Alcohols, ethers and phenols

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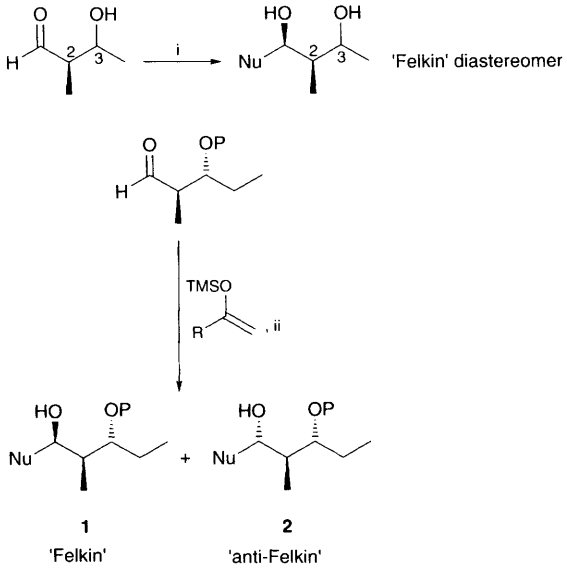
Reviewing the literature published between February 1995 and February 1996
Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 65

1 Preparation of alcohols

1.1 From carbonyl compounds

1.1.1 *via* Carbon–carbon bond-forming reactions

Evans *et al.* have reported the new results of their investigations into the rôle of α- and β-substituents upon the stereochemical course of nucleophilic aldol and allylation reactions of aldehydes.[1] It had been assumed that the proximal stereogenic centre of a 2,3-disubstituted carbonyl compound controls the diastereoselectivity in addition reactions, but the authors found that when the 3-substituent contained a heteroatom, stereocontrol could be exerted by this substituent. Thus, when 2,3-*anti*-disubstituted aldehydes were reacted with nucleophiles, Felkin products **1** were favoured due to a 'matched' diastereomeric preference of the 2- and 3-substituents (**Scheme 1** and **Table 1**). When 2,3-*syn*-substrates were used, the diastereomeric preferences of the substituents were opposed, and upon reaction when enol silanes derived from non-bulky ketones, the authors observed the first examples of non-chelate-controlled Mukaiyama aldol reaction in which the diastereomeric bias is in favour of the *anti*-Felkin product **4** (**Scheme 2** and **Table 2**).



Scheme 1 *Reagents*: i, Nu:; ii, BF_3•OEt_2 (1 equiv.), CH_2Cl_2, –78°C

Table 1

R	P	Yield/%	Ratio **1**:**2**[a]
Bu^t	PMB[b]	94	99:1
Pr^i	PMB	98	98:2
Me	PMB	86	97:3
Bu^t	Bu^{t}SiMe$_2$	93	99:1
Pr^i	Bu^{t}SiMe$_2$	88	95:5
Me	Bu^{t}SiMe$_2$	92	71:29

[a]Ratios determined by GC. [b]PMB = (4-methoxyphenyl)-methyl.

Silicon-centred chirality directs the stereoselective nucleophilic attack of vinyllithiums upon monochiral acylsilanes such as **5** (**Scheme 3**).[2] The monochiral allylic alcohol products of these reaction were subsequently used in asymmetric Ireland ester–enolate rearrangement reactions.

The first reports of Nozaki reaction which does not require stoichiometric amounts of chromium(II) have appeared. Thus, reaction of iodides with aldehydes in the presence of nickel dichloride, chromium chloride and manganese powder in polar solvent gives alkylated products in good yield.[3] It is proposed that the mixture of metallic reagents establishes a multi-component redox system, which effects the alkylation.

Functionalized organozincs react with alkynyl aldehydes in the presence of (1*R*,2*R*)-1,2-di(triflyl-

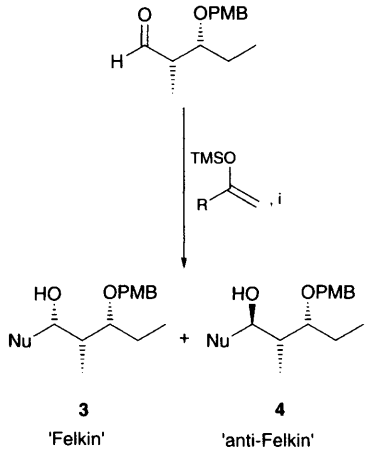
amido)cyclohexane and titanates to give chiral prop-2-ynyl alcohols of good to excellent ee ($\geq$82%).[4] 2-Bromoacroleins also generate these products upon sequential treatment with the same alkylating ingredients and sodium hydride.

Permethylated cyclodextrins catalyze the asymmetric addition of diethylzinc to aldehydes: ees of the resulting alcohols are low.[5]

N-Allenylpyrrole may be deprotonated at moderately low temperature; the resulting anion undergoes nucleophilic addition to carbonyl compounds to give products arising from α- and γ-attack, with the products of α-attack predominating (**Scheme 4**).[6]

Pentaarylantimony species react with aldehydes and ketones to give alcohols; yields for the two examples reported are moderate or excellent.[7]

syn-1,2-Amino alcohols may be prepared in two steps from *N*-benzyl imines **6** by a deprotonation–alkylation–imine hydrolysis protocol (**Scheme 5**).[8] Yields for the overall transformation from imine to amino alcohol are moderate to good.

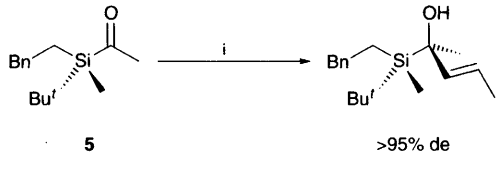


Scheme 2 *Reagents:* i, BF_3•OEt_2 (1 equiv.), CH_2Cl_2 or $PhCH_3$, −78 °C

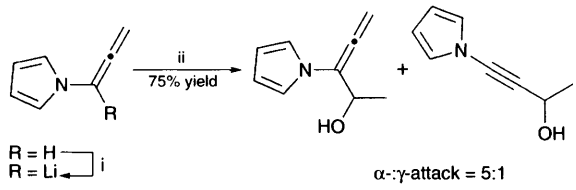
Table 2

R	Solvent	Yield/%	Ratio **3**:**4**[a]
Bu^t	$PhCH_3$	75	88:12
Pr^i	$PhCH_3$	86	36:68
Me	$PhCH_3$	92	6:94
Bu^t	CH_2Cl_2	89	96:4
Pr^i	CH_2Cl_2	98	56:44
Me	CH_2Cl_2	82	17:83

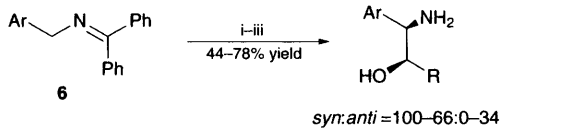
[a]Ratios determined by GC.



Scheme 3 *Reagents:* i, prop-1-enyllithium, Et_2O, −90 °C

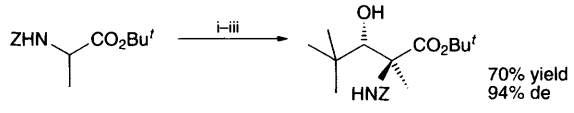


Scheme 4 *Reagents:* i, Bu^{n}Li, −10 to −30 °C; ii, MeCHO



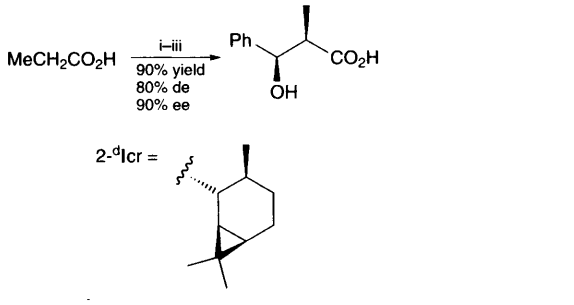
Scheme 5 *Reagents:* i, Bu^{t}Li, THF, −78 °C; ii, RCHO; iii, $MeONH_3Cl$, MeOH

Direct alkylations of simple 2-amino acid derivatives are frequently inefficient; enolates of sterically demanding amino acids are reported to undergo *anti*-selective aldol reactions in the presence of chlorotitanium triisopropoxide.[9] In particular, bulky aliphatic aldehydes react in high yield (**Scheme 6**).



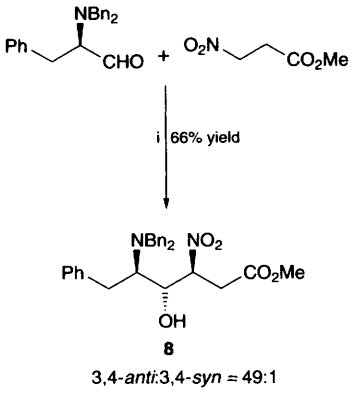
Scheme 6 *Reagents:* i, LDA, THF, −78 °C; ii, $ClTi(OPr^i)_3$; iii, Bu^{t}CHO

Treatment of carboxylic acids with base and isocaranylchloroborane [(2-^{d}Icr)$_2$BCl] **7** generates a chiral boron enolate which undergoes selective aldol reaction with benzaldehyde (**Scheme 7**).[10]



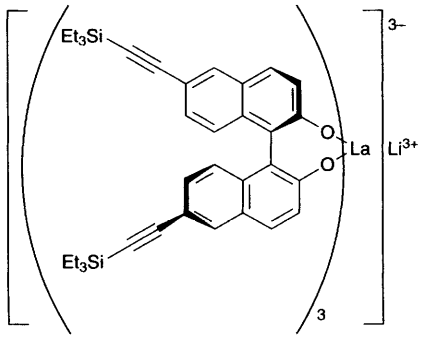
Scheme 7 *Reagents:* i, LDA, THF, −78 °C, 2 h; ii, **7**, THF, −78 to 0 °C; iii, PhCHO, THF, −78 °C

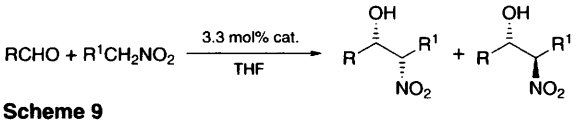
Nitroaldol reactions of monochiral 2-amino acid-derived amino aldehydes are highly stereocontrolled, leading to 1,2-*anti*-2,3-*anti*-3-dibenzylamino-2-hydroxynitroalkanes (such as **8**) in generally good yields (**Scheme 8**).[11] The nature of the base employed is crucial.



Scheme 8 *Reagents*: i, TBAF hydrate, 0 °C, THF, 10–30 min

Shibasaki and co-workers have reported their latest advances in catalysis using bimetallic lanthanide BINOL-derived complexes, with the description of the highly selective nitroaldol reactions of alkyl nitro compounds with aldehydes.[12] Thus, 6,6′-disubstituted BINOL complexes (such as **9**) catalyze the formation of 1,2-*syn*-hydroxynitroalkanes in good to excellent yield and with generally excellent ee (**Scheme 9** and **Table 3**).





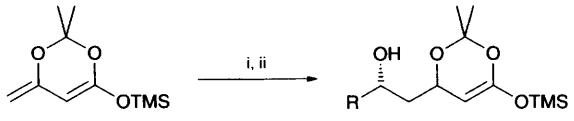
Scheme 9

Table 3

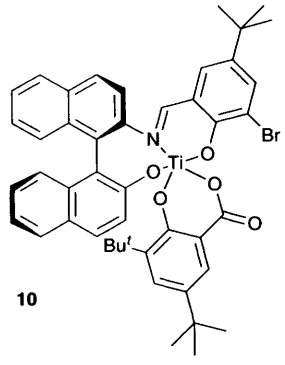
R	R^1	Yield	*syn*:*anti*	ee/%[a]
Ph	Me	70	89:11	93
Ph		85	93:7	95
Ph	HO	97	92:8	97
	HO	96	92:8	95

[a]Of *syn*-isomer.

Aldol reactions of dienolate equivalents to aldehydes are catalyzed by asymmetric binaphthyl titanate **10** (**Scheme 10** and **Table 4**).[13] The acetoacetate aldol adducts isolated are obtained in good to excellent yield and with a minimum of 80% ee. The products of the reaction may be used as precursors to HMG-CoA reductase inhibitors.[14]



Scheme 10 *Reagents*: i, RCHO, Et_2O, **10** (1–3 mol%), 0 °C; ii, TFA, THF

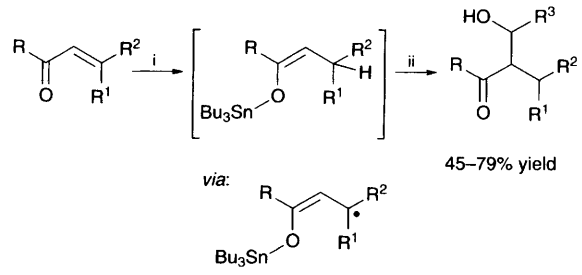


10

Table 4

R	Yield/%	ee/%
Pr^i_3Si	86	91
Bu^tSiMe_2O	97	94
	88	92
	95	92
Ph	83	84
Ph	97	80
Bu_3Sn	79	92

The reaction of α,β-unsaturated ketones with tributylstannane under homolytic initiation conditions generates stannyl enolates *via* the corresponding allylic *O*-stannyl ketyls; these enolates undergo reaction with aldehydes to give aldol products in moderate to good yields (**Scheme 11**).[15]

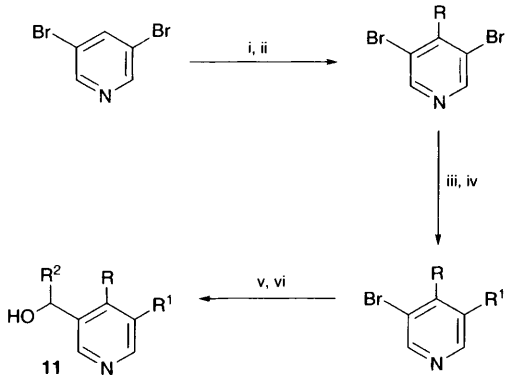


Scheme 11 *Reagents*: i, Bu_3SnH, PhH, AIBN, 80 °C; ii, R^3CHO

A stereoselective migration process resulting in desilylative phenylation of acylsilanes has been reported (**Scheme 12**).[16]

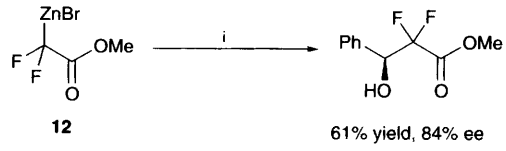
Scheme 12 *Reagents*: i, KF, DMSO, room temp., 5 h

Selective metal–halogen exchange of symmetrical dibromopyridines gives access to lithiated derivatives which can be alkylated and reacted with aldehyde to give hydroxymethylpyridines **11** in good overall yield (**Scheme 13**).[17]



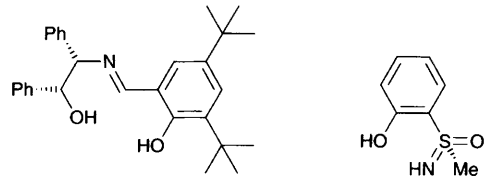
Scheme 13 *Reagents*: i, LDA, THF, −78 °C; ii, RX; iii, Bu^nLi, −100 °C; iv, R^1X; v, Bu^nLi, THF, −78 °C; vi, R^2CHO

An enantioselective Darzens reaction using chiral lithium amide bases has been reported by Koga *et al.*[18] The enantioselectivity of the reaction (even when performed at very low temperature) is moderate. An enantioselective Reformatsky reaction of bromodifluoroacetate has been described.[19] Thus, *N*-methylephedrine catalyzes the stereoselective addition of zinc enolate **12** to aldehydes with moderate levels of enantiomeric control (**Scheme 14**). Yields are acceptable.



Scheme 14 *Reagents*: i, PhCHO, *N*-methylephedrine, THF, 0 °C, 40 h

Asymmetric trimethylsilylcyanation of aldehydes may be accomplished using a titanium(IV) catalyst whose asymmetry is derived from Schiff base **13**; enantio-excesses of the product cyanohydrins are poor.[20]



13 **14**

A more selective silylcyanation of aldehydes employs a catalyst derived from $Ti(OPr^i)_4$ and asymmetric sulfoximine **14**: enantiomeric excesses of the cyanohydrin products are good.[21]

syn-1,2-Dihydroxyphosphonates are prepared with high levels of stereoselectivity by the Lewis acid mediated hydrophosphonylation of 2-benzyloxy-aldehydes by dialkyl (dimethyl-*tert*-butyl)silyl phosphites (**Scheme 15** and **Table 5**).[22]

Scheme 15 *Reagents*: i, TBDMSO–$P(OR^1)_2$, $TiCl_4$, CH_2Cl_2, −78 °C

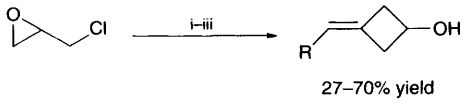
Table 5

R	R^1	Yield/%	*syn*:*anti*
$PhCH_2$	Me	72	>98:<2
Pr^i	Me	73	>98:<2
$PhCH_2$	Et	75	88:12
Pr^i	Et	72	91:9
Me	Me	88	84:16
Me	Et	66	80:20
Me	Pr^i	43	75:25

Pinacol-type couplings involving samarium-based reagents continue to proliferate. In a slight variation on the theme, aromatic dimethyl acetals undergo a reductive coupling and/or reductive demethoxylation

using samarium diiodide under Brønsted or Lewis acid catalysis.[23] Yields of 1,2-diaryl-1,2-dimethoxyalkanes are generally good to excellent. Dialdehydes and keto aldehydes undergo a radical pinacol coupling upon reaction with tributylstannane under conditions which encourage homolysis.[24]

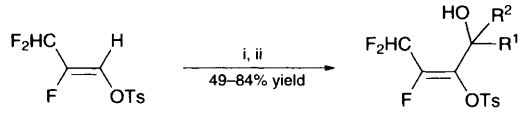
Unsaturated cyclobutanols may be prepared by sequential reaction of epichlorohydrin with methylene triphenylphosphorane, base and an aldehyde (**Scheme 16**).[25]



Scheme 16 *Reagents*: i, $Ph_3P{=}CH_2$, toluene, 0 °C, 20 min; ii, Bu^{n}Li, 0 °C; iii, RCHO, toluene, –40 °C, 1 h

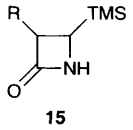
Trimethylphosphite reacts with acrolein in the presence of trimethylsilyl chloride to give dimethyl 2-(trimethylsilyloxy)allyl phosphonate in good yield.[26]

2,3,3-Trifluoro-1-tosyloxyprop-1-enyllithium may be prepared by deprotonation of the parent alkene: this anion is alkylated in moderate to good yield, to give 2-tosyloxy allylic alcohols (**Scheme 17**).[27]



Scheme 17 *Reagents*: i, Bu^{n}Li, –78 °C; ii, $R^1R^2C{=}O$

In a new synthetic method to allow preparation of functionalized β-lactams, the latently nucleophilic carbon–silicon bond of substituted 4-trimethylsilylazetidin-2-one **15** reacts at ambient temperature under fluoride instigation to alkylate aldehydes in good yield.[28]



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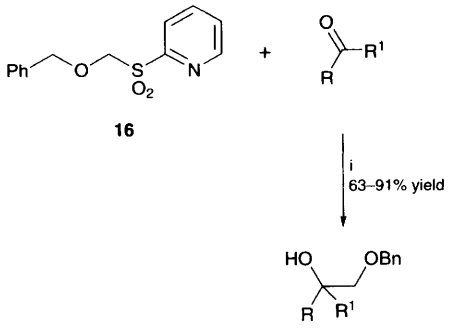
Benzyloxymethyl pyridyl sulfone **16** reacts instantaneously with samarium diiodide to produce a nucleophilic benzyloxylating reagent which alkylates carbonyl compounds in good to excellent yield (**Scheme 18** and **Table 6**).[29]



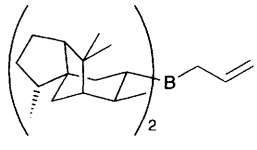
Scheme 18 *Reagents*: i, SmI_2, THF

Table 6

R	R^1	Yield/%
	$-(CH_2)_4-$	91
	$-(CH_2)_5-$	86
Et	Et	87
H	n-C_7H_{15}	84
H	Cyclohexyl	75
H	Pr^i	81
H	$(CH_2)_3OBz$	76

1.1.1a Allylation

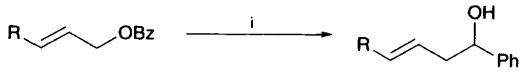
As ever, allylation of carbonyl compounds continues to occupy the attention of many researchers. The latest monochiral allylborane to be utilized in asymmetric carbonyl allylation is allyl (diisocedryl) borane **17**.[30] This borane allylates representative aldehydes to give homoallylic alcohols of poor to mediocre ee.



17

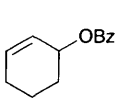
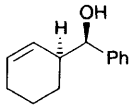
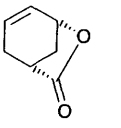
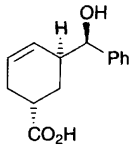
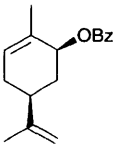
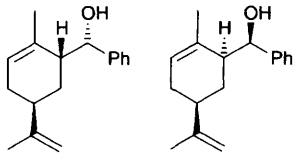
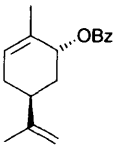
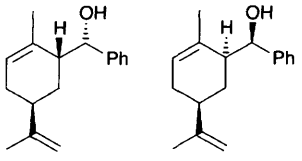
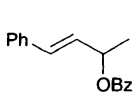
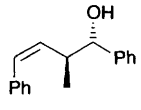
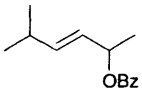
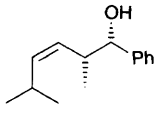
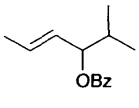
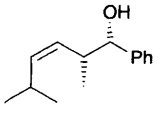
Hydrated copper(II) chloride mediates Barbier-type allylation of aldehydes in the presence of elemental magnesium.[31] The same system reduces carbonyl compounds in the absence of allyl bromide. Alkynes react with aldehydes in the presence of gallium(III) iodide and a tertiary amine to give prop-2-ynyl alcohols, generally in good yield. The process is simple and effective for a wide range of substrates.[32] Alkynyl aluminates have been demonstrated to be highly chemoselective in reactions with carbonyl compounds to prepare prop-2-ynyl alcohols in good yields.[33]

Allyl benzoates provide a source of nucleophilic allylating reagents upon reaction with diethylzinc and tetrakis(triphenylphosphine)palladium(0). These species react slowly with benzaldehyde in a highly stereoselective fashion (**Scheme 19** and **Table 7**).[34] The mechanism proposed to account for the stereoselectivity is shown in **Scheme 20**.

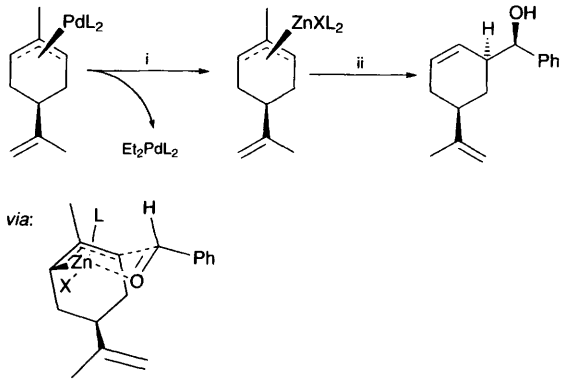


Scheme 19 *Reagents*: i, PhCHO, Et_2Zn, $Pd(PPh_3)_4$ (0.05 mmol) THF, room temp.

Table 7

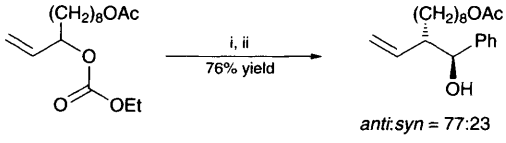
Benzoate	Product	Yield/%
		76
		95
		80/12
		26/72
		60
	 (*anti:syn* = 89:11)	60
	 (*anti:syn* = 86:14)	62

Allyltitanium reagents are accessible from the corresponding halide or alcohol upon reaction of



Scheme 20 *Reagents*: i, Et_2Zn; ii, PhCHO

the latter with isopropyl titanate and a hindered Grignard reagent, allowing a novel method for preparation of homoallylic alcohols (**Scheme 21**).[35] The formation of the allyltitanium species proceeds by an oxidative addition (**Scheme 22**). Allyltitanates are also accessible by desulfurative titanation of allyl sulfides.[36]



Scheme 21 *Reagents*: i, $Ti(OPr^i)_4$, Pr^iMgBr, −50 → −40 °C, 1 h; ii, PhCHO, −40 °C

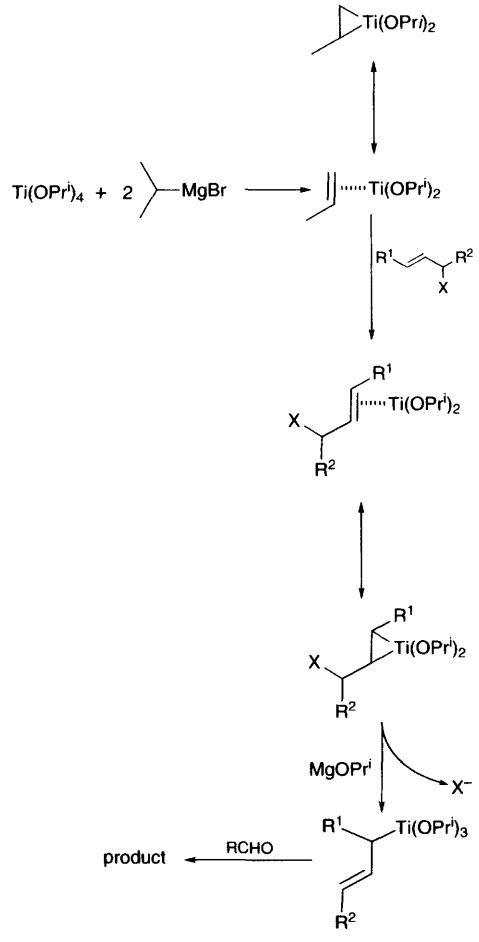
α-Methylene lactones are accessible from bromomethylacrylate in a two-step procedure involving transient formation of (2-methoxycarbonylallyl)-trichlorosilane.[37] Thus, treatment of the allyl bromide with trichlorosilane in the presence of copper(I) salts generates the indicated acryloylating silane **18** which reacts with representative aldehydes in polar solvent in good yield (**Scheme 23**). Ring-closure to the lactone must, however, be carried out subsequently.

Active zinc powder is produced in the reaction of zinc(II) chloride with sodium in liquid ammonia: such zinc is highly efficient in the Barbier reaction of allyl bromide with aldehydes.[38] The reaction may also be performed in THF, rather than liquid ammonia. Chiral (acyloxy)borane catalysis enables an asymmetric synthesis of 2-methylene-3-hydroxy ketones, *via* a face selective conjugate addition of a phenylsulfanyl nucleophile to unsaturated conjugated ketones.[39] The intermediate enolic species generated by the addition undergoes aldol reaction to give *syn*-3-hydroxy-2-(phenylsulfanylmethyl) ketones of high enantiomeric excess: oxidation followed by thermolytic elimination furnishes the products in moderate overall yield.

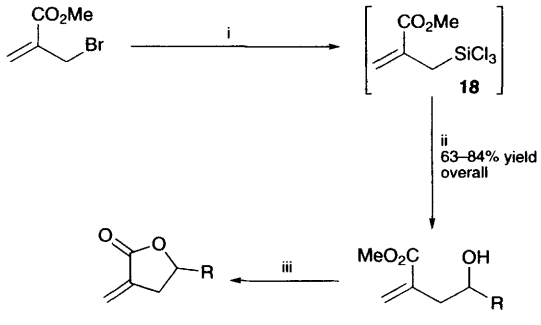
Catalysis of allylation reactions of aldehydes using allylstannanes has occupied the attention of several groups. For instance, Yamamoto *et al.* have described their use of bis(triphenylphospine)-

platinum dichloride.[40]

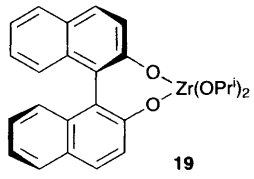
Asymmetric allylation reactions involving allylstannanes continue to be of interest: Tagliavini and co-workers have extended their original study of allylation of aldehydes using asymmetric titanates[41] to include the corresponding zirconate **19** (prepared in either enantiomeric form by reaction of the diol with $Zr(OPr^i)_4 \cdot Pr^iOH$).[42] Enantiomeric excesses in allylation of aldehydes are good to excellent.



Scheme 22



Scheme 23 *Reagents*: i, $HSiCl_3$, CuCl, Pr^iNEt_2, Et_2O, reflux; ii, RCHO, DMF–CH_3CN, 0 °C; iii, H^+

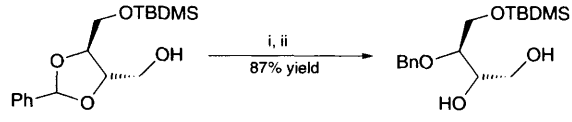


19

1.1.2 Reductive addition

Meerwein–Verley–Ponndorf reactions continue to occupy the attention of many researchers:[43] the interest in asymmetric variants of the reaction, in particular, continues to burgeon.[44] What is described as the first truly catalytic Meerwein–Verley–Ponndorf reaction has been reported, using approximately 8 mol% of aluminium isopropoxide.[45] Yields of reduced products are mediocre to excellent.

Although not, strictly speaking, a reduction of carbonyl groups *per se*, the reduction of acetals is worthy of mention in this section of the article. Thus, for instance, benzylidene acetal **20** reacts with the combination of borane–DMS complex and boron trifluoride–diethyl ether to effect regiospecific acetal cleavage followed by reduction to give differentially-protected tetrol **21** in good yield.[46] Reduction occurs at the C–O bond nearer to the pre-existing hydroxy group.

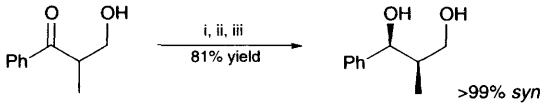


20 **21**

Scheme 24 *Reagents*: i, $BH_3 \cdot SMe_2$, 1 h; ii, $BF_3 \cdot OEt_2$, 5 min

Diisopropoxytitanium borohydride reduces a wide range of carbonyl compounds to the corresponding alcohols, generally in good yields and with excellent chemoselectivity.[47]

The selective reduction of 3-hydroxy ketones using borane–pyridine complex relies upon the use of $TiCl_4$ or BCl_3 as Lewis acids (**Scheme 25**).[48] Thus, the reduction of representative ketones at low temperature is rapid (reaction times often as short as 30 min), favouring the *syn*-isomer, where appropriate.



Scheme 25 *Reagents*: i, $TiCl_4$, −78 °C; ii, pyridine•BH_3, −78 °C; iii, HCl, −78 °C to room temp.

2-Keto esters of monochiral *cis*-1-tosylamidoindan-2-ols are asymmetrically reduced by L-Selectride™ in the presence of a Lewis acid.[49]

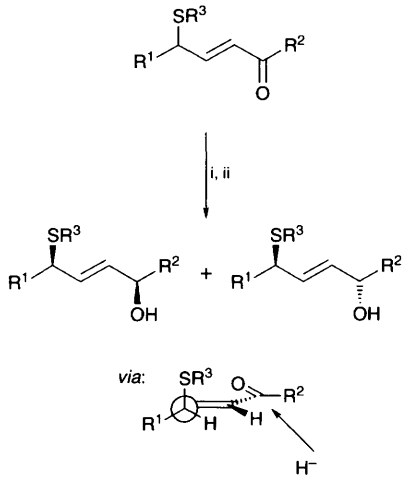
Enantioexcesses of the 2-hydroxy ketones liberated after hydrolytic removal from the auxiliary are high (≥90%). Titanocene borohydride has been reported as a carbonyl reducing agent.[50] Yields of alcohols are high.

In contrast to the usual stereochemical preference in reductions in the presence of Lewis acid, 2-alkyl-3-keto esters are reduced to *anti*-3-hydroxy esters upon reaction with trimethylstannane and titanium tetrachloride.[51] In order to obtain highest selectivity, very low temperatures are required.

Zinc borohydride carries out the reduction of acids to primary alcohols in good yield.[52]

Lithium hydride reacts with nickel(II) acetate to give a new hydride reducing agent which reduces (*inter alia*) carbonyl compounds efficiently.[53]

4-Substituted enones are reduced by L-Selectride™ with (in many cases) high levels of stereoselectivity (**Scheme 26** and **Table 8**).[54] The authors ascribe the high preference for 1,4-*syn*-products which is observed to the transmission of chiral information through the conjugated π-system, which is held in an s-*cis* conformation.

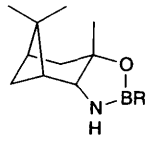


Scheme 26 *Reagents*: i, LiBu$^s_3$BH, THF, −78 °C, 30 min; ii, 30% H_2O_2, NaOH

Table 8

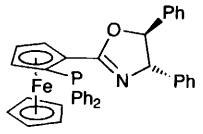
R^1	R^2	R^3	Yield/%	*syn*:*anti*
Bu^t	Bu^t	Ph	96	97:3
Pr^i	Bu^t	Ph	91	96:4
Me	Bu^t	Ph	82	95:5
Bu^t	Pr^i	Ph	82	94:6
Bu^t	Me	Ph	98	91:9
n-C_7H_{15}	*n*-C_5H_{11}	Ph	71	93:7
n-C_6H_{13}	Bu^t	Ph	100	93:7

Prochiral ketones undergo asymmetric reduction by the oxazaborolidine **22** (available in both antipodes) derived from α-pinene.[55] Enantiomeric excesses are variable (42–96% ee), with best selectivity observed in the reduction of aryl alkyl ketones.



22

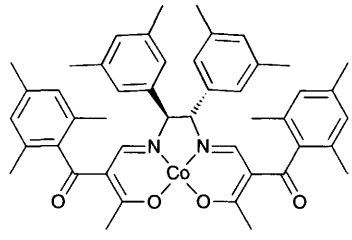
R = H, Me, Bu, Ph



23

The chiral oxazolinylferrocenylphosphine hybrid ligand **23** asymmetrically catalyses the hydrosilylation of prochiral ketones in good yield and with high enantioselectivity.[56]

Mukaiyama and co-workers have reported the utility of monochiral cobalt complex **24** in the enantioselective reduction of ketones using sodium borohydride.[57] Enantiomeric excesses are good to excellent.



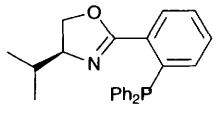
24

Ruthenium[58] catalysts based on bidentate aminophosphines catalyse enantioselective reduction of prochiral carbonyl compounds. As frequently observed in such processes, best selectivities are obtained in the reduction of aryl alkyl ketones (**Scheme 27** and **Table 9**).

Scheme 27 *Reagents*: i, H_2, catalyst, 82 °C

Table 9

R^1	R^2	Catalyst	Ee/% (abs. config.)
Ph	Me	$RuCl_2(PPh_3)_3$–**25**	94 (*R*)
Ph	Et	$RuCl_2(PPh_3)$–**26**	91 (*R*)
Ph	Me	$RuCl_2(PPh_3)$–**26**	93 (*R*)
Cyclohexyl	Pr^i	$RuCl_2(PPh_3)$–**26**	60 (*S*)



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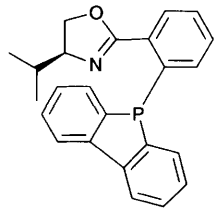
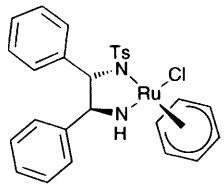


26

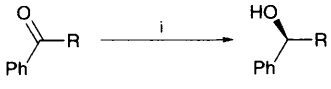
Noyori's contributions to asymmetric hydrogenation continue. Thus, reduction of prochiral aryl

ketones *via* Meerwein–Verley–Ponndorf-type reaction occurs enantioselectivity in the presence of a ruthenium catalyst (**27**, characterized by X-ray) prepared *in situ* and derived from [$RuCl_2$ (η^2-mesitylene)] and (1*S*,2*S*)-1,2-diphenylethylenediamine.[59] Enantioselectivities are impressive (generally greater than 90% ee).



27

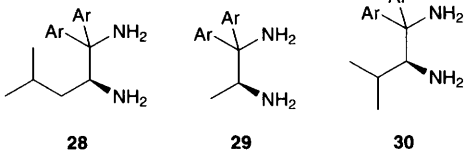
The same group have used the combination of $RuCl_2$[(*S*)-BINAP] and a range of asymmetric 1,2-diamine ligands to enable a highly practical reduction of aryl alkyl ketones, with excellent ee (usually >98% ee).[60] This modified procedure circumvents one of the drawbacks to BINAP reductions, *viz*, the requirement for the hydrogenation substrate to contain a ligating sub-unit. Using a combination of (*S*)-BINAP and (*S*)-TolBINAP and chiral, enantiomerically pure 1,2-diphenylamines, simple aryl alkyl ketones are reduced with good enantioselectivity (**Scheme 28** and **Table 10**).



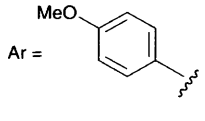
Scheme 28 *Reagents*: i, H_2, cat.

Table 10

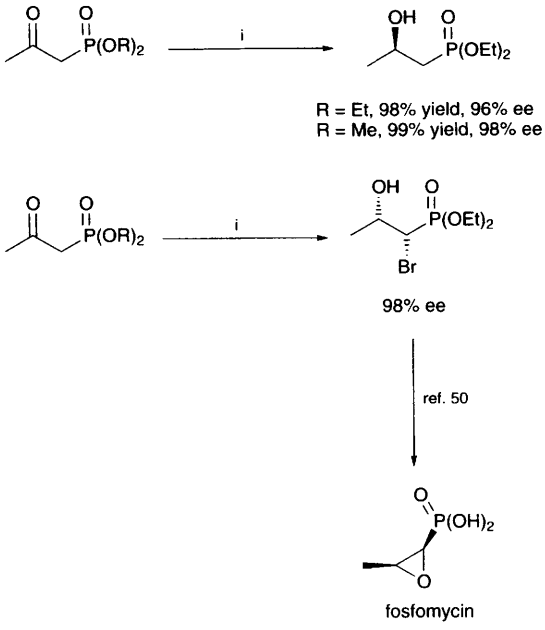
R	Catalyst	Yield/%	Ee/%
Me	(*S*)-BINAP–**28**	>99	87
Bu^n	(*S*)-BINAP–**29**	>99	90
Pr^i	(*S*)-BINAP–**30**	>99	95
Bu^t		no reaction	



28 **29** **30**



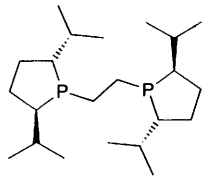
A similar protocol from another research group, in this case employing (*S*,*S*)-1,2-*N*,*N*′-dimethyldiphenylethylenediamine and an achiral rhodium catalyst proceeds with lower selectivity.[61] Noyori reduction of 3-keto phosphonates[62] has allowed a synthesis of fosfomycin, a clinically-used antibiotic natural product (**Scheme 29**).[63]



Scheme 29 *Reagents*: i, [(*R*)-BINAP]Ru, H_2 (4 atm), 25 °C

A modified procedure for performing Noyori reduction of 3-keto esters allows the reaction to be performed at atmospheric pressure, compared to the high pressures often required. Enantiomeric excesses are as impressive as in the high pressure reaction.[64]

The asymmetric reduction of 3-keto esters may also be accomplished by use of asymmetric bisphosphine (*R*,*R*)-Pr^i-BPE **31** in the presence of ruthenium(II) bromide: relatively high hydrogen pressures must be employed.[65]



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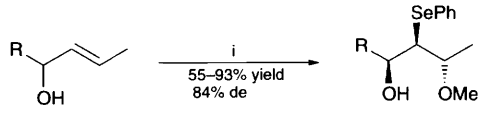


Scheme 30 *Reagents*: i, PhSeBr, MeOH, 2,6-di-*tert*-butylpyridine

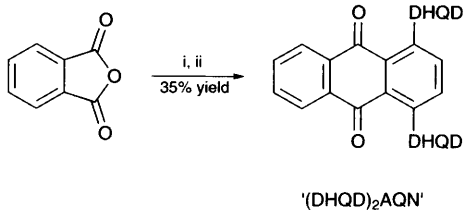
1.2 By addition to alkenes

In the presence of hindered base in methanolic solution, acyclic allylic alcohols react with benzeneselenenyl bromide to give predominantly 1,2-*syn*-2,3-*anti*-2-phenylselanyl-3-methoxy alcohols in good yield (**Scheme 30**).[66]

Alkenes react with NO_2–diphenyl diselenide to give products arising from addition of O_2NO–SePh

to the double bond.[67] The reaction is highly regioselective, with the selanyl moiety in the product being attached where possible to the least hindered carbon of the alkene. The resulting nitrate esters of 2-hydroxy-1-phenylselanylalkanes are hydrolyzed on silica gel to give the corresponding alcohols in moderate to good yield overall.

Developments continue in the asymmetric dihydroxylation reaction of alkenes. In the first of back-to-back papers, Becker and Sharpless have described yet another class of ligand, based upon 1,4-dihydroxyanthraquinone, for the AD reaction.[68] The ligands are prepared *via* Friedel–Crafts reaction of 1,4-difluorobenzene with phthalic anhydride, followed by nucleophilic substitution by the requisite alkaloid. These new ligands have properties complementary to those of known ligands, and offer improvement in AD reactions of terminal alkenes, including halogenated compounds (**Scheme 31** and **Table 11**). Alkenes are dihydroxylated in poor to excellent ee.



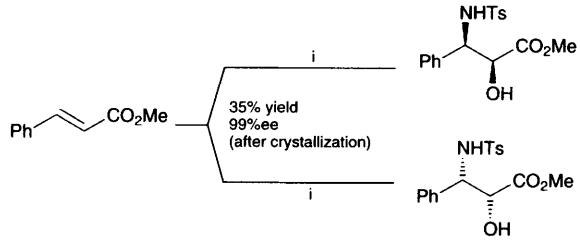
'$(DHQD)_2AQN$'

Scheme 31 *Reagents*: i, 1,4-difluorobenzene, $AlCl_3$, polyphosphoric acid, 48 h, reflux; ii, dihydroquinuclidine (DHQD, 2 equiv.), BuLi (2 equiv.), THF, 15 h

Table 11

Akene	Ee/% (previous best)	Diol config.
Cl	90 (63)	*S*
Br	89 (72)	*S*
TsO	83 (40)	*S*
F_3C	81 (64)	*S*
BnO, O	88 (77)	*S*
Bu^n	87 (87)	*R*
	86 (96)	*R*
Ph	45 (72)	1*R*,2*S*
Ph	78 (96)	*R*

Use of the $(DHQ)_2$-PHAL AD catalyst system in the presence of chloramine-T trihydrate effects asymmetric 1,2-aminohydroxylation (AA) of alkenes.[69] Enantiomeric excesses are, at best, moderate (<81% ee) (**Scheme 32** and **Table 12**).

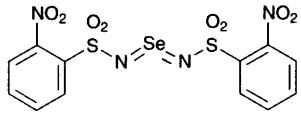


Scheme 32 *Reagents*: i, $K_2OsO_2(OH)_4$ (4 mol%), ligand (5 mol%), chloramine-T (3 equiv.), 0.07 M olefin, CH_3CN–H_2O

Table 12

Akene	Ee	
	$(DHQ)_2$ PHAL	$(DHQD)_2$ PHAL
CO_2Et	74	60
MeO_2C, CO_2Me	77	53
Ph, Ph	62	50
	33	48

Sharpless and his co-workers have also shown that the diimido nosylselenium reagent NsN=Se=NNs **32** (where Ns = nosyl = *p*-nitrophenylsulfonyl) can effect both allylic amination and 1,2-diamination of alkenes, on a multigram scale.[70] Conjugated dienes react under the conditions to give 1,2-diaminoalk-3-enes (**Scheme 33**).



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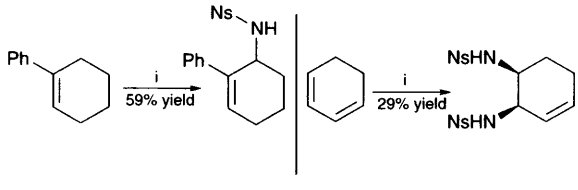
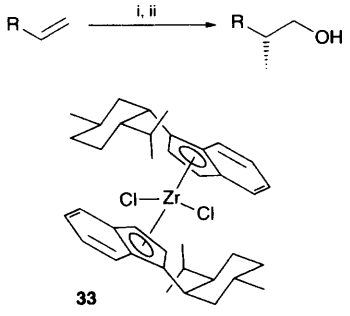


Scheme 33 *Reagents*: i, $NsNCl_2$ (4 mmol), $NsSO_2NHNa$ (2.05 equiv.), Se (1.05 equiv.), 3 Å mol. sieves, alkene (2 equiv.), room temp.

Dichlorobis(1-neomenthylindenyl)zirconium **33** mediates the asymmetric carboalumination of

terminal alkenes (**Scheme 34** and **Table 13**).[71] Reaction of the so-formed alkyldimethylalane with oxygen gives, overall, the product of alkylative primary hydroxylation in good yield. Enantiomeric excesses are generally moderate.

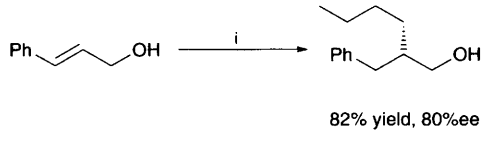


Scheme 34 *Reagents*: i, Me_3Al, **33**; ii, O_2

Table 13

R	Yield	Ee/%
n-C_6H_{13}	88	72
Pr^i	92	74
Cyclohexyl	80	65
$PhCH_2$	77	70
$Et_2(CH_2)_3$	68	71
$HO(CH_2)_4$	79	75

(−)-Sparteine mediates an asymmetric addition of butyllithium to cinnamyl alcohol.[72] The reaction is effective for ethers and primary and secondary cinnamyl amines (40–82% yield, 0–85% ee) (**Scheme 35**).

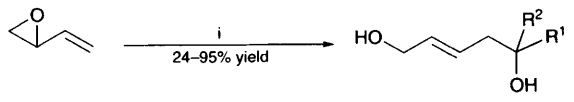


Scheme 35 *Reagents*: i, BuLi, (−)-sparteine, cumene, 0 °C

Hayashi's H-MOP ligand has been reported to effect highly stereoefficient hydrosilylation of arylethenes.[73] Peroxidative cleavage of the initially produced benzylsilane gives 2-arylethanols in good to excellent yield and with high ee.

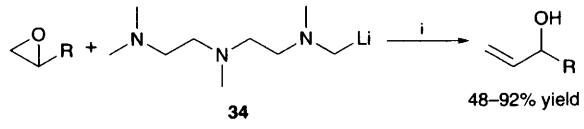
1.3 By ring-opening of epoxides

Ketyl radicals produced using samarium diiodide react in an S_H2' manner with vinyl epoxides, to give 1,5-dihydroxyalk-2-enes (**Scheme 36**).[74]



Scheme 36 *Reagents*: i, $R^1R^2C{=}O$, SmI_2, HMPA, −40 °C, THF

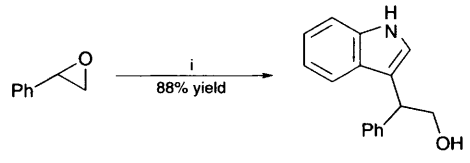
N-Lithiomethyl-*N*,*N*′,*N*″,*N*″-tetramethyldiethylenetriamine **34** reacts with epoxides to give products of methylene transfer (**Scheme 37**).[75]



Scheme 37 *Reagents*: i, pentane, room temp.

Zeolites may be used to effect regiospecific eliminative ring-cleavage of glycidyl esters to give the corresponding 2-hydroxy but-3-enoates in acceptable yield.[76]

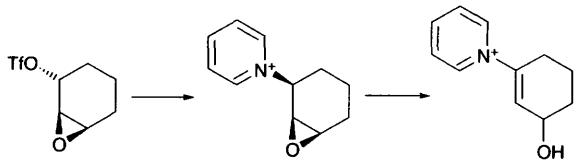
The details of the high-pressure mediated reaction of epoxides with nitrogen-containing heterocycles have been chronicled in full (**Scheme 38**).[77]



Scheme 38 *Reagents*: i, indole, silica gel, CH_2Cl_2, room temp., 7 d

Functionalized epoxides undergo reductive ring-opening upon reaction with a mixture of tributylstannane, tributylstannyl iodide and phosphine oxides.[78] The regiochemistry of the reduction depends on the nature of the substituent: adjacent multiple bonds direct reduction to the allylic position. Notably, chlorine substituents survive the process intact.

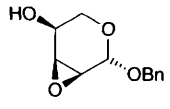
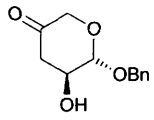
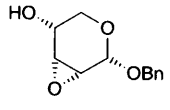
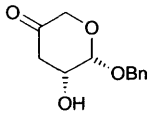
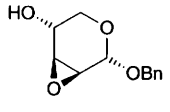
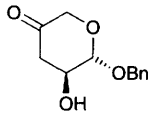
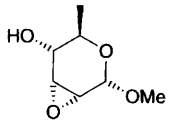
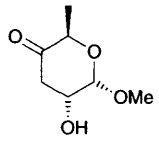
The triflic anhydride-promoted displacement of hydroxy groups adjacent to epoxides leads to 2-pyridinium epoxides in excellent yield[79] These pyridinium ions (such as **35**) activate the epoxide ring to eliminative ring-opening (**Scheme 39** and **Table 14**).



35

Scheme 39

Table 14

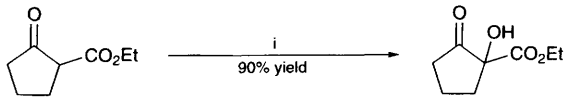
Alcohol	Product	Yield/%
		82
		80
		84
		76

These activated carbonyl equivalents may be converted to the apposite carbonyl compounds, also in excellent yield. Overall, the synthetic method allows high-yielding stereo- and regio-specific conversion of 3-epoxy alcohols to 3-keto-2-deoxy 1-alcohols.

1.4 Oxidative methods

Full details of the oxidative conversion of alkyl-(phenyl)dimethylsilanes to the corresponding alcohols have appeared.[80]

Dimethyldioxirane (DMDO) hydroxylates 1,3-dicarbonyl compounds in the presence of $Ni(acac)_2$.[81] Thus, 2-ethoxycarbonylcyclopentanone reacts in excellent yield at ambient temperature to give tertiary alcohol **36** (**Scheme 40**).

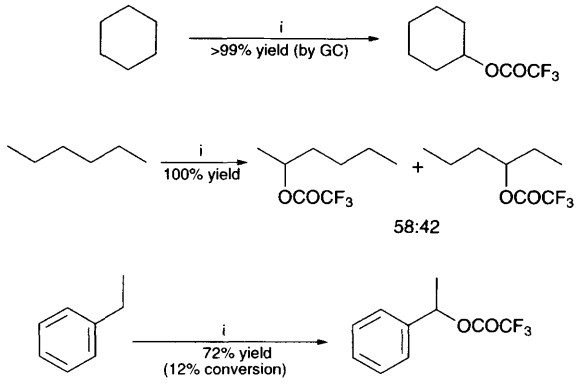


36

Scheme 40 *Reagents*: i, $Ni(acac)_2$ (0.1 equiv.), DMDO

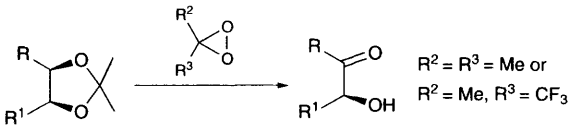
The same reagent oxidizes acyclic vinylsilanes to the corresponding epoxides, but cyclic vinylsilanes react to give mixtures of epoxides and products arising from allylic oxidation (proceeding *via* C–H insertion).[82]

Methyl(trifluoromethyl)dioxirane efficiently monohydroxylates alkanes, yielding trifluoroacetates in good to excellent yield (**Scheme 41**).[83]



Scheme 41 *Reagents*: i, methyl(trifluoromethyl)dioxirane, 0 °C, CH_2Cl_2 (10 equiv.), TFAA

The same oxidant selectively oxidizes ketals of monochiral 1,2-diols to give 2-hydroxy ketones in excellent ee (**Scheme 42** and **Table 15**).[84]



Scheme 42

Table 15

R	R^1	Yield/%	Ee/% (configuration
Me	Me	>96	98 (*R*)
Bu″	Bu″	80	96 (*R*)
$-(CH_2)_6-$		98	99 (*R*)
Ph	Ph	99	97 (*R*)
Ph	Me	60[a]	92 (*R*)

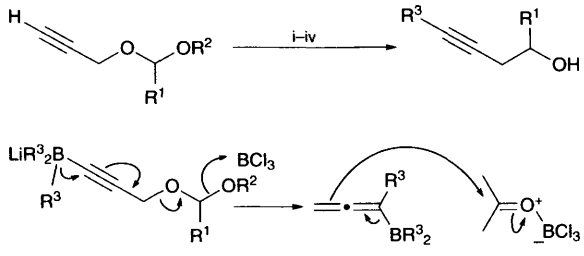
[a]Plus 35% 1,2-dione.

A synthetic kinetic resolution of secondary alcohols has been reported.[85] Thus, a binaphthyl-derived nitroxyl catalyst selectively oxidises (*S*)-2-phenylethanol to acetophenone, leaving behind the (*R*)-alcohol, which is obtained with an enantioexcess of 87% at 69% conversion.

1.5 By rearrangement reactions

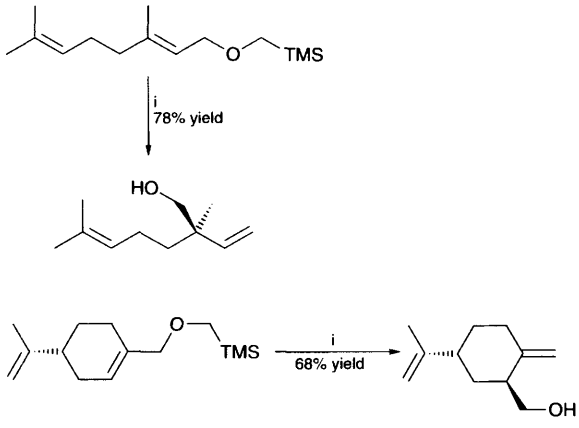
Lithiated alkynylborates derived from prop-2-ynyl acetals rearrange to give but-3-ynyl alcohols in good

yield.[86] The reaction involves a complex sequence of cleavage–readdition processes (**Scheme 43**).



Scheme 43 *Reagents*: i, BuLi; ii, $BR^3{}_3$; iii, BCl_3; iv, HOONa

(Trimethylsilyl)methyl allyl ethers undergo a previously unreported [2,3]-rearrangement (Wittig rearrangement) at temperatures lower than ambient to give homoallylic alcohols in acceptable to good yield (**Scheme 44**).[87]

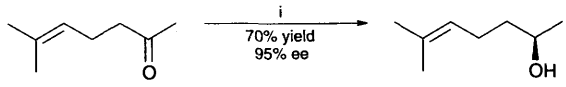


Scheme 44 *Reagents*: i, Bu^nLi, THF, −5 to +5 °C

1.6 Using biotransformations

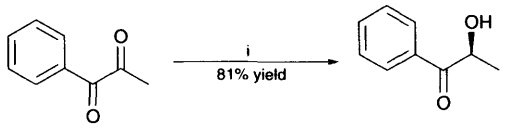
The aldol reaction of glyceraldehyde and sodium pyruvate proceeds under the influence of 2-keto-3-deoxy-6-phosphogluconate (KDPG) aldolases to give sodium (4*S*,5*R*)-4,5,6-trihydroxy-2-oxohexanoate in mediocre yield but excellent enantioselectivity. The reaction is, however, slow, requiring four days for complete reaction to be attained.[88]

A microbial reduction of ketones which seemingly violates Prelog's rule has been reported. *Yarrowia lipolytica* reduces prochiral ketones to (*R*)-alcohols in variable yield and with poor to excellent enantiomeric excess (**Scheme 45**).[89]



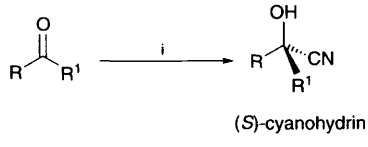
Scheme 45 *Reagents*: i, *Y. lipolytica*

Highly enantio- and regio-selective reduction of 1,2-diketones may be carried out using bakers' yeast (**Scheme 46**).[90]



Scheme 46 *Reagents*: i, bakers' yeast, pH 7, 30 °C, 3 h

The scope of the well-known enzyme-catalyzed addition of HCN to aryl aldehydes has been extended with the recent announcement of the first use of a recombinant hydroxynitrile lyase. MeNHL is such an enzyme isolated from *Manihot esculenta* and overexpressed in *Escherichia coli*. A wide range of aldehydes react with this enzyme, to give (*S*)-cyanohydrins in good to quantitative yield of mediocre to excellent ee (**Scheme 47** and **Table 16**).[91]



Scheme 47 *Reagents*: i, (*S*)-MeNHL [EC4.1.2.37], nitrocellulose, $Pr^i{}_2O$, HCN

Table 16

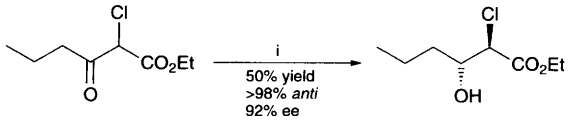
R	R^1	Yield/%	Ee/%
Et	H	86	91
Et	Me	91	18
Bu″	H	100	91
Bu″	Me	36	69
Pr^i	H	91	95
Bu′	H	80	94
Bu′	Me	81	28
$CH_2{=}CH$	H	100	47
$CH_3CH{=}CH$	H	100	92
Cyclohexyl	H	100	92
Ph	H	100	98
Ph	Me	13	78
2-Furyl	H	98	92

Catharanthus roseus cell cultures convert racemic 1-pyridyl alcohols into the corresponding enantiomerically pure species in excellent yield.[92]

Full details[93] of the efficient kinetic resolution of racemic hydroperoxides *via* selective reduction of

one enantiomer using horseradish peroxidase[94] have appeared.

2-Chloro-3-keto esters are reduced with high diastereo- and enantio-selectivity by a reductase from *Mucor plumbeus*.[95] *anti*-2-Chloro-3-hydroxy esters are the favoured products of the reaction (**Scheme 48**).

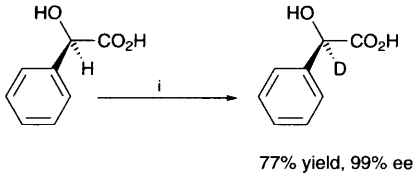


Scheme 48 *Reagents*: i, *M. plumbeus* CBS 110–116 biomass, pH 6, 24 h

The use of diketene as an acylating agent in kinetic asymmetric esterification of racemic chiral alcohols has been reported.[96]

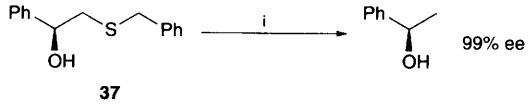
1.7 Miscellaneous methods

A remarkable isotopic labelling experiment allows an asymmetric sonication-promoted H–D exchange reaction to occur in optically active α-hydroxy acids *with retention of configuration* (**Scheme 49**).[97] The enantiomeric excess of the deuterated hydroxy acid produced in the reaction of (*R*)-mandelic acid with D_2O and cobalt–aluminium alloy in the presence of mild inorganic base, for instance, is virtually complete. The yield of the process is good. The authors offer no comment on the mechanism of this interesting reaction.



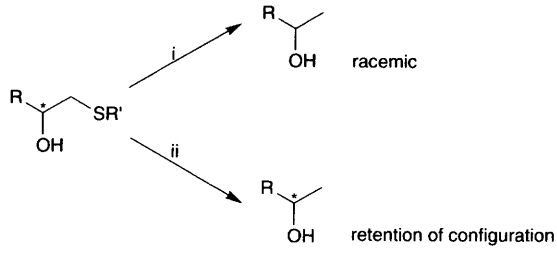
Scheme 49 *Reagents*: i, ultrasound, Ni–Co alloy, Na_2CO_3, D_2O, 60 °C, Ar, 2 h

Transformations which employ Raney nickel as a desulfurizing reagent are notoriously prone to side-reactions, so the report of such a reaction which leaves untouched an optically active and benzylic alcohol represents a useful synthetic method. Thus, reaction of (4*R*)-4-hydroxy-1,4-diphenyl-2-thiabutane **37** with Raney nickel under buffered conditions proceed in good yield to give (*S*)-2-phenylethanol with very high enantioselectivity (**Schemes 50** and **51** and **Table 17**).[98]



37

Scheme 50 *Reagent*: i, Raney Ni



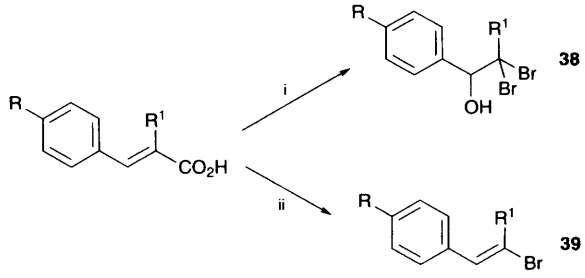
Scheme 51 *Reagents*: i, Raney nickel W-2; ii, Raney nickel W-2, $NaPHO_2O_2$, pH 5.2

Table 17

R	R'	Yield/%	Ee/%
Ph	Bn	84	99
Ph	Ph	98	99
Ph	*p*-Tolyl	82	99
n-C_6H_{13}	Bn	85	91
n-C_6H_{13}	Ph	84	91
n-C_6H_{13}	*p*-Tolyl	82	91

In an interesting modification of the Hunsdiecker reaction, manganese(II) acetate catalyzes the reaction of NBS with 3-arylpropenoic acids producing 1,2-dibromo-2-hydroxy-2-arylethanes **38** when one equivalent of brominating reagent is used, and giving the authentic Hunsdiecker product **39** when two equivalents of NBS are employed

(**Scheme 52** and **Table 18**).[99] The yields of both reactions are generally good.



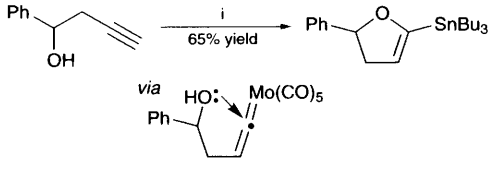
Scheme 52 *Reagents*: i, NBS (1 equiv.), $Mn(OAc)_2$ (0.1 equiv.), MeCN–H_2O, room temp.; ii NBS (2 equiv.), $Mn(OAc)_2$ (0.1 equiv.)

Table 18

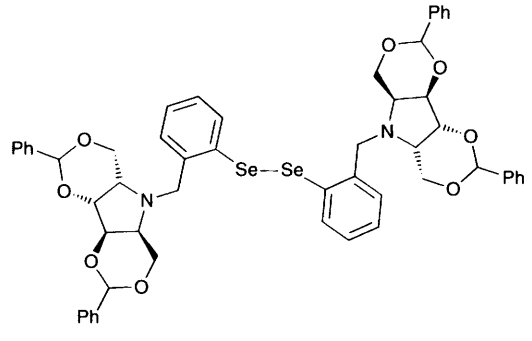
R	R^1	Yield of **38**/%	Yield of **39**/%
Me	H	82	83
H	H	78	73
OMe	H	87	91
OMe	Me	98	95
Cl	H	37	35

2 Preparation of ethers

But-3-ynyl alcohols react with tributylstannyl triflate and molybdenum hexacarbonyl in what is, formally, a 5-*endo-dig* process to give 2-stannyl-4,5-dihydrofurans in acceptable yield (**Scheme 53**).[100]



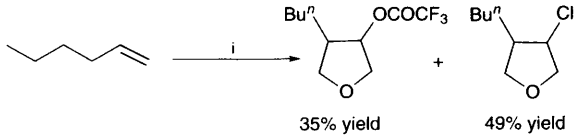
Scheme 53 *Reagents*: i, $Mo_2(CO)_6$, *hv*, Et_3N, Bu_3SnOTf, Et_3N,



40

2-Methoxy-1-arylselanyl alkanes may be prepared enantioselectively by reaction of alkenes with a chiral selanylating reagent prepared *in situ* from monochiral diselenide **40**, itself prepared from D-mannitol.[101]

Tetrahydrofurans may be prepared by a Prins reaction in the presence of TMS chloride and TFA (**Scheme 54**).[102]



Scheme 54 *Reagents*: i, CF_3CO_2H, Me_3SiCl, $(HCHO)_n$

2.1 Preparation of epoxides

Th unusual reactivity of perfluoroalkenes is illustrated in the newly reported epoxidation of such species by diethylhydroxylamine, a reagent not renowned for its oxidizing power.[103] These epoxidations proceed in good to excellent yield. An apparently serendipitous but most efficient epoxidation reaction utilizing a polypeptide has been reported: the reaction (first reported by Julia *et al.*) involves the reaction of electron-deficient alkenes with basic hydrogen peroxide in the presence of poly-(L)- or -(D)-leucine to give either α- or β-epoxides in excellent yield and with good to virtually complete enantiocontrol.[104] Two groups have independently reported the methyltrioxorhenium-(MTO) mediated use of the urea–hydrogen peroxide (UHP) adduct to epoxidize alkenes (**Scheme 55** and **Table 19**[105] and **Scheme 56**[106]).

Formaldehyde dithioacetals are monoalkylated to give sulfonium salts, which react with aromatic aldehydes to give 1-thioalkyl-2-aryl epoxides in moderate to good yield (**Scheme 57**).[107] The products are labile and undergo rearrangement under a variety of reaction conditions (**Scheme 58**).

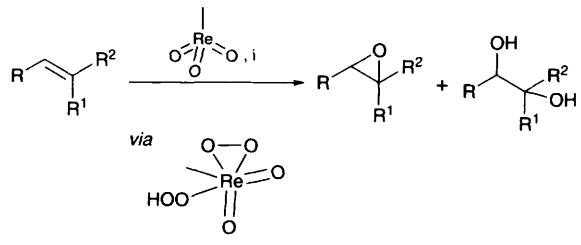
Dimethyl sulfate reacts with DMSO at 100 °C to generate the trimethylsulfonium cation which reacts with aldehydes and ketones in the usual fashion to produce epoxides.[108]

Two reports have appeared from the Jacobsen labs which deal with some of the drawbacks of the existing asymmetric epoxidation protocols developed by this group. Thus, tetrasubstituted alkenes may be epoxidized with high enantioselectivity using (1*R*,2*S*)-diaminodiphenylethane-derived manganese–salen complex **41** in the presence of hypochlorite and 4-phenylpyridine *N*-oxide[109] while a similar catalyst **42** allows epoxidation of unfunctionalized alkenes using peracids in place of hypochlorite.[110]

Full details of the use of KF to promote epoxidation of electron-deficient alkenes by Bu^tO_2H have appeared.[111]

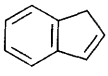
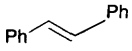
Chiral sulfimine **43** reacts with carbonyl compounds in the presence of base to give epoxides of moderate ee.[112]

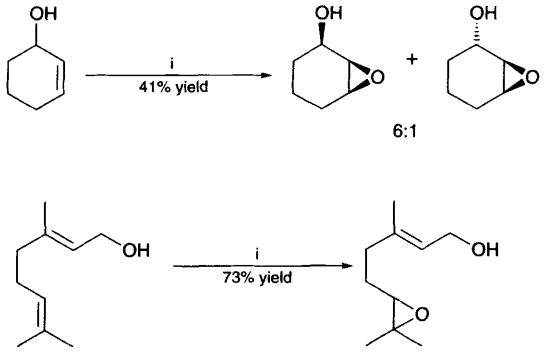
Electron-neutral alkenes may be enantioselectively epoxidized by an asymmetric dioxirane **44**



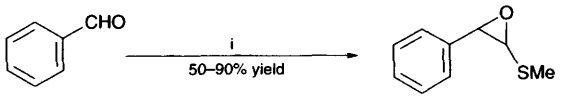
Scheme 55 *Reagents*: i, urea, H_2O_2, 20 °C

Table 19

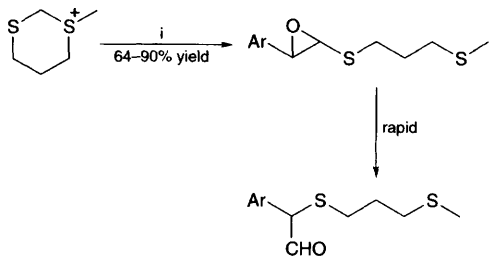
Alkene	Yield of epoxide/%	Yield of diol/%	Conversion
	99	1	98
	96	4	88
	≥95	0	46
	≥95	0	51
	≥95	0	44



Scheme 56 *Reagents*: i, UHP (3 equiv.), MTO (0.05 equiv.), CH_2Cl_2, 20 °C



Scheme 57 *Reagents*: i, $MeSCH_2S^+Me_2$, NaOH, DMF



Scheme 58 *Reagents*: i, ArCHO

derived from the corresponding binaphthyl ketone. Enantiomeric excesses of the products are poor to moderate (5–87% ee).[113]

The asymmetric dioxirane **45** (prepared from Mosher's acid) epoxidizes alkenes in good yield, but with poor ee.[114] Methyl(trifluoromethyl)dioxirane, prepared *in situ* from 1,1,1-trifluoroacetone in the presence of EDTA disodium salt, epoxidizes alkenes in good to excellent yield.[115]

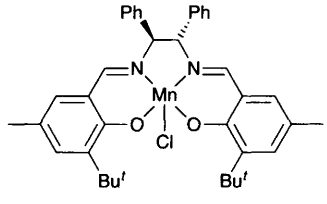
Full details of a new catalyst for dioxirane epoxidation of alkenes using (amongst others) *in situ*-generated ammonium dioxirane **46** have been documented by Denmark *et al.*[116]

Vinyl epoxides undergo hydrogenation without ring-opening upon reaction under high pressure with hydrogen in the presence of either binuclear palladium or cationic iridium catalysts.[117] Yields of saturated epoxides are moderate to excellent.

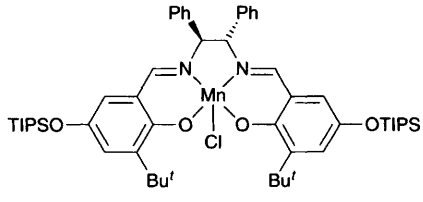
Tetracyanoethylene mediates the epoxidation of alkenes by hydrogen peroxide.[118]

2.1.1 Preparation of epoxides using biotransformations

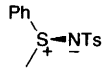
1,1-Disubstituted alkenes may be epoxidized in moderate ee by chloroperoxidase.[119] Hydrogen



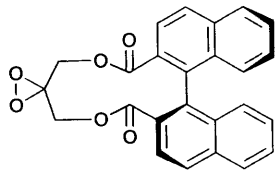
41



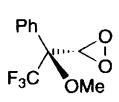
42



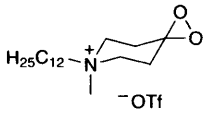
43



44



45

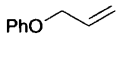
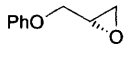
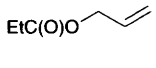
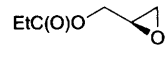
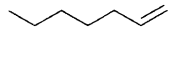
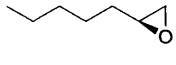
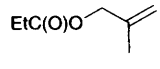
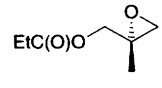
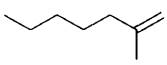
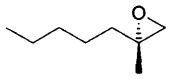


46

peroxide provides the oxidizing source (**Scheme 59** and **Table 20**).

Scheme 59 *Reagents*: i, chloroperoxidase, H_2O_2

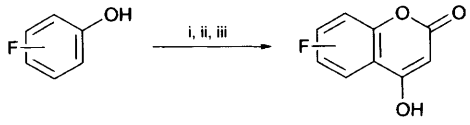
Table 20

Alkene	Epoxide	Yield/%	Ee/%
		89	49
		55	89
		1	46
		12	24
		2	10
		34	94
		23	95

3 Preparation of phenols

4-Hydroxycoumarins which are fluorinated in the benzenoid ring may be prepared in good overall yield by a three-step reaction of fluorophenols.[120]

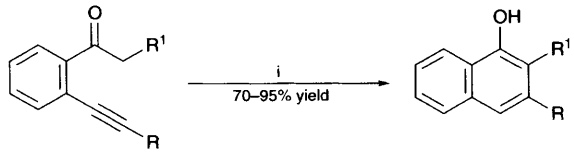
Thus, symmetrical fluorinated diphenyl esters of malonic acid react under Lewis acid catalysis at high temperature to give 3-(2-carboxyacetyl)-4-hydroxycoumarins, which may be deacylated to give the parent hydroxycoumarins (**Scheme 60**).



Scheme 60 *Reagents*: i, $POCl_3$, $CH_2(CO_2H)_2$; ii, $AlCl_3$, 180 °C, 10 min; iii, H_2SO_4, 180 °C

Full details have appeared describing how arenes may be hydroxylated in moderate to good yield under electrolytic conditions to give phenols.[121] In certain cases, complex mixtures of isomeric products result.

3-Alkyl-1-naphthols are prepared in good to excellent yield by the 6-*endo-dig* cyclization of 2-(1-alkynyl)benzophenones (**Scheme 61**).[122]



Scheme 61 *Reagents*: i, $KN(SiMe_3)_2$, toluene, −78 to 80 °C

The carbon–silicon bond of a disilane may be considered as a hydroxy equivalent: such disilanes react with TBAF and hydrogen peroxide to give phenols in moderate to good yield.[123]

Arylboronic acids are rapidly oxidized at temperatures lower than ambient to the corresponding phenols upon reaction with dimethyldioxirane.[124]

The Fries rearrangement of acyloxynaphthalenes is catalyzed by scandium tris(triflate) in refluxing toluene.[125]

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