Alcohols, phenols, and ethers

JOSEPH SWEENEY

School of Chemistry, The University, Cantock's Close, Bristol BS8 1TS, UK

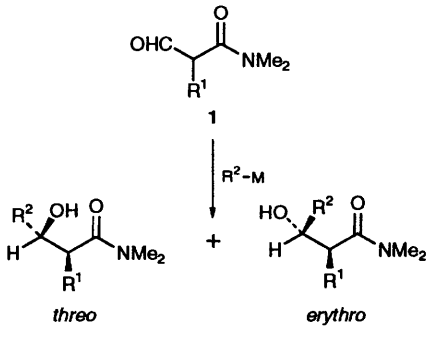
Reviewing the literature published between July 1992 and July 1993

This review seeks to identify new synthetic methods for the preparation of alcohols, phenols, and ethers and covers only those articles describing novel techniques or interesting modifications to existing protocols.

1 Preparation of alcohols

1.1 From carbonyl compounds *via* carbon–carbon bond formation

The chelation-controlled alkylation of β-keto- and β-formyl-esters has been extended to encompass reactions of 2-alkyl-2-formylamides **1** (**Scheme 1**);[1]

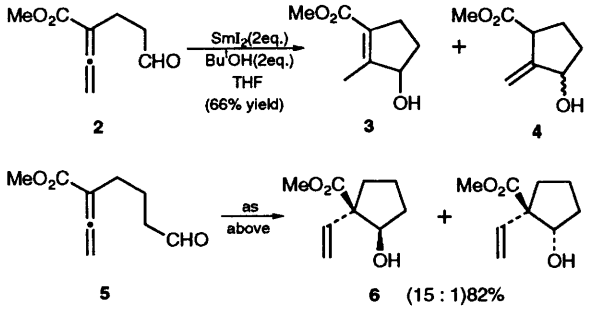


R^1	R^2–M	*threo* : *erythro*
Me	Me Al Cl_2	97 : 3
	Et Al Cl_2	96 : 4
	Ph Al Cl_2	93 : 7
	Ph Ti Cl_3	4 : 96
Pr^i	Me Al Cl_2	99 : 1
	Et Al Cl_2	99 : 1
	Ph Al Cl_2	99 : 1

Scheme 1

these substrates are of particular interest due to the possible peptidomimetic properties of the alkylated products. The scheme illustrates the general reaction: alkyl and aryl aluminium dichlorides delivered carbon ligands from the less hindered face in good yields, and with excellent selectivity. The use of phenyltitanium trichloride in the reaction was capricious; in some circumstances, a reversed selectivity was observed.

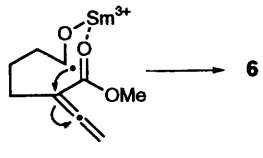
In the reaction of electron-deficient ω-formyl allenes with samarium di-iodide, an interesting divergence in regioselectivity was observed between homologues (**Scheme 2**).[2]



Scheme 2

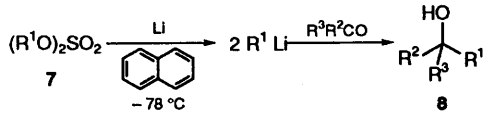
Thus, when 1-(2′-formylethyl)-1-methoxycarbonylallene **2** was treated with samarium(II) iodide in tetrahydrofuran, a 2:1 mixture of *endo*- and *exo*-cyclopentenecarboxylates **3** and **4**, respectively, was obtained. The *exo*-methylene compound **4** was a 2:1 mixture of diastereoisomers, and so the reaction had exhibited poor selectivity. However, when the higher homologue **5** was reacted under the same conditions, a highly selective 5-*exo* cyclization took place to give *cis*-2-hydroxy-1-methoxycarbonyl-1-vinylcyclopentane **6** as the almost exclusive diasteroisomer. This 5-*exo* cyclization contrasts with previously reported 6-*endo* radical cyclizations of similar compounds.[3]

Chelation control, mediated by Sm^{3+} (**Scheme 3**) was suggested to explain the stereoselectivity since a parallel reaction using tributylstannane as radical agent gave a product of much lower diastereopurity (~ 5:1 ratio).



Scheme 3

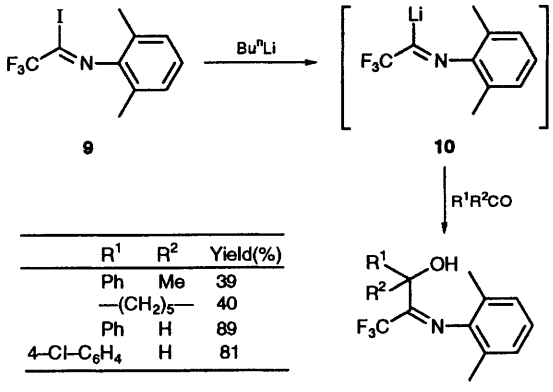
The previously reported conversion of allylic and benzylic mesylates to the corresponding allyl- and benzyl-lithiums[4] has been extended to provide a new route to organolithium reagents (**Scheme 4**).[5] Thus, primary and secondary dialkylsulfates **7**, prepared by Sharpless's method,[6] reacted with an excess of lithium powder, in the presence of a catalytic amount of naphthalene at low temperature, to give two equivalents of a primary or secondary organolithium reagent. These reacted with carbonyl compounds to give alcohols **8** in moderate to excellent yield. The reaction of cyclic sulfates under these conditions gave alkenes, *via* the intermediacy of 1-lithio-2-sulfonates.



R^1	R^2	R^3	Yield 8(%)
Me	Ph	H	52
Et	Ph	H	73
Pr^i	Ph	H	40
Et	—$(CH_2)_5$—		41

Scheme 4

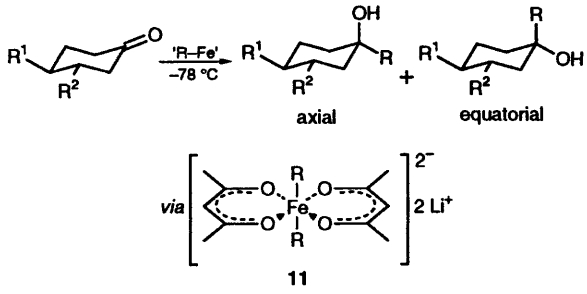
The halogen–metal exchange reaction of iodoimines **9** derived from trifluoroacetaldehyde provided a useful entry to umpoled species **10**, which reacted with ketones in moderate yield and with aldehydes in better yield (**Scheme 5**).[7]



R^1	R^2	Yield(%)
Ph	Me	39
—$(CH_2)_5$—		40
Ph	H	89
4-Cl-C_6H_4	H	81

Scheme 5

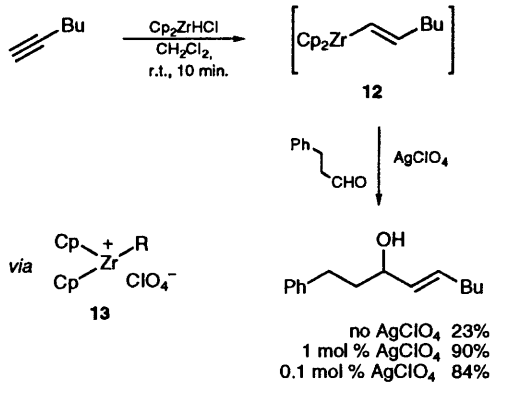
An unprecedented stereoselectivity was observed in the addition of organoiron (II) reagents to cyclohexanones (**Scheme 6**).[8] It was proposed that the combination of organolithium and iron salts gave octahedral iron reagents, *e.g.* **11**, which delivered alkyl groups with high facial selectivity to substituted cyclohexanones, the nucleophile ending up in the equatorial position in the product. The authors proclaim that 'essentially complete stereocontrol in the formation of axial alcohols is possible for the first time'. The use of organomagnesium reagents led to lower selectivity.



R^1	R^2	'R–Fe'	axial : equatorial
Bu^t	H	2 MeLi, $FeCl_3$	98 : 2
Bu^t	H	3 MeLi, $FeCl_3$	99 : 1
Bu^t	H	4 MeLi, $FeCl_3$	98 : 2
Bu^t	H	2 MeLi, $Fe(acac)_2$	99 : 1
H	Me	3 MeLi, $FeCl_3$	99 : 1

Scheme 6

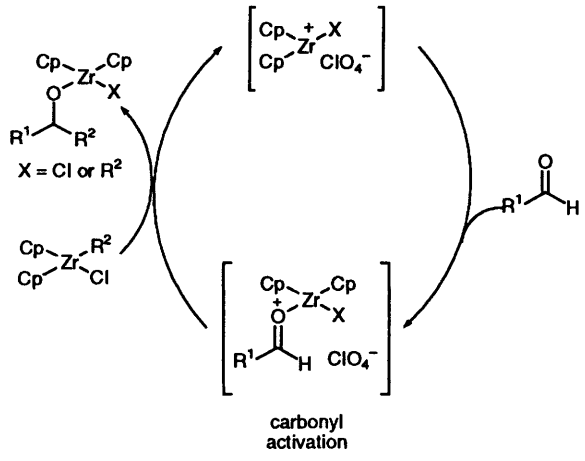
The Grignard-type addition of alkenyl- and alkyl-zirconocene chlorides to aldehydes is subjected to a remarkable acceleration in rate in the presence of silver perchlorate.[9] As an example, under normal conditions the reaction of the hexenylzirconium reagent **12** with 3-phenylpropionaldehyde gave a low yield of addition product. However, when silver perchlorate was added, yields were excellent (**Scheme 7**). Even 0.1 mol% perchlorate was sufficient to give good yields. The authors proposed the intermediacy of a cationic zirconium species **13** to explain their observations.



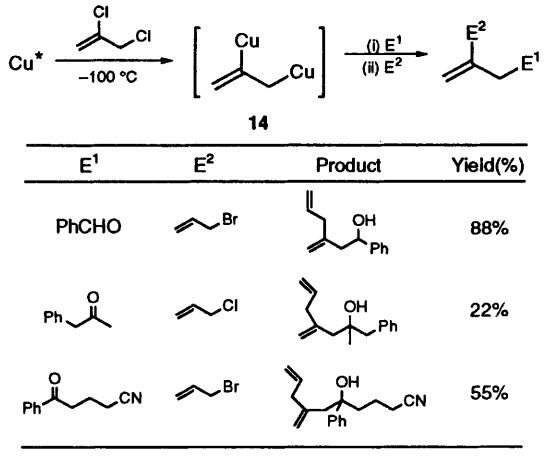
Scheme 7

A similar enhancement was observed in the reaction of alkylzirconocene chlorides with aldehydes, but two equivalents of the alkylzirconocene dichloride must be used along with a ten-fold increase in the level of perchlorate. For alkenylzirconium reagents, the reaction was complete in ten minutes; alkyl zirconium species typically required several hours to react. The authors proposed the cyclic mechanism shown in **Scheme 8** to illustrate the importance of perchlorate to the reaction.

A highly active form of copper(0), generated *in situ* from a copper(I) cyanide/lithium chloride complex, reacted at very low temperature with 1,2-dichloropropene to generate the 1,2-dimetallated propene **14**.[10,11] This underwent sequential reaction with electrophiles to give homoallylic alcohols (**Scheme 9**) in moderate to good yields.



Scheme 8



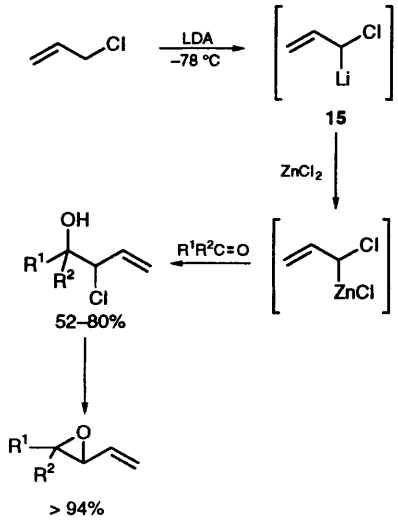
E^1	E^2	Product	Yield(%)
PhCHO			88%
			22%
			55%

Scheme 9

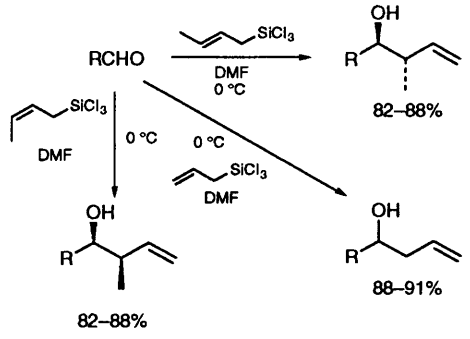
There appears to be some restriction regarding the range of electrophiles which will react in the second alkylation step, and only active electrophiles, *e.g.* allylic halides, react efficiently.

The α-lithiated allylchloride **15** reacts non-regioselectively with electrophiles.[12] It has been reported that the addition of freshly fused zinc chloride to **15** allows for exclusive α-reactivity with carbonyl compounds (**Scheme 10**).[13] The product chlorohydrins were exclusively *syn*-isomers when the carbonyl compounds were aromatic aldehydes. Epoxides were formed in high yield when desired.

The stereoselective allylation of aldehydes occurred, without the need for a catalyst, by reaction with allyltrichlorosilanes in *N,N*-dimethylformamide (**Scheme 11**).[14] The dimethylformamide was found to be essential for the reaction, presumably due to complexation between silicon and the amide. The well known[15] propensity of α-monosubstituted allylic chromium reagents to undergo *anti*-selective addition reactions with aldehydes was overcome by the use of allylic phosphates to prepare the chromium reagents.[16] This allowed for a *stereodivergent* alkylative protocol.

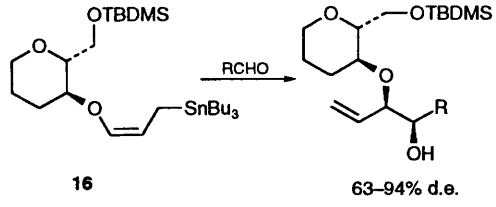


Scheme 10



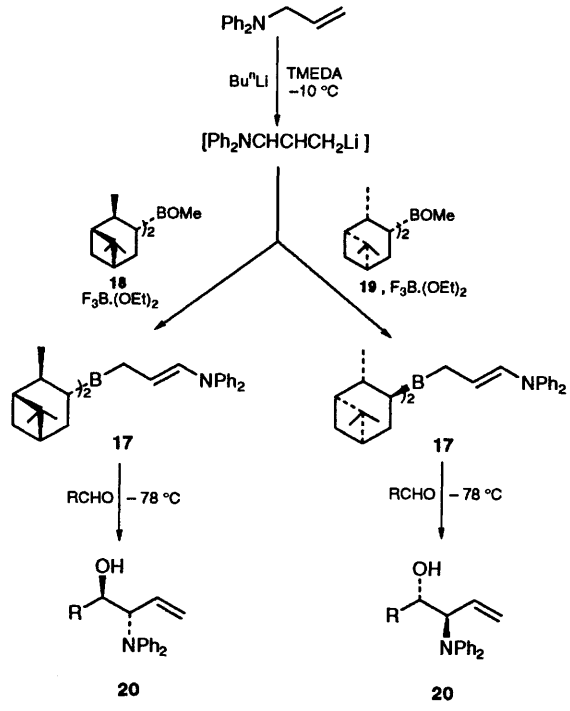
Scheme 11

A selective allylation of aldehydes was effected by use of 3-(tetrahydropyranyloxy)-propenylstannanes **16**.[17] The allylated products were obtained in moderate to good d.e. (**Scheme 12**), although the removal of the chiral auxilary hampered the overall efficacy of the process.



Scheme 12

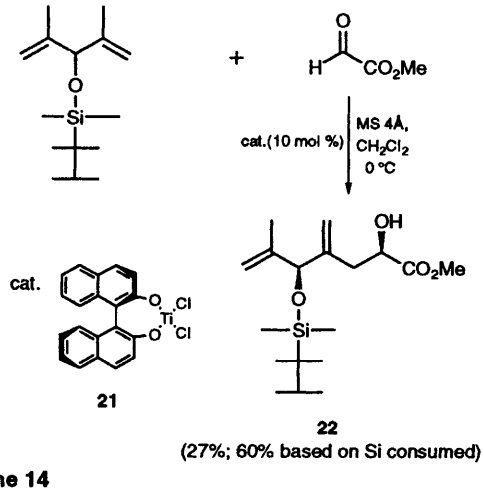
Barrett *et al.* recently reported the use of 3-silylpropenylboranes for the efficient and enantioselective preparation of *anti*-alk-1-ene-3,4-diols.[18] The same group have now disclosed *B*-[(*E*)-(diphenylamino)prop-2-enyl]-diisopinocampheylboranes **17** as highly selective reagents for the synthesis of *anti*-2-(diphenylamino)-3-hydroxy-1-alkenes **20** (**Scheme 13**).[19]



Scheme 13

Deprotonation of 3-(diphenylamino)propene, followed by reaction of the allyllithium species so formed with the methoxyboranes **18** and **19** derived from pinene, allowed *in situ* formation of both enantiomers of the (aminoallyl)borane **17**. Upon reaction with aldehydes at low temperature, *anti*-1,2-aminoalcohols **20** were then formed with uniformly excellent diasteroisomeric and enantiomeric excess. There was one exception to this rule: the acetonide of (*S*)-glyceraldehyde, when a mismatched substrate reacted with poor diastereoselectivity.

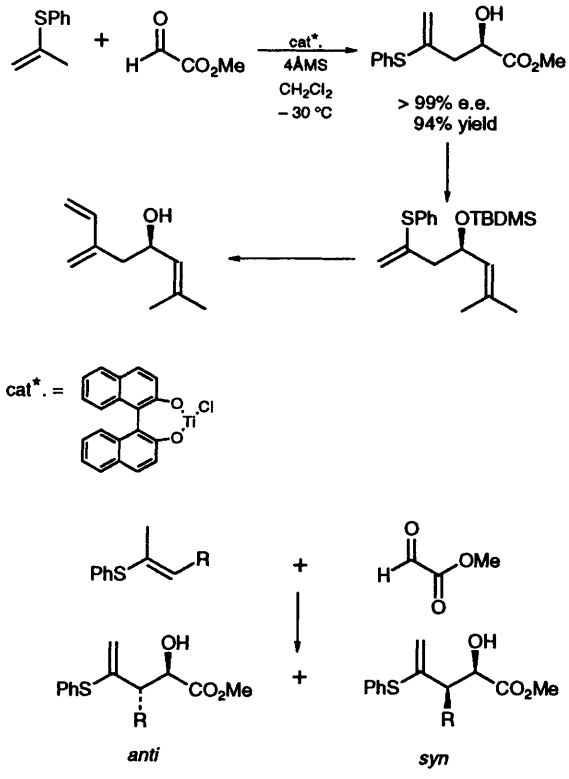
Developments in the area of asymmetric glyoxalate-ene reactions continue. The previously reported work,[20] utilizing homochiral BINOL-derived titanium dichloride **21**, described the reaction of mono-alkenes with methyl glyoxalate; the reaction of symmetrical bis-alkenes allows for a desymmetrizing reaction (**Scheme 14**).[21]



Scheme 14

In the products **22**, high *syn*-selectivity was shown (> 99% *syn*) and enantiomeric selectivity was excellent, but conversions were poor. The reaction may be used kinetically to resolve racemic allylic alcohols.

The asymmetric variant of the glyoxalate-ene reaction has been extended to embrace the use of vinyl selenides and sulfides as the alkene components of the process (**Scheme 15**).[22] The reaction exhibited good enantiocontrol when a variety of alkenes was used. With non-terminal alkenes, the reaction had poor to excellent diastereoselectivity, but the *anti*-diastereoisomers were obtained with high enantiopurity. *syn*-Diastereomers were produced with moderate to high e.e.

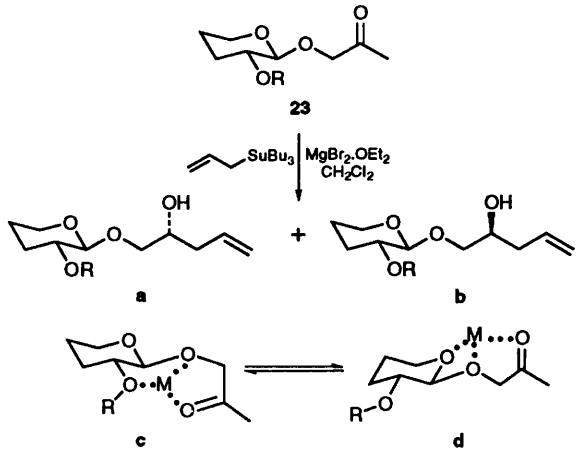


R	*anti* e.e.(%)	*syn* e.e.(%)
Me	45 (99)	55 (78)
Et	81 (99)	19 (84)
Bu^n	91 (>99)	9 (>90)
Bu^i	95 (>99)	5 (>90)

Scheme 15

An interestingly selective preparation of homoallylic alcohols from hydroxyacetone relied on an unusual remote protecting group effect (**Scheme 16**).[23] Thus the use of a protecting group, R in **23**, which was predisposed to coordinate strongly to a cation favoured conformer **c**, and led to (*Re*)-face attack, producing isomer **a**. The authors proposed that the use of a less-coordinating or bulkier protecting group, such as a trialkylsilyl moiety, favoured conformer **d** in which the ring-oxygen atom coordinated the metal, thereby leading to (*Si*)-facial

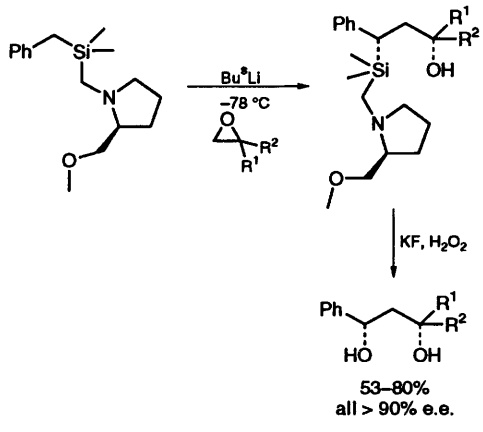
attack and the formation of isomer **b**. In these reactions, the group causing the effect was six atoms away from the reacting centre, an unusually distant influence.



R	a : b	Yield(%)	Temp.
Bn	93.7 : 6.3	93	– 20 °C
Pr^i_3Si	12 : 88	88	–20 °C
Bn	97.6 : 2.4	92	–55 °C→r.t.
Pr^i_3Si	7.2 : 92.8	90	–55 °C→r.t.

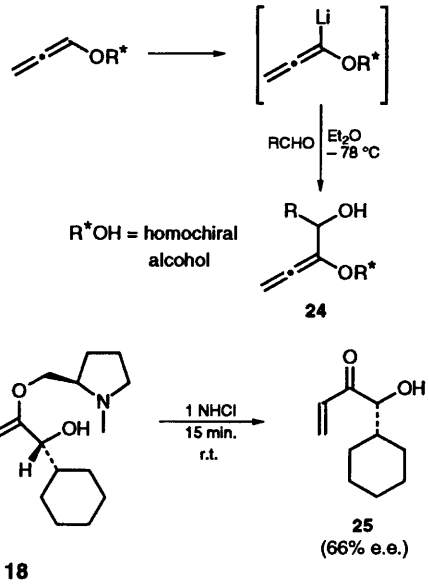
Scheme 16

A similarly distant stereocentre facilitated the highly enantioselective ring-opening of epoxides by α-silylbenzylic anions (**Scheme 17**).[24] Chan and co-workers improved upon their previous report[25] of enantioselective alkylation of proline-derived aminosilanes, and described the preparation of homochiral *syn*-1,3-diols *via* the regiospecific ring-opening of disubstituted epoxides. Yields were good and stereocontrol complete.



Scheme 17

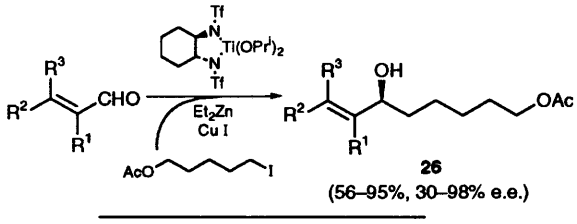
The utility of chiral ligands as mediators of enantioselective addition reactions of carbonyl compounds has continued to attract interest. When propargyl ethers, obtained from propargylation of homochiral alcohols (norephedrine, prolinol, menthol, diacetone glucose, among others), were treated with potassium t-butoxide, homochiral alkoxyallenes were obtained (**Scheme 18**).[26]



Scheme 18

These ethers, when deprotonated and reacted with aldehydes, gave (1-hydroxyalkyl)allenyl ethers **24** in good yield but with only moderate diastereoselectivity (< 50–85% d.e.). Acidic hydrolysis of **24** gave enantiomerically enriched (hydroxyalkyl) vinyl ketones, *e.g.* **25**, which are useful synthetic intermediates for use in cycloaddition reactions.

The utility of the previously reported work by Knochel on the novel preparation of polyfunctionalized dialkylzinc reagents[27] was hampered by two drawbacks: firstly, a large excess (five equivalents) of diethylzinc had to be used to allow efficient reaction and, secondly, scale-up of the reactions was accompanied by incomplete conversion of starting material. An improved protocol has now been reported to overcome these serious limitations.[28] When a functional alkyl iodide was treated with diethylzinc and a catalytic amount of a copper(I) salt (either CuI or CuCN were employed), a functionalized dialkylzinc was formed which reacted with α,β-unsaturated aldehydes in the presence of a homochiral catalyst (derived from *trans*-1,2-diaminocyclohexane) to give functionalized secondary allylic alcohols **26** with moderate to excellent chemical yields and enantiomeric excesses (**Scheme 19**).

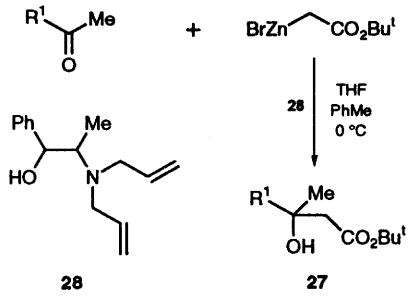


R^1	R^2	R^3	Yield(%)	e.e.(%)
Me	Me	H	70	98
H	Pr	H	75	83
Me	EtO_2C	H	78	80
Br	Pr	H	95	94
Br	Me	Me	68	68
Br	Me	H	77	80

Scheme 19

A two-fold increase in the rate of reaction was observed compared with the previous method, and only a 50% excess of diethylzinc was required to achieve > 95% conversion of starting material, in both small- and large-scale reactions. The authors noted that α-bromoaldehydes reacted to give products with higher e.e.'s than non-halogenated substrates, as noted before in enantioselective cycloaddition reactions,[29] due to more restricted conformations.

An enantioselective Reformatsky reaction mediated by the naturally occurring diamine(−)-sparteine was first reported in the early 1970's although the stereoselectivity of this pioneering work was poor (7–39% e.e.).[30] The Reformatsky reaction of aryl methyl ketones with t-butylbromoacetate has since been found to be more selective when the reaction is carried out in the presence of *N*,*N*-diallylephedrine **28** (**Scheme 20**).[31] The use of (1*S*, 2*R*)-ephedrine gave (*S*)-2-hydroxyesters **27** with moderate enantioselectivity.



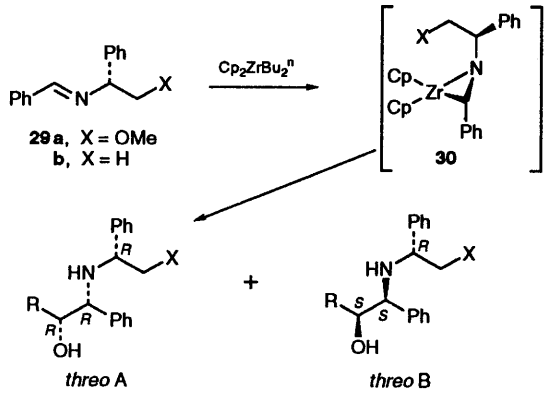
R^1	e.e.(%)
Ph	74
2-Napth	75
F-	73

Scheme 20

Finally in this section, an extremely interesting example of a counter-intuitive effect of temperature upon selectivity has been observed during the reaction of chiral aldimines with dialkylzirconocenes (**Scheme 21**). Thus, when dibutylzirconocene was reacted with imines such as **29** in tetrahydrofuran or toluene, a zirconoaziridine **30**[32,33] was generated.
This metalloheterocycle reacted with aldehydes to yield exclusively *threo*-1,2-aminoalcohols in good yield.[34] The authors found that the facial selectivity could be completely reversed by increasing the temperature of the reaction; however, the reversal in selectivity was only possible when imines **29a**, derived from phenylglycinol, were used. When simpler imines, such as **29b**, underwent the reaction, selectivity was merely diminished and not reversed.

1.2 By oxidation

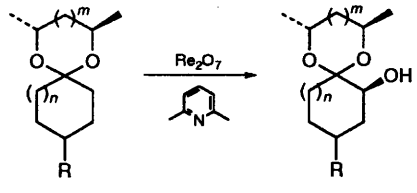
(*S*)-2-Hydroxycycloalkanones were prepared with virtually complete enantioselectivity *via* the rhenium-mediated oxidation of cycloalkanone ketals **31** derived from homochiral 1,2- and 1,3-diols

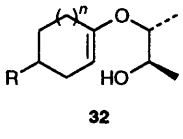


R	Reaction *T*	Solvent	A : B
Ph	0° C	THF	94 : 6
Ph	reflux	THF	5 : 95
Ph	23 °C	PhMe	88 : 12
Ph	60 °C	PhMe	4 : 96
Me	23 °C	PhMe	87 : 13
Me	60 °C	PhMe	5 : 95

Scheme 21

(**Scheme 22**).[35] That this reaction proceeded through the (2-hydroxyalkyl)enol ether was demonstrated when the preformed enol ethers **32**, prepared *via* silylative ketal cleavage,[36] were oxidized using the rhenium (VII) oxidant; the same levels of diastereoselectivity were observed.

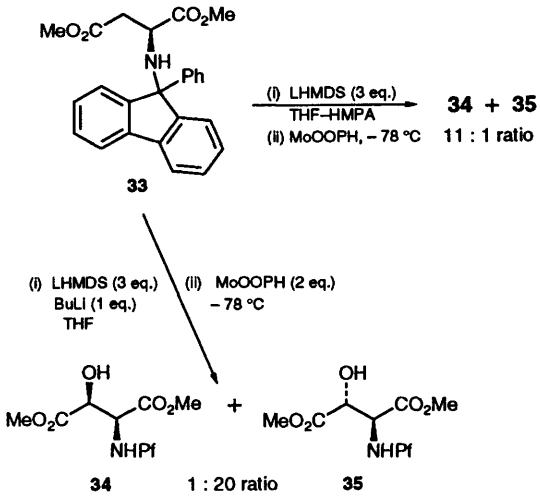




m	*n*	R	Yield(%)	d.e.(%)
0	1	H	88	> 98
0	0	H	98	> 98
1	1	H	56	> 98
1	0	H	49	> 98
0	1	Bu^t	80	0

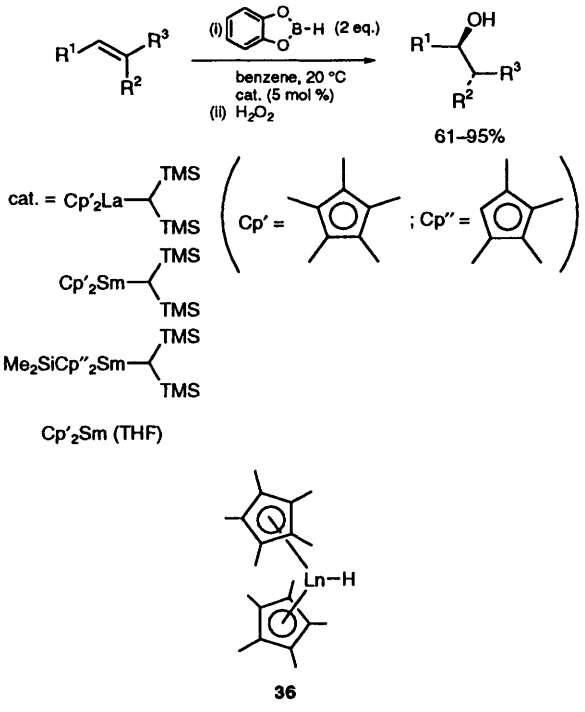
Scheme 22

Alkylations of dianions derived from *N*-9-phenylfluorenyl aspartic acid diesters **33**[37] have been employed in the stereodivergent preparation of (3*R*)- and (3*S*)-3-hydroxy aspartates (**Scheme 23**).[38] Such specifically hydroxylated compounds are of significance in many biological systems and the preparation of both diastereoisomers of these compounds is feasible using MoOOPH oxidation. When no excess of HMPA was employed, the (2*S*,3*R*)-isomer **35** was produced in > 90% d.e.; when the phosphonamide was present, the (2*S*,3*S*)-diastereoisomer **34** predominated (85% d.e.). The authors employed the fact that the enolate derived from **33** exists as a mixture of open and chelated forms, the chelate being favoured in poorly coordinating solvents.



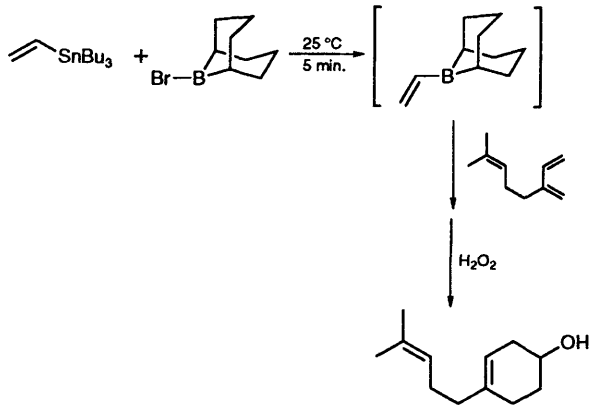
Scheme 23

Organolanthanides are the latest organotransition metal derivatives to be utilized as catalysts for olefin hydroboration.[39] A variety of lanthanide complexes mediate the reaction, a common feature to all of the catalysts being the use of polymethylated cyclopentadienyl ligands (**Scheme 24**).
The mechanistic fulcrum of the process is the formation of a dicyclopentadienyl-lanthanide hydride **36** which adds regiospecifically across the alkene, producing an alkyl-lanthanide which is converted by a second equivalent of catechol borane into an alkyl boronate.



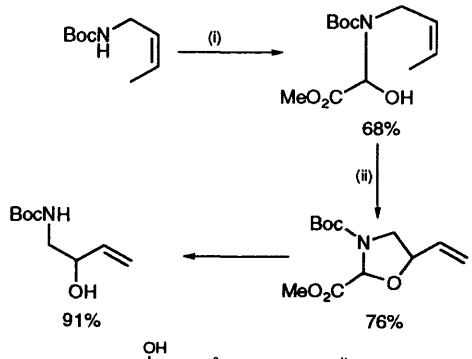
Scheme 24

A useful application of, and improvement to, the recently disclosed[40] use of vinyl boranes as dienophiles, has been reported (**Scheme 25**).
The improvement in the methodology was in the preparation of the requisite vinyl borane, which is frequently pyrophoric and not easily handled. Singleton *et al.*[41] employed a coupling reaction of commercially available reagents to allow a facile *in situ* preparation of vinyl-9-BBN, and reacted the dienophile with a variety of dienes to yield, after the usual peroxidative treatment, 1-hydroxycyclohex-3-enes which had not previously been reported or whose previous syntheses were laboured. The regiocontrol in the cycloaddition reaction was high, usually > 90% in favour of the *para*-cycloadduct.



Scheme 25

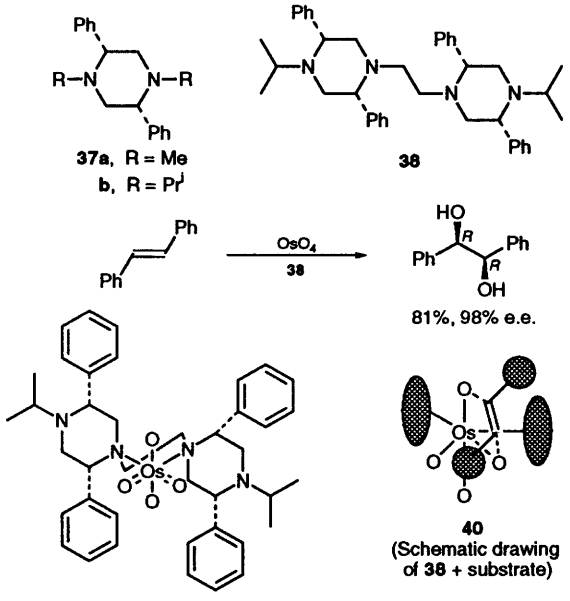
Transition-metal activation of alkenes has been used by Speckamp and Hiemstra in a novel synthetic approach to 1-amino-3-alken-2-ols (**Scheme 26**).[42] Thus, carbamate-protected allylic amines were converted into hemi-aminals by reaction with glyoxalate hemi-acetals, and these were oxidatively cyclized under palladium catalysis to give oxazolidines in good yields. The oxazolidines were converted in a one-pot, four-step process (including an electrolytic decarboxylation) to aminoalkenols in excellent yield. However, where diasteroisomerism is possible, mixtures were generally obtained, although amines derived from cycloalkenes showed high *cis*-selectivity.



Scheme 26

The development of asymmetric dihydroxylation (AD) reactions continues to result in improved methodology. The known asymmetry of the addition of alkylzincs in the presence of homochiral piperazines, such as **37**, led to the development[43] of asymmetric

cis-dihydroxylation of olefins employing dimers of **37** (**Scheme 27**). Thus, treatment of prochiral olefins with OsO_4 in the presence of stoichiometric amounts of **37a** gave *cis*-diols in low chemical yield and with unsatisfactory e.e.'s.

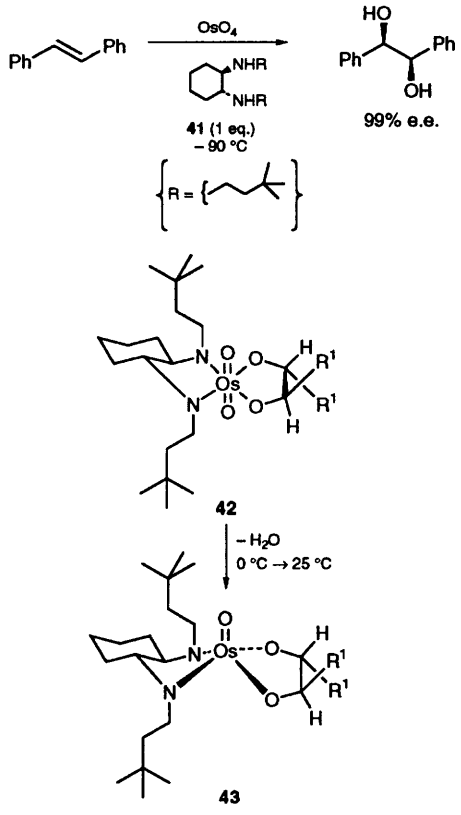


Scheme 27

This result was rationalized by the authors as being due to energetically disfavoured coordination to osmium, caused by the severe distortion of the ligand necessary to achieve good bonding to the metal atom. To obviate this problem, the workers developed bis-piperazine **38**, in which the dimeric structure allowed efficient formation of an osmium-ligand complex **39**. Whether or not **39** is an accurate representation of the species involved in the reaction, the dihydroxylation of representative olefins in the presence of **38** proceeded in good chemical yield and with good to excellent enantiomeric excesses (see **40**). As previously noted in such dihydroxylations, the best substrates for the reaction were *trans*-1,2-disubstituted alkenes in which at least one of the substituents is aromatic.

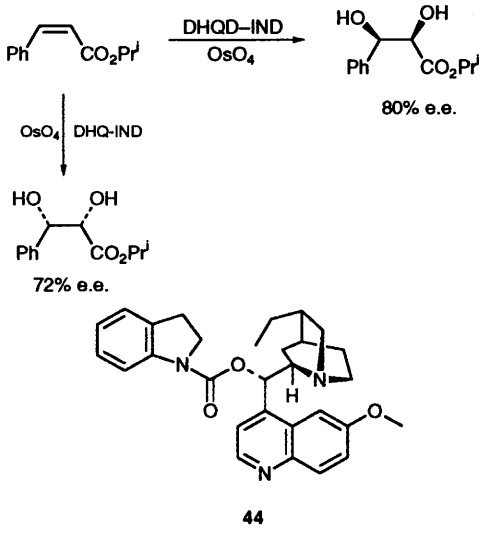
The limiting feature of this work was the need for stoichiometric quantities of ligand. A similar drawback was present in the system offered by Hanessian *et al.*[44] Thus, osmylation of *trans*-stilbene in the presence of homochiral *trans*-[*N*, *N'*-di-(3,3-dimethylbutyl)] cyclohexane-1,2-diamine **41** at very low temperature was enantioselective (**Scheme 28**). Although in this reaction *cis*-substrates reacted poorly (as is usual), there were several which reacted with greater efficiency than in previously reported systems. Thus, fumarates react with high e.e. (96%) as do other previously unreactive AD substrates. The authors isolated a derivative **43** of the first product of the reaction, presumed to be osmate **42**, and solved its structure by *X*-ray analysis.

Sharpless has published full details of the preparation and crystal structures of the cinchona alkaloids used in AD-mix reactions.[45] The same group



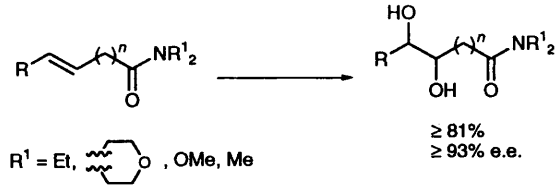
Scheme 28

has also tackled the often referred to weakness of asymmetric dihydroxylations, *viz.* reaction of *cis*-1,2-disubstituted substrates. They have maintained their search for improvement of reaction conditions and discovered that the use of indolinyl derivatives of dihydroquinidines vastly improved the enantioselectivity of the dihydroxylation of these difficult substrates.[46] Whereas previous e.e.'s were poor, < 35%, the new ligands gave acceptable e.e.'s (**Scheme 29**). DHQD-IND **44** gave the products of β-attack as expected, and DHQ-IND gave the α-products, the difference in selectivity between the two systems being the most pronounced discovered to date.

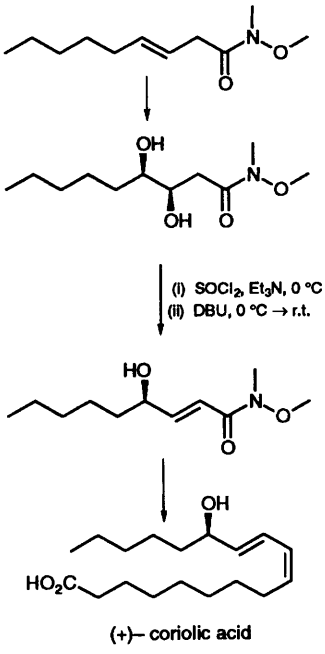


Scheme 29

The AD-mix reaction of β,γ- and γ,δ-unsaturated esters has been shown to be highly enantioselective,[47] and has been used to synthesize all four isomers of disparlure.[48] To accomplish highly selective hydroxylation of α,β- and β,γ-unsaturated amides, a modified AD-mix employing a five-fold increase in the ligand and potassium osmate was required.[49] When this new, improved mix was used, both α,β- and β,γ-unsaturated amides reacted in good chemical yield and with high levels of enantioexcess (**Scheme 30**). The products of these reactions were easily dehydrated to give homochiral γ-hydroxy-α,β-unsaturated amides (**Scheme 31**).[50] Sharpless has utilized this oxidation–elimination process to prepare (+)-coriolic acid in four steps.[50]

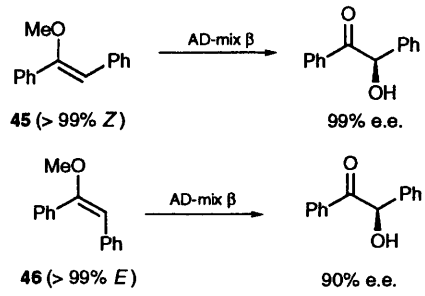


Scheme 30



Scheme 31

Further work from the group has revealed an interesting nuance when the AD protocol is applied to enol ethers.[51] α-Hydroxyketones are produced in high enantiomeric purity, but the reaction of enol ethers derived from phenylbenzylketone gives the same absolute stereochemistry at the new chiral centre, *regardless of enol ether geometry* (**Scheme 32**). So, (*Z*)-enol ether **45** gives the (*R*)-hydroxyketone, as does the (*E*)-enol ether **46**. These substrates were expected to give enantiomeric products.

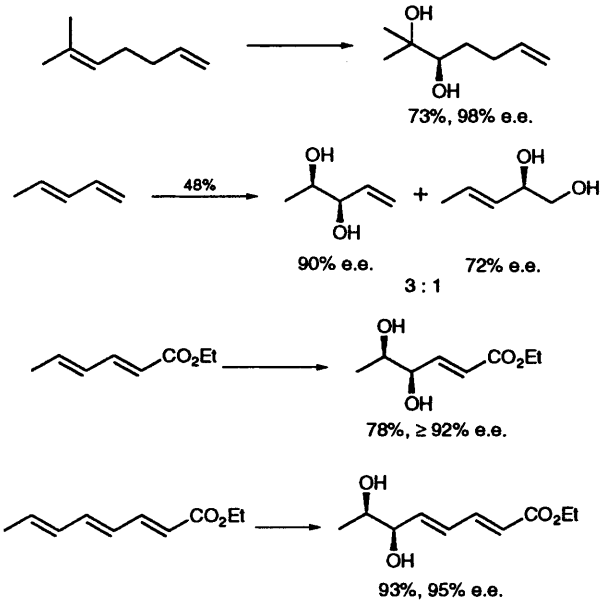


Scheme 32

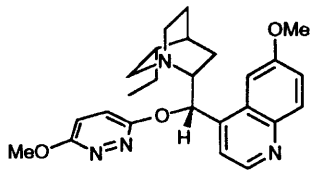
The selective asymmetric dihydroxylation of dienes is a highly viable and valuable synthetic process (**Scheme 33**).[52] Both conjugated and non-conjugated dienes react selectively, with the olefin of greater substitution reacting preferentially. When an electron-withdrawing substituent lies in conjugation with the diene, the olefin most distant from the substituent is hydroxylated. Trienes also react selectively.

Corey has examined the origins of the high enantioselectivity in the AD reaction,[53] and prepared monomeric derivatives of cinchona alkaloids, *e.g.* **47**, for use in dihydroxylations. AD reactions using **47** were one-hundred-fold slower than the reactions in which dimeric alkaloids were employed. The Harvard workers used this evidence to support their suggestion that the bridged osmium complex **48** is the active ingredient of AD-mixes.

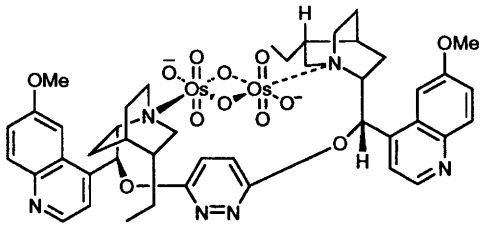
Finally, a review has appeared covering asymmetric dihydroxylation.[54]



Scheme 33



47

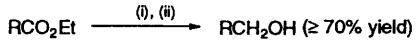


48

1.3 Reductive methods of alcohol synthesis

Although not strictly speaking a reduction of carbonyl compounds, the unusual reactivity shown by borane towards tetrahydropyranyl ethers is a useful reductive method for the direct preparation of 5-hydroxyethers.[55] *N,N*-Methoxy-*N*-methyloxamides were reduced in excellent yield to 1,2-diols with borohydride.[56] Simple dialkylamides were reduced to α-hydroxyamides. A new system for reduction of ketones, aldehydes, and acid halides used cadmium chloride and magnesium in water.[57] Simple carbonyl compounds were reduced to alcohols, while acid chlorides were reduced to aldehydes in good yield. Some epoxides were regioselectively, reductively cleaved.

Buchwald previously reported the reduction of esters using titanocene as catalyst;[58] a new 'second generation catalyst system' for ester hydrosilylation, employing (tetraisopropyloxy)-titanium as the transition metal component (**Scheme 34**), has been described.[59]

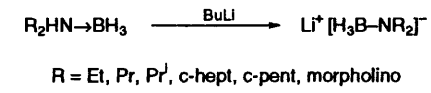


Reagents: (i) Et_3SiH, $Ti(OPr^i)_4$, (5 mol. %), 55 °C
(ii) 1 N NaOH, THF, r.t.

Scheme 34

The authors claim several advantages for their system over the reagents available for such transformation: the catalyst is self-activating, the process requires no solvent, and the catalyst may be used and generated without the need for an inert atmosphere. *O*-Benzyloximes have been reduced to the corresponding hydroxylamines using an excess of titanium tetraisopropoxide and diphenylsilane.[60]

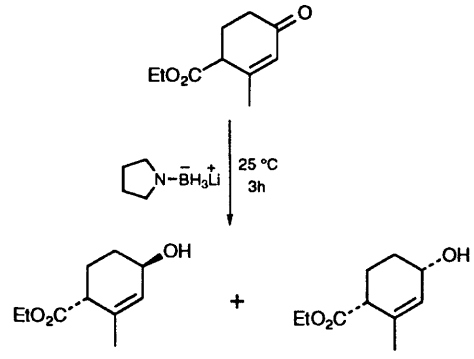
Lithium aminoborohydrides have been reported as a new class of powerful reducing agents. They exhibit similar levels of reactivity to lithium aluminium hydride but they are non-pyrophoric and air-stable, and were prepared by reaction of borane-amine complexes with butyl lithium (**Scheme 35**).[61] A range of amines may be used.



R = Et, Pr, Pr^i, c-hept, c-pent, morpholino

Scheme 35

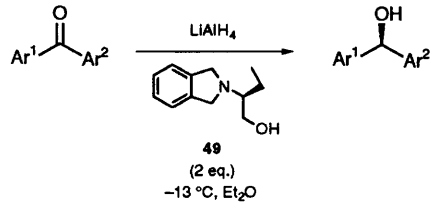
Lithium pyrrolidinoborohydride is a highly useful reagent for the chemoselective 1,2-reduction of enones (**Scheme 36**).[62]



61 : 39
94%

Scheme 36

Sodium diethylpiperidinohydroaluminate (prepared from commercially available sodium diethylaluminium dihydride) has also been prepared as a new selective reducing agent.[63] Esters, *N,N*-dialkylamides and nitriles were reduced to aldehydes in excellent (GC) yield. (*R*)-(−)-2-(2-isoindolinyl)butan-1-ol **49** has been used as an asymmetric mediator in reduction of benzophenones (**Scheme 37**).[64] The products were obtained in up to 95% e.e., but the authors made no assignment of the absolute stereochemistry generated in the reaction.

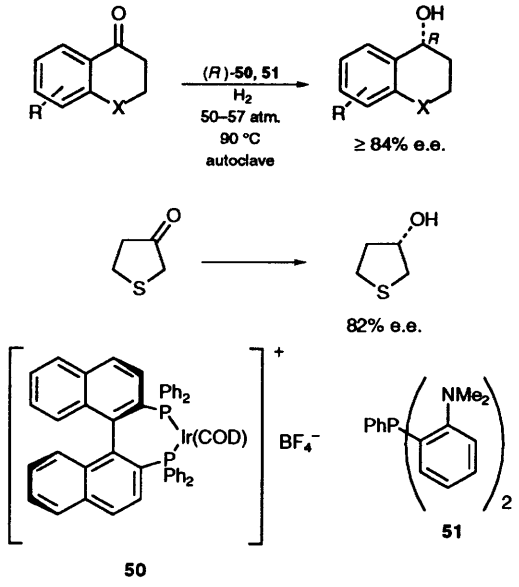


49
(2 eq.)
−13 °C, Et_2O

Scheme 37

Biaryl ligands continued to be of utility in catalytic asymmetric reactions. To solve the difficulty associated with hydrogenation of ketones which do not contain another coordinating group, a combination of the cationic BINAP-derived iridium complex **50** and a mixed P,N-donor ligand **51** has been prepared.[65] Thus, the hydrogenation at high pressure of bicyclic ketones proceeded with good e.e. (often ≥ 92%) (**Scheme 38**). The reduction of monocyclic ketones was less selective. When ligand **51** was omitted from reaction mixtures, lower enantioselectives were obtained.

para-Cymene derivatives **52** of bisphenylphosphine similarly catalysed the hydrogenation of phenyl glyoxalate and glyoxamides to mandelates and mandelamides.[66] Yields were good and enantiopurities were excellent (≥ 93% e.e.).

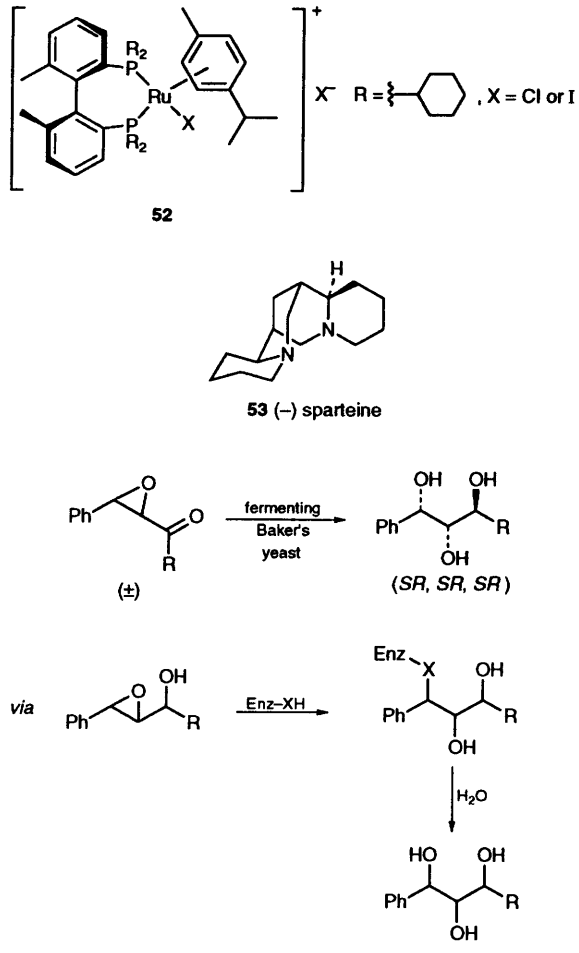


Scheme 38

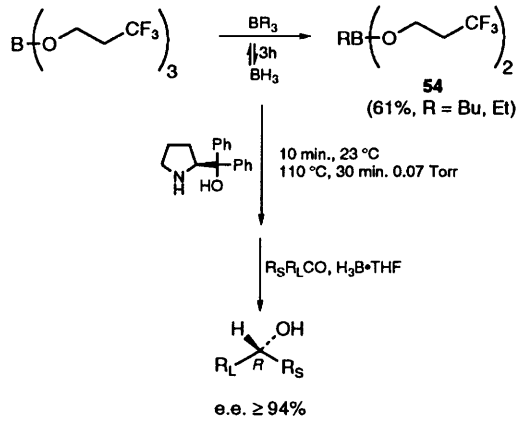
Rhodium (I) complexes containing (−)-sparteine ligands **53** have been used in the enantioselective hydrosilylation of prochiral ketones.[67] Enantioselectivities were uniformly low. An efficient Baker's-yeast-mediated reduction of 3-aryl-2,3-epoxy ketones has been reported (**Scheme 39**).[68] The epoxide ring was cleaved stereospecifically by fermenting yeast *after* the carbonyl had been stereoselectively reduced. Only one of the eight diastereoisomeric triols possible was produced in the reaction. The authors investigated the mechanism and suggested that the carbonyl reduction was followed by a regiospecific epoxide ring-opening, caused by a hydrolytic moiety present in the yeast. Water then displaced the endogenous nucleophilic species to give the product.

Oxazaborolidines continue to be of widespread interest. Corey has described a new process for the generation of 1,3,2-oxazaborolidines (**Scheme 40**).[69] Previous methods of preparing these heterocyclic catalysts used the reaction of aminoalcohols with the borane-THF complex or substituted boronic acids, and such processes require long reaction times. Corey has devised bis(trifluoropropyl) alkylboronates **54** as more reactive alkylboronic acid equivalents, and the use of these species thereby speeds catalyst formation. The paper described a new synthesis of **54** and the procedures using **54** for *in situ* formation of oxazaborolidine catalysts. The enantiomeric excesses obtained using catalysts prepared by this new method equal those seen before.[70]

The addition of amines to Corey oxazaborolidine reductions has been found to have an influence upon the levels of enantiomeric excess (**Scheme 41**).[71] Thus, when a series of ketones was reduced using Corey conditions, e.e.'s were up to 20% lower than when the reaction was performed in the presence of triethylamine. The reason for the improved selectivity was in the availability of more than one equivalent of hydride from the chiral intermediate **55**.
It was proposed that the product **56** arising from the

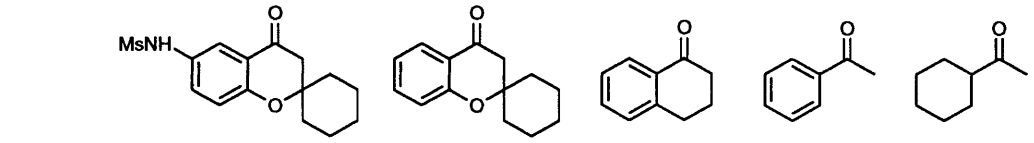


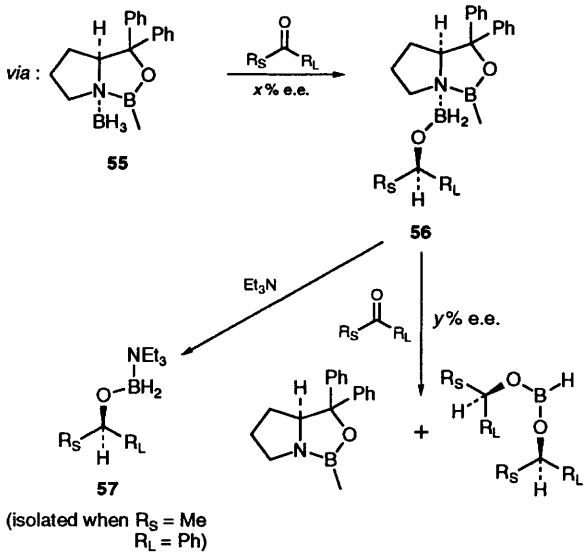
Scheme 39



Scheme 40

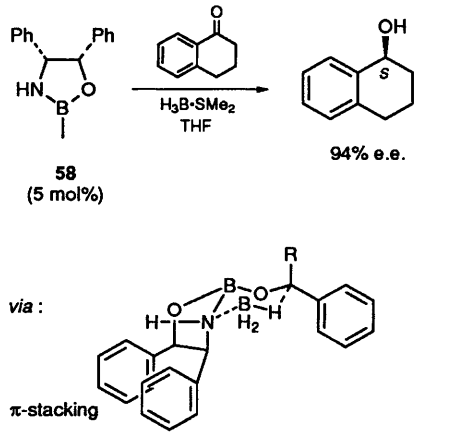
first hydride transfer then itself acted as a possible, less selective reducing agent. There would then be two distinct reductions, one of e.e. x% and one of y%; the observed e.e. in the alcohol product would then be $[(x+y)/2]$%. When triethylamine was added to the product, intermediate **56** was converted into **57**, which could be isolated and fully characterized, thus preventing a second, less selective hydride transfer occurring.





Scheme 41

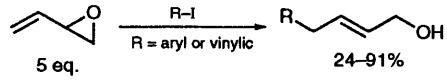
Liotta has performed MNDO Hamiltonian calculations in an attempt to ascertain the origins of the enantioselectivity observed in oxazaborolidine ketone reduction.[72] These calculations showed that the most favoured situation was that in which hydride transfer occurred *via* a chair transition state, with the oxazaborolidine and ketone substituent effects reinforcing each other. Four papers have appeared describing quantum chemical modelling of chiral catalysis by oxazaborolidines.[73–76] The first of these was concerned with the role of alkoxyboranes in CBS carbonyl reduction, the second discussed the relative stability of dimer homochiral oxazaborolidines, and the third and fourth described the effects controlling the coordination of borane to oxazaborolidines during reductive processes and the conformational constraints of the reduced species, respectively. A review of the uses of homochiral oxazaborolidines in asymmetric synthesis has appeared.[77] Quallich and Woodall have introduced a new oxazaborolidine catalyst **58**, available in both antipodes, which reduced arylalkylketones with high enantioselectivity. The sense of chiral induction was predictive (**Scheme 42**) and the selectivity was proposed to arise from the highly ordered transition state arising from π-stacking. Only arylalkylketones were reduced with high selectivity.[78]



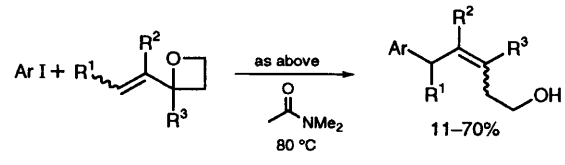
Scheme 42

1.4 Preparation of alcohols from epoxides

Two reports by Larock *et al.* have extended the palladium-catalysed heterocycle cleavage (**Scheme 43**).[79,80] Thus, palladium acetate in the presence of sodium formate, tetrabutylammonium chloride, and Hunig's base catalysed the cross-coupling of vinylic epoxides with aryl or vinyl halides to give allylic alcohols. This complemented the previous work on ring cleavage of unsaturated epoxides by aryl iodides.[81] The second report illustrated in **Scheme 43** extended the previously described S_N2' ring-opening of vinylic oxetanes by organometallic species in the presence of palladium; the new process[82] allows the replacement of organometallics by aryl iodides (two examples of aryl iodides), but a five-fold excess of vinyl oxetane was necessary to obtain even moderate yields. The process was again successful when 1-(triflyloxy)cyclohexene was used as the pro-nucleophile. Homoallylic alcohols were obtained in 11–70% yields although many yields were moderate.



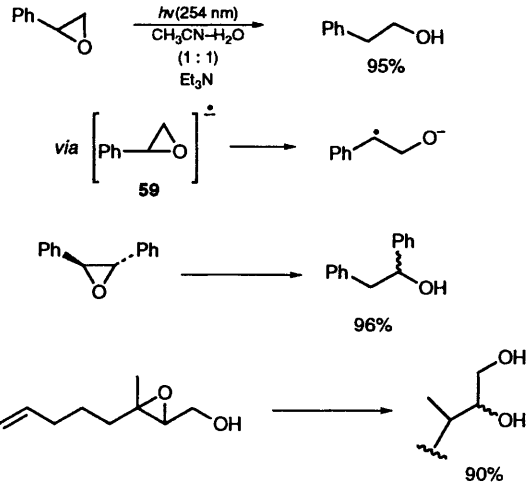
Reagents: 10% $Pd(OAc)_2$, 5 eq. NaO_2CH, Bu_4NCl, Pr^i_2NEt



Scheme 43

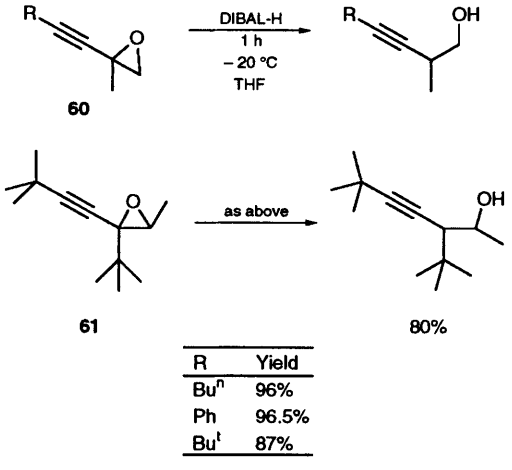
An *anti*-Markovnikoff hydration of olefins may be efficiently carried out by a two-step epoxidation–reductive ring-opening process involving a photochemical ring-cleavage reaction (**Scheme 44**).[83] Thus, when an epoxide was photolysed under nitrogen in a Rayonet apparatus, in the presence of sodium

borohydride in acetonitrile–water solvent, a non-stereospecific but regiospecific reductive ring-opening occurred.[83] The reaction proceeded *via* radical anions such as **59**; $NaBH_4$ suppressed the formation of by-products arising from other radical reactions.



Scheme 44

The best method previously reported for the preparation of 2-substituted 3-butyn-1-ols was that of Seebach[84] which used titanium acetylides to ring-open epoxides nucleophilically; a new method of accomplishing the preparation of such alkynols uses a reductive ring-opening of 1-substituted 1-alkynyl-epoxides **60** (**Scheme 45**).[85]



R	Yield
Bu^n	96%
Ph	96.5%
Bu^t	87%

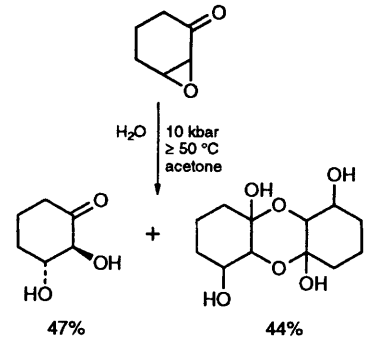
Scheme 45

Only DIBAL-*H* reacted regiospecifically to give products arising from nucleophilic hydride attack at the more hindered carbon. Even extremely hindered substrates (such as **61**) reacted regioselectively.

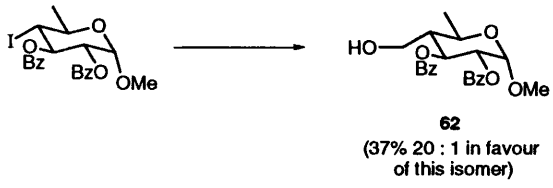
High pressure was used to catalyse the hydrolysis of epoxides (**Scheme 46**).[86] Yields were moderate to good.

1.5 Miscellaneous methods of alcohol synthesis

It is known that radical alkylation of carbon monoxide under high pressure gives aldehydes;[87] when Kahne *et al.* employed these conditions in an attempt to prepare analogues of carbohydrates seen in calichemycins, very poor yields of the hydroxymethylated product **62** were obtained.[88] To circumvent this problem, the authors utilized an *in situ* generated germane instead of the stannane previously used. Under these conditions, a much better (though still low) yield of **62** was obtained. The authors claim their improvement represents a general method for direct introduction of a hydroxymethyl group *via* intermolecular trapping of CO (**Scheme 47**).



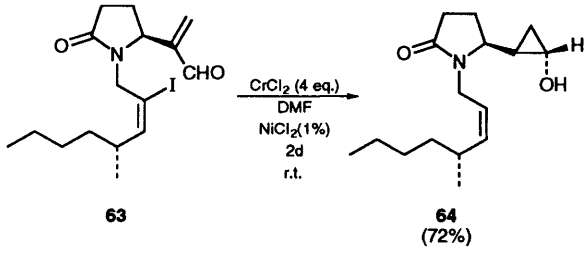
Scheme 46



Reagents: Ph_3GeH(0.1eq.), AIBN (0.1eq.), $NaBH_3CN$(2.9eq.), benzene–THF (50 :1), 1400 p.s.i. CO, 105 °C, 12 h

Scheme 47

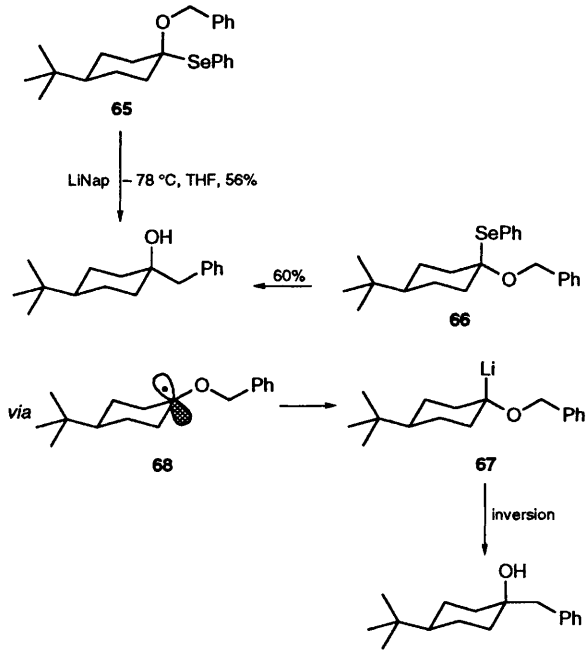
When Stevenson *et al.* attempted a Cr^{II}-mediated intramolecular alkylative cyclization of **63**, the only product isolated was the reduced cyclopropyl alcohol **64**[89] (**Scheme 48**). The reaction was general for α-monosubstituted acroleins but not generally useful for terminally substituted systems. The process was similar to the intramolecular addition of allylbromides to α,β-unsaturated aldehydes reported by Still.[90]



Scheme 48

When O,Se-ketals (prepared from the corresponding dibenzylketals and $Et_2AlSePh$) **65** and **66** were treated with lithium naphthalenide, both isomers generated anion **67** *via* radical **68**.[91,92] This anion then underwent a [1,2]-Wittig rearrangement to

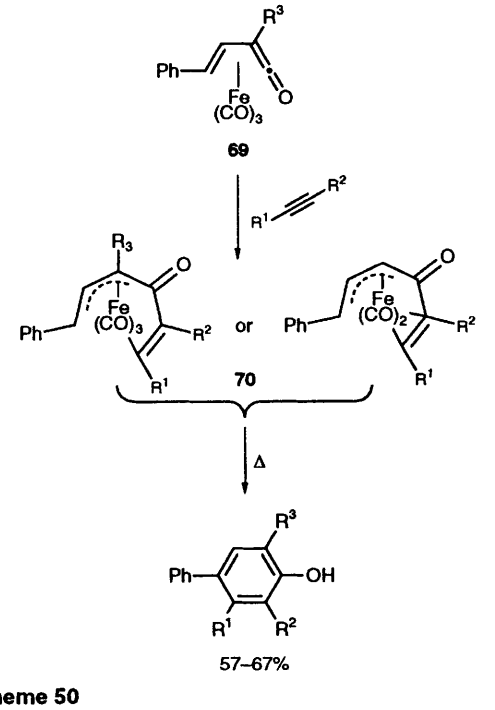
give an axial alcohol. This overall process offered an improved route to such axial alcohols (for instance, reaction of 4-t-butylcyclohexanone with benzylmagnesium bromide gave equal amounts of axial and equatorial product) (**Scheme 49**).



Scheme 49

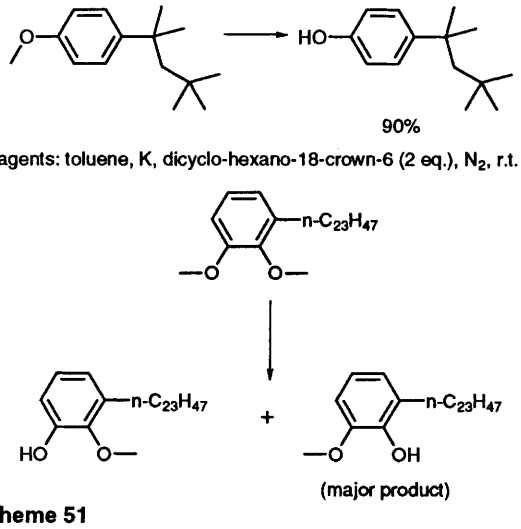
2 Preparation of phenols and ethers

Tricarbonyl(vinyl ketene)iron(0) complexes **69** reacted with alkynes to give stable and isolable di- and tri-carbonyl iron(0) adducts **70** (**Scheme 50**). When these compounds were heated, phenols were produced in good yield.[93]



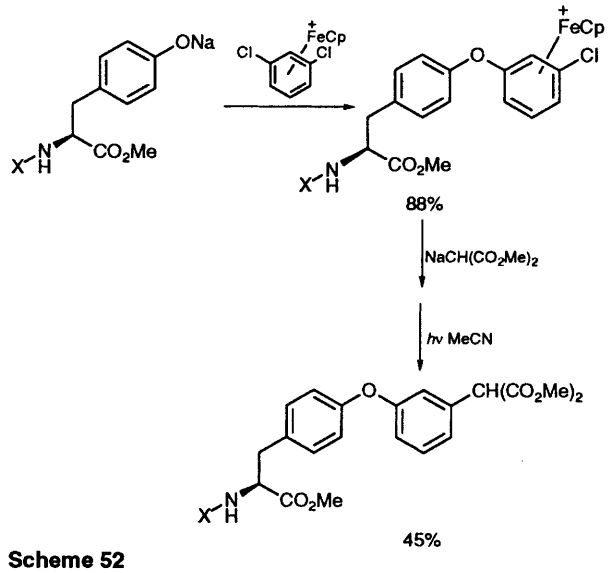
Scheme 50

When toluene solutions of methoxybenzenes and crown ethers were reacted with potassium and then treated with isopropanol, a high-yielding demethylation reaction occurred (**Scheme 51**). The toluene radical anion was the reactive species; in the reaction of dimethoxybenzenes, the less hindered ether was demethylated.[94]



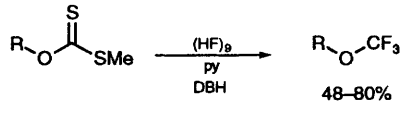
Scheme 51

Diarylethers may be prepared *via* the nucleophilic attack of phenolates on chloroarene-metal π-complexes.[95] After decomplexation, moderate to good yields of ethers were obtained (**Scheme 52**).[96] If dichlorinated arenes were used, the second chloride was also displaced by nucleophiles.



Scheme 52

Trifluoromethyl ethers may be prepared by a desulfurative fluorination of xanthates (**Scheme 53**).[97]



Scheme 53

3 References

1 H. Fujii, M. Taniguchi, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1992, **33**, 4579.
2 T. Gillmann, *Tetrahedron Lett.*, 1993, **34**, 607.
3 J.K. Crandall and T.A. Ayers, *Tetrahedron Lett.*, 1991, **32**, 3659.
4 D. Guijarro, B. Mancheno, and M. Yus, *Tetrahedron*, 1992, **48**, 4593.
5 D. Guijarro, B. Mancheno, and M. Yus, *Tetrahedron Lett.*, 1992, **33**, 5597.
6 Y. Gao and K.B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538.
7 H. Watanabe, F. Yamashita, and K. Uneyama, *Tetrahedron Lett.*, 1993, **34**, 1941.
8 M.T. Reetz and S. Stanchen, *J. Chem. Soc., Chem. Commun.*, 1993, 328.
9 H. Maeta, T. Hashimoto, T. Hasegawa, and K. Suzuki, *Tetrahedron Lett.*, 1992, **33**, 5965.
10 D.E. Stack, B.T. Dawson, and R.D. Rieke, *J. Am. Chem. Soc.*, 1992, **114**, 5110.
11 D.E. Stack and R.L. Rieke, *Tetrahedron Lett.*, 1992, **33**, 6575.
12 A. Doucoure, B. Mauze, and L. Miginiac, *J. Organomet. Chem.*, 1982, **236**, 139.
13 K. Mallaiah, J. Satyanarayana, I. Iia, and H. Junjappa, *Tetrahedron Lett.*, 1993, **34**, 3145.
14 S. Kobayashi and K. Nishio, *Tetrahedron Lett.*, 1993, **34**, 3453.
15 T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 561.
16 C. Jubert, S. Nowotny, D. Korneman, I. Antes, C.E. Tucker, and P. Knochel, *J. Org. Chem.*, 1992, **57**, 6384.
17 Y. Yamamoto, K. Kobayashi, H. Okano, and I. Kadota, *J. Org. Chem.*, 1992, **57**, 7003.
18 A.G.M. Barrett and J.W. Malecha, *J. Org. Chem.*, 1991, **56**, 5243.
19 A.G.M. Barrett and M.A. Seefeld, *J. Chem. Soc., Chem. Commun.*, 1993, 339.
20 K. Mikami, M. Terada, and T. Nakai, *J. Am. Chem. Soc.*, 1990, **112**, 3949.
21 K. Mikami, S. Narisawa, M. Shimizu, and M. Terada, *J. Am. Chem. Soc.*, 1992, **114**, 6566.
22 M. Terada, S. Matsukawa, and K. Mikami, *J. Chem. Soc., Chem. Commun.*, 1993, 327.
23 A.B. Charette, C. Mellon, L. Rouillard, and E. Malenfant, *Synlett*, 1993, 81.
24 T.H. Chan and K.T. Nwe, *J. Org. Chem.*, 1992, **57**, 6107.
25 T.H. Chan and S. Lamothe, *Tetrahedron Lett.*, 1991, **32**, 1847.
26 P. Rochet, J.-M. Vatèle, and J. Goré, *Synlett*, 1993, 105.
27 M.J. Rozema, A. Sidduri, and P. Knochel, *J. Org. Chem.*, 1992, **57**, 1956.
28 M.J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, and P. Knochel, *Tetrahedron Lett.*, 1993, **34**, 3115.
29 E.J. Corey and T.-P. Loh, *J. Am. Chem. Soc.*, 1991, **113**, 8966.
30 M. Guette, J. Capillon, and J.-P. Guette, *Tetrahedron*, 1973, **29**, 3659.
31 K. Soai, A. Oshio, and T. Saito, *J. Chem. Soc., Chem. Commun.*, 1993, 811.
32 S.L. Buchwald, B.T. Watson, M.W. Wannamaker, and J.C. Dewan, *J. Am. Chem. Soc.*, 1989, **111**, 4486.
33 M. Jensen and T. Livinghouse, *J. Am. Chem. Soc.*, 1989, **111**, 4495.
34 H. Ito, T. Taguchi, and Y. Hanzawa, *Tetrahedron Lett.*, 1992, **33**, 4469.
35 S. Tang and R.M. Kennedy, *Tetrahedron Lett.*, 1992, **33**, 7823.
36 R.D. Miller and D.R. McKean, *Tetrahedron Lett.*, 1982, **23**, 323.
37 P. Dunn, R. Häner, and H. Rapoport, *J. Org. Chem.*, 1990, **55**, 5017.
38 F.J. Sardina, M.M. Paz, E. Fernández-Megia, R.D. deBoer, and M.P. Alvarez, *Tetrahedron Lett.*, 1992, **33**, 4637.
39 K.N. Harrison and T.J. Marks, *J. Am. Chem. Soc.*, 1992, **114**, 9220.
40 D.A. Singleton, J.P. Martinez, and J.V. Watson, *Tetrahedron Lett.*, 1992, **33**, 1017.
41 D.A. Singleton, J.P. Martinez, and G.M. Ndip, *J. Org. Chem.*, 1992, **57**, 5768.
42 R.A.T.M. Van Bentham, H. Hiemstra, and W.N. Speckamp, *J. Org. Chem.*, 1992, **57**, 6083.
43 K. Fuji, K. Tanaka, and H. Miyamoto, *Tetrahedron Lett.*, 1992, **33**, 4021.
44 S. Hanessian, P. Maffre, M. Girard, S. Beaudoin, J.-Y. Sancéau, and Y. Benani, *J. Org. Chem.*, 1993, **58**, 1991.
45 W. Amberg, Y.L. Bennani, R.K. Chadha, G.A. Crispino, W.D. Davis, J. Hartung, K.-S. Jeong, Y. Ogino, T. Shibata, and K.B. Sharpless, *J. Org. Chem.*, 1993, **58**, 844.
46 L. Wang and K.B. Sharpless, *J. Am. Chem. Soc.*, 1992, **114**, 7568.
47 Z.-M. Wang, X.-L. Zhang, K.B. Sharpless, S.C. Sinha, A. Sinha-Bagahi, and E. Keinan, *Tetrahedron Lett.*, 1992, **33**, 6407.
48 E. Keinan, S.C. Sinha, A. Sinha-Bagchi, Z.-M. Wang, X.-H. Zhang, and K.B. Sharpless, *Tetrahedron Lett.*, 1992, **33**, 6411.
49 Y.L. Bennani and K.B. Sharpless, *Tetrahedron Lett.*, 1993, **34**, 2079.
50 Y.L. Bennani and K.B. Sharpless, *Tetrahedron Lett.*, 1994, **34**, 2083.
51 T. Hashiyama, K. Morikawa, and K.B. Sharpless, *J. Org. Chem.*, 1992, **57**, 5067.
52 D. Xu, G.A. Crispino, and K.B. Sharpless, *J. Am. Chem. Soc.*, 1992, **114**, 7570.
53 E.J. Corey, M.C. Noe, and S. Sarshar, *J. Am. Chem. Soc.*, 1993, **115**, 3828.
54 B.B. Lohray, *Tetrahedron: Asymmetry*, 1992, **3**, 1317.
55 J. Cossy, V. Bellosta, and M.C. Müller, *Tetrahedron Lett.*, 1992, **33**, 5045.
56 M.P. Sibi and R. Sharma, *Synlett*, 1992, 497.
57 M. Bordoloi, *Tetrahedron Lett.*, 1993, **34**, 1681.
58 S.C. Berk, K.A. Kreutzer, and S.L. Buchwald, *J. Am. Chem. Soc.*, 1991, **113**, 5093.
59 S.C. Berk and S.L. Buchwald, *J. Org. Chem.*, 1992, **57**, 3751.
60 K.C. Nicolaou, E.P. Schreiner, and W. Stahl, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 585.
61 G.B. Fisher, J. Harrison, J.C. Fuller, C.T. Goralski, and B. Singaram, *Tetrahedron Lett.*, 1992, **33**, 4533.
62 J.C. Fuller, E.L. Stangeland, C.T. Goralski, and B. Singaram, *Tetrahedron Lett.*, 1993, **34**, 257.
63 N.M. Yoon, J.H. Ahn, D.K. An, and Y.S. Shon, *J. Org. Chem.*, 1993, **58**, 1941.
64 E. Brown, A. Leze, and J. Touet, *Tetrahedron: Asymmetry*, 1992, **3**, 841.
65 X. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, and H. Takaya, *J. Am. Chem. Soc.*, 1993, **115**, 3318.
66 T. Chiba, A. Miyashita, H. Nohira, and H. Takaya, *Tetrahedron Lett.*, 1993, **34**, 2351.
67 Y. Goldberg and H. Alper, *Tetrahedron: Asymmetry*, 1992, **3**, 1055.
68 G. Fouché, R.M. Horak, and O. Meth-Cohn, *J. Chem. Soc. Chem. Commun.*, 1993, 119.
69 E.J. Corey and J.O. Link, *Tetrahedron Lett.*, 1992, **33**, 4141.

70 E.J. Corey, *Pure Appl. Chem.*, 1990, **62**, 1209.
71 D. Cai, D. Tschaen, Y.-J. Shi, T.R. Verhoeven, R.A. Reamer, and A.W. Douglas, *Tetrahedron Lett.*, 1993, **34**, 3243.
72 D.K. Jones, D.C. Liotta, I. Shinkai, and D.J. Mathre, *J. Org. Chem.*, 1993, **58**, 799.
73 V. Nevaleinen, *Tetrahedron: Asymmetry*, 1992, **3**, 921.
74 V. Nevaleinen, *Tetrahedron: Asymmetry*, 1992, **3**, 933.
75 V. Nevaleinen, *Tetrahedron: Asymmetry*, 1992, **3**, 1441.
76 V. Nevaleinen, *Tetrahedron: Asymmetry*, 1992, **3**, 1563.
77 S. Wallbaum and J. Martens, *Tetrahedron: Asymmetry*, 1992, **3**, 1475.
78 G.J. Quallich and T.M. Woodall, *Tetrahedron Lett.*, 1993, **34**, 4145.
79 R.C. Larock and S. Ding, *J. Org. Chem.*, 1993, **58**, 804.
80 R.C. Larock and W.-Y. Leung, *J. Org. Chem.*, 1990, **55**, 6244.
81 R.C. Larock and S.K. Stolz-Dunn, *Tetrahedron Lett.*, 1989, **30**, 3487.
82 R.C. Larock, S. Ding, and C. Tu, *Synlett*, 1993, 145.
83 G.A. Epling and Q. Wang, *J. Chem. Soc., Chem. Commun.*, 1992, 1133.
84 N. Krause and D. Seebach, *Chem. Ber.*, 1988, **121**, 1315.
85 P. Nussbaumer and A. Stütz, *Tetrahedron Lett.*, 1992, **33**, 7507.
86 H. Kotsuki, M. Kataoka, and H. Nishizawa, *Tetrahedron Lett.*, 1993, **34**, 4031.
87 I. Ryu, K. Kusano, N. Masumi, H. Yamakazi, A. Ogawa, and N. Sonoda, *Tetrahedron Lett.*, 1990, **31**, 6887.
88 V. Gupta and D. Kahne, *Tetrahedron Lett.*, 1993, **34**, 591.
89 D. Montgomery, K. Reynolds, and P. Stevenson, *J. Chem. Soc., Chem. Commun.*, 1993, 363.
90 W.C. Still and D. Mobilio, *J. Org. Chem.*, 1983, **48**, 4785.
91 R.W. Hoffmann and R. Brückner, *Chem. Ber.*, 1992, **125**, 1957.
92 R.W. Hoffmann, T. Rückert, and R. Brückner, *Tetrahedron Lett.*, 1993, **34**, 297.
93 K.G. Morris, S.P. Saberi, and S.E. Thomas, *J. Chem. Soc., Chem. Commun.*, 1993, 209.
94 T. Ohsawa, K. Hatano, K. Kayoh, J. Kotabe, and T. Oishi, *Tetrahedron Lett.*, 1992, **33**, 5555.
95 A.J. Pearson, J.C. Park, and P.Y. Zhu, *J. Org. Chem.*, 1992, **57**, 3583.
96 A.J. Pearson, H.S. Lee, and F. Gouzoules, *J. Chem. Soc., Perkin Trans. I*, 1990, 2251.
97 M. Kuroboshi, K. Suzuki, and T. Hiyama, *Tetrahedron Lett.*, 1992, **33**, 4173.