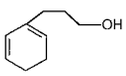
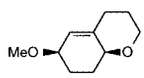
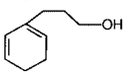
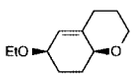
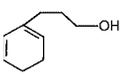
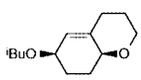
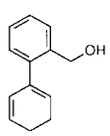
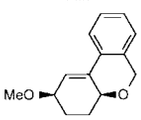
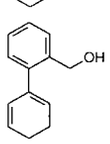
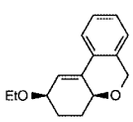
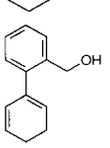
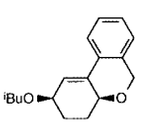
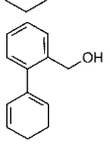
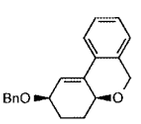


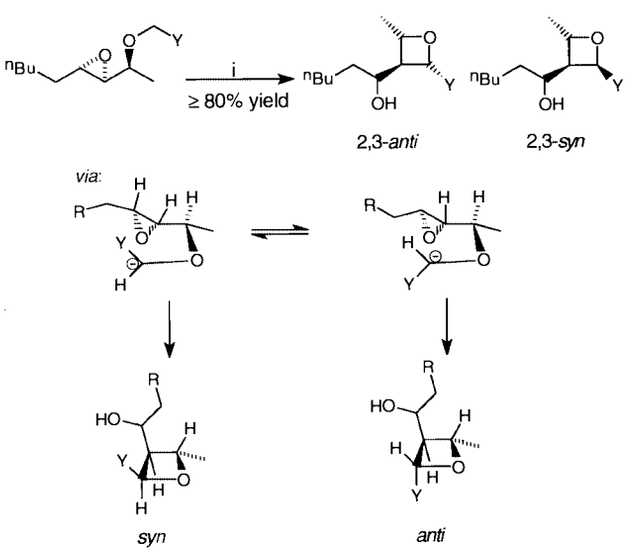
Scheme 141

The previously-reported cyclization of benzylic and allylic glycidols to give hydroxyalkyloxetanes has been extrapolated to encompass reaction of 1-alkyl-2,3-epoxyalcohols, thereby generating trisubstituted oxetanes in high yield (Scheme 142 and Table 97).[119]

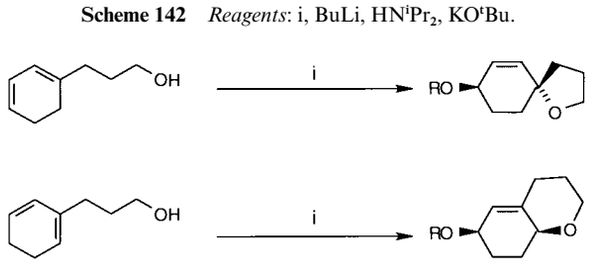
Bäckvall and his co-workers have described their stereoselective approach to fused bicyclic hydropyrans and spiroethers *via* palladium-catalysed intramolecular 1,4-dialkoxylation of cyclohexa-1,3-dienes.[120] Thus, cyclohexadienes bearing pendant alcoholic functionality cyclize to give fused ethers in which the newly-formed C–O bonds are *cis*-conformed (Scheme 143 and Table 98).

Table 98

Starting material	Solvent	Product	Yield (%)	Stereo-chemistry
	MeOH		76	>97% *cis*
	EtOH		87	>97% *cis*
	^{i}BuOH		96	>97% *cis*
	MeOH		90	92% *cis*
	EtOH		77	>97% *cis*
	^{i}BuOH		96	95% *cis*
	BnOH		80	82% *cis*



Scheme 142 *Reagents*: i, BuLi, $HN^{i}Pr_2$, $KO^{t}Bu$.



Scheme 143 *Reagents and conditions*: i, $Pd(OAc)_2$ (5 mol%), $MeSO_3H$ (10 mol%), benzoquinone (2 eq.), ROH, rt, 73%.

Bicyclic ketoethers may be prepared in moderate yield by the reaction of oxoallyl carbocations (generated from dibromopenta-2-one with diethylzinc) and furans (Scheme 144 and Table 99).[121]

Table 99

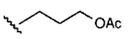
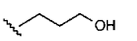
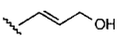
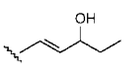
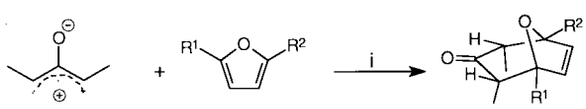
R^1	R^2	Yield (%)
H		55
H		56
H		46
CH_2OH		8
H		29

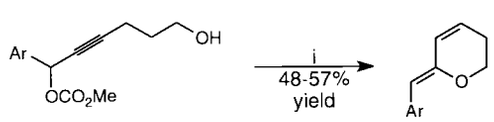
Table 100

Solvent	R	Yield (%)	*cis*:*trans*
CH_2Cl_2	$PhCH_2$	28	68:32
CH_2Cl_2 (with $HfCl_4$)	$PhCH_2$	18	65:35
CH_2Cl_2	$^{n}C_5H_{11}$	53	70:30
CH_2Cl_2	$^{c}C_6H_{11}$	32	70:30
CH_2Cl_2	$BnOCH_2$	67	45:55
$PhCH_3$	$BnOCH_2$	80	55:45
$PhCH_3$	$TBDMSOCH_2$	75	86:14
$PhCH_3$	$TIPSOCH_2$	80	77:23
$PhCH_3$	$TBDMSOCH_2CH_2$	56	50:50



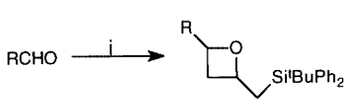
Scheme 144 *Reagents and conditions*: i, benzene, rt 8–20 h.

2-Methylenedihydropyrans may be prepared in moderate yield by means of the reaction of 1-aryl-6-hydroxyhex-2-ynyl carbonates with a palladium(0) catalyst (Scheme 145).[122]



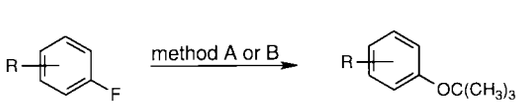
Scheme 145 *Reagents and conditions*: i, Pd(0), dppb, THF, 50 °C.

Zirconium(IV) chloride promotes the cycloaddition of allylsilanes to aldehydes, yielding oxetanes in variable yield.[123] The stereoselectivity of the reaction is mediocre (Scheme 146 and Table 100).



Scheme 146 *Reagents*: i, allyl-*tert*-butyldiphenylsilane, $ZrCl_4$, solvent.

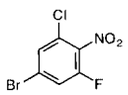
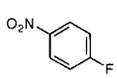
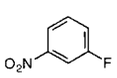
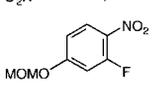
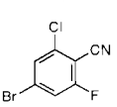
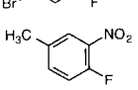
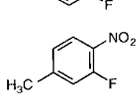
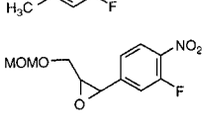
Tertiary ethers of phenols may be prepared in good yield by *ipso* nucleophilic substitution of activated aryl fluorides.[124] The method is effective even using relatively electron-rich arenes, and is applicable to the preparation of a range of chiral ethers (Schemes 147 and 148, Tables 101 and 102).



Scheme 147

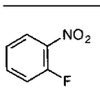
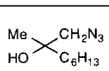
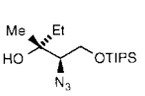
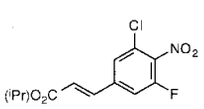
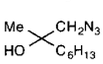
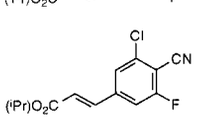
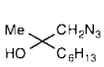
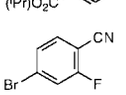
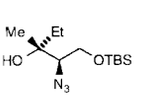
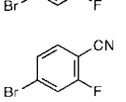
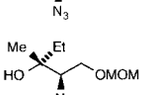
Allyl aryl ethers undergo a rearrangement reaction when heated with molybdenum hexacarbonyl in toluene.[125] The product of the reaction is a 2-substituted dihydrobenzofuran,

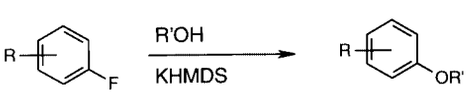
Table 101

Substrate	Method A[a]	Method B[b]
	99	99
	87	87
	94	95
	0	0
	94	94
	99	95
	92	n/d
	92	93
	0	0
	71	n/d

[a] Method A: the aryl fluoride was dissolved in THF, cooled to 0 °C, treated with KO^{t}Bu (1.2 eq.) and allowed to warm to 23 °C. [b] Method B: the aryl fluoride and *tert*-butyl alcohol were dissolved in THF, cooled to 0 °C, treated with KHMDS (1.1 eq.) and allowed to warm to 23 °C.

Table 102

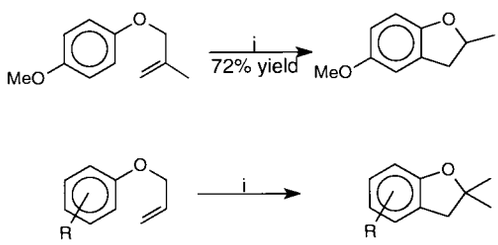
Substrate	Alcohol	Yield (%)
		86
		75
		75
		30 Low yield due to competing transesterification
		60
		91



Scheme 148

Table 103

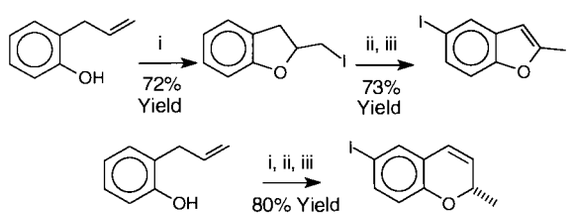
R	$Mo(CO)_6$/mol %	Yield (%)
4-OMe	40	91
3-Me	40	71
3,5-Me_2	40	85
4-Et	40	72
4-^{i}Pr	40	70
4-^{t}Bu	40	75



Scheme 149 *Reagents and conditions*: i, $Mo(CO)_6$, toluene, 110 °C, 55 h.

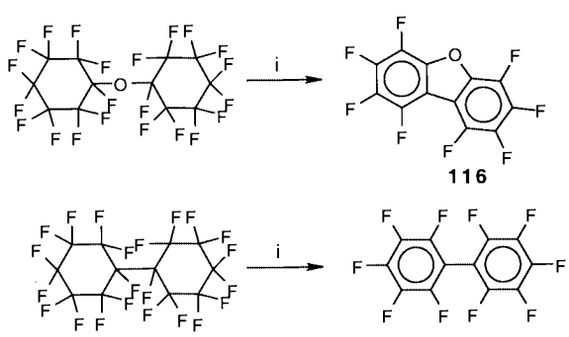
produced *via* a sequential Claisen rearrangement/cyclization process (Scheme 149 and Table 103).

Dihydrobenzofurans may be prepared by reaction of 2-allylphenols with tin(IV) chloride and elemental iodine.[126] Dehydroiodination of the reaction products gives benzofurans in good yield. The presence of terminal substituents on the alkene changes the regioselectivity of the C–O bond-forming reaction and benzopyrans are the products obtained after dehydroiodination (Scheme 150).



Scheme 150 *Reagents and conditions*: i, $SnCl_4$, I_2, CH_2Cl_2, rt; ii, HgO, I_2, CH_2Cl_2, rt; iii, NaOH, MeOH, reflux.

Perfluorinated dicyclohexyl ethers react with the benzophenone radical anion to give octafluorodibenzofuran **116**.[127] The corresponding dicyclohexane gives a perfluorobiphenyl rather than a perfluorofluorene (Scheme 151).



Scheme 151 *Reagents*: i, Na, Ph_2CO, THF.

Reaction of 3-phenylpropan-1-ol with (diacetoxyiodo)-benzene using photolytic initiation gives dihydrobenzopyrans in acceptable yield.[128] The reaction proceeds, it is proposed, *via* the intermediacy of alkoxy radicals. The authors suggest that the reaction allows ready preparation of flavonoid and vitamin E analogues (Scheme 152 and Table 104).

(*S*)-(+)-3-*p*-Tolylsulfinylbut-3-en-2-one **117** has been described as a "spectacular" heterodiene, due to its highly diastereo- and enantioselective cycloaddition reactions with

Table 104

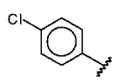
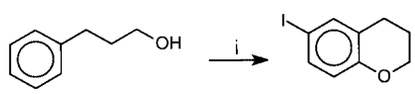
Ar	R	Yield (%)
Ph	CF_3	0
Ph	CH_3	64
p-Tol	CH_3	63
	CH_3	64

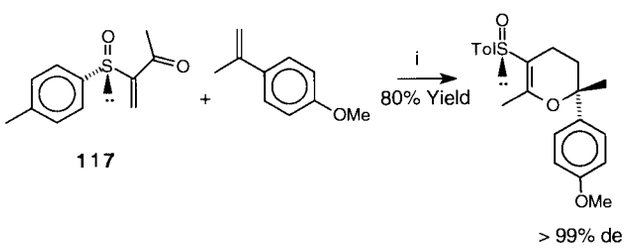
Table 105

R	R′	Yield **119** (%)	Ee **119** (%)	Yield **120** (%)	Ee **120** (%)
Me	Me	37	94	12	56
H	Me	13	70	3	27
Me	Et	73	97	9	88
H	Et	29	97	14	88



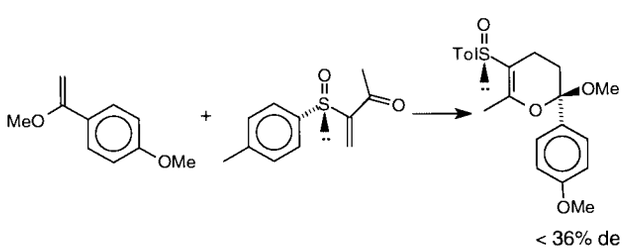
Scheme 152 *Reagents and conditions*: i, $ArI(OCOR)_2$ (2.2 eq.), I_2 (1.1 eq.), W lamp, 60–70 °C.

styrenes.[129] Thus, in particular, electron-rich styrenes react with **117** in good yield and with >99% de (Scheme 153).



Scheme 153 *Reagents and conditions*: i, CH_2Cl_2, 40 °C.

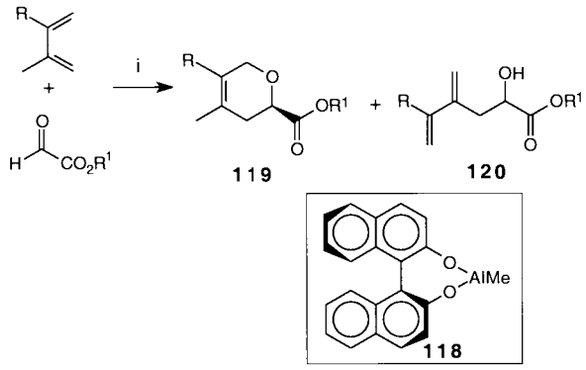
When other, electron-rich, alkenes are used as dienophiles, the diastereoselectivity shown in the cycloaddition is spectacular due to its mediocrity. The authors deduce that (especially in the case of methoxystyrene) the primary structure factor underlying the stereocontrol (or lack of it) is the nature of the aromatic group (Scheme 154).



Scheme 154

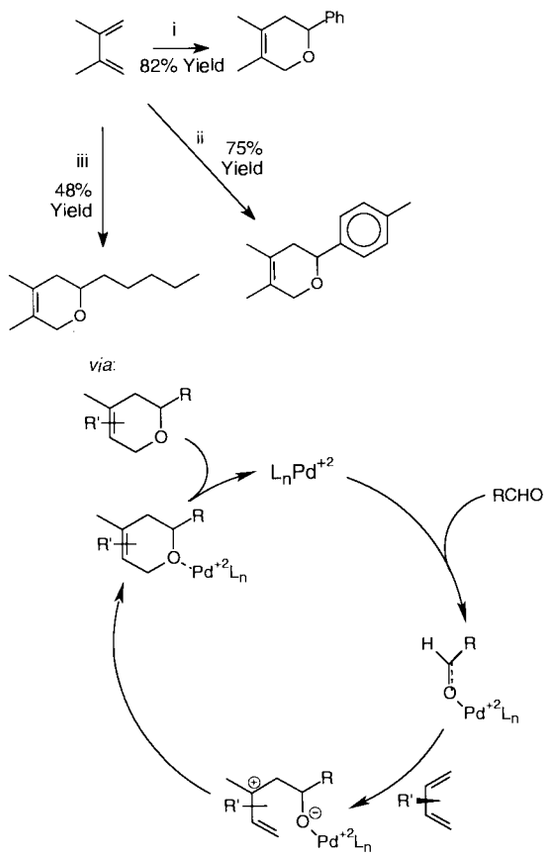
(*S*)-BINOL-derived Lewis acid **118** asymmetrically catalyses the hetero Diels–Alder reaction of unactivated dienes with glyoxalates.[130] The enantiocontrol shown in the reaction is impressive (usually >90% ee) but the products **119** are always contaminated by the alternative product **120** (arising from an asymmetric "ene" reaction) leading to low yields (Scheme 155 and Table 105).

Cationic palladium(II) complexes catalyse the hetero Diels–Alder cycloaddition reaction of unactivated dienes with aldehydes.[131] 5,6-Dihydro-2*H*-pyrans are produced in generally



Scheme 155 *Reagents*: i, **118** (10 mol%), solvent.

good yields. Of the two possible mechanistic rationales (concerted pericyclic reaction *versus* stepwise ionic reaction) the authors plump for the stepwise mechanism shown since this tallies best with the experimental observations (Scheme 156).



Scheme 156 *Reagents and conditions*: i, $[Pd(dppf)(PhCN)_2](BF_4)_2$ (0.02 mol%), $CHCl_3$, 50 °C, 20 h, PhCHO; ii, $[Pd(dppf)(PhCN)_2](BF_4)_2$ (0.02 mol%), $CHCl_3$, 50 °C, 20 h, 4-methylbenzaldehyde; iii, $[Pd(dppf)(PhCN)_2](BF_4)_2$ (0.02 mol%), $CHCl_3$, 50 °C, 20 h, hexan-1-al.

Tungsten dihydropyranylidene carbenes **121** are obtained in mediocre yield when alk-1-yn-5-ols are reacted with pentacarbonyltungsten–THF complex; these metal carbenes react with tributylstannyl triflate to give 6-tributylstannyl-3,4-dihydro-2*H*-pyrans in excellent yield (Schemes 157 and 158, Table 106).[132]

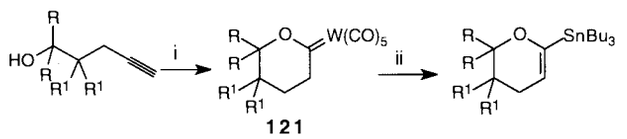
Spiroacetal enol ethers may be prepared by a base-induced double cyclization of 1-methyloxycarbonyl-9-hydroxy-5-oxo-non-1-ynes **122**.[133] The product of the reaction is usually the more thermodynamically sable (*E*)-enoate, but judicious choice of conditions can allow the (*Z*)-isomer to predominate (Scheme 159 and Table 107).

Table 106

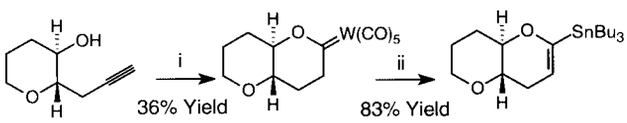
R	R′	Yield **121** (%)	Yield dihydropyran (%)
H	H	42	84
H	Me	41	85
H, Me	H	34	78
Me	H	35	100

Table 107

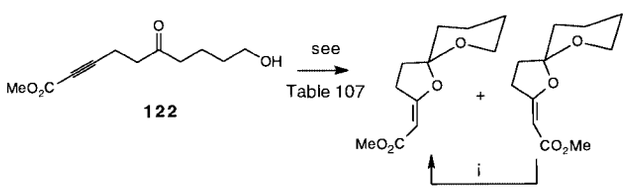
Conditions	Yield (%)	(*E*):(*Z*)
^{t}BuOK, THF, 4 °C, 1 min	73	52:1
^{t}BuOK, ^{t}BuOH, rt, 5 min	97	25:1
Na_2CO_3 (10 eq.), MeOH–H_2O, rt, 50 min	65	1:2.5



Scheme 157 *Reagents*: i, (THF)$W(CO)_5$, THF; ii, Bu_3SnOTf, Et_3N, Et_2O.

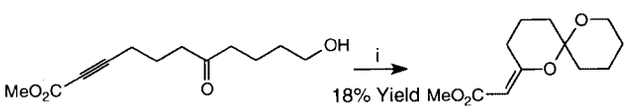


Scheme 158 *Reagents*: i, (THF)$W(CO)_5$, THF; ii, Bu_3SnOTf, Et_3N, Et_2O.



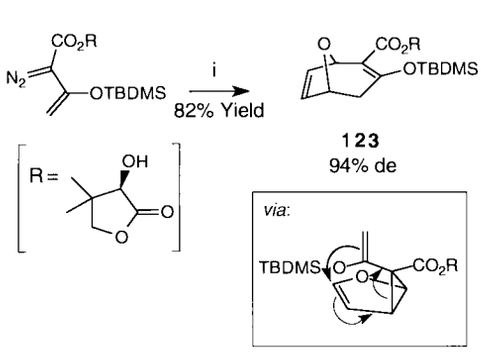
Scheme 159 *Reagents and conditions*: i, ^{t}BuOK, THF, 4 °C, 1 min.

The corresponding decynes do not undergo efficient double cyclization (Scheme 160).



Scheme 160 *Reagents and conditions*: i, NaH, THF, 4 °C to rt, 20 min.

Asymmetric vinyl diazomethanes react with furans in the presence of rhodium(II) carboxylates to give 8-oxabicyclo-[3.2.1]octa-2,6-diene derivatives **123**.[134] Although an apparent [3 + 4] cycloaddition, the process is actually thought to be a tandem cyclopropanation–Cope rearrangement (Scheme 161).

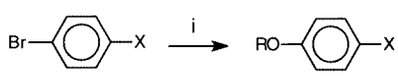


Scheme 161 *Reagents*: i, Furan, $Rh_2(OOct)_4$.

Table 108

X	R	Yield (%)
Bz	^{t}Bu	63
CN	^{t}Bu	90
^{t}Bu	^{t}Bu	<1
Bz	Me	76
CHO	Me	55
CN	Me	58
CHO	TBDMS	98
CN	TBDMS	96

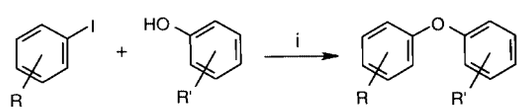
In an extension to the author's previous studies, it has been reported that nickel catalysis allows for direct displacement of halide by alkoxides without the usual prerequisite for strongly electron-withdrawing groups to be present upon the aromatic ring.[135] Thus, in the presence of $Ni(COD)_2$, *o*-alkylphenols may be prepared in good yields by reaction of sodium alkoxides with aryl bromides and chlorides. Certain bromides also react with sodium siloxides, yielding silyl aryl ethers in good yield (Scheme 162 and Table 108).



Scheme 162 *Reagents and conditions*: i, $Ni(COD)_2$ (15 mol%), DPPF (30 mol%), NaOR, toluene, 95 °C.

Non-activated aryl halides react with phenols in refluxing dioxane or toluene to give diaryl ethers in good yield, when phosphaazene P_4-^{t}Bu base and copper(I) bromide are used to catalyse the process.[136]

Thus, even electron-rich iodides (*cf*. **124**) react under the conditions to give good yields of product. The authors are unable to assign a precise mechanistic role to the base, but point out that its presence in the reaction medium dramatically enhances the dissolution of the copper(I) salt (which is otherwise only sparingly soluble under the reaction conditions) (Scheme 163 and Table 109).



Scheme 163 *Reagents and conditions*: i, P_4-^{t}Bu, CuBr, toluene, reflux.

2.1 Preparation of epoxides

The fructose-derived non-racemic ketone **125**[137] effects enantioselective mono-epoxidation of conjugated dienes in the presence of Oxone™.[138] Thus, the intermediate chiral dioxirane reacts *via* transition state **126**, usually giving a mono-epoxide (mono-:diepoxide ≥12:1). Where unsymmetrical dienes were used, the less-hindered bond normally reacted, whilst electron-deficient dienes reacted preferentially at the least electron-deficient position (Scheme 164).

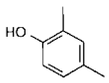
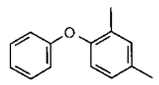
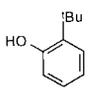
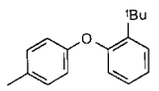
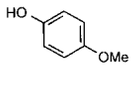
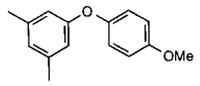
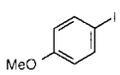
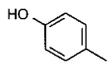
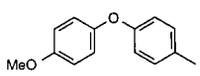
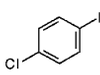
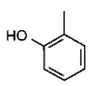
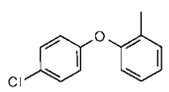
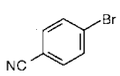
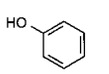
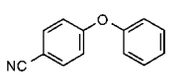
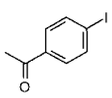
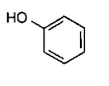
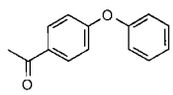
The results of a study into some of the factors controlling the diastereoselectivity of epoxidation of cyclohexane derivatives by dimethyldioxirane have been published.[139]

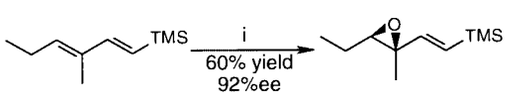
Glycidic esters may be prepared with moderate to good enantiocontrol by Darzens reaction of chiral esters of chloro acetic acid and ketones.[140] In all of the reactions carried out, (2*R*)-configured glycidates predominated and highest enantiocontrol was observed using an (−)-8-phenylmenthyl ester. The authors rationalize the stereoselectivity witnessed as being due to a preference for *Si-Si* approach of the reactants (Scheme 165 and Table 110).

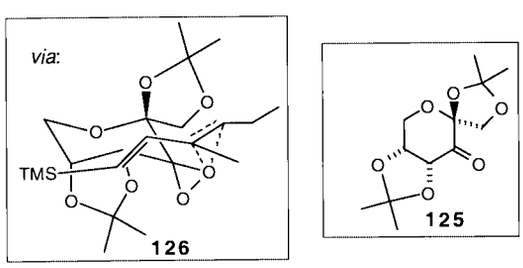
When asymmetrically-substituted ketones were used in the reactions, mixtures of *cis*- and *trans*-epoxides were obtained.

A novel asymmetric Darzens reaction between chloroketones and aldehydes gave 2,3-epoxyenones in moderate ee.[141] The

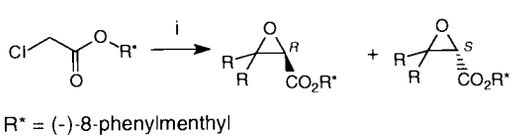
Table 109 Reaction performed on 1 mmol scale; aryl halide–phenol–CuBr = 1:2:2 in toluene. Yields in parentheses refer to the reaction under catalytic conditions for Cu(I) (20 mol% CuBr)

Halide	Phenol	Product	Yield (%)
			81 (73)
			56
			81 (72)
 124			70 (25)
			80
			76 (80)
			61



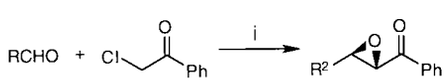


Scheme 164 *Reagents*: i, Oxone, **125** (<30 mol%), H_2O–solvent.



Scheme 165 *Reagents and conditions*: i, ^tBuOK, R_2CO, CH_2Cl_2, −70 to 0 °C.

reaction is mediated by *N*-(4-trifluoromethyl)benzylcinchonine **127** (Scheme 166 and 167 and Table 111).



Scheme 166 *Reagents and conditions*: i, **127** (10 mol%), $^nBu_2O$, $LiOH·H_2O$, 4 °C.

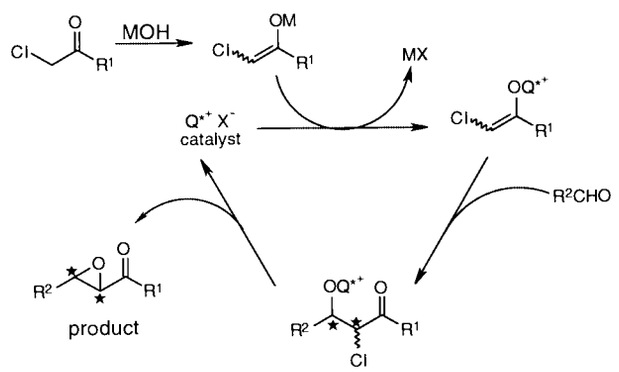
N-Anthracenylmethylcinchona alkaloid derivatives catalyze the enantioselective epoxidation of enones by sodium hypochlorite.[142] *trans*-α,β-Epoxyketones are obtained, in generally good yields, with good diastereoselectivity and good enantiocontrol (Scheme 168 and Table 112).

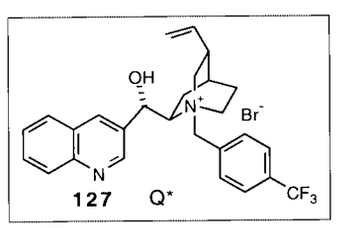
Table 110

R	Yield (%)	De (%)
Me	64	87
Et	47	81
$-(CH_2)_4-$	45	80
Ph	48	77

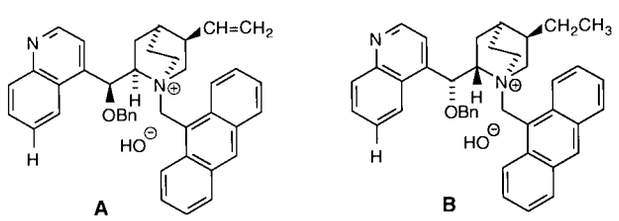
Table 111

Aldehyde	Time/h	Yield (%)	Ee (%)
^{i}Pr	60	80	53
Et	117	32	79
^{n}Pr	60	82	57
^{i}Bu	134	73	69
^{t}BuCH$_2$	91	50	62
Et_2CHCH_2	117	76	58
$Ph(CH_2)_2$	114	83	44
c-Hexane	61	47	63
Ph	69	43	42





Scheme 167



Scheme 168

Aggarwal *et al.* have described copper(I)-catalysed epoxidation *via* reaction of 2-diazoacetamides in the presence of tetrahydrothiophene (THT).[143] Thus, aryl and aliphatic aldehydes undergo reaction with *N*,*N*-diethyl-2-diazoacetamide in the presence of sub-stoichiometric amounts of THF and $Cu(acac)_2$ to give 2,3-epoxyamides in moderate to good yield and with good diastereoselectivity (dr *trans*:*cis* = >90:<10) (Scheme 169, Table 113 and Scheme 170, Table 114).

Peroxycarboximidic acid epoxidation of alkenes is promoted by layered hydrotalacite $Mg_{10}Al_2(OH)_{24}CO_3$.[144] A range of alkenes is epoxidized in good yield by this two-phase reaction (Scheme 171 and Table 115).

Table 112

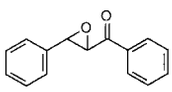
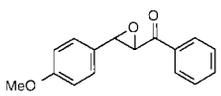
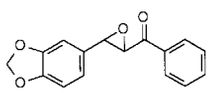
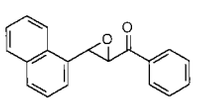
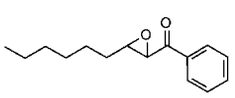
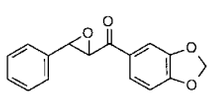
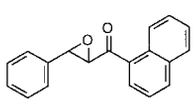
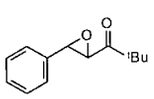
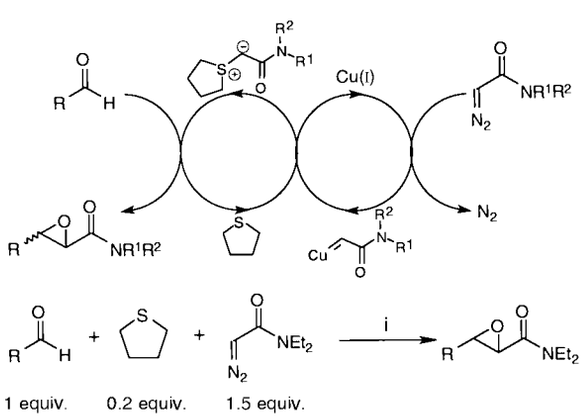
Product	Catalyst	De (%)	Ee (%)	Yield (%)
	**A**	≥95%	81 (−)	90
	B	≥95%	86 (+)	90
	**A**	≥95%	81 (−)	86
	B	≥95%	82 (+)	87
	**A**	≥95%	82 (+)	92
	B	≥95%	83 (−)	97
	**A**	≥95%	82 (+)	92
	B	≥95%	82 (−)	86
	**A**	≥95%	76 (−)	75
	B	≥95%	77 (+)	92
	**A**	≥95%	86 (−)	93
	B	≥95%	89 (+)	95
	**A**	≥95%	69 (+)	75
	B	≥95%	71 (−)	77
	**A**	≥95%	87 (−)	42
	B	≥95%	85 (+)	40

Table 113

Aldehyde	Yield (%)	*trans*:*cis*
p-Cl-C_6H_4CHO	79	>95:5
PhCHO	79	>95:5
p-NO_2-C_6H_4CHO	71	>95:5
p-Me-C_6H_4CHO	63	>95:5
p-MeO-C_6H_4CHO	44	>95:5
Valeraldehyde	64	>90:10
c-$C_6H_{11}CHO$	64	>90:10



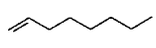
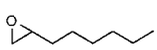
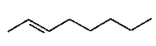
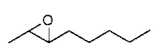
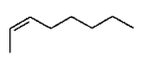
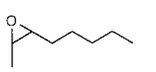
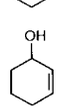
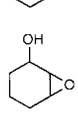
Scheme 169 *Reagents and conditions*: i, $Cu(acac)_2$ (5 mol%), MeCN, 3 h addition, 60 °C.

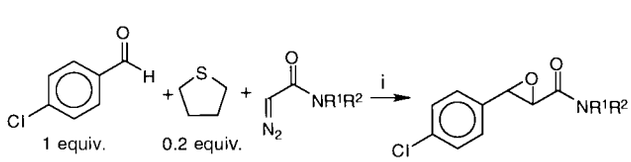
Menthol-derived oxathianes have been employed in an asymmetric synthesis of enantiomerically-pure *trans*-diaryl-epoxides.[145] As judged by NMR, the reaction furnishes enantiomerically-pure epoxides directly, as (*R*,*R*)-isomers (Scheme 172).

Table 114

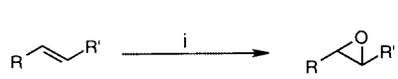
R^1	R^2	Yield (%)	*trans*:*cis*
Et	Et	79	>95:5
Me	Me	78	>95:5
	$-C_4H_8-$	75	>95:5
Me	OMe	40	>95:5

Table 115

Substrate	Product	Conversion (%)	Yield (%)
		95	95
		100	96
		94	93
		100	95
		100	>99
		100	94
		99	95
		100	>99 (*exo* only)
		97	92
		84	84
		90	89 (*syn*:*anti* = 80:20)



Scheme 170 *Reagents and conditions*: i, $Cu(acac)_2$ (5 mol%), MeCN, 3 h addition, 60 °C.



Scheme 171 *Reagents and conditions*: i, olefin (3.9 mmol), benzonitrile (10.5 mmol), $Mg_{10}Al_2(OH)_{24}CO_3$ (0.05 g), MeOH (10 ml), 30% aq. H_2O_2 (2.4 ml), 60 °C, 24 h.

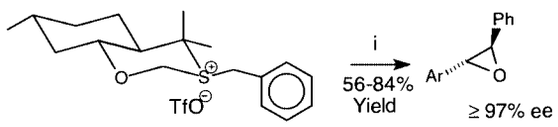
If so desired, the precious chiral auxiliary can be recycled in greater than 78% yield. C_2-symmetric thiolane **128** mediates an asymmetric Darzens-like epoxidation of aryl aldehydes,[146] *via* chiral sulfonium ylide **129**. Predominantly *trans*-(*S*,*S*)-epoxides are obtained from the process, but diastereo- and enantio-selectivities are moderate to good. The authors rationalize the observations as proceeding *via* conformation **129b** of the intermediate chiral sulfonium ylide (Schemes 173 and 174 and Tables 116 and 117).

Table 116

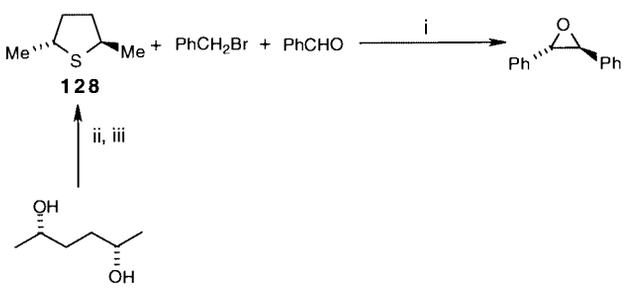
Solvent	Time/days	Yield (%)	De (*trans*) (%)	Ee (*S*,*S*) (%)
9:1 $CH_3CN:H_2O$	1	92	88	84
9:1 $^tBuOH:H_2O$	2	92	86	88
9:1 $^iPrOH:H_2O$	8	59	86	90
9:1 $EtOH:H_2O$	3	15	84	94
H_2O	4	90	74	86

Table 117

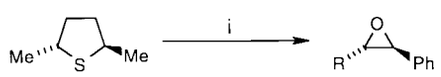
R	Time/ days	Yield (%)	De (*trans*) (%)	Ee (%) (configuration)
Ph	2	92	88	88 (*S*,*S*)
$4\text{-}ClC_6H_4$	2	89	84	86 (*S*,*S*)
$4\text{-}CH_3C_6H_4$	2	88	84	88 (*S*,*S*)
$^cC_6H_{11}$	2	87	30	94



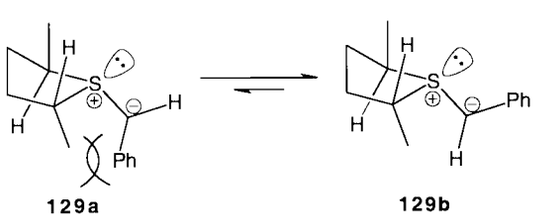
Scheme 172 *Reagents*: i, NaH, ArCHO, CH_2Cl_2.



Scheme 173 *Reagents and conditions*: i, NaOH, rt; ii, MsCl, Et_3N, CH_2Cl_2, −20 °C; iii, Na_2S, EtOH, rt.



Scheme 174 *Reagents and conditions*: i, $PhCH_2Br$, RCHO, NaOH, rt.

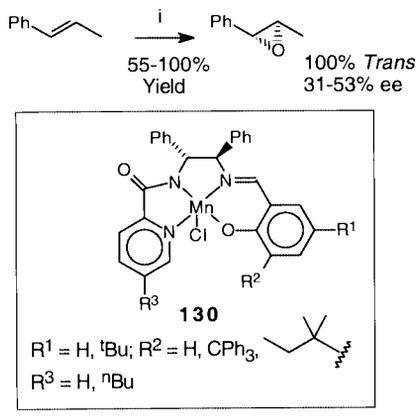


A new class of tetradentate ligands useful in asymmetric manganese-based epoxidation has been described.[147] Thus, (*R*,*R*)-1,2-diphenylethylene-1,2-diamine-derived ligands **130** have been used to prepare manganese complexes exhibiting higher turnover numbers than similar salen complexes during epoxidation of unfunctionalized alkenes. The enantioselectivity of epoxidation using these newer catalysts is moderate, at best (Scheme 175).

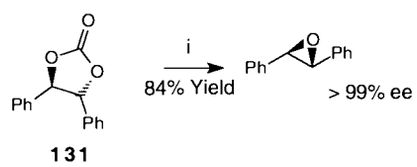
Chang and Sharpless have described a molar-scale preparation of enantiomerically-pure stilbene oxide from the corresponding diol.[148] The reaction involves ring-opening of C_2-symmetric cyclic carbonate **131** by chloride ion, followed by decarboxylative ring-closure (Scheme 176).

Table 118

Additive	Temp/°C	Time/h	Yield (%)	Ee (%)	Configuration
—	−20→20	12	81	—	Racemic
132	−20→10	0.67	97	25	(*S*,*S*)
134	−20→20	1	68	50	(*R*,*R*)
134	0	1	74	51	(*R*,*R*)
134	−20→20	12	90	66	(*R*,*R*)
134	−80	3	23	27	(*R*,*R*)
135	−20→20	12	87	10	(*R*,*R*)

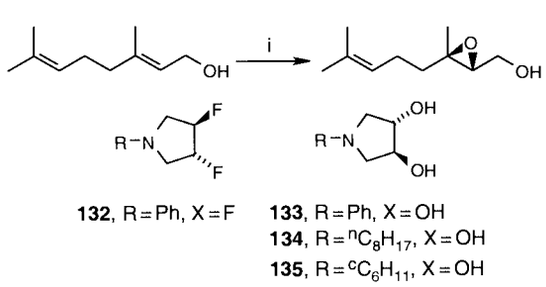


Scheme 175 *Reagents*: i, **130**, NaOCl.



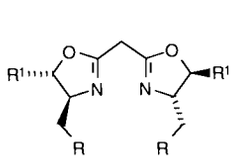
Scheme 176 *Reagents*: i, LiCl, DMF.

Chiral difluoro and dihydroxylated pyrrolidines **132**–**135** catalyse asymmetric epoxidation of allylic alcohols; the enantiomeric purity of the product epoxyalcohols produced is moderate (Scheme 177 and Table 118).[149]



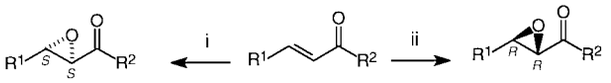
Scheme 177 *Reagents and conditions*: i, ^tBuOOH, $Ti(O^iPr)_4$, **132** (10 mol%), −20 to 20 °C, 12 h.

Chiral bisoxazoline-based catalysts have been reported to mediate asymmetric epoxidation *via* Tiffenau reaction of phenyldiazomethane with a range of aryl aldehydes in good yield and with high levels of diastereocontrol.[150] Thus, bisoxazolines **136**–**141** were screened in the reaction, but uniformly low ees were observed (ee = 0–24%). The product 1,2-diarylepoxides were obtained primarily as *trans*-diastereoisomers (dr = 92–100 : 8–0 *trans* : *cis*).



136 R = CH_2SMe, R^1 = H
137 R = SMe, R^1 = H
138 R = OH, R^1 = Ph
139 R = OMe, R^1 = Ph
140 R = SMe, R^1 = Ph
141 R = SPh, R^1 = Ph

The Julià–Colonna epoxidation using polyleucine as chiral mediator[151] was believed to be an efficient asymmetric process only when chalcones were used as substrates. However, Roberts *et al.* have shown that a much wider range of substrates undergoes epoxidation, some with excellent stereoselectivity (Scheme 178 and Table 119).[152]



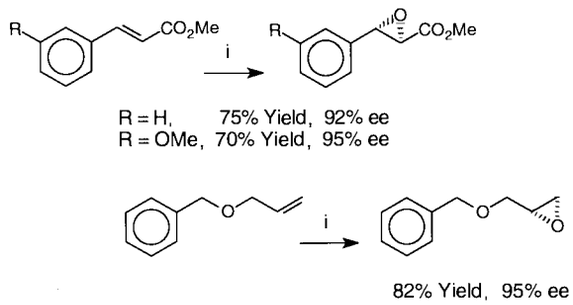
Scheme 178 *Reagents*: i, poly-(L)-leucine (PLL), NaO_2H; ii, poly-(D)-leucine (PDL), NaO_2H.

Allylic and homoallylic alcohols are epoxidized in good yield upon reaction with ^{t}BuOOH in the presence of a variety of transition metal catalysts in liquid CO_2.[153] Sharpless epoxidation is feasible in this solvent, but the enantioselectivity of the asymmetric epoxidation is low (Scheme 179 and Table 120).

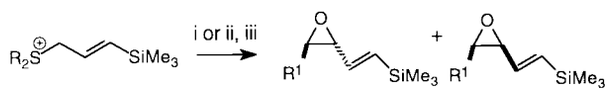
Epoxidation using 'liposomized' *m*-chloroperbenzoic acid has been reported to be an effective synthetic process.[154] A range of alkenes undergo enantioselective epoxidation using MCPBA encapsulated in liposomes derived from egg phosphatidyl-chlorine (EYPC), some with excellent enantioselectivity. The origins of the stereoselectivity observed lie, it is suggested, in the highly selective interactions between the alkenic substrate and the hydrophobic centres of the liposomes (Scheme 180).

Scheme 179 *Reagents and conditions*: 24 h reaction in liquid CO_2 (10.3 bar), 1.47 mM $VO(O^iPr)_3$ (3.5 mol%), 0.42 mM substrate, 100 mM ROOH.

The recent work examining the utility of sulfonium salts in epoxidation and aziridination has been extrapolated to allow for synthesis of both *trans*- and *cis*-(trimethylsilyl)vinyl-epoxides from aldehydes.[155] Thus, (3-trimethylsilyl)allyldimethyl sulfonium salts undergo sequential reaction with solid KOH and an aldehyde to give predominantly *trans*-2-trimethylsilyl-vinyl epoxides, while the analogous diphenyl sulfoniums react with KHMDS and aldehydes at low temperature furnishing mainly *cis*-vinylepoxides (Scheme 181). The authors suggest that the dimethylsulfonium salt reacts *via* an open transition state to give the thermodynamically-favoured product, while the diphenylsulfonium salt reacts under aprotic conditions through the ubiquitous six-membered transition state to give the *cis*-configured product (Scheme 182 and Table 121).



Scheme 180 *Reagents*: i, EYPC–MCPBA liposomes.



Scheme 181 *Reagents and conditions*: i, R^1CHO, KOH(s), MeCN, rt; ii, KHMDS, THF, −90 °C; iii, R^1CHO, LiBr, THF, −90 °C to rt.

Table 119

R^1	R^2	Peptide	Yield (%)	Ee (%)
Ph	^{t}Bu	PLL	92	>98
Ph	^{t}Bu	PDL	90	>86
Ph		PLL	70	63
Ph	^{i}Pr	PLL	60	62
		PLL	73	74
		PLL[a]	52	98

[a] Immobilized polypeptide used.

Table 121

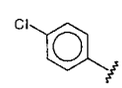
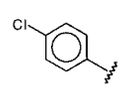
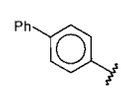
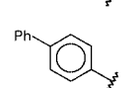
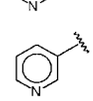
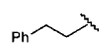
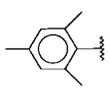
R	R′	Yield (%)	*trans*:*cis*
Me		95	98:2
Ph		96	6:94
Me	Ph	91	87:13
Ph	Ph	96	15:85
Me		84	80:20
Ph		93	7:93
Me		91	87:13
Ph		81	5:95

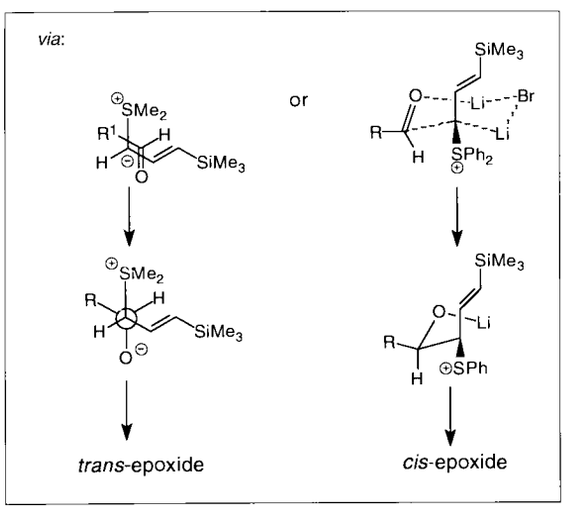
Table 120

R^1	R^2	*n*	Conversion (%)	Yield (%) Epoxide	Yield (%) Aldehyde
Me	H	1	>99	85	15
$Me(CH_2)_2$	H	1	>99	>99	—
Me	Me	1	>99	86	—
$Me_2C{=}CH(CH_2)_2$	Me	1	>99	>95	—
Me	$Me_2C{=}CH(CH_2)_2$	1	>99	>99	—
H	Et	2	>99	89	—
Et	H	2	>99	89	—
H	$Me(CH_2)_4$	2	>99	99	—

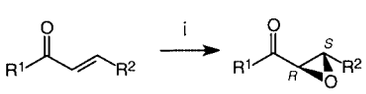
Table 122

R^1	R^2	Yield (%)	De (%)	Ee (%)
Ph	Me	96	>99	85
Ph	Et	99	>99	91
Ph	^{n}Pr	99	>99	87
Ph	^{i}Pr	97	>99	92
Ph	Ph	94	>99	61
^{t}Bu		99	>99	90
	Et	94	>99	82

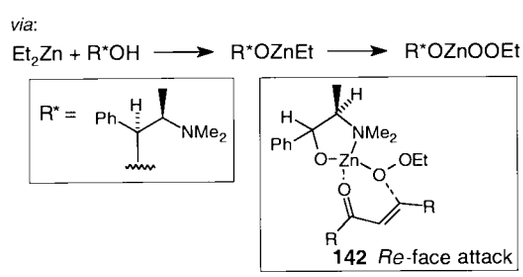
α,β-Unsaturated ketones may be epoxidized enantioselectively by the combination of oxygen, diethylzinc and (*R*,*R*)-*N*-methylpseudoephedrine.[156] The active species is proposed to be chiral peroxyzinc alkoxide **142** and the overall process is, therefore, analogous to the traditional basic hydrogen peroxide protocol. In all cases, (2*R*,3*S*)-epoxyketones were obtained (Schemes 183 and 184, and Table 122).



Scheme 182



Scheme 183 *Reagents and conditions*: i, O_2, Et_2Zn, (*R*,*R*)-*N*-methylpseudoephedrine, toluene, 0 °C.

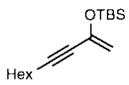
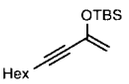
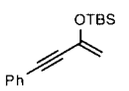
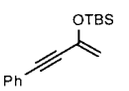
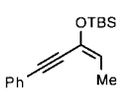


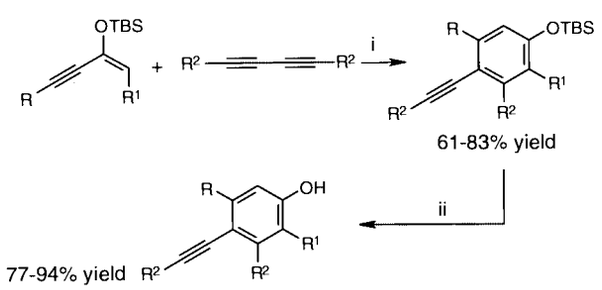
Scheme 184

3 Preparation of phenols

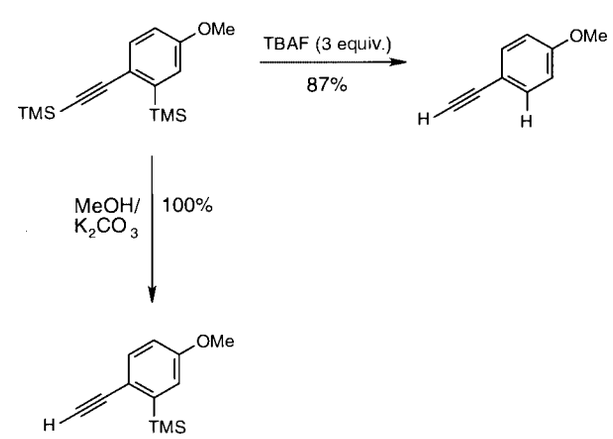
A palladium-catalysed cycloaddition reaction of symmetrical 1,3-diynes with silyl enol ethers of alkynyl ketones leads in good yield to silyl ethers of phenols (Scheme 185 and Table 123).[157] In all the cases studied, the regioselectivity of the reaction was high: the only isomer observed was that in which the alkynyl substituent of the enyne was *ortho*- to the diyne substituent R^1. The phenolic ethers could be deprotected in the same reaction vessels in good yield to give the corresponding phenols and carbon–silicon bonds could be chemoselectively cleaved to yield silylarenes (Scheme 186).

Table 123 Synthesis of phenols *via* the palladium-catalysed enzyne–diyne bensannulation protocol

Enyne	R^2	Yield silyl ether (%)	Yield phenol (%)	Overall yield (%)
	Bu	83	94	78
	Ph	70	77	54
	Bu	79	86	68
	Ph	61	89	54
	Bu	66	92	61



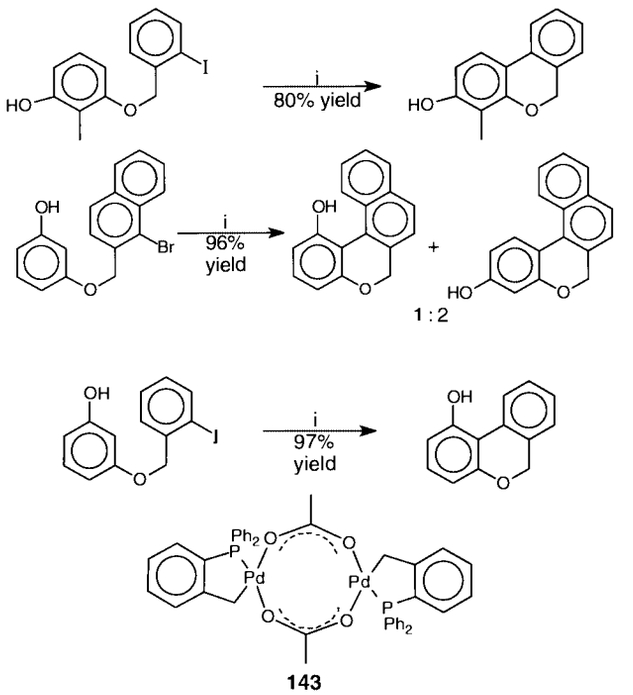
Scheme 185 *Reagents and conditions*: i, $Pd(PPh_3)_4$ (2 mol%), $P(o\text{-Tol})_3$ (20 mol%), THF, 100 °C, sealed vessel; ii, TBAF (2 eq.), THF, rt.



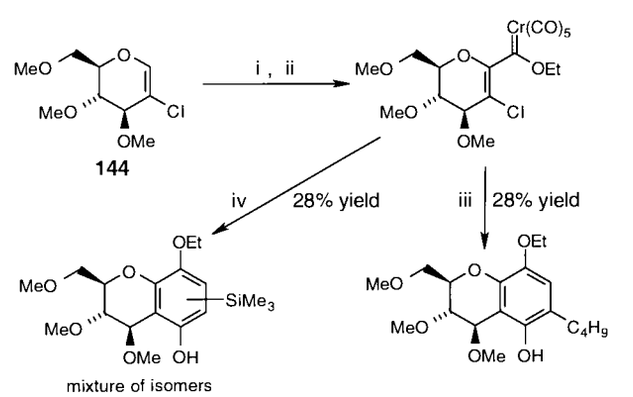
Scheme 186

The intramolecular palladium-coupling of phenols and aryl halides provides a useful method of preparation of (*inter alia*) polycyclic phenols in good yield.[158] Best results were obtained using Herrmann's catalyst **143** (Scheme 187).

3-Chloroglucals **144** are readily deprotonated by ^{s}BuLi: the resulting vinyllithium species reacts with hexacarbonylchromium to give Fischer carbene complexes.[159] These compounds react with alkynes to give phenols, in variable yields. Where non-terminal alkynes were employed, mixtures of regioisomers were obtained (Scheme 188).

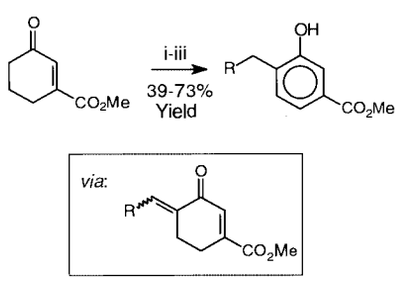


Scheme 187 *Reagents and conditions*: i, Herrmann's catalyst (5 mol%), $CsCO_3$ (3 eq.), DMA, ⩾80 °C.



Scheme 188 *Reagents and conditions*: i, ^{s}BuLi (1.1 eq.), THF, −78 °C; ii, $Cr(CO)_6$ (1 eq.), −78 °C; iii, $C_4H_9C_2H$ (2.2 eq.), THF, 80 °C; iv, TMS acetylene (2.2 eq.), THF, 80 °C.

Esters of 3-oxocyclohex-1-ene-1-carboxylic acid may be converted by means of a three-step reaction sequence into 4-substituted 3-hydroxybenzoates.[160] The sequence involves aldol condensation, dehydration and tautomerism (Scheme 189).



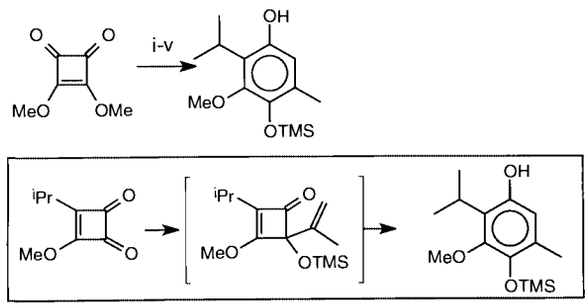
Scheme 189 *Reagents and conditions*: i, (a) LHMDS, THF, −78 °C; (b) RCHO; ii, Burgess' reagent, PhH, Δ; iii, DBU, $PhCH_3$.

Dimethyl squarate undergoes alkylation and ring-expansion upon sequential reaction with a Grignard reagent and a vinyllithium, to give highly substituted phenols (Scheme 190).[161]

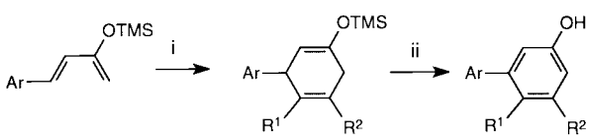
Phenols are prepared in poor to good yield *via* cycloaddition of 2-silyloxybutadienes with electron-deficient alkynes.[162] In particular, the reaction sequence is of some utility in the preparation of biaryls and terphenyls (Scheme 191 and Table 124).

Table 124

Ar	R^1	R^2	Yield (%)
Ph	CO_2Me	CO_2Me	72
Ph	CO_2Me	H	64
Ph	CN	H	72
2-Furyl	CO_2Me	CO_2Me	65
4-C_6H_4-Ph	CO_2Me	CO_2Me	85
1,4-Biphenyl	CO_2Me	H	47
4-C_6H_4-Ph	CN	H	48

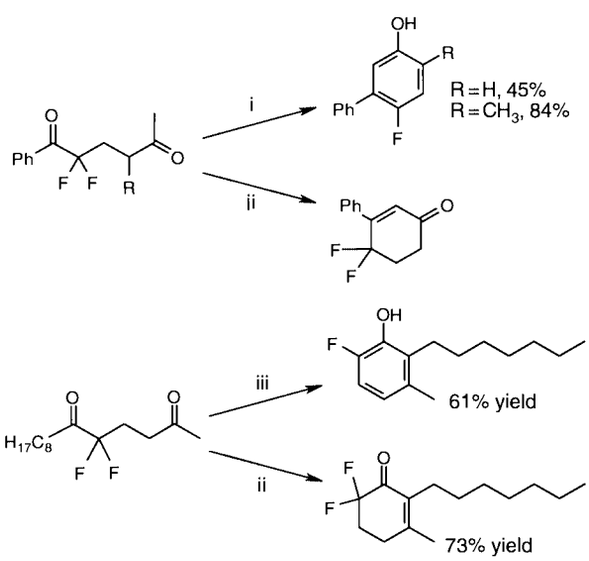


Scheme 190 *Reagents*: i, ^{i}PrMgCl; ii, TFAA; iii, H_2O; iv, 2-lithiopropene; v, TMSCl.



Scheme 191 *Reagents and conditions*: i, $R^2C{\equiv}CR^2$, toluene; ii, DDQ, AcOH, toluene, Δ.

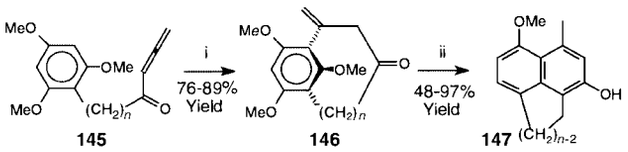
2,2-Difluoro-1,5-diketones (prepared in "one-pot" from acylsilanes and enones) are converted to phenols upon reaction with potassium hydroxide.[163] If a sub-stoichiometric amount of base is employed, the intermediate difluoroketones may be obtained (Scheme 192).



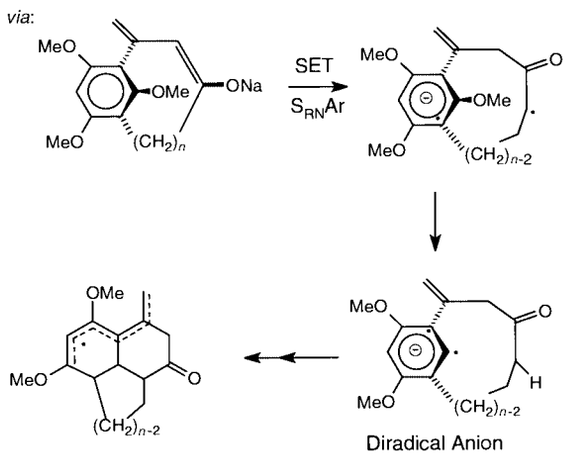
Scheme 192 *Reagents and conditions*: i, KOH (2 eq.), MeOH, 6 h, reflux; ii, KOH (0.1 eq.) MeOH, 24 h, rt; iii, KOH (4 eq.), MeOH, reflux.

Tricyclic β-naphthols may be prepared from electron-rich allenyl aryl alkyl ketones *via* an interesting $S_{RN}Ar$ reaction pathway.[164] Thus, allenyl 2,4,6-trimethoxyphenylalkyl ketone **145** reacts with $B(OTf)_3$ to give chiral (but racemic) metacyclophanes **146**. When these cyclophanes are treated with sodium

hydride in THF, β-naphthols **147** are obtained, generally in good yield (Scheme 193). The rearrangement proceeds *via* a radical mechanism involving intramolecular electron transfer from the enolate to the trimethoxyarene (Scheme 194).

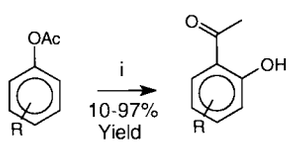


Scheme 193 *Reagents and conditions*: i, $B(OTf)_3$, CH_2Cl_2, −78 °C, 5 min; ii, NaH, THF, reflux.



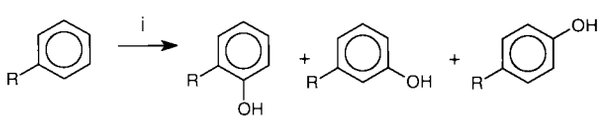
Scheme 194

The *ortho*-Fries rearrangement may be carried out at ambient temperature when mediated by zirconium tetrachloride.[165] The reaction exhibits a high level of regioselectivity, with 2-hydroxyacetophenones being the major product, often representing >95% of the product mixture (Scheme 195).



Scheme 195 *Reagents*: i, $ZrCl_4$ (4 eq.), CH_2Cl_2, 20 °C.

Arenes are monohydroxylated using anodic oxidation in a mixed solvent of trifluoroacetic acid and dichloromethane.[166] The reaction is successful for benzene itself but electron-withdrawing substituents are generally required for high yields to be obtained. The reaction's major drawback is the obtention of mixtures of regioisomers in all cases (Scheme 196 and Table 125).



Scheme 196 *Reagents*: i, TFA, CH_2Cl_2, Et_3N, 2–5 F/mol.

The first report of direct ("one-pot") synthesis of calixarenes has been made.[167] Thus, reaction of 4-benzyloxyphenol with formaldehyde in the presence of alkali metal hydroxides gives a mixture of (4-benzyloxy)calix[8]arene and the corresponding calix[7]arene and calix[6]arene; the calix[8]arene is always the dominant product and its yield is best when NaOH is employed as base (Scheme 197 and Table 126).

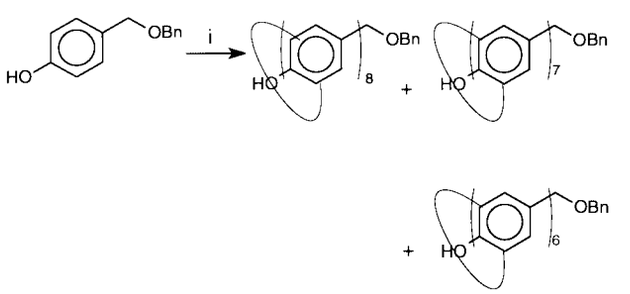
The great insolubility of the calix[8]arene permits its facile separation from the product mixture.

Table 125

R	Yield (%)	*o*:*m*:*p*
Cl	67	32:8:60
Br	87	30:9:61
F	50	67:7:26
CF_3	61	23:63:14
$COCH_3$	43	47:33:20
CO_2Et	89	44:34:22
CHO	33	29:47:24
CN	40	43:27:30
NO_2	18	44:27:29

Table 126

	Relative yield (%)		
MOH	Calix[6]arene	Calix[7]arene	Calix[8]arene
LiOH	20	17	63
NaOH	10	6	84
KOH	7	21	72



Scheme 197 *Reagents*: i, MOH, $H_2C{=}O$.

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