Imines, enamines and related functional groups

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Reviewing the literature published between May 1993 and January 1995

1. Introduction

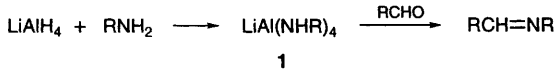
The work described in this review of the literature is largely based around new methodology, although some examples of natural product synthesis are described where they are dependent on imine chemistry and are of general interest.

2. Imines

The synthetic applications of γ-piperidone imines and enamines have been reviewed in a 62-reference review including preparations and reactions of γ-piperidone derivatives.[1] Two reviews on nitrile imines (nitrilimines), looking at their reactions with heterocycles[2] and the work done in identifying them from matrix characterisation to stable compounds,[3] have also been published.

2.1 *N*-Substituted imines

The formation of aldimines is often complicated for aliphatic aldehydes by the tendency of the aldimines to undergo aldol condensation reactions. To avoid this polymerisation it is possible to treat the amines with lithium aluminium hydride. The lithium aluminium amides **1** so formed undergo clean reactions with aldehydes (or ketones) in generally high yields (85–100%) (**Scheme 1**).[4]

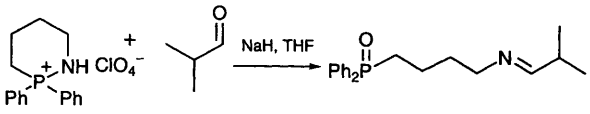


1

Scheme 1

A polyclonal antibody has been shown to catalyse the bimolecular aldimine condensation of pyridoxal with phenylalanine under physiological conditions;[5] in the absence of the antibody no reaction is observed.

The establishment of a synthesis of cyclic amino phosphonium salts, *viz* **2**, has allowed the development of a method for the generation of *N*-substituted imines *via* aza-Wittig reactions with aldehydes.[6] The cyclic phosphonium salts are prepared from (3-cyanopropyl)diphenylphosphine or (3-cyanobutyl)diphenylphosphine in a five-step procedure. Treatment with aldehydes or isocyanates gives imines **3** or carbodiimides (hydrolysed to urea derivatives) respectively (**Scheme 2**).

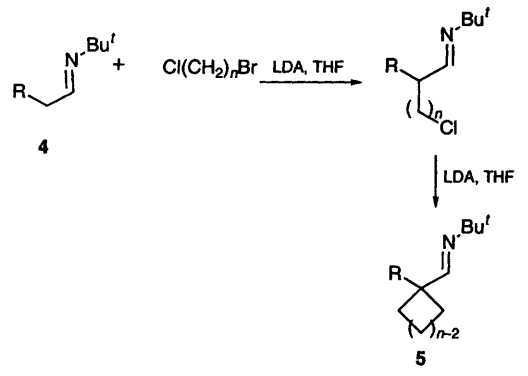


2 **3**

Scheme 2

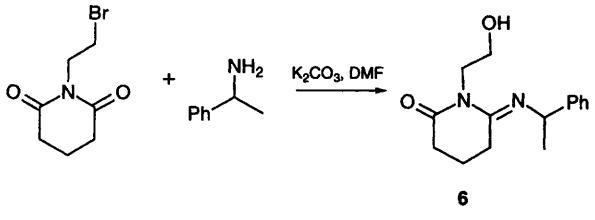
The construction of a cycloalkyl ring at the α-positions of aldehydes *via* the cyclisation of ω-haloaldimines has been established. Thus alkylations of aldimines **4** with α,ω-dihaloalkanes followed by treatment with LDA provides a convenient route to α-cycloalkyl-substituted aldimines **5** (**Scheme 3**), which can be hydrolysed smoothly to the parent α-cycloalkyl-substituted aldehydes.[7]

The reactions of primary amines with *N*-(2-bromoethyl)glutarimide derivatives in the



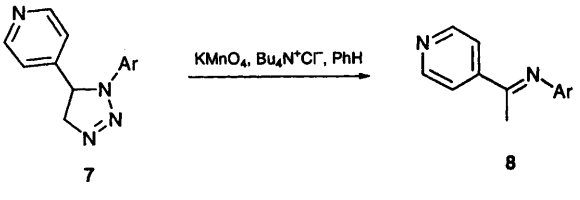
Scheme 3

presence of potassium carbonate in DMF lead to the corresponding *N*-(2-hydroxyethyl)imino-glutamides **6** in good yields (68–80%).[8] The proposed mechanism involves the intermediacy of an oxazolinium ion (**Scheme 4**).



Scheme 4

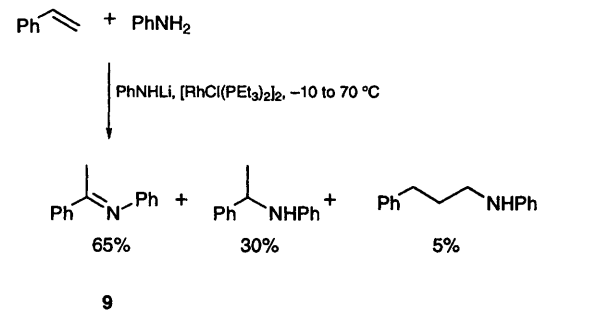
Oxidations of 1-aryl-5-(4-pyridyl)-1*H*-1,2,3-triazolines **7** with potassium permanganate in benzene–water lead to 1-unsubstituted 1*H*-1,2,3-triazolines. If the reactions are run in anhydrous benzene then imines **8** result (**Scheme 5**).[9]



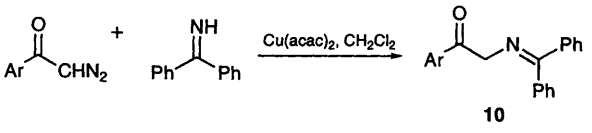
Scheme 5

Aniline reacts with styrene in the presence of lithium anilide and $[(Et_3P)_2RhCl]_2$ to give predominantly the oxidative hydroamination product **9** in 65% yield (**Scheme 6**).[10]

The reactions of α-diazo carbonyl compounds with 1,1-diphenylmethanimine in the presence of $Cu(acac)_2$ as catalyst afford the corresponding *N*-substituted imines **10** *via* the intermediacy of azomethine ylides, (yields 17–32%).[11] Lower yields are obtained when diazo esters are used (*ca.* 4%) (**Scheme 7**).

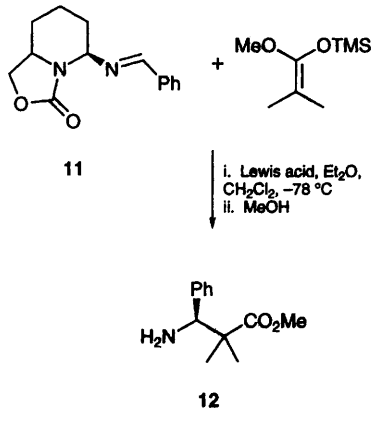


Scheme 6



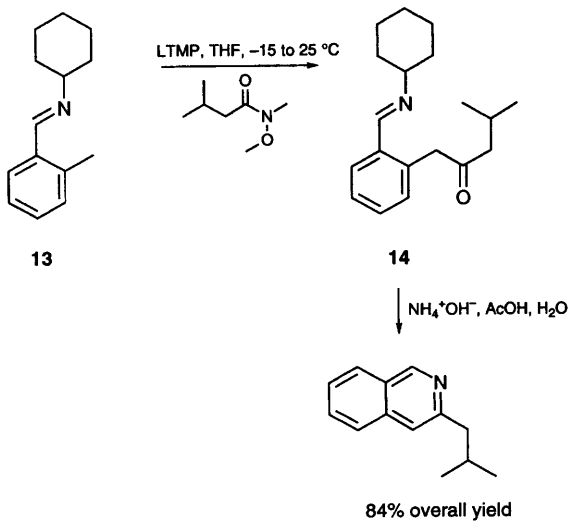
Scheme 7

An optically active α-amino amine can be converted to its Schiff base **11** using benzaldehyde. Mannich reaction of the Schiff base with dimethylketene silyl acetal in the presence of a Lewis acid [zinc chloride, titanium(IV) chloride or boron trifluoride–diethyl ether] then gives the corresponding coupling products which can be hydrolysed to β-amino acid esters **12** (yields 23–93%, ee 72–88%) (**Scheme 8**).[12]



Scheme 8

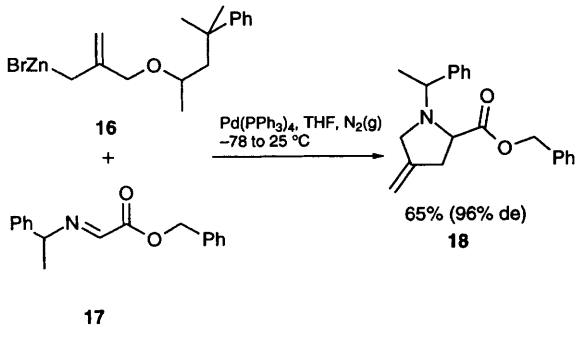
N-Cyclohexyl aromatic aldimines **13** are *o*-lithiated or *o*-methyllithiated when treated with two equivalents of lithium tetramethylpiperidide (LTMP) in THF solution at −15 °C, but a wide variation in yields is observed (40–97%).[13] This work has provided the basis for a two-step synthesis of isoquinolines. The *o*-methylmetallation of *o*-tolualdehyde cyclohexylimines using LTMP in THF solution is followed by trapping with Weinreb amides. This is followed by an intramolecular condensation with the resulting ketone **14**, and the



Scheme 9

isoquinolines **15** are obtained in yields of 57–84% (**Scheme 9**).[14] The method does not suffer from the intrinsic regiochemical limitations of the electrophilic cyclisation process as does the most widely used isoquinoline synthesis, the Pommeranz–Fritsch method.

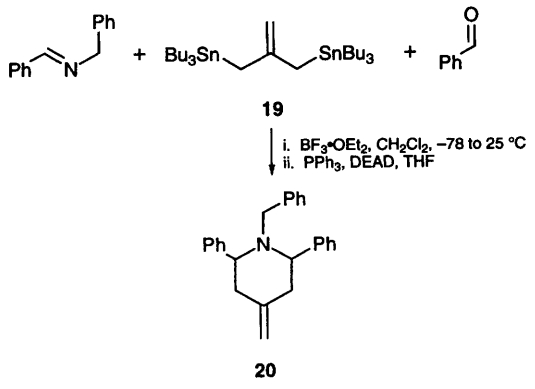
3-Methylenepyrrolidines **18** are formed with high diastereomeric excess in a one-pot process by the addition of allylzinc reagents **16** to imines **17** bearing an alkoxycarbonyl group at the α- or α′-position, followed by a Pd^0 catalysed cyclisation.[15] Yields are of the order of 51–68% and diastereomeric excesses range from 13% to 96% (**Scheme 10**).



Scheme 10

2,6-Disubstituted piperidines **20** may be prepared from imines in a two-step process by the use of 3-tributylstannyl-2-[(tributylstannyl)methyl]propene **19** and an aldehyde to give an amino alcohol which can be subsequently cyclised under Mitsunobu conditions (**Scheme 11**).[16]

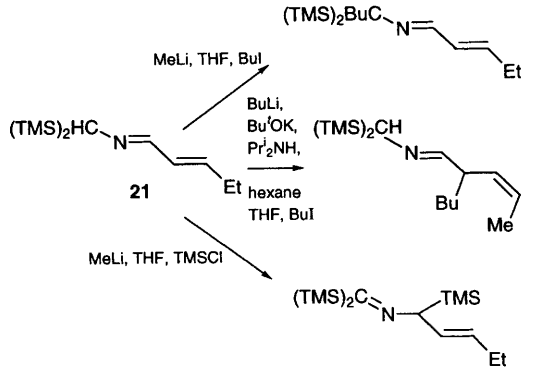
Regioselective functionalisations of bis(trimethylsilyl)methylimines **21**, which are prepared by



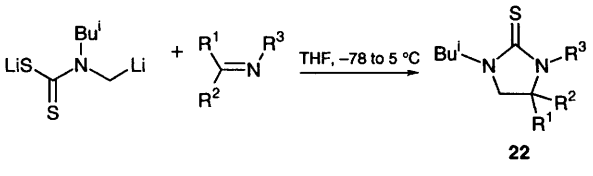
Scheme 11

condensation of bis(trimethylsilyl)methylamine with aldehydes, with a range of electrophiles can be controlled to give either C-1, C-3 or C-4 functionalisation depending on the nature of the electrophile and the base employed (**Scheme 12**).[17]

Imines have also been used to prepare 1,3,4,4-tetrasubstituted imidazolidine-2-thiones **22** (yields of 50–69%) by treatment with lithium *N*-butyl-*N*-lithiomethyldithiocarbamates (**Scheme 13**).[18]



Scheme 12

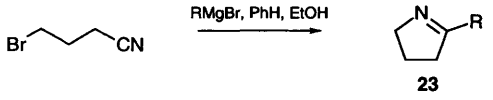


Scheme 13

2.2 Cyclic imines

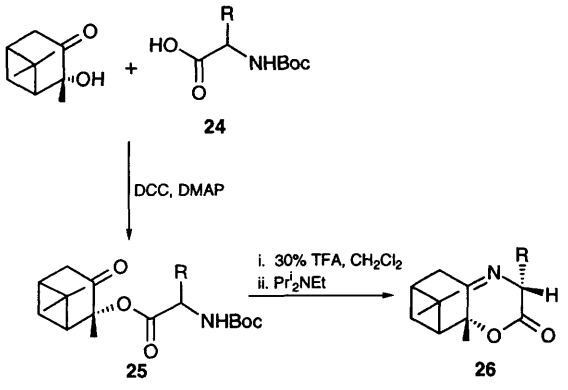
ω-Bromo nitriles can readily undergo a tandem addition–cyclisation reaction sequence upon treatment with Grignard reagents to provide cyclic imines **23** in yields of 10–90% (**Scheme 14**).[19]

The formation of cyclic Schiff bases provide an interesting method for the resolution of amino acids (**Scheme 15**).[20] Thus, coupling of the racemic amino acids **24** with 1-hydroxycamphor, followed by the



23

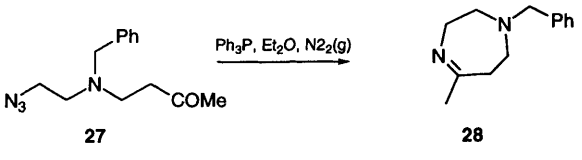
Scheme 14



Scheme 15

cyclisation of the resulting esters **25**, gives the cyclic imines **26**. Only one of the diastereomers cyclises and it can be separated by chromatography. Hydrolysis of the cyclic imines **26** then releases the amino acids in high enantiomeric excesses (yield 48%, ee 98%).

Intramolecular aza-Wittig reactions using the azides **27**, obtained by Michael addition of 1,2-amino azides with α,β-enones, give 2,3,6,7-tetrahydro-1*H*-1,4-diazepines **28** (**Scheme 16**). Greater control in the formation of regioisomers is observed over the corresponding diazepine formation using alkane-1,2-diamines.[21]



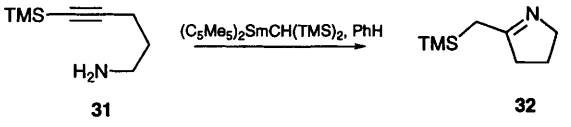
27 28

Scheme 16

The hydrogenolysis of *N*-(2-cyanoethyl)-ε-caprolactam and di-(2-cyanoethyl)amine using Raney nickel in the presence of sodium borohydride at atmospheric pressure leads to the reduction of the cyano groups to give the corresponding amines. These intermediates can then be used to prepare the cyclic imine bases DBU **29** and TBD **30** (1,5,7-triazabicyclo[4.4.0]dec-5-ene).[22]

29 30

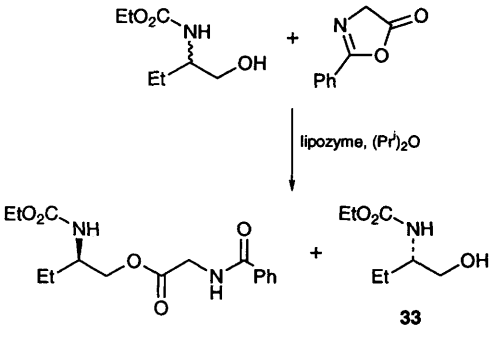
Aromatic and aliphatic amino alkynes **31** undergo a facile, regiospecific cyclisation to the corresponding cyclic imines **32** in the presence of the organolanthanide complex $(C_5Me_5)_2SmCH(TMS)_2$ (**Scheme 17**).[23]



31 32

Scheme 17

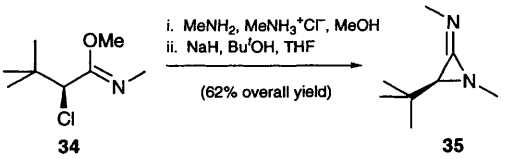
2-Phenyloxazolin-5-one has been shown to act as a derivatising agent for the kinetic resolution of 2-(*N*-ethoxycarbonylamino)butan-1-ol when used in organic solvents in the presence of a lipase (**Scheme 18**).[24] The highest enantiomeric excess is obtained in diisopropyl ether. This method avoids the need for column chromatography, as the product **33** is insoluble in diisopropyl ether, and gives moderate enantioselectivity.



Scheme 18

2.3 Haloimines

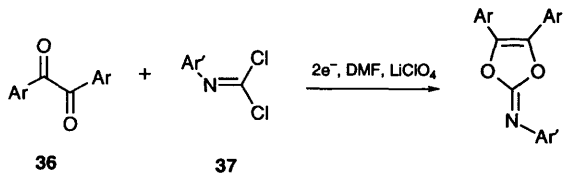
The reaction of 2-chloro imidate **34** with methylamine in the presence of methylammonium chloride yields the 2-chloro amidine in high enantiomeric excess (90%). Subsequent treatment with sodium hydride or potassium *tert*-butoxide with catalytic amounts of *tert*-butyl alcohol then induces the elimination of hydrogen chloride and the formation of the chiral 2-iminoaziridine **35** in an ee of 28% ee, as an *E*/*Z* mixture (**Scheme 19**).[25]



34 35

Scheme 19

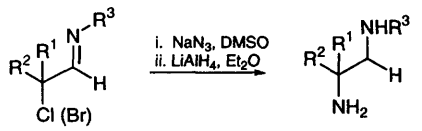
Selective cathodic reductions of diaryl-1,2-diketones **36** in the presence of carbonimidoyl dichlorides **37** provide a new method for the synthesis of enediol iminocarbonates in yields of 83–95% (**Scheme 20**).[26]



36 **37**

Scheme 20

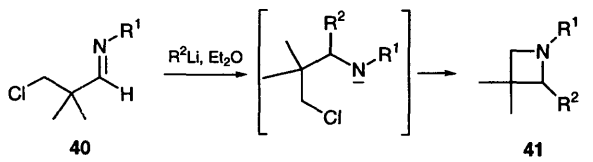
Treatment of α-bromo aldimines, α-chloro aldimines **38** or α-bromo ketimines with sodium azide in DMSO give the corresponding α-azido aldimines or α-azido ketimines in 79–92% yield.[27] Reductions of these α-azido-imines results in the formation of the corresponding 1,2-diamines **39** (**Scheme 21**), which are useful precursors to imidazolidin-2-ones and imidazolidine-2-thiones.



38 **39**

Scheme 21

3-Chloro-2,2-dimethylpropanimines **40** can be treated with alkyllithium or phenyllithium reagents to give 2-alkyl- and 2-phenyl-azetidines **41** respectively (**Scheme 22**).[28] The organometallic reagents add across the imino bond of the β-chloro imines, and this is followed by an intramolecular nucleophilic substitution.

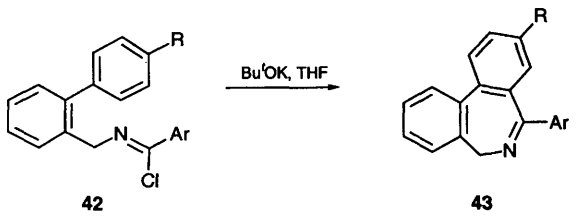


40 **41**

Scheme 22

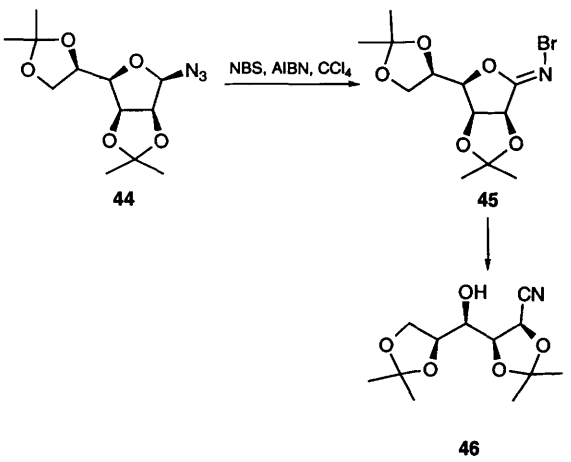
The imidoyl chlorides **42**, prepared by the action of thionyl chloride on *N*-benzoyl-2-arylbenzylamines, can be converted readily to intermediate diene-conjugated nitrile ylides which in turn cyclise to dibenz[*c*,*e*]azepines **43** (**Scheme 23**).[29]

Glycosyl azides **44** have been converted into *N*-bromo glycosylimines **45** by treatment with *N*-bromosuccinimide. The *N*-bromo glycosylimines



42 **43**

Scheme 23



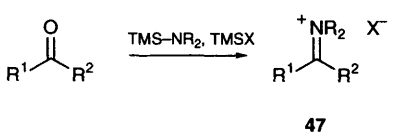
44 **45** **46**

Scheme 24

45 can subsequently be converted into aldonitriles **46** (**Scheme 24**).[30]

2.4 Iminium ions

A method for the synthesis of isolable methyleneiminium and amidinium salts has been developed. The treatment of aldehydes, ketones or amides with a mixture of (dialkylamino)trimethylsilane and TMSCl, or with (dialkylamino)trimethylsilane and TMSTf lead to iminium chlorides or trifluoromethanesulfonates **47** respectively (**Scheme 25**).[31] The former conditions using TMSCl, are restricted to non-enolisable aldehydes and DMF, whereas the latter reagents are also suitable for ketones and substituted amides.



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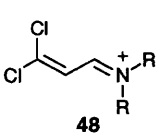
Scheme 25

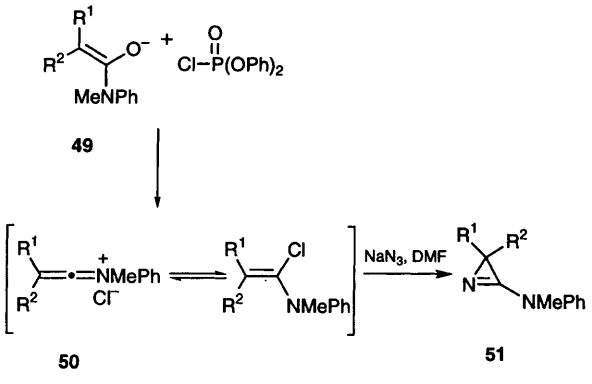
The (dialkylamino)trimethylsilane reagent can also be used for the synthesis of vinylogous Viehe salts **48** by its reaction with α-chloromethyl ethers in diethyl ether.[31]



48

Enaminones can also be used to prepare vinylogous iminium salts and these iminium salts can then be used to synthesise thienylpyrimidines and thienylpyrroles.[32]

2,2-Disubstituted 3-amino-2*H*-azirines **51** can be prepared in good yields (45–94%) by the action of diphenyl phosphochloridate on amide enolates **49** to give the keteniminium salts **50**. Treatment of the keteniminium salts with sodium azide furnishes the 2,2-disubstituted 3-amino-2*H*-azirines **51** (**Scheme 26**).[33] This method avoids the use of phosgene.

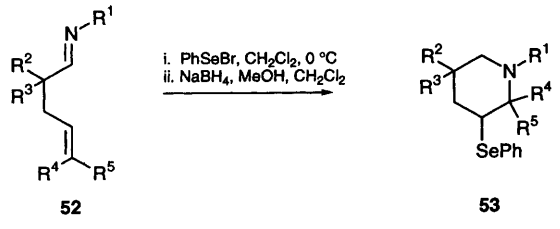


Scheme 26

Iminium ions can be readily generated by the catalytic action of a Lewis acid on an α-methoxyamine. The α-methoxyamines are themselves prepared by electrochemical oxidation of the parent amine in methanol. This chemoselective method for the creation of functionalised moieties for iminium ion cyclisation has been utilised in the synthesis of ACE (angiotensin-converting enzyme) inhibitors (−)-A58365A and (±)-A58365B.[34]

2.5 Cyclic iminium ions

The treatment of γ,δ-alkenyl enamines **52** with benzeneselenyl bromide results in the formation of cyclic iminium salts *via* an electrophile induced cyclisation.[35] The iminium salts may then be reduced to functionalised pyrrolidines (R^4, R^5 = H) or piperidines **53** (R^4, R^5 = Me) (**Scheme 27**).

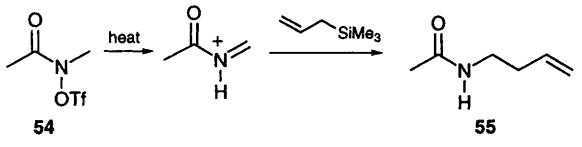


Scheme 27

An approach to the dipiperidine indole alkaloids nitrarine and isonitrarine relies on the stereoselective reduction of the cyclic iminium salts nitramidine and 15,20-epinitramidine with sodium borohydride.[36] The iminium salts are prepared by an oxidative cyclisation reaction.

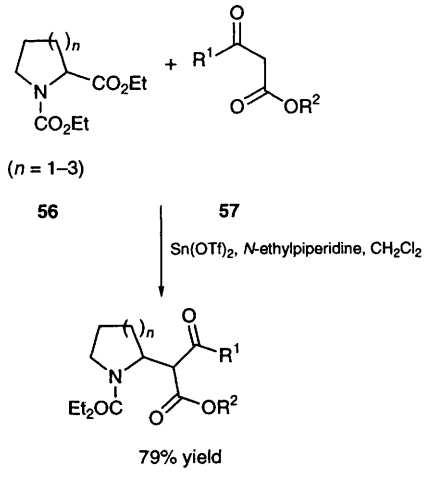
2.6 *N*-Acyl iminium ions

N-Trifluoromethylsufonyloxy amides **54** undergo ionisation in refluxing propan-2-ol to give *N*-acyl iminium ions which can then be trapped by addition of allyltrimethylsilane leading to homoalkyl substituted amides **55** (**Scheme 28**).[37] Alternatively the *N*-acyl iminium salts can be isolated as *N*-(isopropoxy)alkyl amides and then converted back into *N*-acyl iminium ions under a variety of conditions. The latter approach is more versatile than the *in situ* trapping method employed with *N*-trifluoromethylsulfonyloxy amides.



Scheme 28

Tin(II) trifluoromethanesulfonate can be used to form acyl iminium ions from α-ethoxy carbamates **56**. The acyl iminium ions, which are formed *in situ*, can then be trapped with electron rich olefins (35–70% yields), tin(II) enolates (41–70% yields) or active methylene compounds **57** (59–87% yields) (**Scheme 29**).[38]



Scheme 29

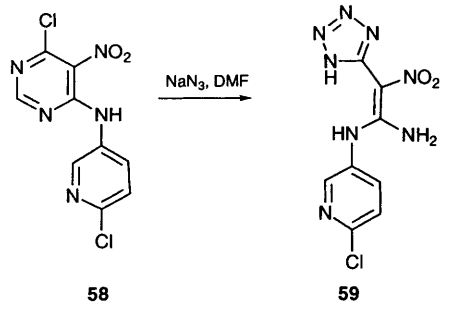
The addition of alkylcopper reagents to chiral *N*-acyl iminium ions gives products with a high *trans* selectivity (58–86% yields), whereas π-nucleophiles give *cis* selectivity.[39]

3 Enamines

A review on heterocyclic ketene aminals (cyclic 1,1-enediamines), covering their synthesis, reactions and applications in the preparations of fused heterocycles, has been published.[40]

If iminium salts which possess an α-CH group are treated with sodium trimethylsilanolate they are deprotonated efficiently. This method provides a route into α-alkenylenamines, prepared from the corresponding iminium trifluoromethanesulfonates (yields 62–91%).[41]

4-Chloro-5-nitropyrimidines **58** can be treated with sodium azide in DMF such that they undergo a multi-step rearrangement to give conjugated tetrazolyl enamines **59** (**Scheme 30**).[42]



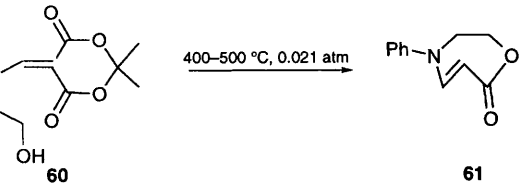
58 59

Scheme 30

Meldrum's acid derivatives of amino alcohols **60** can undergo a thermolysis reaction to give macrocyclic enamino lactones **61** in yields of 22–75% (**Scheme 31**),[43] and enaminonitriles **62** can be treated with nitroketene dithioacetal in refluxing acetonitrile to afford nitro dienamines **63** (**Scheme 32**).[44]

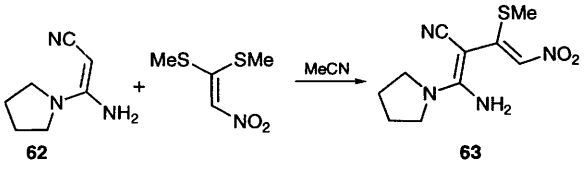
Cyclic imino ethers **64** are in tautomeric equilibrium with the corresponding secondary enamino ethers **65**. These enamino ethers undergo Michael additions to acrylic esters resulting in high yields (70–98%) of the 2-alkyl substituted imino ethers **66** (**Scheme 33**).[45]

Ethoxycarbonylation of 1-pyrrolidinocyclohexene can be effected using *N*-methylimidazolium salts **67** which are formed by the methylation of alkyl-imidazole-2-carboxylates with methyl trifluoromethanesulfonate (**Scheme 34**).



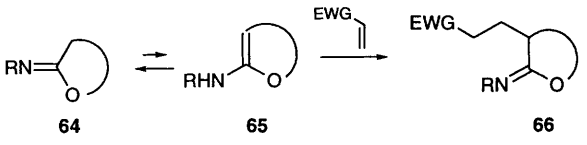
60 61

Scheme 31



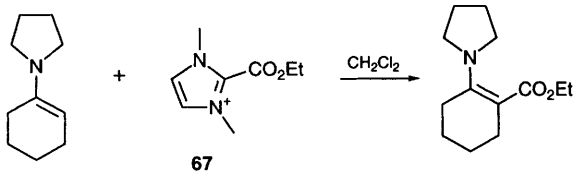
62 63

Scheme 32



64 65 66

Scheme 33



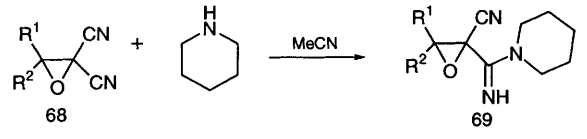
67

Scheme 34

4 Related functional groups

4.1 Amidines and guanidines

The chemoselective nucleophlic attack of amines on tetrasubstituted α,α-dicyano epoxides **68** provides a simple and efficient route to epoxy amidines **69** (**Scheme 35**). However, the degree of substitution on the α,α-dicyano epoxides can lead to either α-amino amides or epoxy amidines.[47] This contrast is seen for α,α-dicyano-β-allyl epoxides, which when treated with amines, lead to α-amino amides.



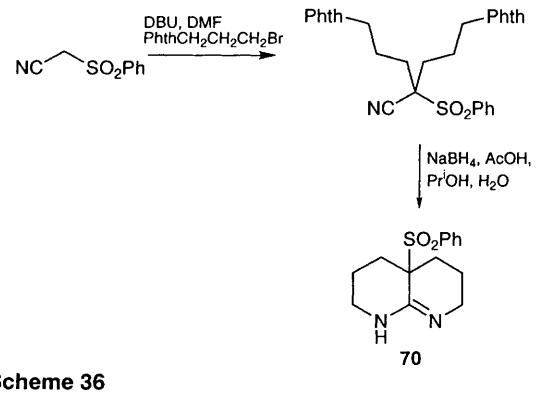
68 69

Scheme 35

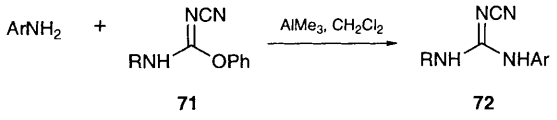
The bicyclic amidine 6-phenylsulfonyl-2,10-diazabicyclo[4.4.0]dec-1-ene **70** has been synthesised from (phenylsulfonyl)acetonitrile and *N*-(3-bromopropyl)phthalimide in a two-step procedure in 57% overall yield (**Scheme 36**).[48]

Cyanoguanidines **72** can be prepared from the trimethylaluminium promoted reaction of *N*-cyano-*O*-phenylisoureas **71** with anilines (**Scheme 37**).[49] The reaction proceeds well for most anilines (yields 44–90%) but those bearing a strong electron withdrawing group (nitro) do not undergo the reaction.

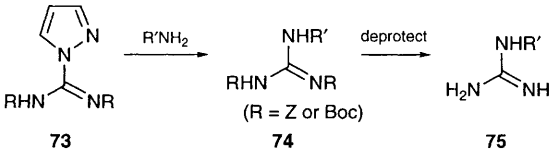
Bis-urethane protected derivatives of 1-guanylpyrazole **73** are found to react with amines giving bis-protected guanidines **74** in good yields.[50] Bis-



Scheme 36



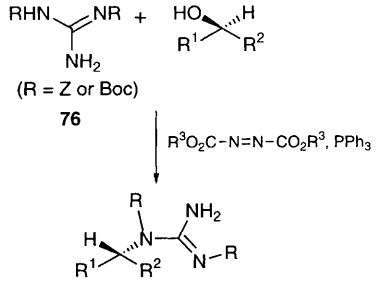
Scheme 37



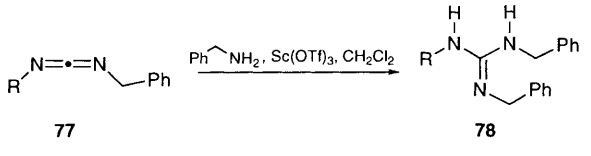
Scheme 38

deprotection concludes this efficient synthesis of monosubstituted guanidines **75** (**Scheme 38**).

Alcohols can be converted into guanidines in a facile, high yielding (64–95%) reaction by using *N,N*-bisprotected guanidines **76** as the nucleophiles in a Mitsunobu procedure (**Scheme 39**).[51] Guanidines **78** can also be synthesised in good yields (60–89%) by the action of amines on carbodiimides **77** in the presence of scandium or ytterbium trifluoromethanesulfonates (**Scheme 40**).[52]



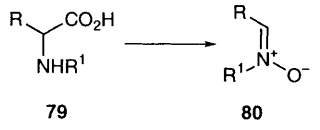
Scheme 39



Scheme 40

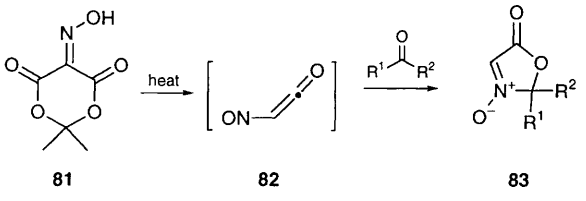
4.2 Nitrones

The tungstate-catalysed decarboxylative oxidation of *N*-alkyl-α-amino acids **79** with hydrogen peroxide provides an efficient method for the regioselective synthesis of nitrones **80** in yields of 52–99% (**Scheme 41**).[53]



Scheme 41

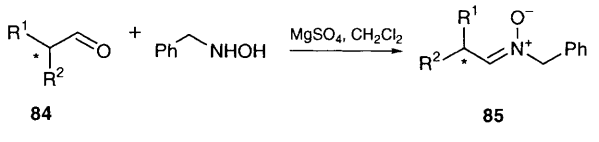
Nitrosoketene **82** is formed by the thermolysis of hydroximino Meldrum's acid **81**. The nitrosoketene may then be treated with ketones to form cyclic nitrones **83** (dihydrooxazole 3-oxides) in yields of 54–62% (**Scheme 42**).[54]



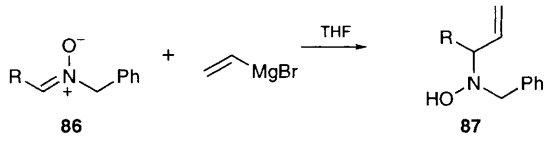
Scheme 42

The reactions of *N*-benzylhydroxylamine with chiral aldehydes **84** in the presence of desiccants (magnesium sulfate results in the shortest reaction times) result in the formation of chiral *N*-benzylnitrones **85** in yields of 59–89% (**Scheme 43**).[55]

N-Benzylnitrones **86** react with allylmagnesium bromide to give the corresponding *N*-benzyl-*N*-allylhydroxylamines **87** (**Scheme 44**).[56]

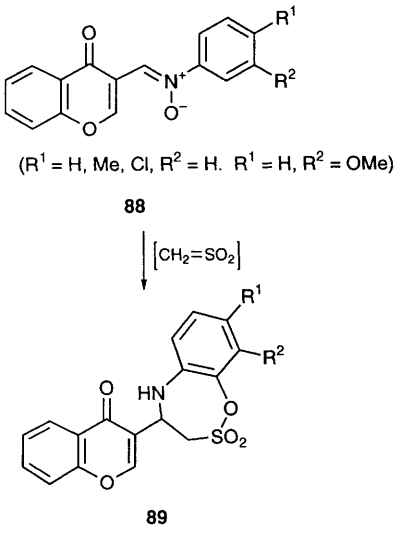


Scheme 43



Scheme 44

A new method for the generation of sulfene (thioformaldehyde dioxide) from chlorosulfonylmethylene(dimethyl)ammonium chloride has been exemplified by cycloaddition reactions with imines, nitrones and 1,3-diazabutadiene derivatives.[57] When nitrones **88** are used, high yields (80–85%) of the corresponding cycloaddition products, benzoxathiazepine 2,2-dioxides **89**, are obtained (**Scheme 45**).

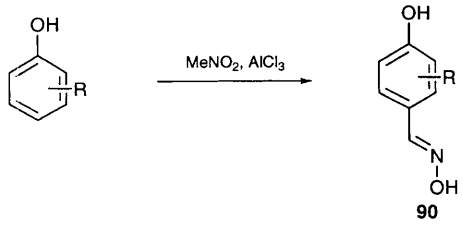


Scheme 45

4.3 Oximes

Two procedures for the synthesis of oximes have been demonstrated on an avermectin analogue. Oximes can be prepared from α-methyl-α,β-enones using zinc chloride and *O*-trimethylsilylhydroxylamine in isopropyl acetate (80%) or by using hydroxylamine hydrogen chloride in propan-2-ol–water at pH 1.8–2.2 (82%).[58]

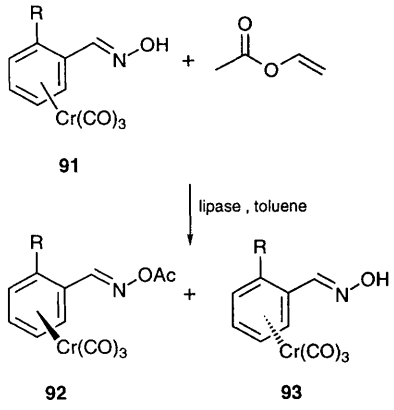
The reactions of nitromethane with aluminium phenolates, derived from the reaction of phenols with $AlCl_3$, provide a mild method for the preparation of salicylaldoximes **90** in yields of 14–85% (**Scheme 46**).[59] This method avoids the use of strongly acidic promoters.



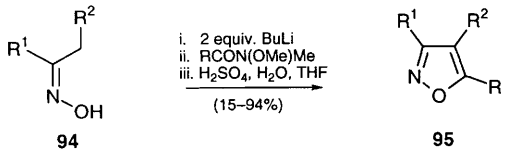
Scheme 46

Enzymatic resolutions of aryl oximes can be accomplished if the aryl unit is first complexed with chromium tricarbonyl to give the chromium–oxime complexes **91**.[60] The enantiomeric excesses of the resulting oximes **92** and **93** range from 7 to 98% and are dependent on solvent, substitution on the aryl group and whether an acylation or a hydrolysis is occurring (**Scheme 47**).

The use of Weinreb amides in conjunction with dianions obtained from oximes **94** results in the production of 3-substituted 5-alkylisoxazoles **95** (**Scheme 48**).[61]

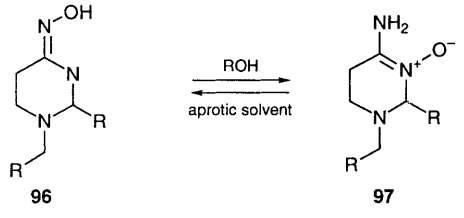


Scheme 47



Scheme 48

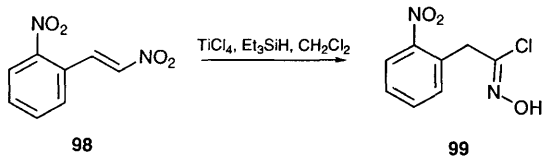
1,2-Disubstituted 4-hydroxyiminohexahydropyrimidines **96** undergo the Dimroth rearrangement in alcohol solvents.[62] The 1,2-disubstituted 4-aminotetrahydropyrimidine 3-oxides **97** so formed (**Scheme 49**) revert to the original 4-hydroxyiminohexahydropyrimidines in aprotic solvents.



Scheme 49

4.4 Hydroximoyl chlorides

A new method for the formation of phenylacetohydroximoyl chlorides **99**, in yields of 52–84%, from the titanium(IV)chloride–triethylsilane mediated conversion of ω-nitrostyrenes **98** has been developed.[63] Stoichiometric amounts of titanium(IV) chloride and triethylsilane are required (**Scheme 50**).

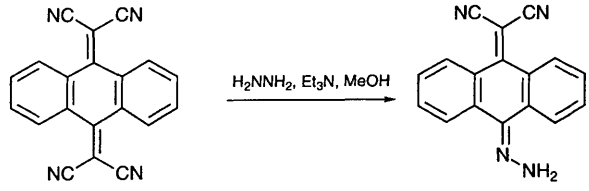


98 99

Scheme 50

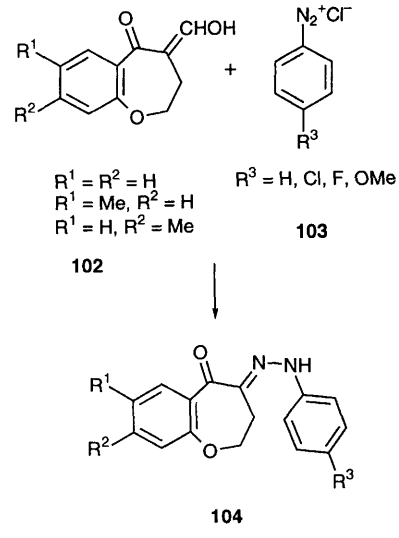
4.5 Hydrazones

A novel reaction of 11,11,12,12-tetracyanoanthraquinodimethane **100** is its transformation into 10-(dicyanomethylene)anthrone hydrazone **101** by its reaction with hydrazine, in 96% yield (**Scheme 51**).[64] 2,3-Dihydro-4-(phenylhydrazono)-1-benzoxepin-5-(4*H*)-ones **104** are convenient precursors to 5*H*,12*H*-[1]benzoxepino[4,3-*b*]indol-6-ones *via* the Fischer indole cyclisation. These intermediates can be prepared from the corresponding β-hydroxy α,β-enones **102** by using the Japp–Klingemann reaction, whereby the hydroxy enone is treated with a diazonium salt **103** to give the desired hydrazone (**Scheme 52**).[65]



100 101

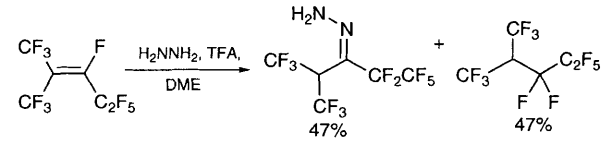
Scheme 51



102 103 104

Scheme 52

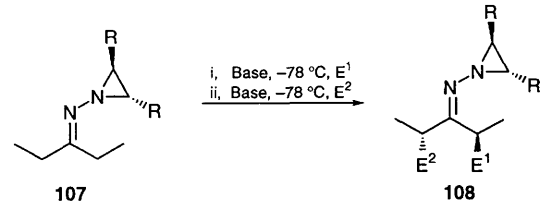
Hexafluoroisopropyl pentafluoroethyl ketone hydrazone **106** can be prepared readily by the action of hydrazine hydrate on perfluoro-2-methylpent-2-ene **105** (**Scheme 53**).[66]



105 106

Scheme 53

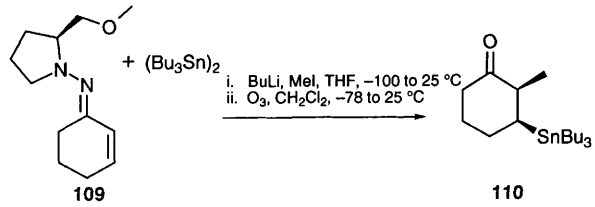
The α-alkylation of *N*-aminoaziridine hydrazones **107** is highly diastereoselective despite the absence of chelating groups (**Scheme 54**).[67] In contrast to other dialkylhydrazones, *N*-aminoaziridine hydrazones exhibit a *syn*-directing effect analogous to that observed for arylsulfonylhydrazones.



107 108

Scheme 54

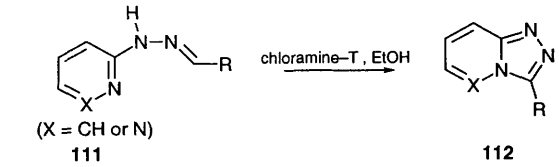
The work of Enders *et al.* into the use of SAMP and RAMP [(*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine] as chiral auxiliaries has shown that regio-, diastereo- and enantio-selective syntheses of 2-substituted 3-trialkylstannylcyclohexanones **110** can be effected by the Michael addition of trialkylstannyllithium to cyclohexanone SAMP or RAMP hydrazones **109** (**Scheme 55**).[68] Subsequent oxidative cleavage of the SAMP/RAMP moiety can then be achieved *via* ozonolysis.



109 110

Scheme 55

The oxidative cyclisation of aromatic and aliphatic aldehyde hydrazones **111** to give 3-substituted [1,2,4]triazolo[4,3-*a*]pyridines **112** (X=CH) and [1,2,4]triazolo[4,3-*b*]pyridazines **112** (X=N) can be achieved using chloramine-T in yields of 39–88% (**Scheme 56**).[69]

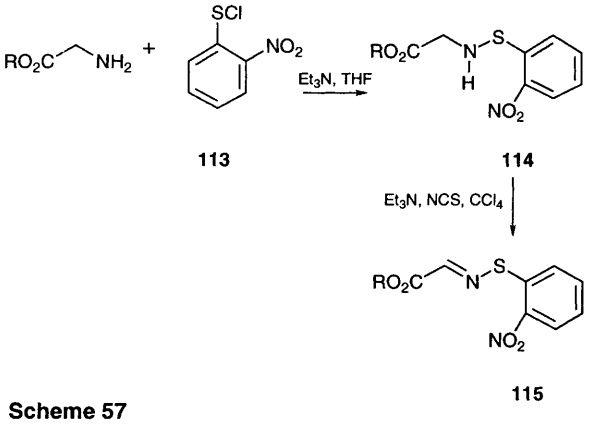


(X = CH or N)
111 112

Scheme 56

4.6 Sulfanyl imines, sulfoximides and sulfinyl imines

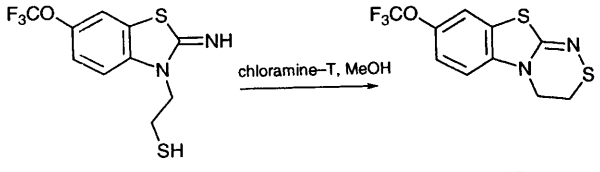
A general synthesis of nitrophenylsulfanyl imines **115** from primary amines has been developed for use in amino acid synthesis. Primary amines undergo a reaction with 2-nitrobenzenesulfenyl chloride **113** to give the corresponding sulfenamides **114**, which can then be converted into the sulfanyl imines **115** using *N*-chlorosuccinimide and triethylamine in carbon tetrachloride (**Scheme 57**).[70] If the primary amine used is a glycine derivative then the resultant sulfinimine can be used as a glycine synthon, *i.e.* to prepare α-amino acids.



113 **114** **115**

Scheme 57

A cyclic sulfanyl imine **117** has been formed by the intramolecular reaction of thiol-containing unsubstituted imine **116** using chloramine-T as the reagent in 75% yield (**Scheme 58**).[71]

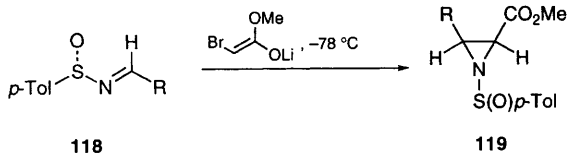


116 **117**

Scheme 58

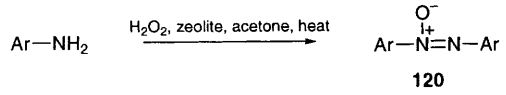
The conjugate addition reactions of lithiated allyl sulfoximides result predominantly in 1,4α-addition (45–92% yields). The 1,4α-addition product is formed exclusively when *N*-*p*-tosyl-*S*-phenyl-*S*-prop-2-enylsulfoximide is used.[72]

Enantiopure sulfinyl imines **118** undergo a Darzens type reaction with the lithium enolate of methyl bromoacetate to give *cis*-aziridine-2-carboxylic esters **119** in yields of 60–77% (**Scheme 59**).[73] These aziridines are themselves useful precursors to *syn*-β-hydroxy-α-amino acids.



118 **119**

Scheme 59



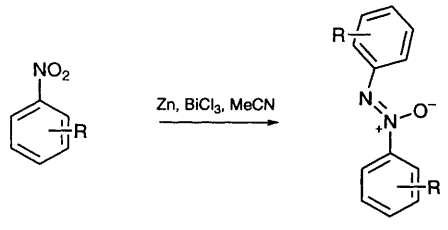
120

Scheme 60

4.7 Azoxybenzenes

The selective catalytic oxidation of arylamines to azoxybenzenes **120** has been demonstrated using hydrogen peroxide and a zeolite in acetone (**Scheme 60**).[74] Titanium silicates exhibit greater selectivity and higher activity than aluminosilicates. The most effective zeolite is TS-1 which gives azoxybenzene in 88% yield.

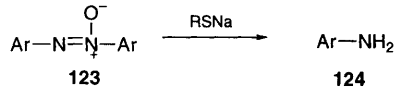
The selective reduction of aromatic nitro compounds **121** to azoxy compounds **122** can be accomplished at room temperature using bismuth(III) chloride and metallic zinc in yields of 70–85%, (**Scheme 61**).[75] Dinitro compounds are reduced to cyclic azoxy compounds under these conditions.



121 **122**

Scheme 61

A novel alkyl thiolate reduction of azoxybenzenes **123** to sulfenamides is accompanied by *in situ* decomposition leading to anilines **124** in yields up to 65% (**Scheme 62**).[76] In the case of sodium *tert*-butylthiolate, sulfenamides are isolated as the major products.

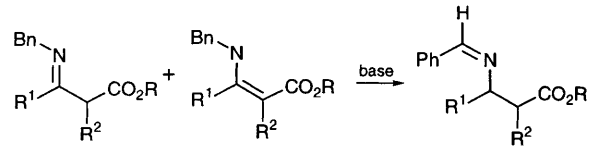


123 **124**

Scheme 62

5 Miscellaneous

A mixture of *N*-benzylimines **125** and *N*-benzylenamines **126** of β-polyfluoroalkyl-β-ketocarboxylic acids, when treated with an organic base (triethylamine or DBU), rearrange to the corresponding *N*-benzylidene derivatives **127** (**Scheme 63**).[77] No

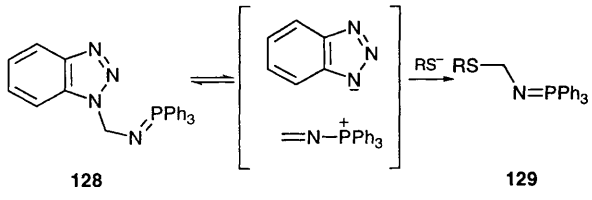


125 126 127

Scheme 63

such rearrangements occur in the non-fluorinated analogues.

Iminophosphoranes **129** can be synthesised readily by the action of a nucleophile on the benzotriazole derivative betmip **128** (**Scheme 64**).[78] If the nucleophile is a thiolate then the resulting *N*-(alkylthiomethyl)iminophosphoranes **129** can be trapped with aldehydes, isocyanates or acid chlorides to give thiomethylimines, thiomethylureas and thiomethylamides respectively.

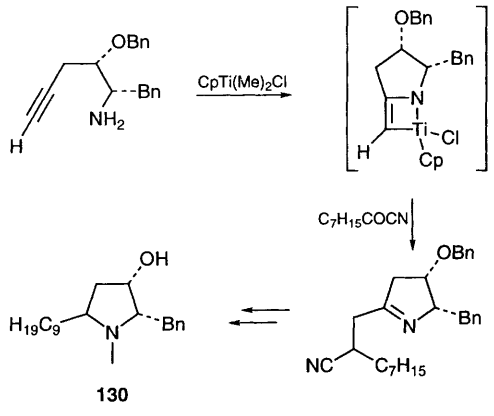


128 129

Scheme 64

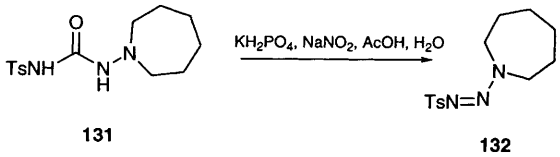
A novel synthesis of the antifungal agent (+)-preussin **130** using a convergent, intramolecular imidotitanium alkyne [2+2] cyclisation has been described (**Scheme 65**).[79] Although this synthesis involved the use of $CpTi(CH_3)_2Cl$, a more thermally stable catalytic titanium species can be prepared by treatment of a primary amine with $CpTiCl_3$ to give the bis(ethylamide) species $CpTiCl(NEt_2)_2$.

Mild nitrosating conditions can transform sulfonylsemicarbazides **131** (*e.g.* the oral antidiabetics Tolazamide and Glisoxepide) to sulfonyl triazenes **132** (**Scheme 66**).[80]



130

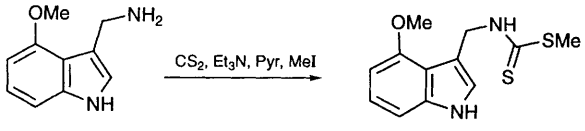
Scheme 65



131 132

Scheme 66

The conversion of 4-methoxy-3-aminomethylindole **133** into the dithiocarbamate 4-methoxybrassinin **134** can be achieved smoothly in 64% yield using carbon disulfide, triethylamine, pyridine and methyl iodide (**Scheme 67**).[81]



133 134

Scheme 67

6 References

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