Imines, enamines and oximes

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Reviewing the literature published between January 1995 and January 1997
Continuing the coverage in *Contemporary Organic Synthesis*, 1997, **4**, 183

1 Introduction

This article reviews modern methodology involving the synthesis and utility of imines, enamines and oximes. A previous paper covering the literature from May 1993 to January 1995 has been published in this journal.[1]

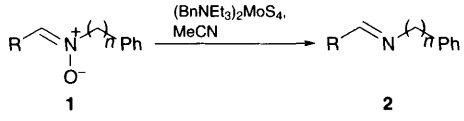
2 Imines

2.1 Formation of imines

An efficient synthesis of aromatic acetonyl imines can be conducted using aromatic amines and 2-methoxypropene using pyridinium toluene-*p*-sulfonate as catalyst. Yields of 97–100% have been obtained.[2]

Trimethyl orthoformate was found to be a mild and effective dehydrating reagent for both solution and solid phase imine formation from amines and aldehydes or ketones (88–100%).[3]

Nitrones **1** react with benzyltriethylammonium tetrathiomolybdate in acetonitrile to give the corresponding imines **2** in 60–88% yields (**Scheme 1**). The reaction is chemoselective and sulfoxides, azoxybenzenes and nitro functions are unaffected.[4]



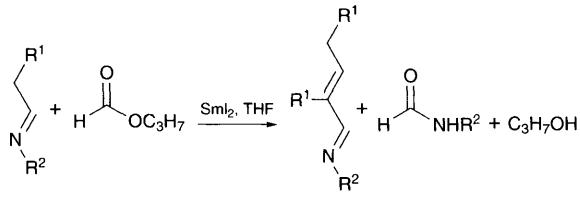
1 **2**

R = Me or aryl
n = 0 or 1

Scheme 1

The condensation of various aldehydes and ketones with amines to prepare imines can be achieved in high yield (65–100%) by conducting the reaction over Algerian bentonite, a natural clay. This method was not successful for aromatic ketones.[5]

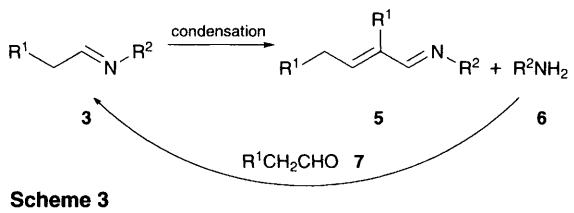
The self condensation of imines **3** was also found to occur when the samarium diiodide catalyst (or samarium triiodide) was used in conjunction with stoichiometric equivalents of propyl formate **4** to form the α,β-unsaturated imines **5** in yields of 42–98% yield (**Scheme 2**).[6]



3 **4** **5**

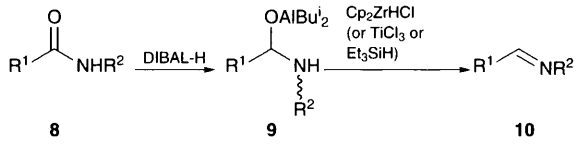
Scheme 2

Trapping of the amine by-product **6** formed during this condensation, when conducted in the absence of propyl formate **4**, with aldehydes **7** results in the regeneration of the starting imines under the reaction conditions. This idea resulted in the aldol condensation of imines **3** in a catalytic process utilising samarium diiodide (10 mol%) to form α,β-unsaturated imines **5** in yields of 23–99% (**Scheme 3**).



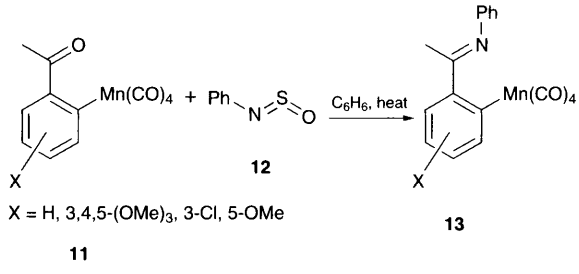
Scheme 3

Secondary carboxamides **8** can be reduced to *N*-substituted imines **10** using diisobutylaluminium hydride to form aluminium amides **9** which can then be reduced with Cp_2ZrHCl in 53–93% yields. Triethylsilane or low-valent titanium species can also reduce the aluminium amides **9** although in lower yields (**Scheme 4**).[7]



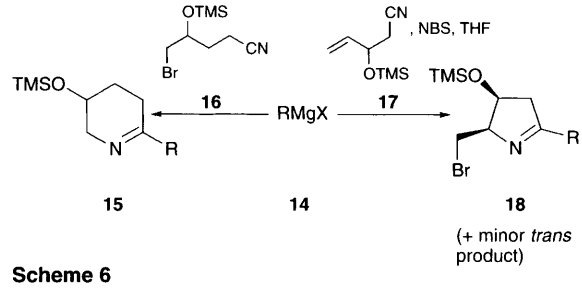
Scheme 4

Ortho-manganated aryl imines **13** can be prepared *via* a new route involving the reaction of *ortho*-manganated acetophenones **11** with PhNSO in 47–62% yields (**Scheme 5**).[8]



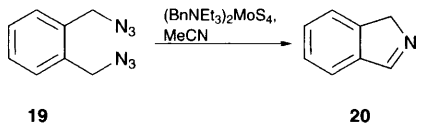
Scheme 5

Functionalised cyclic imines **15** can be prepared by the addition of Grignard reagents **14** to ω-bromonitriles **16**. γ,δ-Unsaturated nitriles **17** react with the Grignard reagents **14** to give the 1,2-addition products which can then undergo cyclisation either directly or *via* addition of *N*-bromosuccinimide (**Scheme 6**).[9]



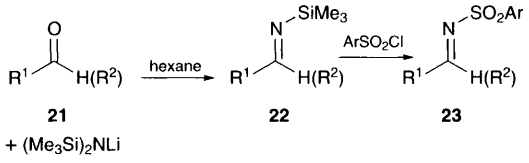
Scheme 6

Bisazides **19** can undergo a reduction with tetrathiomolybdate to form cyclic imines **20** in 65–92% yields (**Scheme 7**).[10]



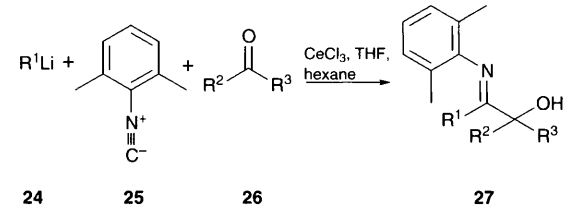
Scheme 7

A facile one-pot conversion of aldehydes or ketones to *N*-sulfonyl imines **23** can be achieved by treating the carbonyl compound with lithium hexamethyldisilazide to form the *N*-trimethylsilylimine **22** which can then be treated with a sulfonyl chloride to give the desired *N*-sulfonyl imines **23** in quantitative yields (**Scheme 8**).[11]



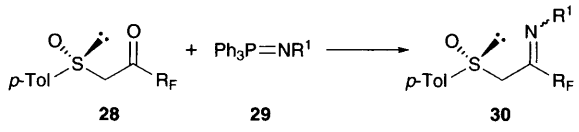
Scheme 8

The addition of alkyllithium reagents **24** to a mixture of an anhydrous lanthanide salt and 2,6-xylyl isocyanide **25** can provide the corresponding (alkanimidoyl)lanthanide(III). The best results were achieved using cerium(III) chloride. Treatment of (alkanimidoyl)cerium(III) with a carbonyl compound **26** results in the formation of the addition product, an α-hydroxy imine **27** in 54–99% yield (**Scheme 9**).[12]



Scheme 9

The synthesis of enantiomerically pure fluoroalkyl(arylsulfinyl)methyl imines **30** can be achieved by the displacement of a chloride from an acetimidoyl chloride with (*R*)-lithiomethyl *p*-tolyl sulfoxide in 70–100% yield. The second route involves an aza-Wittig reaction between *N*-aryliminophosphoranes **29** and (*R*)-γ-fluoroalkyl-β-keto sulfoxides **28** to give the imine product **30** in 32–90% yields (**Scheme 10**).[13]



28 29 30

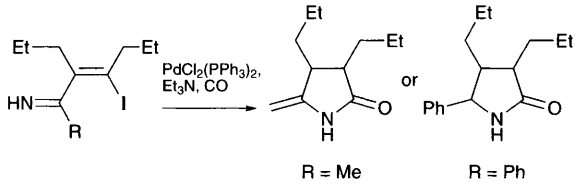
R^1 = Ph, *p*-$MeOC_6H_4$

R_F = CF_3, CF_2Cl, CHF_2, CF_2CF_3, CH_2F

Scheme 10

2.2 Imine cyclisations

The reactions of Z-β-iodo-α,β-unsaturated imines **31** with carbon monoxide in the presence of a palladium - phosphine catalyst can generate γ-lactams **32** and **33** (**Scheme 11**).[14]

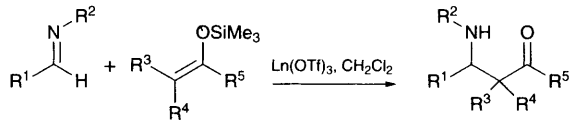


R = Me R = Ph

31 32 33

Scheme 11

The reactions of imines **34** with silyl enolates **35** in the presence of a catalytic amount of lanthanide trifluoromethanesulfonates (triflates) or scandium triflate smoothly provide β-amino ester derivatives **36** (**Scheme 12**). The rare earth metal triflates also catalyse the Diels–Alder reactions of imines with dienes to provide tetrahydropyridine or tetrahydroquinoline derivatives.[15]

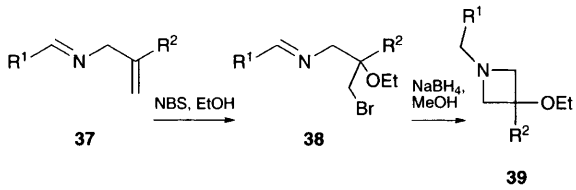


34 35 36

Scheme 12

Imines of α-amino acid esters can undergo thermal 1,3-dipolar cycloaddition reactions to [60]fullerene to give fullerene-fused proline derivatives.[16]

Treatment of 2-substituted prop-2-enyl imines **37** with *N*-bromosuccinimide in ethanol leads to 2-alkoxy-3-bromo-3-substituted imines **38** (71–95%) which are excellent precursors to 3-alkoxyazetidines **39** *via* reduction of the imine **38** with sodium borohydride and subsequent intramolecular nucleophilic substitution in yields of 65–97% (**Scheme 13**).[17]

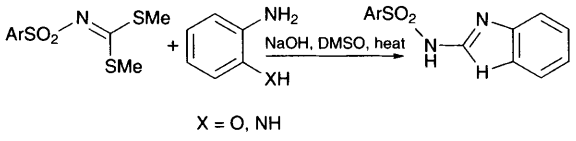


37 38 39

Scheme 13

Diphenylnitrilimine, prepared *in situ* by the action of a base upon *N*-phenyl benzenecarbohydrazonoyl chloride, has been shown to undergo 1,3-dipolar additions with some dipolarophiles at a greater rate when supported on a solid mineral support and subjected to microwave radiation, than when treated in a solvent with heating. Yields of 87–99% were obtained.[18]

Bis-thio sulfonyl imines **40** can undergo reactions with *o*-aminophenol or 1,2-diaminobenzene **41** to give heterocycles **42** in yields of 58–84% (**Scheme 14**).[19]

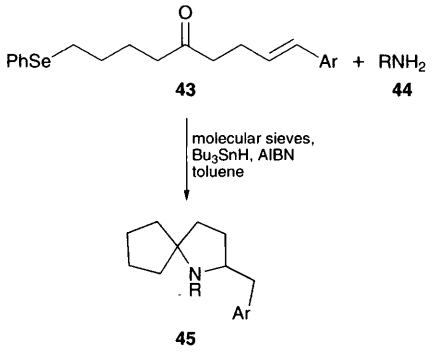


X = O, NH

40 41 42

Scheme 14

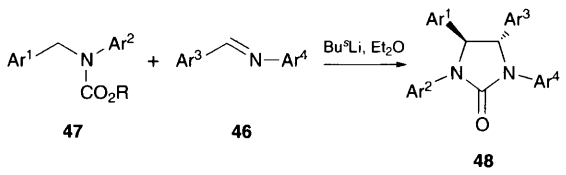
A tandem radical cyclisation of imines has provided a novel synthetic route to bicyclic nitrogen heterocycles **45** involves a radical cyclisation onto the C-centre of the imine to generate intermediate aminyl radicals, which then undergo a second cyclisation onto an alkene. The imines are generated *in situ* from the corresponding ketone **43** and amines **44**. This approach can provide access to spiro bicyclic products (**Scheme 15**).[20]



43 44 45

Scheme 15

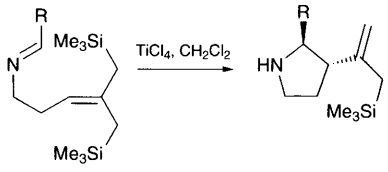
The reaction of imines **46** with α-nitrogen carbanions, prepared from the substituted amines **47**, can lead to the synthesis of *trans*-4,5-disubstituted imidazolidin-2-ones **48** in yields of 22–92% (**Scheme 16**). The *trans*:*cis* ratio varies from 84:16 to >99:1.[21]



47 46 48

Scheme 16

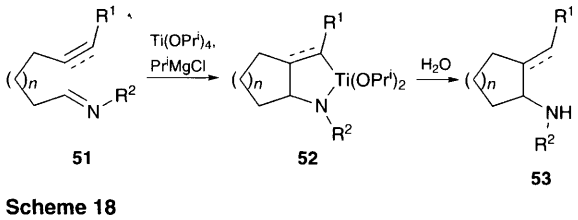
1,3-Bis(silyl)isopropylidene imines **49** can undergo intramolecular cyclisations in an efficient new procedure to provide pyrrolidines **50** in a stereocontrolled manner (**Scheme 17**). Further cyclisations can be conducted using the new functionalities of the amine and the allylic silane to provide isotropanes and bridged pyrrolizidines.[22]



49 50

Scheme 17

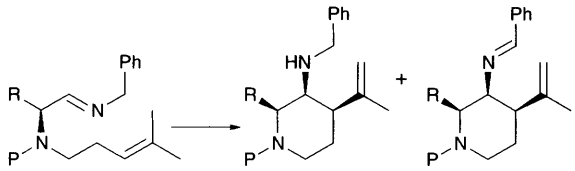
Unsaturated imines **51** can be used for the stereoselective synthesis of cycloalkylamines **53** by treatment with (η^2-propene)Ti(OPr^i)$_2$. The titanium reagent, formed *in situ* by the action of isopropylmagnesium chloride on titanium(IV) isopropoxide, causes a bicyclisation to occur forming the cyclic organotitanium intermediate **52**. Subsequent hydrolysis results in the formation of the desired cycloalkylamines **53** (**Scheme 18**).[23]



51 52 53

Scheme 18

N-Protected-*N*-(4-methylpent-3-enyl)amino aldehyde benzylimines **54** (obtained from alanine, leucine or phenylalanine methyl esters in a five step procedure) can be cyclised diastereoselectively in the presence of Lewis acids to 3-amino-2,4-dialkyl-substituted piperidines **55** and **56** (**Scheme 19**). When the protecting group is benzyl the reactions are more selective than the corresponding toluene-*p*-sulfonates. The product distribution depends upon the the type of Lewis acid and nitrogen protecting group.[24]

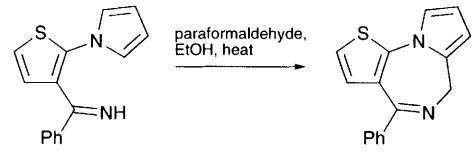


54 55 56

P = Bn, Ts

Scheme 19

4-Phenyl-6*H*-pyrrolo(1,2-*a*)thieno[3,2-*f*][1,4]diazepine **58** has been isolated in a one-step procedure (54% yield) *via* treatment of the imine **57** with paraformaldehyde (**Scheme 20**).[25]

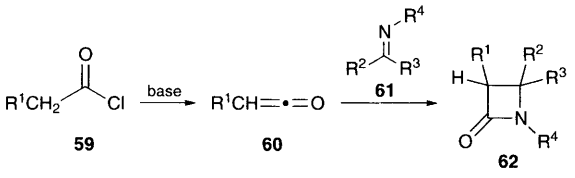


57 58

Scheme 20

2.3 β-Lactam formation from imines

Imines **61** provide a convenient starting material for the preparation of β-lactams **62**. The most common method is to treat the imine with a ketene **60**, formed by the action of a base on an acid chloride **59** (**Scheme 21**).

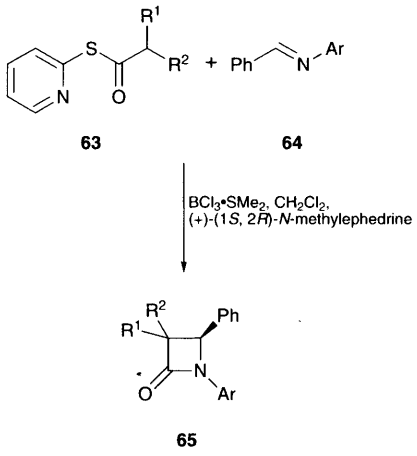


59 60 61 62

Scheme 21

Hence, the chiral imines derived from D-glyceraldehyde and D-threonine derivatives can react with oxglycyl chloride and triethylamine to give optically active *cis*-substituted β-lactams.[26]

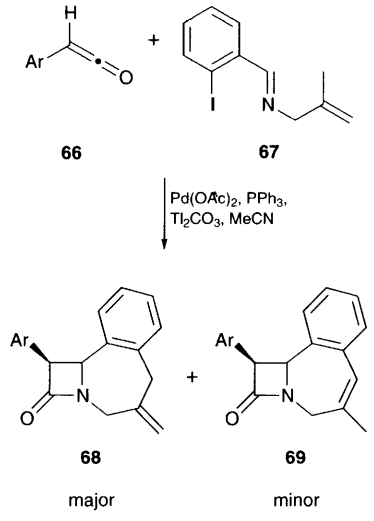
An enantioselective one-pot synthesis of β-lactams **65** can be achieved by treating the enolates derived from achiral 2-pyridyl thioesters **63** and boron trichloride–dimethyl sulfide with an aromatic imine **64** in the presence of an enantiomerically pure amino alcohol. The β-lactam products **65** are obtained in 39–74% yield and 51–78% ee (**Scheme 22**).[27]



Scheme 22

The ester enolate–imine condensation has been studied with different metal enolates formed *via* the use of lithium diisopropylamide or potassium hexamethyldisilazide on chiral esters attached to (+)-camphor derivatives. The lithium or potassium enolates can also undergo transmetallation to provide access to zinc, boron or tin enolates. The 4*R*- or 4*S*-β-lactams are obtained in a highly stereoselective manner if the ester is formed from a chiral alcohol [(+)-camphor derivatives].[28]

Imines **67** can be used to prepare bicyclic β-lactams using ketenes **66** *via* a sequential and cascade imine–ketene [2+2] cycloaddition–palladium catalysed cyclisation. The bicyclic products are formed in 40–62% yield for the major product **68** (**Scheme 23**).[29]



Scheme 23

The [2+2] cycloaddition of ketenes to imines has also been used to prepare structurally diverse β-lactams using solid-supported combinatorial synthesis.[30]

The [2+2] cycloaddition of ketenes to imines has also been used in the total synthesis of Cardmonam (**Fig. 1**)—an antibacterial agent. The cycloaddition took place in 85% yield.[31]

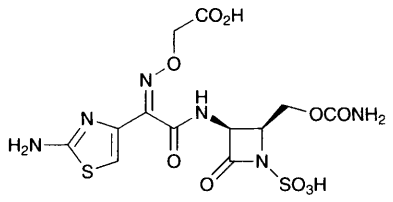
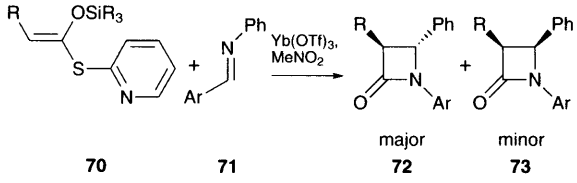


Fig. 1

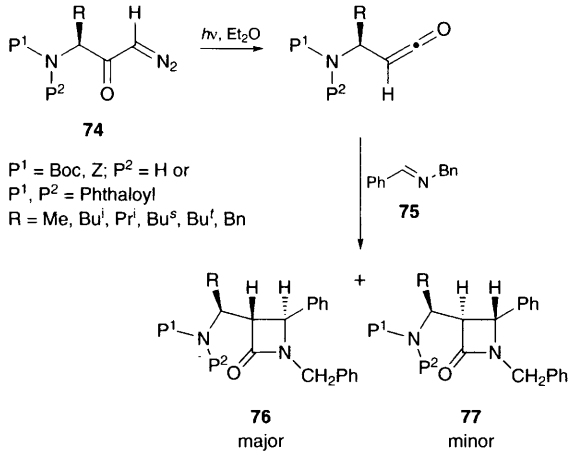
Ytterbium(III) triflate catalyses the synthesis of β-lactams **72** and **73** from silyl ketene thioacetals **70** and imines **71** by a two- or three-component reaction in 16–99% yield with predominantly *trans* products (**Scheme 24**).[32]



Scheme 24

A stereoselective one-pot synthesis of β-lactams can be conducted by the reaction of 2-pyridyl thioesters with imines in the presence of a tertiary amine and aluminium tribromide or ethylaluminium dichloride. Yields of 20–85% are obtained and high *trans* selectivity is observed. The condensation may be conducted without the amine and with sub-stoichiometric amounts of Lewis acid, but lower yields are obtained.[33]

The photochemical rearrangement of α-diazo ketones **74** in the presence of imines led to the diastereoselective formation of aminoalkyl-substituted β-lactams **76** and **77** (Scheme 25) with *trans*:*cis* selectivities of 59:41 to 93:7.[34]

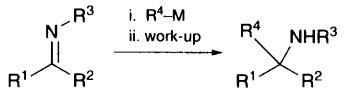


Scheme 25

2.4 Addition of organometallics to imines

A variety of organometallic reagents have been added across the imine bond, which after work-up

leads to the formation of α-substituted amines **79** (**Scheme 26**).



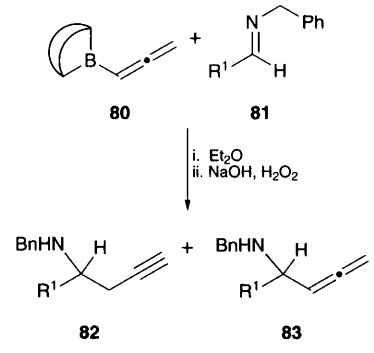
78 **79**

Scheme 26

This reaction becomes an even more useful component in the chemist's arsenal when it is carried out asymmetrically, using either chiral imines or chiral organometallics. The results of several recent experiments are condensed in **Table 1**.

2.5 Boration of imines

B-Allenyl-9-BBN **80** reacts in a highly chemoselective and regiospecific manner with imines **81**, the allenyl moiety undergoing the transfer to the imine carbon atom with allenic to prop-2-ynylic rearrangement while the boron moiety bonds to the nitrogen atom. Subsequent oxidation results in the formation of the corresponding buta-3-ynyl amines **82** in 84–90% yield with very little of the allenic amine **83** formed (4% when $R^1 = Pr^i$, 2% when $R^1 = Ph$) (**Scheme 27**).[57]



80 **81** **82** **83**

Scheme 27

Chirally modified allylboranes undergo enantioselective additions to *N*-(trimethylsilyl)benzaldimine to give 4-amino-4-phenylbutene. The highest enantioselectivity (73% ee) was obtained with (−)-*B*-allyldiisopinocampheylborane which gave the allylic amine product in 70% yield.[58]

Several coinage metal (copper, silver and gold) complexes containing bulky, chelating bis(phosphine) ligands are selective catalysts for the hydroboration of imines using catecholborane.[59]

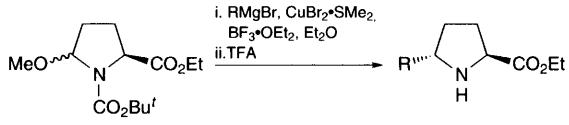
2.6 Reduction of imines to amines

The reduction of imines to the corresponding secondary amines may be conducted in a variety of ways using numerous different methods. The most recent are listed in **Table 2**.

2.7 Iminium species

Preformed iminium salts derived from aldehydes other than formaldehyde have been shown to be effective aminoalkylation reagents for electron rich aromatic compounds (indoles, phenols, *N*,*N*-dimethylaniline).[75]

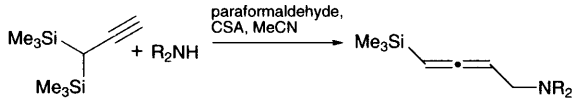
The addition of Grignard derived organocopper reagents to *N*-acyliminium ions obtained from proline or 4-substituted prolines **84** proceeds in high yield and stereoselectivity. The adducts are deprotected with TFA to give the free amines **85** (**Scheme 28**) with diastereoselective excesses of 78–97% over the two steps.[76]



84 **85**

Scheme 28

Iminium ions, formed *in situ* by the action of amines **86** upon paraformaldehyde in the presence of camphorsulfonic acid, can react with 1,1-bis(trimethylsilyl)prop-2-yne **87** to give trimethylsilyl substituted α-allenic amines **88** in 42–67% yield (**Scheme 29**).[77]



87 **86** **88**

Scheme 29

A new approach to the synthesis of 3-substituted tetrahydroisoquinolines **91** *via* nucleophilic addition to N-tosyliminium ions has been reported. The *N*-tosyliminium ions are formed *in situ* by the action of tin(IV) chloride on α-acetylsulfonamides **89** and subsequently trapped with cyanotrimethylsilane **90** to give the α-cyanosulfonamides **91** in 16–99% yields (**Scheme 30**).[78]

Table 1 Organometallic reagent–imine addition

Imine	Organometallic reagents	Yield (%)	Ee/de (%)	Comments	Ref.
Various	Vinylmagnesium bromide and cerium trichloride	38–67	—	2 Equiv. of vinyl magnesium bromide are used to form a synthetic equivalent to a crotyl anion	35
Various	Bu_2SnClH–HMPA + alkylating agent	40–96	—	Hydrostannylation of imines followed by alkylation of intermediate tin amides	36
N-Metallo imines derived from benzaldehyde	Butyllithium + chiral alcohols	52–85	1–52 ee	*N*-Aluminium, *N*-boryl and *N*-silyl imines were used. Best results were obtained with *N*-aluminium imines	37
Chiral imine, using D-(−)-phenylglycine auxiliary	$TiCl_4$ (or TiF_4) + silyl ketene acetal	60–67	—	$TiCl_4$ give predominantly (3*R*)-amino ester products. TiF_4 gives predominantly (3*S*)-amino ester products	38
N-Diphenylphosphinylimine	Diethylzinc	81	95	Alkylation in the presence of stoichiometric (1*R*,2*S*)-*N*-(4-vinylbenzyl)-*N*-methylnorephedrine to give *N*-diphenylphosphinylamine	39
Chiral imine using α-naphthylethyl group as auxiliary	Organolithiums in the presence of boron trifluoride etherate	76–99	26–100	Asymmetric addition	40
N-[(*S*,*S*)-3,5-bis(1-hydroxyethyl)-1,2,4-triazol-4-yl]arylamines	Grignard reagents	60–76	70–99 de	Diastereoselective alkylations	41
Diphenylphosphinoylimine	Diethyl zinc + chiral aziridino alcohols	18–92	3–94 ee	90% of the ligands can be recovered during the work-up procedure	42
Various	Allylstannane + π-allylpalladium chloride dimer	72–99	—	Chemoselective allylation of imines in the presence of aldehydes	43
Various	Allylic tin(IV) + tin(II) chloride	89–91	—	*anti*-Products formed in acetonitrile. *syn*-Products formed in dichloromethanc. The reaction conditions are also effective for aldehydes and ketones	44
Chiral imine, 1-(2-methoxyphenyl)-ethylamine auxiliary	Organolithiums	56–85	90–96 de	Highly diastereoselective addition	45
Various	Organolithium reagents + proline derived catalyst	42–96	10–21 ee	The chiral catalyst, (*S*)-1-methyl-2-(2-methoxy-phenoxymethyl)-pyrrolidine, favours (*S*)-amine formation	46
Various	Reformatsky reagents + trimethylsilyl chloride	53–80	—	A wide variety of substituted β-lactams can be produced using this methodology	47
Various	DIBAH–HMPA + chiral acetylenic ester	34–90	40–98	A new approach to α-aminoalkylacrylic acid derivatives	48
Benzyl imine with dibenzyl-D-glyceraldehyde auxiliary	Methylmagnesium bromide	51	—	Stereoselective synthesis of α-hydroxy-β-amino acids using D-glyceraldehyde as the homochiral source. The optical rotation was used to confirm that a single diasteromer was formed	49
Aldimines using (*S*)-1-phenylethyl auxiliary	Organoallyl reagents	80–100	70–99 de	Diastereoselective addition of allylmetal compounds to imines derived from (*S*)-1-phenylethanamine	50

Table 1 — *continued*

Imine	Organometallic reagents	Yield (%)	Ee/de (%)	Comments	Ref.
Various	Magnesium or zinc + allyl bromide	80–99	—	Magnesium- or zinc-mediated allylation of imines	51
Hydroxy aryl imines	Diallyltin dibromide	55–70	—	Allylation of functionalised imines by diallyltin dibromide	52
Various	Samarium + allyl bromide	52–80	—	Allylation of imines with samarium allyl bromide system	53
Aldjmines	Allylic barium reagents	42–99	—	α-Adducts are obtained at low temperatures (−78 °C), γ-adducts are obtained at higher temperatures (0 °C)	54
Imines derived from glyoxylate and (*R*)- or (*S*)-1-phenylethylamine	Allyltrichlorostannanes	72–76	80–90 de	The transmetallation of 4- and 5-benzyloxypent-2-enyl(tributyl)stannanes with tin(IV) chloride and subsequent addition to imines results in 1,5-asymmetric induction	55
Various	Allyltributylstannane + lanthanide triflates	29–73	—	Lanthanide triflates are effective catalysts for the formation of homoallylamines from imines using allyltributylstannane	56

Iminium salts **92** can be treated with imines **93** under acidic conditions to regioselectively and diastereoselectively synthesise β-amino ketones **94** in yields of 62–78% (**Scheme 31**).[79]

A new preparation of *N*-acyliminium salts **97** uses the reaction of nitrilium salts **95** with non-enolisable ketones **96** to give the desired *N*-acyliminium salts **97** in 67–91% yields (**Scheme 32**). Ketones without electron donating substituents react only with *N*-arylnitrilium salts (**95**, R = Ar).[80]

An *in situ* formation of an acyliminium ion, from the action of toluene-*p*-sulfonic acid in acetic acid on the correponding amide, provided a new entry into the erythrinane skeleton *via* a tandem Diels–Alder–*N*-acyliminium cyclisation in 70% yield.[81]

N-Acyliminium salts, formed *in situ* by the action of triflic anhydride upon *bis*carbamates **99**, can react with 1,1-difluorovinyl methyl ethers **98** to generate β-amino-α,α-difluoro ketones **100** in 54-88% yield (**Scheme 33**).[82]

2.8 Sulfonyl imines, sulfanyl imines and sulfinyl imines

Sulfonyl imines **101** can undergo a novel catalytic asymmetric reaction to form aziridines *via* mediation with sulfur ylides. The sulfonyl imine is treated with a rhodium carbenoid, generated *in situ*, in the presence of a chiral sulfur ylide (**Scheme 34**) to generate the aziridines **103** in 70–88% yields.[83]

N-Sulfonyl imines **101** can react with 3-(alkoxycarbonyl)propenyldimethylsulfonium bromide **104** in the presence of potassium carbonate in acetonitrile [or with the preformed dimethylsulfonium 3-(alkoxycarbonyl)allylides] to generate *N*-sulfonyl-2-[(*E*)-2-(alkoxycarbonyl)ethenyl]-3-arylaziridines **105** in 42–62% yields (**Scheme 35**).[84]

Sulfonyl imines **101** can react with alkynyl sulfides **106** to afford α,β-unsaturated thioimidates **107** in 40–100% yields (**Scheme 36**).[85]

A facile preparation of β-phenylvinylaziridines **109** uses the reaction of *N*-sulfonyl imines **101** with cinnamyl bromide **108** in the presence of catalytic dimethyl sulfide and solid potassium carbonate in acetonitrile. The aziridines **109** are prepared in 30–72% yields and with 24–42% diastereoselectivity (**Scheme 37**).[86]

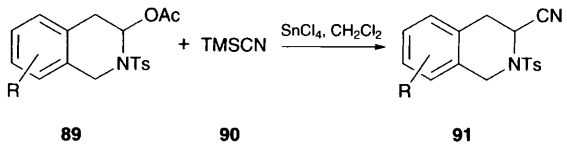
Another route to aziridines from sulfonyl imines uses a phenacyl transfer from dimethylsulfonium phenacylide to produce 2-benzoyl-1-arylsulfonyl-aziridines in yields of 30–38%.[87] Prochiral sulfides **110** undergo a novel asymmetric catalytic transformation to sulfonyl imines **112** by the reaction with PhI=NTs **111** in the presence of a catalytic amount of copper iodide and 2,2-bis[(4*R*)-phenyl-4,5-dihydro-1,3-oxazol-2-yl]propane ligands in 37–82% yields and 9–65% ee (**Scheme 38**).[88]

Sulfonyl imines derived from camphor can be treated with organometallic reagents to produce sulfenamides asymmetrically in high optical purity and with yields of 68–76%.[89]

The reaction of perfluoroalkanesulfonyl amides **113** with dialkyl sulfides in the presence of stoichiometric amounts of lead tetraacetate produces *N*-perfluoroalkanesulfonyl sulfimides **114** in yields of 46–77% (**Scheme 39**).[90]

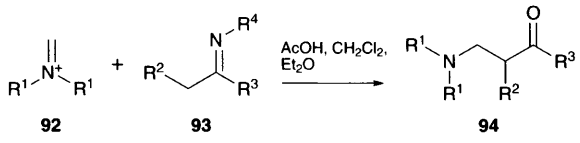
Table 2 Reduction of imines

Imine	Reduction conditions	Yield (%)	Ee/de (%)	Comments	Ref.
Various	$Ni(OAc)_2$, 1-(2-hydroxy benzylidene)thiosemi carbazide, triethylsilane, DMSO	24–98	—	Hydrosilyation of imines is followed by a basic work-up to provide the secondary amines	60
Various	Cp_2MoH_2, AcOH, toluene, and a basic work-up	48–89	—	In the presence of a ketone only the imine was reduced	61
Various	Rh^+(1,5-COD) (η^6-$PhBPh_3^-$), 1,4-bis(diphenylphosphino)-butane, THF, MeOH, H_2 (200–600 psi)	27–95	—	The extent of imine reduction is highly dependent on the substrate structure and solvent employed	62
C,*N*-Diphenyl imine	Iridium complexes of orthometallated triaryl phosphites, MeOH, $ClCH_2CH_2Cl$, H_2 (30 atm)	99	—	—	63
N-Tosylimines	Ru[(*R*)-BINAP]$(OAc)_2$, THF, H_2 (71.5 atm)	48–82	17–84	Asymmetric hydrogenation of *N*-tosylimines	64
C-Aryl-*N*-benzyl imines	Rh[(2*S*,4*S*)-bdpp](NBD)-ClO_4, C_6H_6, H_2 (70 atm), reverse AOT micelles (NBD = norborna-2,5-diene; AOT = aerosol OT or bis(2-ethylhexyl) sodium sulfosuccinate)	96–99	59–92	Asymmetric imine hydrogenation in the presence of reverse micelles. The presence of halides causes an inversion of the enantioselectivity	65
Cyclic imines (β-enamino esters)	$NaBH_4$, AcOH, MeCN	60–95	—	A method of synthesising *trans* disubstituted pyrrolidines	66
Various	(*S*,*S*)-Ethylenebis(η^5-tetra-hydroindenyl)titanium difluoride, Ph_3SiH, pyrrolidine, MeOH, THF	64–97	86–99	Acidic work-up in conjunction with a highly enantioselective imine hydrosilylation to produce secondary cyclic amines	67
N-Aryl imines	$[Ir(COD)Cl]_2$, $NaClO_4$, (*R*,*R*)-2,6-bis(1-diphenyl-phosphinoxyethyl)-pyridine, H_2 (59.2 atm)	0–100	7–55	Asymmetric hydrogenation of prochiral imines using tridentate C_2 symmetrical diphosphine complexes of iridium(I) and rhodium(I)	68
N-(α-Methyl-benzylidene)benzyl-amine and 2-phenyl-3,4,5,6-tetrahydro-pyridine	$[Ir(COD)Cl]_2$, protic amine, BINAP (or Tol-BINAP), MeOH, H_2	3–100 (by HPLC)	23–91	Protic amines act to improve catalyst performance	69
N-Methylbenzaldimine	$CpTiCl_2$[2Ph_2P-6-$C(CH_3)_3$-C_6H_3)], BuLi, $PhSiH_3$, THF, hexane	100	—	The *o*-phosphinophenol ligand system can have its steric or electronic properties tuned independently	70
1-Alkyl-3,4-dihydro-isoquinolines	$[Ir(COD)Cl]_2$, chiral diphosphines, phthalimide, toluene, H_2 (100 atm)	22–100	3–93	Five-membered imides improve the enantioselectivity and catalytic activity of the Ir complex	71
N-Aryl imines	Carboxylato(diphosphine)-iridium(III) complexes, THF, CH_2Cl_2, H_2 (39.5 atm)	29–100	2–90	Asymmetric hydrogenation of prochiral imines	72
Various	BH_3·SMe_2, (2*R*,5*R*)-2-phenyl-3-oxa-1-azaphosphinabi-cyclo[3.3.0]-octane–borane complex, toluene and a basic work-up	51–81	42–63	Enantioselective borane reduction of imines is catalysed by oxazaphospholide–borane complex to provide secondary amines	73
Various	RuCl[(1*S*,*S*)-*p*-TsNCH(Ph)-CH(Ph)NH_2] (η^6-*p*-cymene), formic acid, triethylamine, MeCN	82–99	77–97	Asymmetric transfer hydrogenation of imines	74



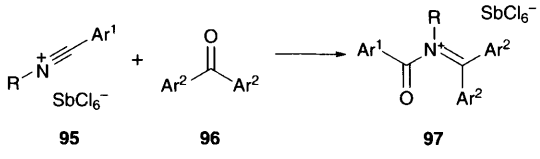
89 90 91

Scheme 30



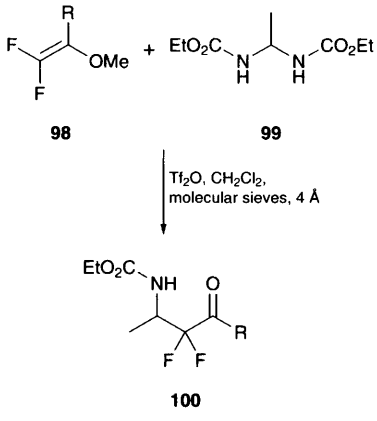
92 93 94

Scheme 31



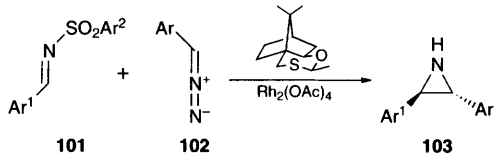
95 96 97

Scheme 32



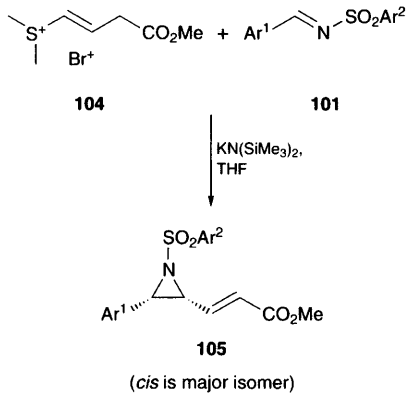
98 99 100

Scheme 33



101 102 103

Scheme 34



104 101 105

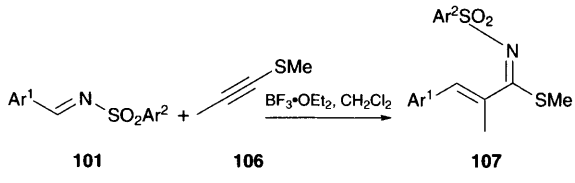
(*cis* is major isomer)

Scheme 35

S-Ethenylsulfimides **115** can be used to synthesise allyl vinyl ethers **117** in a two-step process. Treatment of the *S*-ethenylsulfimides with an allylic alcohol in the presence of sodium hydride leads to an intermediate ether which is then treated to a distillation at reduced pressure (0.66 atm) to give the allyl vinyl ether **117**.[91] If the *S*-ethenylsulfimides are treated with an amide then 2-substituted 4,5-dihydrooxazoles **116** are produced in yields of 53–98% (**Scheme 40**).[92]

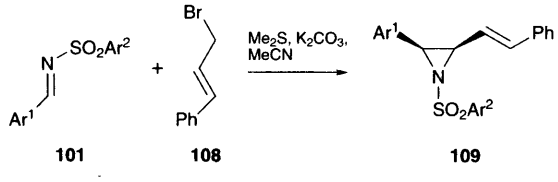
A diastereoselective rearrangement of *β*-substituted *δ*-hydroxy *N*-tosyl allylic sulfoximides **118** produces allylic amides **119** and **120** in the presence of a palladium(0) catalyst (**Scheme 41**).[93]

Chiral *N*-alkylidenesulfinamides **121** can be treated with allylmagnesium bromide to give the addition product **122** with complete stereoselectivity



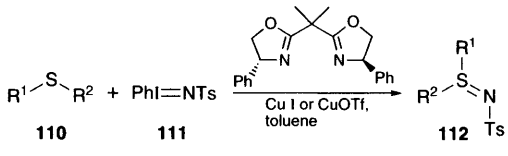
101 106 107

Scheme 36



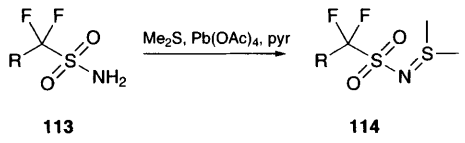
101 108 109

Scheme 37



110 111 112

Scheme 38

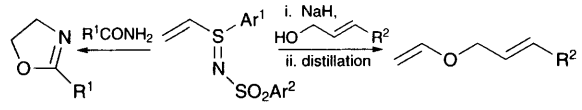


113 114

Scheme 39

(**Scheme 42**). Subsequent hydrolysis can lead to the formation of enantiomerically pure α-amino acids.[94]

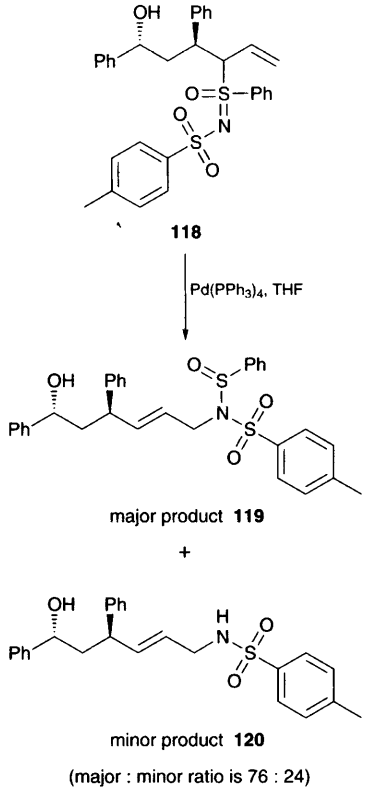
Non-racemic sulfinamides **124** can undergo a [3+2] cycloaddition with allyl sulfone **123** to give 2-aryl-3-pyrrolines **125** and **126** in yields of 62–74% and with 50–76% de (**Scheme 43**).[95]



115 117

116

Scheme 40



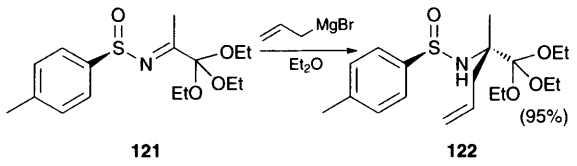
major product **119**

+

minor product **120**

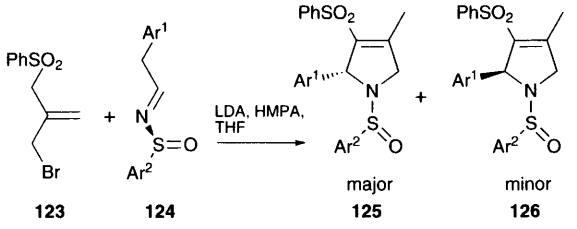
(major : minor ratio is 76 : 24)

Scheme 41



121 122

Scheme 42



123 124 major 125 minor 126

Scheme 43

The addition of α-phosphonate carbanions to (*S*)-sulfimides affords *N*-sulfinyl β-amino-phosphonates with diasteromeric ratios of 5:1 to 10:1. Separation of the major diastereomer and its conversion to the corresponding β-amino-phosphonates with acid allowed the stereochemistry of the new stereogenic centre to be determined as (*R*).[96]

Diethylaluminium cyanide reacts with enantiopure sulfimides to afford the corresponding *N*-sulfinyl α-cyano derivatives which can be hydrolysed with acid to give the corresponding α-amino acids in 80–95% de in a modified asymmetric Strecker reaction.[97]

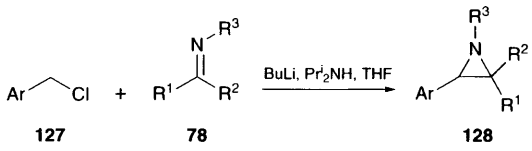
The addition of dimethyloxosulfonium methylide to optically pure sulfimides can afford *N*-sulfinyl aziridines in 58–70% de and with yields of 51–68%.[98]

Chiral sulfimides can be treated with sulfur ylides to provide access to aziridines asymmetrically. The stereochemical outcome of the aziridination is dependent on the nature of the methylene transfer reagent.[99]

2.9 Aziridination

A new asymmetric catalytic synthesis of aziridines *via* carbenoid transfer to imines yields the substituted aziridines in 17–37% yields and up to 67% enantiomeric excess by using the diazoacetates in the presence of the homochiral catalyst (*S*,*S*)-2,2-*bis*(4-phenyl-4,5-dihydrooxazol-2-yl)propane–Cu(MeCN)$_4$PF$_6$.[100]

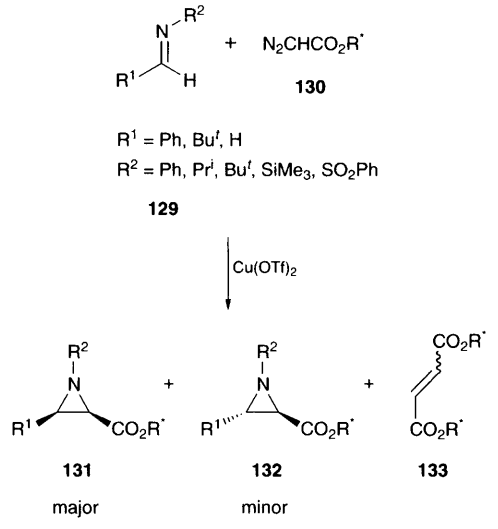
Imines **78** have also been used to synthesise aziridines **128** *via* a Darzens approach, involving the use of (heteroarylchloromethyl)lithium species. The substituted aziridines **128** are obtained in 30–85% yield (**Scheme 44**).[101]



127 78 128

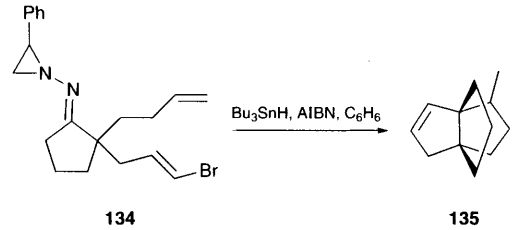
Scheme 44

A second asymmetric synthesis of aziridines **131** and **132** *via* the reactions of imines **129** with chiral diazoacetates **130** and copper complexes [*e.g.* copper(II) triflate] leads to the products **131** and **132** in 5–95% yield, with *cis*:*trans* ratios ranging from 0.4:1 to >20:1 (**Scheme 45**). Those imines possessing bulky or electron withdrawing groups on the nitrogen atom afford lower yields. Dialkyl maleate and dialkyl fumarate **133** are common by-products, produced in low yields.[102]



Scheme 45

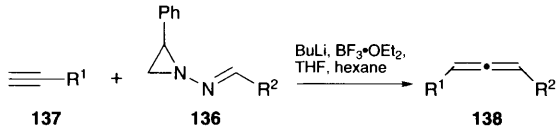
N-Aziridinyl imines **134** can be readily prepared by the reaction of *N*-aziridinyl amines with ketones. The resultant *N*-aziridinyl imines **134** can undergo tandem radical cyclisations to form [3.3.3]propellanes **135** (**Scheme 46**).[103]



134 135

Scheme 46

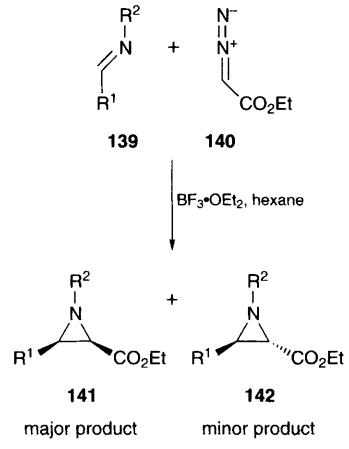
N-Aziridinylimines **136** can react with alkynylboranes, formed *in situ* from the corresponding alkynes **137**, to produce allenes **138** in 42–83% yields (**Scheme 47**).[104]



137 136 138

Scheme 47

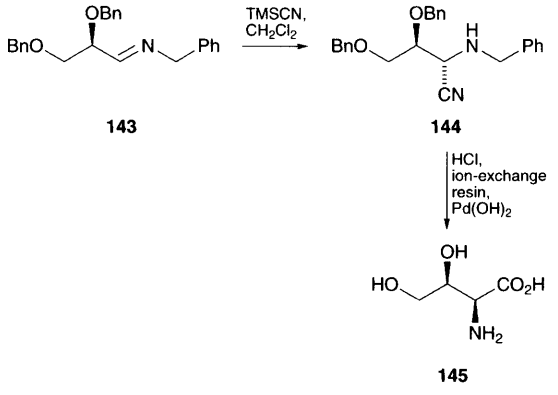
Aziridines can be formed by the action of ethyl diazoacetate **140** on imines **139** in the presence of the catalyst methylrhenium trioxide in yields of 87–96% with a preference for *trans* products.[105] The same reactions can be conducted using the Lewis acid boron trifluoride–diethyl ether instead of $MeReO_3$ to give aziridines **141** and **142** in 51–93% yields with predominantly *cis* stereochemistry (**Scheme 48**).[106]



Scheme 48

2.10 Miscellaneous

A diastereoselective Strecker reaction of imines **143** derived from D-glyceraldehyde provided a new route to β-hydroxy-α-amino acids **145** *via* the α-cyano amine **144** (**Scheme 49**).[107]

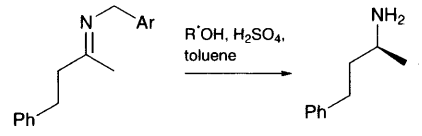


143 144 145

Scheme 49

The [1,3]-proton shift isomerisation of prochiral *N*-benzylimines **146** can be catalysed by chiral alcohols and amino alcohols to give enantiomeric-

ally enriched (up to 44% ee) *N*-benzylidene derivatives, which can be hydrolysed to the corresponding amines **147** (**Scheme 50**).[108]



Ar = C_6H_5, 4-ClC_6H_4

146 **147**

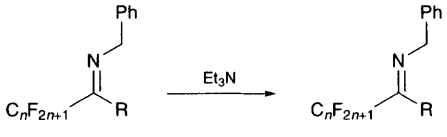
Scheme 50

A (1,3)-proton shift isomerisation of the *N*-benzylimines **148** derived from fluorinated aldehydes or ketones can be achieved using triethylamine to give the corresponding *N*-benzylidene derivatives **149** in 74–96% yields (**Scheme 51**).[109]

Cobalt complexes can catalyse the oxidation of imines to oxaziridines using molecular oxygen as the terminal oxidant in the presence of aliphatic aldehydes (no reaction was observed when aryl aldehydes were used), the oxaziridines were obtained in 47–90% yields.[110]

A highly enantioselective imino pinacol coupling was observed when *p*-anisylbenzylimine was treated with (+)-camphorsulfonic acid in the presence of zinc-copper couple in DMF to give the (*R,R*)-1,2-diphenylethylenediamine in 97% ee.[111]

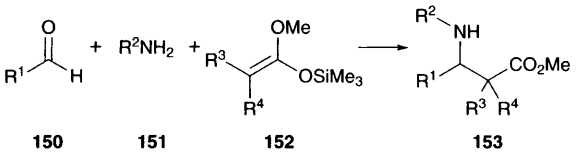
A one-pot synthesis of β-amino esters **153** from a mixture of aldehydes **150**, amines **151** and silyl enolates **152** using ytterbium(III) triflate proceeds by way of *in situ* imine formation followed by imine aldol condensation in 62–96% yields (**Scheme 52**).[112]



148 **149**

Scheme 51

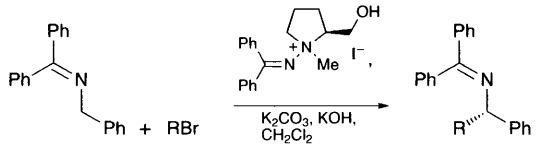
The enantioselective phase-transfer alkylation of *N*-benzyldiphenylmethylene imine **154** using a chiral quaternary benzophenone hydrazonium salt derivative provides the corresponding α-substituted chiral imines **155** in high enantiomeric excess (**Scheme 53**).[113]



150 **151** **152** **153**

Scheme 52

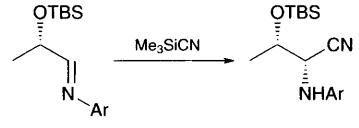
The addition of trimethylsilyl cyanide to *N*-substituted lactaldehyde imines **156** affords chiral α-amino β-hydroxy nitriles **157** with high *syn* diastereofacial selectivity. The propensity for *syn* selectivity is maintained with different Lewis acids and is even observed in the non-catalysed reaction (**Scheme 54**).[114]



154 **155**

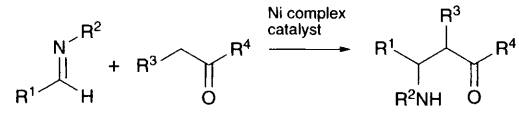
Scheme 53

Activated imines **158** react in imine aldol condensations with pronucleophiles (*e.g.* **159**) when catalysed by the nickel complexes $NiCl_2(PPh_3)_2$ or $NiBr_2(PPh_3)_2$ to give 43–99% yields of the β-amino carbonyl compounds **160** (**Scheme 55**).[115]



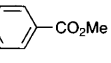
156 **157**

Scheme 54



158 **159** **160**

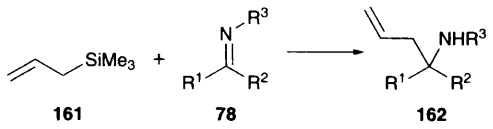
R^1 = aryl or cyclohexyl

R^2 = 

Scheme 55

Treatment of $(Cp^*_2SmH)_2$ with aromatic imines derived from aldehydes or ketones results in *ortho*-metallation of the aromatic moiety in 22–70% yields.[116]

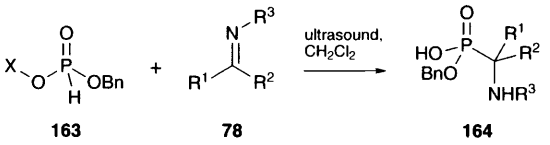
Tetrabutylammonium triphenyldifluorosilicate acts as a fluoride source to induce an intermolecular coupling between allyltrimethylsilane **161** and imine derivatives **78** to give the allyl amines **162** (**Scheme 56**).[117]



161 78 162

Scheme 56

Imines **78** can be condensed with Wang resin bound phosphonates **163** to afford the corresponding α-amino phosphonates **164** in high yields using Lewis acid or ultrasound catalysis in yields of 25–100% (**Scheme 57**).[118]

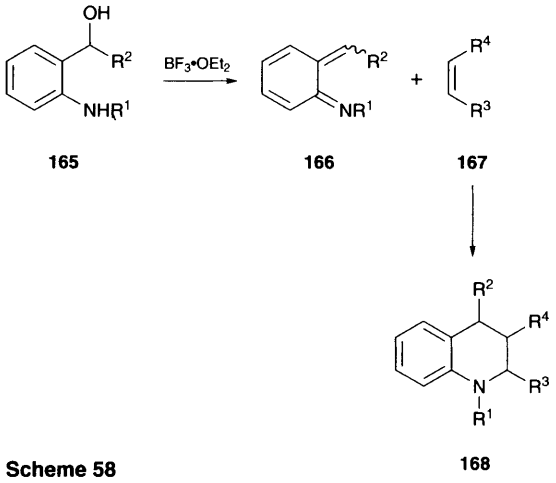


163 **78** **164**

X = resin

Scheme 57

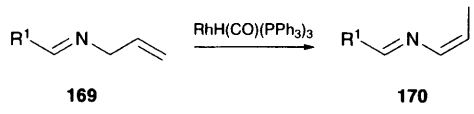
The intra- and inter-molecular Diels–Alder reactions of olefins **167** with *ortho*-quinomethane imines **166**, prepared from the corresponding aryl amines **165**, efficiently provide tetrahydroquinolines **168** in 56–97% yields (**Scheme 58**).[119]



165 **166** **167** **168**

Scheme 58

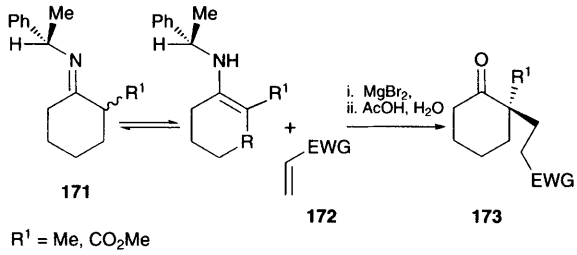
Treatment of *N*-allylimines **169** with $RhH(CO)(PPh_3)_3$ in benzene at 100 °C (sealed ampoule) results in the formation of the corresponding 2-aza-1,3-dienes **170** in 70–88% yields (**Scheme 59**).[120]



169 **170**

Scheme 59

The Michael addition of imines **171**, derived from 2-substituted cyclohexanones and optically active 1-phenylethylamine, to Michael acceptors **172** results in alkylation predominantly at the more substituted α-side of the imine in up to 80% yield (**Scheme 60**).[121]



171 **172** **173**

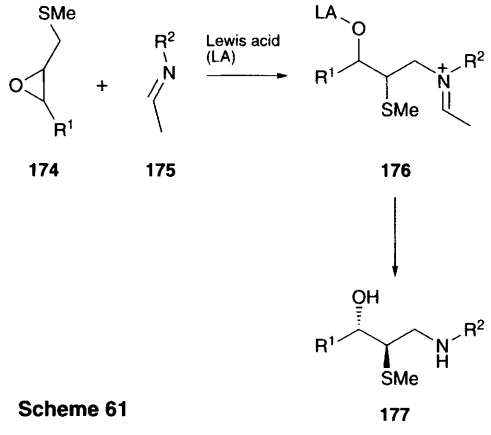
R^1 = Me, CO_2Me

EWG = COR, CO_2R

Scheme 60

Imines react smoothly with silyl ketene acetals in the presence of catalytic amounts of TiX_4 (X = Br or I) to give the corresponding β-amino esters in high yield (54–99%) and with a preference for *anti* selectivity, (*anti*:*syn* ratio varies from 46:54 to 99:1).[122]

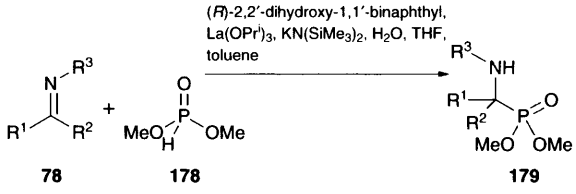
Imines **175** act as selective nucleophilic trapping agents for thiiranium ions generated *in situ* from 2,3-epoxy sulfides **174** under Lewis acid conditions. Hydrolysis of the intermediate iminium ions **176** generates the secondary amines **177** in 40–70% overall yields (**Scheme 61**).[123]



174 **175** **176** **177**

Scheme 61

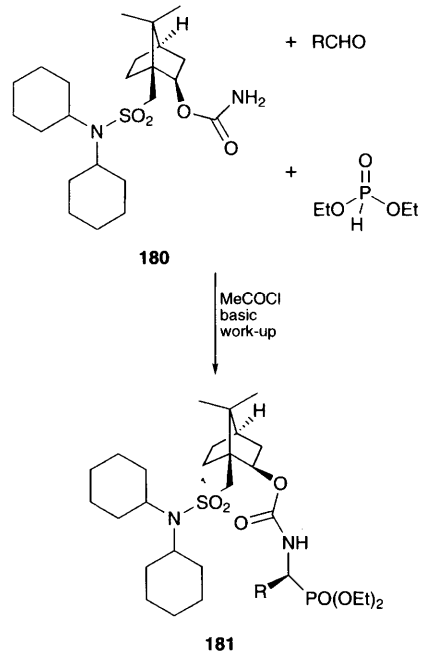
Imines **78** undergo asymmetric hydrophosphonylation reactions using catalytic lanthanide–potassium BINOL complexes to give the α-amino phosphonates **179** in 47–87% yield and 66–96% ee (**Scheme 62**).[124]



Scheme 62

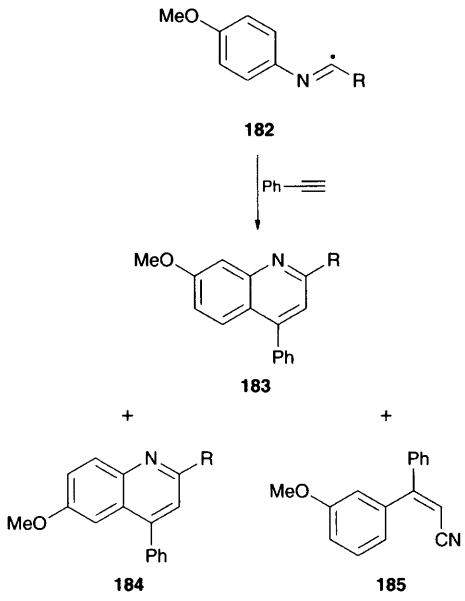
The electrophilic fluorination of imines with *N*-fluoro-*bis*(trifluoromethylsulfonyl)imide produced the monofluoro ketones in 22–38% yields and/or difluoroketones in 58–83% yields without the need of a strong base to generate the imine anions.[125]

Chiral imines, formed *in situ* from homochiral (1*S*)-(+)-camphorsulfonamide-derived carbamate **180** and aldehydes can react with diethyl phosphite to produce chiral α-amino phosphonates **181** in 75–79% yields with >99% de (**Scheme 63**).[126]



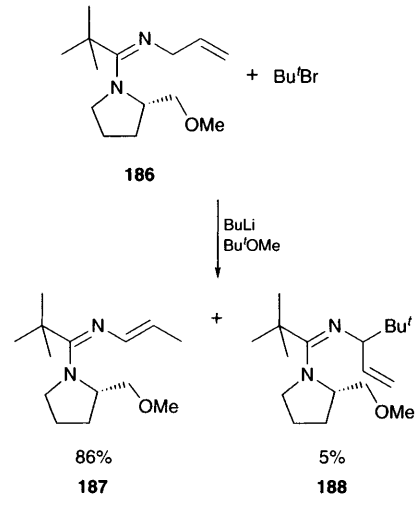
Scheme 63

Aromatic aldimines can be treated with diisopropyl peroxydicarbonate (DPDC) to generate imidoyl radicals **182**. For those imidoyl radicals **182** where R can undergo a homolytic cleavage to generate a stable radical (R˙) then isonitriles are generated (80% yield when R = CPh_3). If R does not form stable radicals from this homolytic cleavage then the imidoyl radical can be trapped with an alkyne to generate quinolines **183** and **184**, and unsaturated nitriles **185** (**Scheme 64**).[127]



Scheme 64

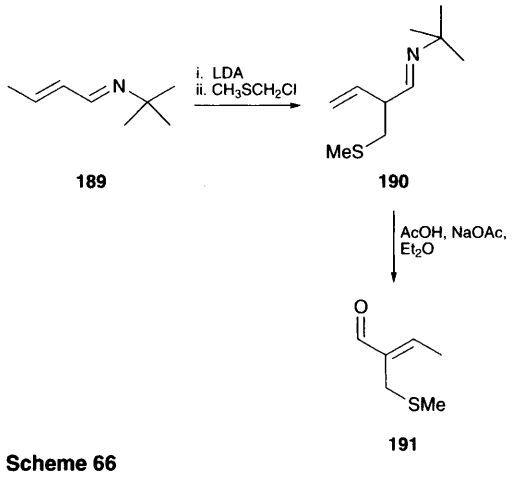
N-Allylimines **186** bearing a chiral auxiliary at C-1 can be deprotonated with butyllithium and subsequent transmetallation with magnesium bromide can be followed by alkylation. Alkylation with primary alkyl halides leads mainly to 3-substituted *N*-allylimines **188**. Secondary and tertiary alkyl halides preferentially give 5-substituted 2-azapenta-1,3-dienes **187** (**Scheme 65**).[128]



Scheme 65

2,2-Dimethyl-3-azahepta-3,5-diene **189** can be treated with LDA to form the α-anion. Alkylation with chloromethyl methyl sulfide gave the α-substituted product **190** in 100% yield, which then underwent imine hydrolysis to give the desired flavour

impact compound 2-[(methylthio)methyl]but-2-enal **191** (**Scheme 66**).[129]

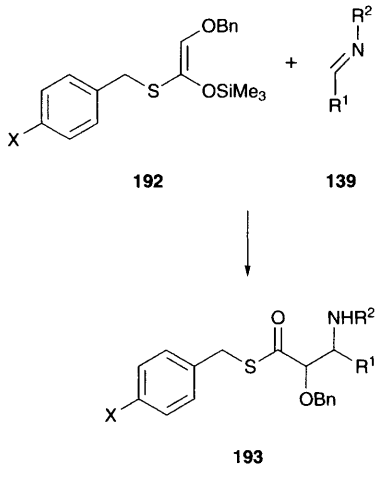


189 **190** **191**

Scheme 66

An electron withdrawing group on the phenyl moiety of imines derived from benzyl trifluoromethyl ketone facili ates the (1,3)-proton shift reaction.[130]

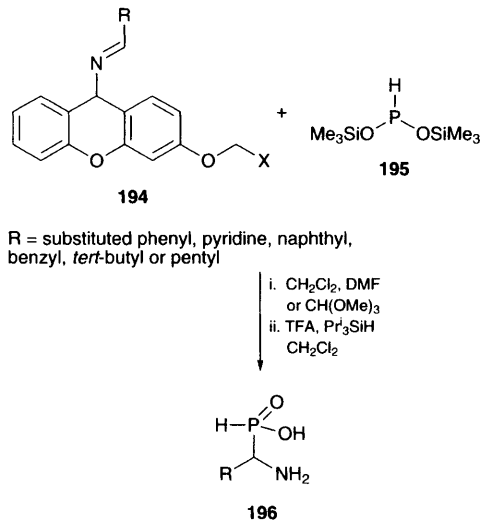
Polymer supported thioketene silyl acetals **192** react with imines **139** in the presence of catalytic amounts of scandium(III) triflate to afford β-amino thioesters **193** (**Scheme 67**).[131]



192 **139** **193**

Scheme 67

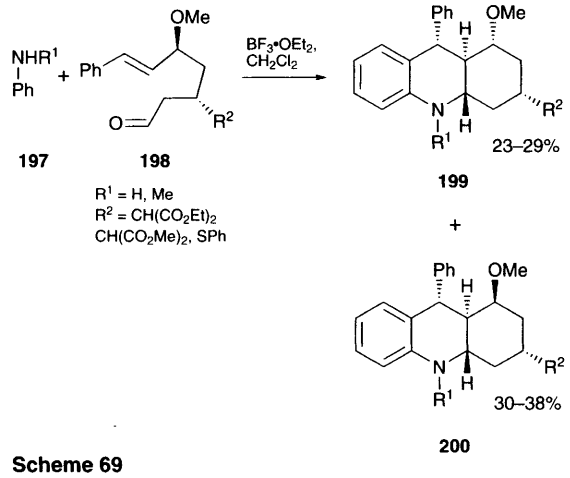
9-Alkyl- or aryl-iminoxanthen-3-yloxymethylpolystyrene **194** undergoes a facile addition to bis(trimethylsilyl) phosphonite **195** to produce the resin bound racemic *N*-substituted 1-aminophospinic acids. Acid hydrolysis delivers racemic 1-aminophosphinic acids **196** in yields of 71–100% (**Scheme 68**).[132]



194 **195** **196**

Scheme 68

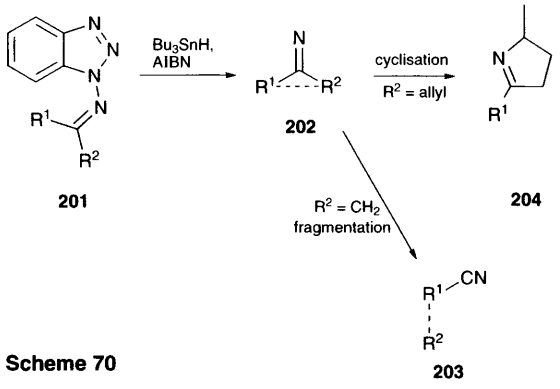
The domino imine condensation–intramolecular ($4\pi^+ + 2\pi$) cycloaddition of anilines **197** with ω-unsaturated aldehydes **198** leads to a diastereoselective synthesis of octahydroacridines **199** and **200** with five stereogenic centres (**Scheme 69**).[133]



197 **198** **199** **200**

Scheme 69

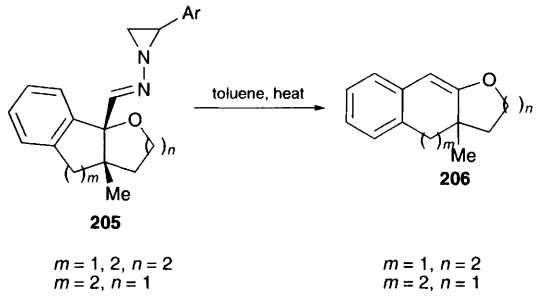
N-Benzotriazolylimines **201** are precursors for the formation of iminyl radicals **202**. The radicals, once formed, can undergo fragmentation reactions to provide nitriles **203** or cyclisation reactions to provide substituted cyclic imines **204** (**Scheme 70**).[134]



Scheme 70

Ruthenium complexes $Ru_3(CO)_{12}$ can catalyse the addition of olefins across the *ortho* carbon–hydrogen bond of aromatic aldimines or ketimines to give the *o*-alkyl derivatives in yields of 16–97%.[135]

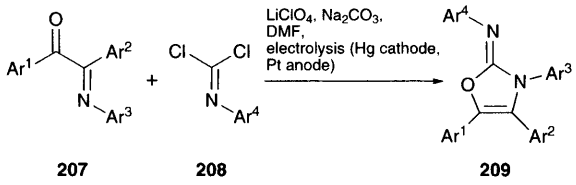
α-Oxetanyl-*N*-aziridinylimines undergo a ring expansion on heating to afford dihydropyrans in 55–69% yields. Heating α-tetrahydrofuranyl and α-tetrahydropyranyl *N*-aziridinyl imines **205** produces the ring expanded cyclic enol ethers **206** in 62-91% yields (**Scheme 71**).[136]



Scheme 71

Iminosulfonyl chlorides can be prepared in yields of 33–78% by the action of chlorosulfonyl isocyanate with styryl cyclopropyl ketones.[137]

The selective cathodic reduction of benzil monoimines **207** in the presence of stoichiometric *N*-arylcarbonimidoyl dichlorides **208** provides 3,4,5-triaryl-2-aryliminooxazolines **209** in yields of 60–94% (**Scheme 72**).[138]

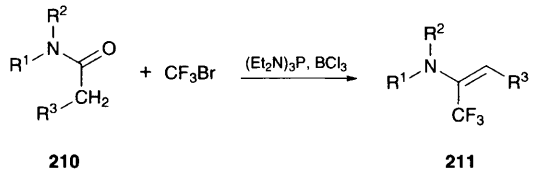


Scheme 72

3 Enamines

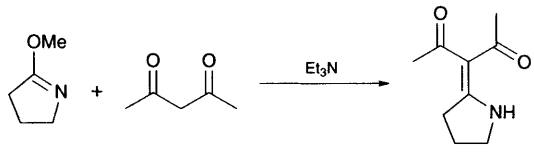
3.1 Formation of enamines

A one-pot synthesis of α-trifluoromethyl substituted enamines **211** can be achieved by the *C*-trifluoromethylation of dialkylamides **210** with tris(diethylamino)phosphine and bromotrifluoromethane in the presence of boron trichloride (**Scheme 73**) in yields of 25–36%.[139]



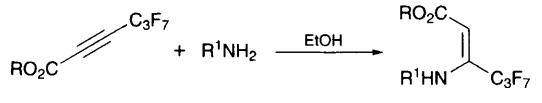
Scheme 73

Acetyl substituted heterocyclic enamines **213** have been prepared by the action of acetylacetone on lactim ethers **212** (**Scheme 74**).[140]



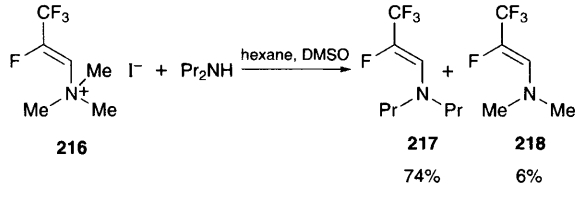
Scheme 74

The reaction of fluoroalkynes **214** with ammonia or benzylamine results in the formation of perfluoroalkylated enamines **215** with predominantly the *Z* configuration in yields of 42–76% (**Scheme 75**).[141]



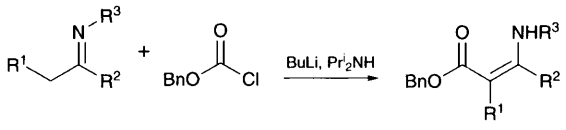
Scheme 75

A stereoselective synthesis of β-trifluoromethylated enamines **217** (and **218**) has been implemented using the reactions of quaternary ammonium salts **216** having a polyfluoroalkenyl group with secondary amines (**Scheme 76**).[142]



Scheme 76

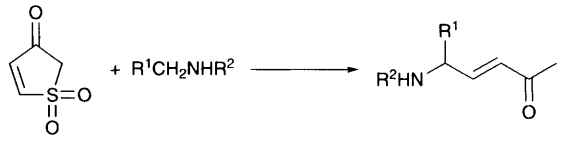
A versatile route to β-enamino esters **220** involves the acylation of lithium enamines, available by the action of butyllithium on the corresponding imine **219**, with diethyl carbonate or benzyl chloroformate (**Scheme 77**).[143]



219 220

Scheme 77

The addition of amines to 3-thiophen-3(2*H*)-one 1,1-dioxide **221** occurs with extrusion of sulfur dioxide to furnish the enamines **222** in 73–92% yields (**Scheme 78**). The rates of the Michael addition and subsequent loss of sulfur dioxide are dependent upon the solvent used.[144]



221 222

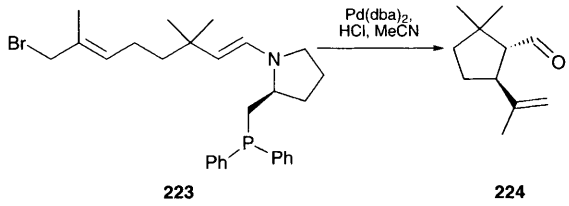
Scheme 78

4-Formylpyridines, or 4,4′-diformyl-2,2′-bipyridines, have been prepared in a two-step process involving enamine intermediates. The intermediate 4-dimethylaminovinylpyridines, or 4,4′-dienamine-2,2′-bipyridines, are prepared by the action of bis(dimethylamino)methyl *tert*-butyl ether on 4-methyl pyridines, or 4,4′-dimethyl-2,2′-bipyridines, in DMF at 140 °C. Sodium periodate cleavage of the enamine double bond results in the formation of the 4-formyl pyridines.[145]

The formation of enamino ketones from the condensation of bulky amines with ethyl acetoacetate or pentane-2,4-dione can be achieved either under high pressure or by catalysis with ytterbium triflate with yields ranging from 12–95%.[146]

3.2 Enamine cyclisations

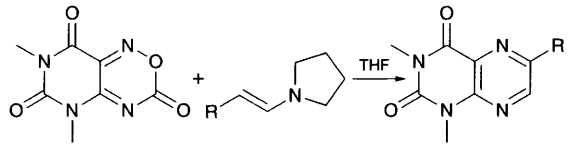
Palladium catalysed intramolecular asymmetric allylations of chiral enamines **223**, imines and hydrazones bearing phosphine groups at the stereogenic centre proceed with high asymmetric induction (**Scheme 79**).[147]



223 224

Scheme 79

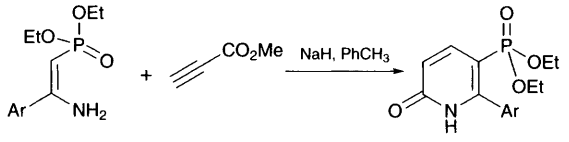
A regioselective synthesis of alkylated lumazines **227** can be accomplished by the hetero Diels–Alder addition between an oxadiazinone **225** and an enamine **226**. The reaction proceeds in a stepwise manner by cycloaddition, decarboxylation and deamination to give the 6-alkylated lumazines **227** in 22–79% yield (**Scheme 80**).[148]



225 226 227

Scheme 80

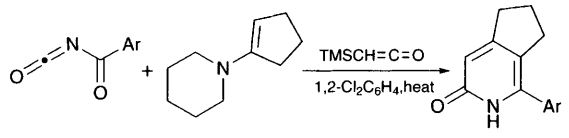
Primary β-enamino phosphonates **228** can be obtained by the action of metallated diethyl methylphosphonate on nitriles. The enamines **228** can then undergo a reaction with ethyl propiolate or dimethyl acetylenedicarboxylate to give adducts in 68–83% yields which can then rearrange either thermally or with sodium hydride to give pyridones **229** (**Scheme 81**).[149]



228 229

Scheme 81

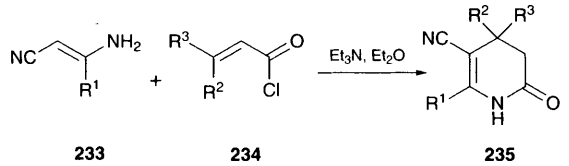
The enamines **231** of cycloalkanones react smoothly with 4-trimethylsiloxy-1,3-oxazin-6-ones (prepared *in situ* by the action of trimethylsilylketene on acyclic isocyanates **230**) to give bicyclic 2-pyridones **232** in 32–96% yield (**Scheme 82**).[150]



230 231 232

Scheme 82

α,β-Unsaturated acid chlorides **234** can react with primary enaminonitriles **233** in the presence of triethylamine to produce polysubstituted 3,4-dihydro-2(1*H*)-pyridones **235** regiospecifically under mild conditions in 70–80% yield (**Scheme 83**).[151]

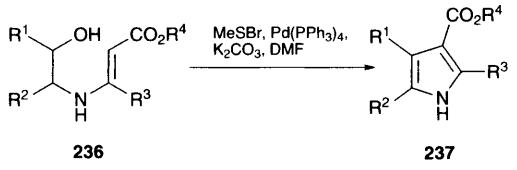


233 234 235

Scheme 83

A palladium catalysed oxidation of hydroxy enamines **236** has been shown to result in the formation of polysubstituted pyrroles **237** and

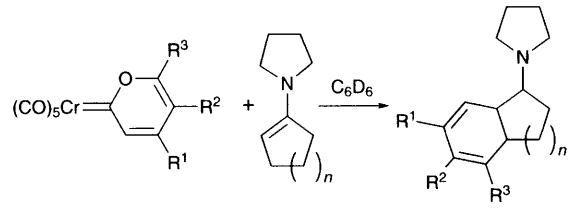
4,5,6,7-tetrahydroindoles in yields of 27–85% (**Scheme 84**).[152]



236 **237**

Scheme 84

Pyran-2-ylidene complexes **238** of tungsten or chromium can react with cyclic enamines **239** to generate 5-aminocyclohexa-1,3-dienes **240** by the elimination of $M(CO)_6$ (**Scheme 85**). This methodology can be used to synthesise steroids.[153]

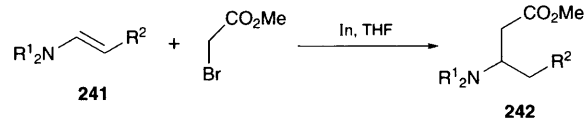


238 **239** **240**

Scheme 85

3.3 Addition of organometallics to enamines

Novel reactions were observed when enamines **241** were treated with allyl bromide or methyl bromoacetate in the presence of indium powder in THF to give homoallylamines and β-amino esters **242** respectively in yields varying from 5–82% (**Scheme 86**).[154]

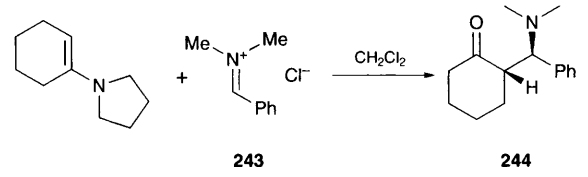


241 **242**

Scheme 86

3.4 Miscellaneous

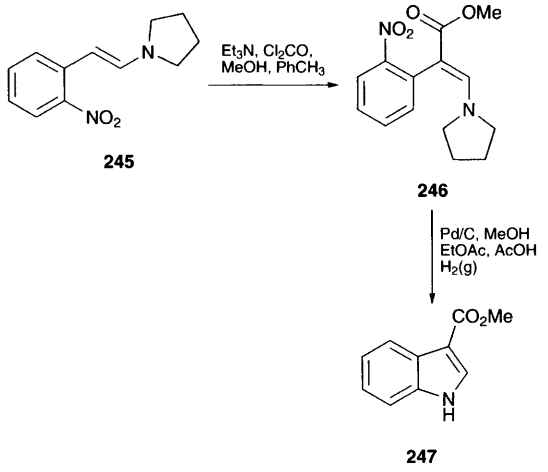
Diastereomerically pure Mannich bases **244** have been obtained by the addition of enamines to ternary iminium salts **243** in yields of 72–94% and with an *anti*:*syn* ratio of 99:1 (**Scheme 87**).[155]



243 **244**

Scheme 87

A convenient synthesis of 3-substituted 1*H*-indoles **247** in yields of 58–65% has been devised. This approach is based on Leimgruber–Batcho methodology but the intermediates **246** are prepared by the functionalisation of enamines **245** with phosgene (**Scheme 88**).[156]



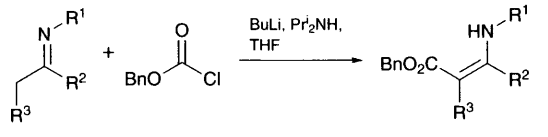
245 **246** **247**

Scheme 88

A facile dehomologation procedure for α-substituted aldehydes to ketones has been demonstrated using β,β-disubstitued enamines as intermediates. The methodology uses potassium dichromate mediated oxidative cleavage of the enamine. The best cleavage conditions were a biphasic mixture of diethyl ether and chromic acid. Yields of the isolated ketones were 73–88%.[157]

The hydroboration of acyclic and cyclic enamines, formed from aldehydes or ketones, followed by an oxidative work-up results in the formation of β-amino alcohols in high yields. If asymmetric hydroboration reagents are used (monoisopinocampheylborane or diisopinocampheylborane) then the newly created stereogenic centre is formed with 50–86% ee.[158]

β-Enamino esters **250** can be readily prepared by the action of butyllithium on aldimines or ketimines **248** to give lithiated enamines; a subsequent reaction with diethyl carbonate or benzyl chloroformate **249** provides the desired β-enamino esters **250** in yields of 34–76% (**Scheme 89**).[159]

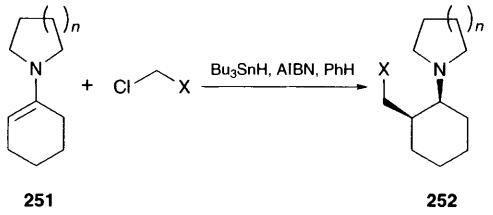


248 **249** **250**

Scheme 89

The radical reductive alkylation of enamines **251** can be achieved using α-cyanomethyl chloride or phenylsulfonylmethyl chloride in the presence of tributyltin hydride and catalytic AIBN to produce the *syn* alkylated products **252** (**Scheme 90**). The alkylated products can be further manipulated to give alkenes (*via* oxidation of the amine to *N*-oxide

and Cope elimination) or primary amines (double β-elimination).[160]



251 252

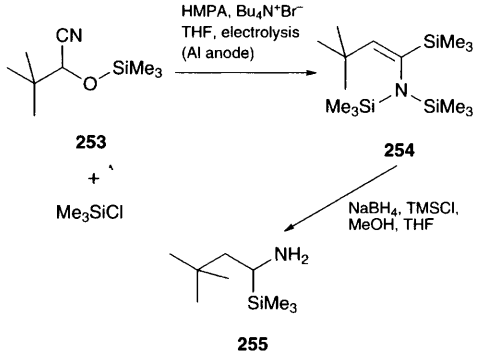
$n = 1,2$ X = CN, SO_2Ph

Scheme 90

1-Trifluoromethyl enamines can be treated with bromine or iodine to give the corresponding iminium salts. Subsequent treatment with methanol converts the iminium salts into the α-bromo trifluoromethyl and α-iodo trifluoromethyl ketones in yields of 40–85%.[161]

The reaction of pyrrolidine with 2-methylcyclohexanone has led to the formation of the corresponding enamine in 98% yield. This enamine can then be trapped with 4-methoxybenzyl chloride and subsequently be used to prepare 2-(4-hydroxybenzyl)-6-methylcyclohexanone which is an intermediate in the synthesis of insect juvenile hormone bioanalogues.[162]

The reaction of 1-cyano-2,2-dimethylpropyl trimethylsilyl ether **253** with trimethylsilyl chloride under electrochemical reductive silylation conditions results in the formation of a silylated enamine **254** (59–82% yield) which can be subsequently reduced to produce the α-(trimethylsilyl)alkylamines **255** (**Scheme 91**).[163]



253 254 255

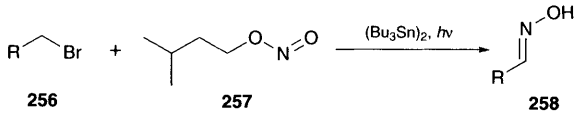
Scheme 91

In the synthesis of a vicinal tricarbonyl amide derivative of L-phenylalanine, sodium periodate was used to cleave an enamine to the corresponding ketone and *gem*-diol in a combined yield of 79%.[164]

4 Oximes

4.1 Formation of oximes

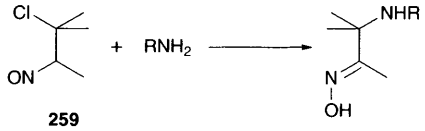
A novel radical induced C–N bond formation led to the discovery of a new route to oximes **258** from alkyl halides **256** in yields of 61–84%.[165] Bis(tributylstannane) in the presence of light from a tungsten lamp was used to conduct the reaction (**Scheme 92**).



256 257 258

Scheme 92

Treatment of an α-chloronitroso substrate **259** with primary amines has been shown to lead to α-amino oximes **260** (**Scheme 93**). This approach was used to prepare propylene amine oximes (PnAOs).[166]



259 260

Scheme 93

A catalytic oxidation of benzylic and allylic amines to the corresponding oximes has been demonstrated to be highly selective when a titanium silicate–hydrogen peroxide system was used.[167]

The oxidative decarboxylation of α-amino acids, $RCH(NH_2)CO_2H$, using dimethyl dioxirane, generated *in situ* from acetone–oxone, has led to the formation of the corresponding oximes, RCHNOH, as the major components.[168]

A general methodology for the synthesis of α,β-unsaturated oximes from phosphine oxide allenes has been achieved.[169] Hydroxylamine addition to allene phosphine oxides yields β-oximo phosphine oxide derivatives which may then undergo olefination reactions with aldehydes and ketones to give the desired products.

4.2 Reduction to amines

The reduction of oximes to amines can be achieved using several approaches. Aromatic oximes may be reduced in yields of 68–94% using borohydride supported on an ion exchange resin in the presence of nickel acetate in methanol.[170]

The *O*-acyl derivatives of oximes can be reduced using the sodium borohydride–iodine system (64–90% yields).[171]

Zinc in trifluoroacetic acid is also an effective medium for this reduction (59–98% yields)[172] as is Raney nickel under hydrogen pressure, although in the case of Raney nickel higher temperatures (100 °C) and longer reaction times (10 h) are required.[173]

4.3 Oxidation to nitro

Oximes may be oxidised to nitro compounds. Treatment of certain oximes with *Caldaromyces fumago* (*i.e.* a chloroperoxidase), potassium bromide and

hydrogen peroxide leads to the corresponding *gem*-bromonitro compounds (23–82% yields).[174]

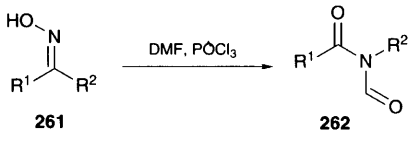
Ketoximes have also been converted to nitroalkanes using a molybdenum(VI) oxodiperoxo complex as oxidant in acetonitrile.[175]

4.4 Conversion to aldehydes and ketones

The conversion of oximes to aldehydes and ketones may be achieved using a variety of different reagents. Cupric nitrate supported on silica gel has been shown to be particularly adept at this transformation.[176] Activated manganese dioxide has also been shown to rapidly and effectively oxidise the oxime (70–92% yields) although benzyloximes and those oximes derived from α-keto esters do not undergo the reaction.[177] 3-Carboxypyridinium chlorochromate is an inexpensive, stable reagent that achieves the conversion of oximes to their corresponding carbonyl compounds in yields of up to 97%.[178] The oxidative deoximation can also be achieved using sodium perborate in glacial acetic acid, thus avoiding metal contaminated effluents, although aldoximines give lower yields and need extended reaction times.[179] Layered zirconium sulfophenyl phosphonate $[Zr(O_3PMe)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}]$ has also been shown to be an efficient heterogeneous catalyst for the hydrolysis of oximes: the parent carbonyls are obtained in yields ranging from 70–95%.[180]

4.5 Beckmann rearrangements

The Beckmann rearrangement is a well recognised and trusted method for the transformation of oximes to amides. This technology has been extended to the synthesis of *N*-formyl amides **262** using the Vilsmeier reagent, in yields of 30–60% (**Scheme 94**).[181]



261 **262**

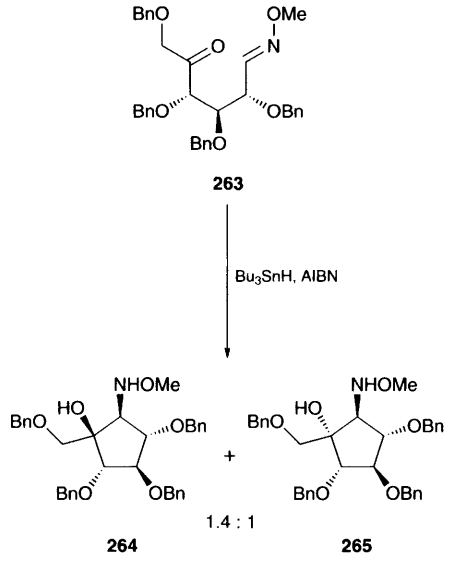
Scheme 94

The mixing of an oxime with K-10 montmorillonite, in the absence of solvent, and its subsequent irradiation with microwaves provides an extremely rapid Beckmann rearrangement.[182]

A Beckmann type oxime fragmentation was also pivotal in a recent synthesis of the milbemycin SB-201561.[183]

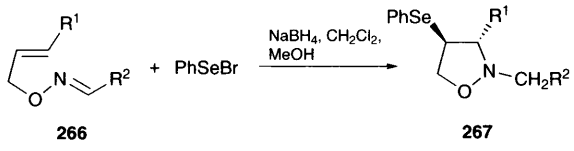
4.6 Oxime cyclisations

Numerous cyclisations involving oximes have been reported in the literature. A concise synthesis of aminocyclopentitol and 1-deoxynojirimycin has been reported.[184] The methodology for these syntheses is dependent upon a radical cyclisation of an oxime ether **263** (**Scheme 95**), which proceeds in 68% yield.



Scheme 95

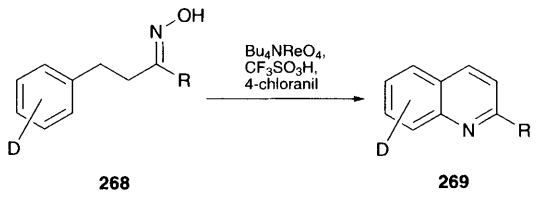
A selenium induced cyclisation of *O*-allyl oximes **266** provides a synthetic route to *N*-alkyl isoxazolidines **267**. Benzeneselenenyl bromide undergoes a ready reaction with *O*-allyl oximes **266** to produce cyclic iminium bromides, which are then reduced *in situ* with sodium borohydride to give the desired *N*-alkyl isoxazolidines **267** in yields of 50–95% (**Scheme 96**).[185] The *O*-allyl oximes can also be used to form isoxazolidines *via* an organoselenium induced ring closure reaction which again gives cyclic iminium salts. These cyclic iminium salts can then be treated with water to give the isoxazolidines.[186]



266 **267**

Scheme 96

A synthetic approach to quinolines **269** *via* intramolecular cyclisation of the benzylacetone oxime derivative **268** proceeds in 49–89% yields (**Scheme 97**). The cyclisation uses tetrabutylammonium perrhenate, trifluoromethanesulfonic acid and 4-chloranil in refluxing 1,2-dichloroethane.[187]

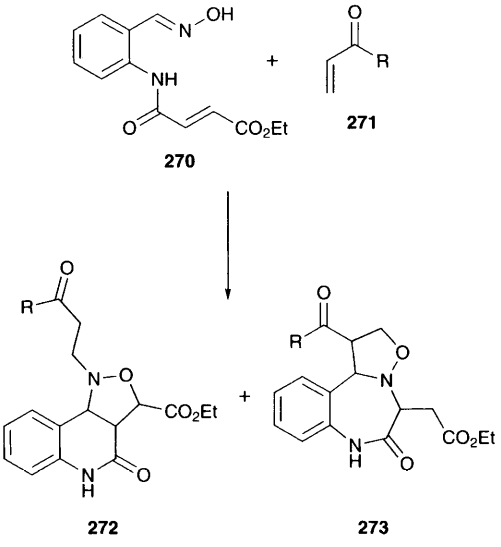


268 269

D = electron donating group
R = Me, Et

Scheme 97

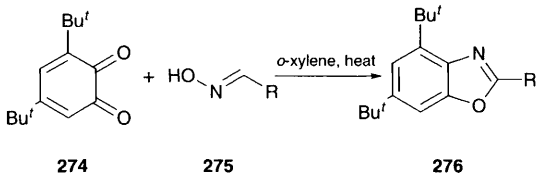
Oximes **270** have also been used in the synthesis of certain quinolin-4(5*H*)-ones **272** and benzodiazepin-6(5*H*)-ones **273**. The product distribution pattern is dependent upon the reacting olefin **271** and the nature of the substitution pattern of the acrylate moiety (**Scheme 98**).[188]



272 273

Scheme 98

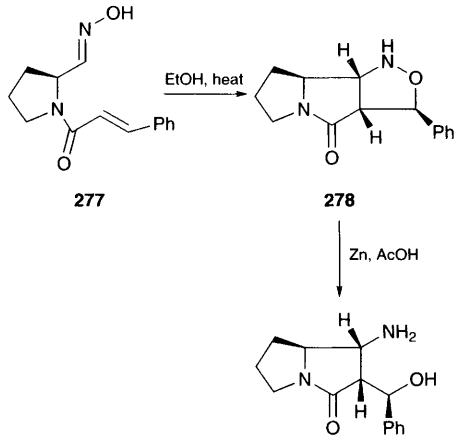
Benzoxazoles **276** can be prepared by the action of aldoximes **275** on 3,5-di-*tert*-butyl-1,2-benzoquinone **274** in yields of 27–66% (**Scheme 99**).[189]



274 275 276

Scheme 99

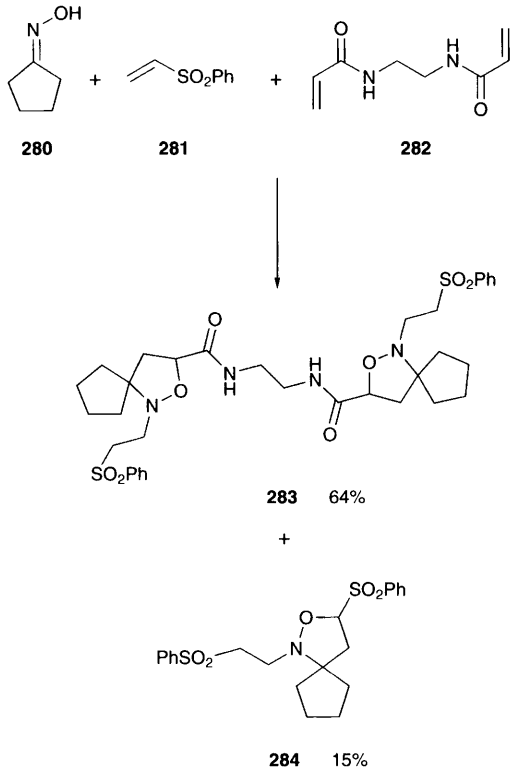
An intramolecular oxime–olefin cycloaddition provides a useful tool for an asymmetric approach to pyrrolidinones and pyrrolizidinone systems. The stereoselective cycloaddition initially provides fused isoxazolidines **278** (68–90% yields) which are then reduced using zinc in acetic acid to provide pyrrolidin-2-ones **279** (**Scheme 100**) or with lithium aluminium hydride to provide the pyrrolidines.[190]



277 278 279

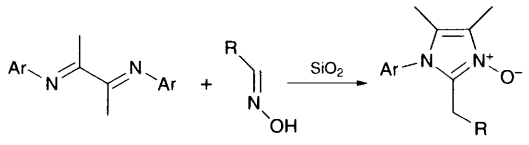
Scheme 100

Symmetrically linked bisisoxazoles **283** have been prepared from a three-component one-pot reaction. The methodology uses oximes **280** in conjunction with bifunctional dipole generating components **282** and dipole trapping components **281** *e.g.* **Scheme 101**.[191]



Scheme 101

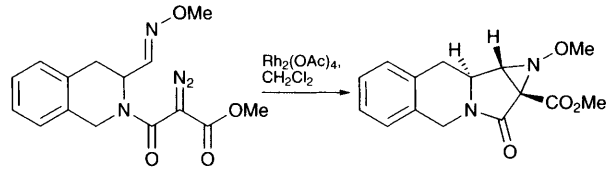
The reaction of 1,2-diimines **285** with oximes **275**, under solvent free conditions, using silica gel or aluminium oxide as both supports and catalysts leads to the generation of imidazole *N*-oxides **286** (**Scheme 102**) under mild conditions with easier work-ups and higher yields than the corresponding solution phase reactions.[192]



285 275 286

Scheme 102

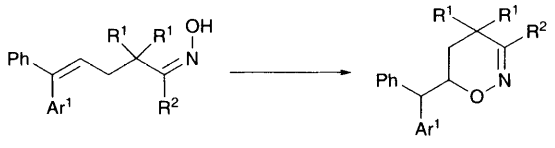
Oximino ethers **287** have been used to prepare aziridines **288** by their intramolecular reaction with α-diazoamide moieties in the presence of a metal catalyst (**Scheme 103**).[193]



287 288

Scheme 103

γ,δ-Unsaturated oximes **289** have been irradiated (400 W medium pressure mercury arc lamp) in the presence of the electron acceptor sensitiser 9,10-dicyanoanthracene to provide 5,6-dihydro-4*H*-1,2-oxazines **290** in 21–53% yields (**Scheme 104**).[194]

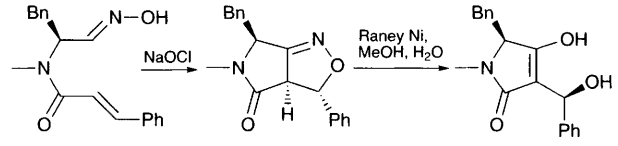


289 290

R^2 = Me, R^1 = H, Ar^1 = Ph
R^2 = H, R^1 = H, Ar^1 = Ph
R^2 = H, R^1 = Me, Ar^1 = H

Scheme 104

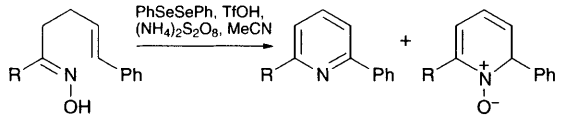
Substituted enamido oximes **291** can undergo intramolecular nitrile oxide cycloadditions (INOC) and subsequent reduction and hydrolysis of the bicyclic intermediates **292** provides 3,4-dehydropyrrolidin-2-ones **293** (**Scheme 105**).[195]



291 292 293

Scheme 105

δ-Phenyl-γ-alkenyl oximes **294** can be converted into 2-phenylpyridines **295** using catalytic amounts of diphenyl diselenide with excess ammonium persulfate and trifluoromethane sulfonic acid in acetonitrile. 2-Phenylpyridine *N*-oxides **296** are formed in significant amounts as by-products (**Scheme 106**). The combined yields of the two products range from 64–75%.[196]



294 295 major 296 minor

Scheme 106

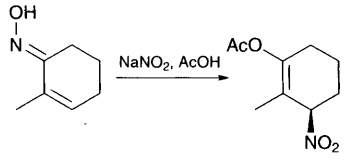
An efficient conversion of conjugated oximes **297** to substituted pyridines **298** under Vilsmeier conditions (**Scheme 107**) has been reported to proceed in 71–82% yields.[197]

297 298

Scheme 107

4.7 Miscellaneous

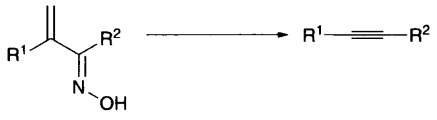
Certain α,β-unsaturated oximes **299** possessing the 2-methyl-3-hydroxyiminocyclohexene structure provide access to allylic nitro compounds **300** by their reaction with sodium nitrite in acetic acid (**Scheme 108**).[198]



299 300

Scheme 108

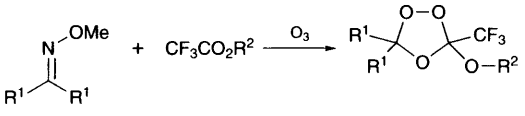
Sodium nitrite in aqueous acetic acid can also be used for the conversion of α,β-unsaturated oximes **301** to alkynes **302**, although in low yield (20%, **Scheme 109**).[199]



301 302

Scheme 109

If *O*-methyloximes **303** are treated with ozone in the presence of esters of trifluoroacetic acid **304** or acyl cyanides then ozonides **305** are formed in yields of 4–67% (**Scheme 110**).[200]



303 304 305

Scheme 110

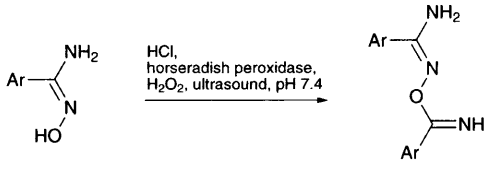
α-Sulfinylketoximes **306** can be diastereoselectively reduced to give *N*-methylamino sulfoxides **307** with L-Selectride in yields of 40–87% (**Scheme 111**).[201]

306 307

S:*R* ratio 90:10 to 97:3

Scheme 111

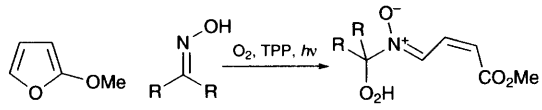
O-(Arylimidoyl)arylamidoximes **309** can be readily prepared in 27–68% yields by the oxidation of arylamidoximes **308** with hydrogen peroxide in the presence of horseradish peroxidase (**Scheme 112**).[202]



308 309

Scheme 112

The reaction of 2-methoxyfuran **310** with oximes **311** in the presence of oxygen, tetraphenylporphyrin (TPP) and light (650 W halogen super-hot lamp) gave rise to hydroperoxynitrones **312** in 20–80% yields (**Scheme 113**).[203]



310 311 312

Scheme 113

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