REVIEW

Imines, enamines and oximes

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Received (in Cambridge, UK) 16th September 1999

Covering: January 1997 to December 1998
Continuing the coverage in *Contemp. Org. Synth.*, 1997, 4, 517

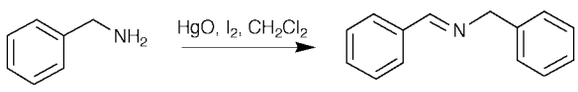
1 Introduction

This review covers areas of current interest in the use of imines, enamines and oximes. It is complementary to two reviews published in *Contemp. Org. Synth.*[1] The research covered revolves around new reagents, novel transformations and new methodology.

2 Imines

2.1 Formation of imines

Treatment of benzylamine with a catalytic amount of binuclear copper(II) complex of 7-azaindole under an oxygen atmosphere at room temperature produced a mixture of *N*-benzylbenzaldimine and benzonitrile. Under the same dehydrogenation conditions *n*-propylamine, dibenzylamine and 1-pyrrolidine all gave imine products.[2] Alkylamines also give self-condensed dimeric imines *via* oxidation with $YBa_2Cu_3O_7$.[3] Secondary amines are oxidised by 1-*tert*-butylperoxy-1,2-benziodoxol-3(*1H*)-one in the presence of potassium carbonate to give imines as the dehydrogenation products in 56–84% yield.[4] Treatment of benzylamines **1** with mercury oxide–iodine reagent in dichloromethane results in dimerisation occurring to give the imine products **2** in 76–98% yields (Scheme 1).[5]



1 **2**

Scheme 1

The reductive cyclisation of ω-azido carbonyl compounds is mediated by tetrathiomolybdate to give 5-, 6- and 7-membered cyclic imines in 67–90% yields.[6]

Imines are formed by the action of catalytic scandium or lanthanide triflates on a mixture of acetals and primary amines in toluene with molecular sieves in 41–96% yields.[7]

Formamidines are prepared in 38–95% yields by the action of primary amines on *N*,*N*-dimethylformamides when arenesulfonyl chlorides are used as coupling agents.[8]

Aldehydes react directly with 1,2-diaminoethane in chloroform to give imines in 75–98% yields.[9]

Aldehydes and ketones readily react with primary amines to give imines in 80–97% yields by using microwave irradiation with envirocat EPZG(R) as a catalyst under solvent free conditions. Reaction with secondary amines under these conditions leads to enamines.[10] Similarly, the reaction of primary amines with ketones and aldehydes is accelerated by microwaves under solvent free conditions in the presence of Montmorillonite K10 clay to afford imines in 95–98% yields. Under the same reaction conditions secondary amines give enamines.[11] In another example of microwave-assisted imine formation, heterocyclic amines and aldehydes are coupled in 65–95% yields using a domestic microwave oven and a basic solid support [poly(4-vinylpyridine)] in the absence of solvent.[12]

2.2 Addition to imines

A review covering the asymmetric synthesis of amines by nucleophilic 1,2-addition of organometallic reagents to the CN-double bond has been published.[13]

Enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines is promoted by 2-azanorbornylmethanol† ligands. Stoichiometric amounts of ligand led to enantioselective excesses of up to 92% using (1*S*,3*R*,4*R*)-2-benzyl-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane, and using 0.25 equivalents of the ligand gave ee's up to 85%.[14] Chiral diimines, diamines and dendrimers possessing 2, 4 and 8 ephedrine derivatives have also been utilised as chiral ligands for the enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines to afford *N*-diphenylphosphinylamines in 27–54% yields with 74–93% ee.[15]

Reaction of enantiopure methyl *N*-benzylidene-(*S*)-valinate with 2-methylallyl- or prenyl‡ zinc reagents affords homoallylic amines with *S*,*S* configuration in up to 100% de and 94–95% yields. Allylboron reagents gave the diastereomeric (*R*,*S*)-amine.[16]

† The IUPAC name for norbornane is bicyclo[2.2.1]heptane.
‡ The IUPAC name for prenyl is 3-methylbut-2-enyl.

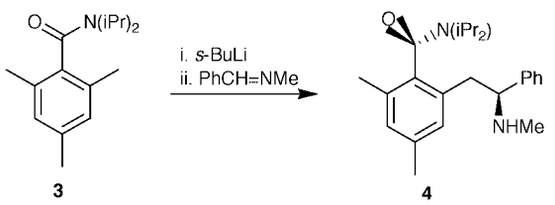
Organolanthanum reagents, generated *in situ* from $LaCl_3$ and alkyllithium or allylmagnesium species, undergo regioselective 1,2-addition to *N*-alkyl-α,β-unsaturated imines to give predominantly allylamines.[17]

(−)-Sparteine induced asymmetric addition of organolithium reagents to α,β-unsaturated imines has been used to prepare α,β-unsaturated amines in 35–86% yields and 16–88% ee.[18]

Organolithium reagents undergo an enantioselective addition to imines when mediated by C-2 symmetrical bis(aziridine) ligands {*e.g.* 1,2-bis[(2*S*,3*S*)-diphenylaziridin-1-yl]ethane}. Yields range between 39 and 90% with 5–89% ee.[19]

A preparative method for α-difluoromethylornithine and α-trifluoromethylornithine utilises the regioselective alkylation of an imine with lithiumpropargylamine.[20]§

Lithiation of *N*,*N*-diisopropyl-2,4,6-trimethylbenzamide **3** with *sec*-butyllithium followed by addition to *N*-methylbenzaldimine gave the amine as a single atropisomer **4** with complete (1,5)-asymmetric induction (Scheme 2).[21]



3 4

Scheme 2

The enantioselective addition of silyl enol ethers to imines is catalysed by palladium(II) diaquo complexes {*e.g.* Pd[(*R*)-tolbinap](H$_2$O)$^{2+}$$_2$(BF$_4^-$)$_2$} to give optically active acylalanine derivatives in 62–95% yields and 53–90% ee.[22]

The allylation of imines with allyltributylstannane and the reaction of imines with silyl enol ethers is catalysed by group 4 metal triflates, Zr(OTf)$_4$ or Hf(OTf)$_4$, to give the amine products in 83–92% and 77–95% yields respectively.[23] Chiral bis π-allylpalladium complexes enable the catalytic asymmetric allylation of imines with allyltributylstannane in 30–69% yields and 40–82% ee.[24] α-Trifluoromethylated amines are prepared by the action of triethylgermyl sodium and trifluoromethylthiobenzene on imines in 94–98% yields.[25]

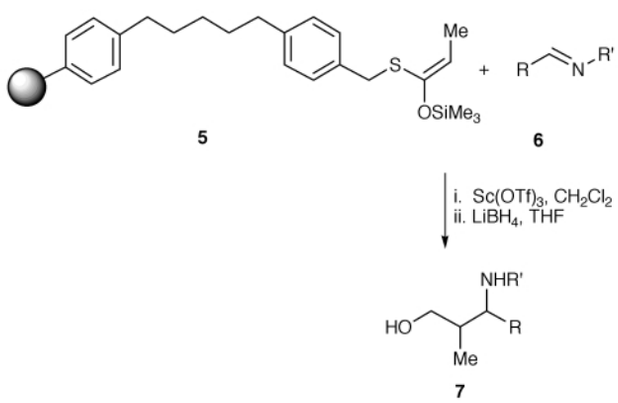
The Lewis acid promoted addition of silyl enol ethers to chiral imines derived from (*R*)-phenylglycinol produced (*R*,*R*)-β-aminoester derivatives in 42–85% yields and 72–98% de.[26]

The reaction of an allylzinc species with enantiopure imine species attached to polystyrene proceeds with >99% de and 97–98% yields to provide polymer supported chiral homoallylic amines.[27] *N*-(Trimethylsilyl)benzaldehyde imine undergoes an enantioselective allylation (up to 89% ee, 99% yield) using polymer supported chiral allylboron reagents.[28] 5-(4′-Chloromethylphenyl)pentylpolystyrene resin (CMPP resin) supported silyl enol ethers **5** undergo a reaction with imines **6** under Lewis acid conditions to give the amine products **7** in 72–100% yields (Scheme 3). These yields are approximately 10–30% higher than for the corresponding reaction using Merrifield resin.[29]

The asymmetric catalytic cyanosilylation of *N*-benzylbenzaldimine using a chiral binaphthol–titanium(IV) complex gave the α-cyanoamine product in 60% yield and 30% ee. The procedure is also effective for the cyanosilylation of aldehydes.[30]

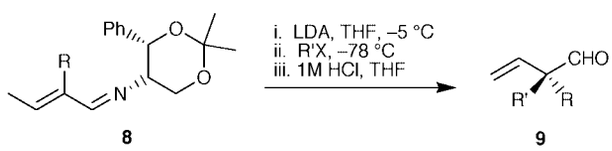
(4*S*,5*S*)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane [(4*S*,5*S*)-ADPD] was used to prepare chiral 2-alkylbut-2-ene (4*S*,5*S*)-ADPD imines **8** in 85–86% yields. Deprotonation with LDA of the imine **8** followed by alkylation at −78 °C and hydrolysis gives the α-alkylated aldehydes **9** in 42–78% yields with 40–81% ee (Scheme 4).[31]

Reduction of ferrocenylaldimines, prepared from ferrocenecarbaldehyde with valinol or phenylglycinol, with alkyllithium gives the inverse configuration at the stereogenic centre to that obtained by reduction of ferrocenylketimines, prepared from ferrocenylketone and valinol or phenylglycinol, with sodium borohydride.[32]



5 6 7

Scheme 3

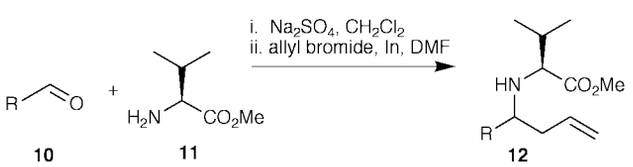


8 9

Scheme 4

Ketimines react with 4-*tert*-butylcatecholborane in THF to afford multiply borated products when catalysed by Wilkinson's catalyst. If bis(*tert*-butylbenzenediolato)diboron is used then *N*-bornylenamines are formed.[33] The allylboration of 1,1,1-trimethyl-*N*-(phenylmethylene)silanamine with chirally modified allylboron reagent prepared from triallylboron and *N*-tosyl-(−)-norephedrine gave (*S*)-α-(prop-2-enyl)benzenemethanamine in 89% yield and 92% ee.[34]

A one-pot procedure to give chiral homoallylic amines **12** in 52–80% yields from aldehydes **10** and L-valine methyl ester **11** proceeds in 91–98% de *via* the formation of imines *in situ* followed by alkylation with an allylindium species (Scheme 5).[35]



10 11 12

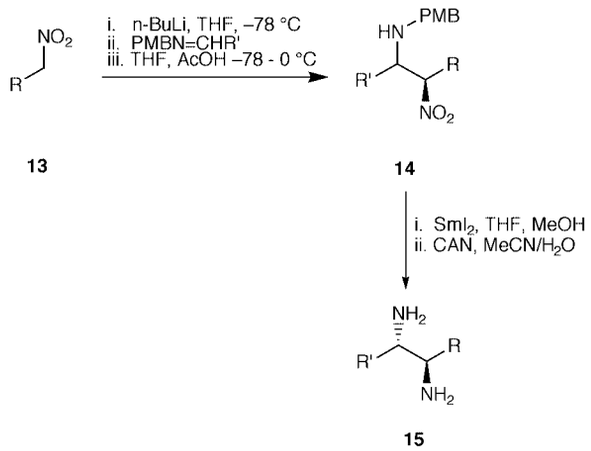
Scheme 5

Imines react with cyanotrimethylsilane (TMSCN) to afford α-aminonitriles using lanthanide triflates as catalysts. To avoid preparing and isolating the imines the reaction can be conducted using aldehydes, amines and TMSCN in a one-pot procedure, to give the desired α-aminonitriles in 78–100% yields.[36]

The treatment of alkyl nitrones **13** with butyllithium to give alkyl nitronate anions and their subsequent addition to *N*-(4-methoxybenzyl)imines in the presence of a Brønsted acid proceeds with 20–82% de favouring the *anti*-diastereomer. The β-nitroamines **14** are converted to 1,2-diamines **15** in a 2 step procedure (Scheme 6).[37]

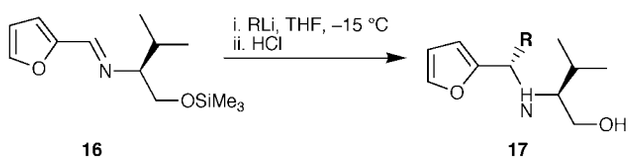
The addition of allylic zinc reagents, prepared by fragmentation of sterically hindered tertiary homoallylic alcohols with butyllithium and zinc chloride, to imines proceeds in 63–97% yields.[38] Addition of diethylzinc to imines in the presence of a Lewis acid affords secondary amines in 29–96% yields.[39] Addition of organometallics (allylzinc bromide, methyllithium or phenyllithium) to imines **16** derived from (*S*)-valinol and furaldehyde proceeds in 77–96% yields with high diastereo-

§ The IUPAC name for propargyl is prop-2-ynyl.



Scheme 6

selectivity to give the amines **17**. The resultant chiral amines were subsequently converted to α-amino acid derivatives (Scheme 7).[40]



Scheme 7

A Barbier type allylation of optically active imines using metallic samarium, a catalytic amount of iodine and allyl bromide proceeds at room temperature in THF in 47–93% yields and 24–98% de to give the homoallylic amines.[41]

Addition of alkyl radicals to the imine derived from methyl glyoxylate and 1-phenylethylamine gave the desired α-amino-esters in 40–67% yields but with only 16–40% de. Conducting the same chemistry on cyclic glyoxylate imine derivatives (dihydro-1,4-oxazin-2-ones) gave similar diastereoselectivities but in one case complete stereocontrol was observed.[42]

α-Aminophosphonates are prepared by the action of dimethyl phosphite on imines using tetramethylguanidine as a catalyst in 73–81% yields. This methodology may also be applied to α,β-unsaturated carbonyl compounds, alkenenitriles, aldehydes and ketones to provide ready access to a variety of phosphonate synthons.[43]

2.3 Reduction of imines to amines

A review on the asymmetric reduction of imines has recently been published.[44]

The hydrosilylation of imines using a chiral titanium difluoride complex with a silane is greatly enhanced by the addition of primary amines. Acidic work-up of the chiral *N*-silylamines provides the desired amines in high yield with 91–99% ee.[45]

A ruthenium complex with (oxazolinylferrocenyl)phosphine acts as a catalyst for the asymmetric hydrosilylation of a cyclic secondary imine to give a pyrrolidine in 60% yield and 88% ee after an acidic work-up.[46]

$Ni[P(OPh)_3]_4$ is an effective catalyst for transfer hydrogenation of *N*-phenyl-4-methoxybenzaldimine using ammonium formate. The amine product is obtained in 73% yield.[47] Imine hydrogenation can also be achieved using iridium complexes.[48] Furthermore, the asymmetric hydrogenation of imines is catalysed by an iridium-chiral diphosphine ligand (BICP) in the presence of imides (phthalimide) with up to 95% ee.[49]

Rhodium pyridylphosphine complexes are active in the catalytic hydrogenation of imines (75% yield in the reduction of *N*-phenylbenzaldimine), aldehydes and olefins.[50]

Organolanthanide catalysed imine hydrogenation has been shown to proceed in 16–98% yields with acyclic imines.[51]

A stereoselective reduction of an imine tetracycle was achieved in 68% yield using lithium aluminium hydride and aluminium chloride, although 29% of the undesired diastereomer was also obtained.[52]

An efficient approach to (3*S*,4*S*)-6,7-dimethoxy-4-hydroxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline uses sodium borohydride to reduce an enantiomerically pure imine in 98% yield.[53] Imines are chemoselectively reduced over esters by the use of tetrabutylammonium borohydride in chloroform in 95% yield.[54] The enantioselective reduction of *N*,*S*-heterocyclic imines (thiazolines and *2H*-1,4-benzothiazine) under different conditions has been studied. An enantioselectivity of 44% ee was obtained in one example when $Na(Boc\text{-}Pro)_3BH$ was used.[55] Imines are reduced by zinc borohydride supported on silica gel in 85–95% yields, and this method provides a highly diastereoselective synthesis of substituted cyclohexylamines.[56]

Imines can be reduced to amines in 69–94% yields *via* a titanium catalysed hydromagnesation reaction. *n*-Butylmagnesium chloride is employed as the stoichiometric reducing agent and Cp_2TiCl_2 as a catalyst. The reduction is not tolerant of bulky nitrogen substituents or primary or secondary enolizable protons on the imine.[57]

Zinc in acetic acid has been used for the reduction of an imine intermediate (83% yield) in a synthesis of 5-amino-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine—which shows antiulcer and antiarrhythmic activity.[58] Imines are also reduced by zinc powder in 5% aqueous sodium hydroxide solution without any organic solvents to give the amines in 53–88% yields.[59]

Treatment of imines with catalytic *n*-butyltris(2-ethylhexanoate)tin and stoichiometric polymethylhydrosiloxane in ethanol at room temperature provides the amine products in 75–84% yields.[60]

2.4 Sulfur imines

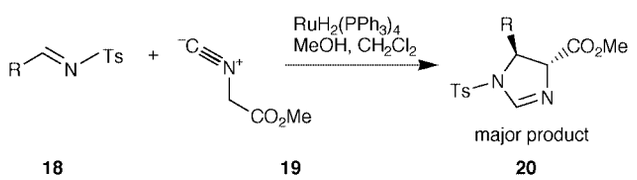
A review on *N*-sulfonyl imines has been published.[61]

The addition of phosphites to enantiopure sulfimines proceeds in 50–82% yields and with 90–97% de at −78 °C in THF. Cleavage of the resultant sulfinamide N–S bond by acid catalysed methanolysis leads to α-amino phosphonic acids.[62]

N-Tosylbenzaldimine is methylated effectively (95% yield) with a catalytic amount of $Ni(acac)_2$ using trimethylaluminium as the alkylation agent. The reaction is accelerated by phosphine or phosphite ligands when methylating aldehydes.[63] The regioselective addition of α,β-unsaturated organozinc reagents with *N*-(phenylsulfanyl)iminoesters proceeds in 55–98% yields.[64]

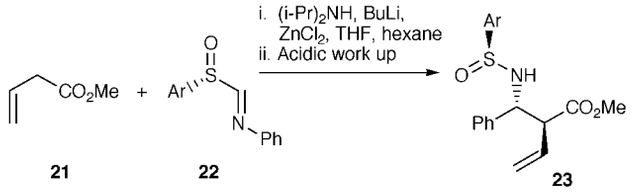
A catalytic amount of triphenylphosphine allows the [3 + 2] cycloaddition of methyl buta-2,3-dienoate with aromatic or heteroaromatic *N*-tosylimines in 53–98% yields at room temperature.[65]

The ruthenium(II) catalysed reaction of *N*-sulfonylimines **18** and methyl isocyanoacetate **19** proceeds to give *trans*-2-imidazoles **20** under neutral, mild conditions in 75–95% yields with *trans*:*cis* ratios of 84:16 to 95:5 (Scheme 8).[66]



Scheme 8

The lithium dienolate of but-3-enoic methyl ester **21** reacts in 34–90% yields with enantiomerically pure *N*-phenylaryl-sulfinylimines **22** at the 2-position of the dienolate to give the homoallylic amines **23** (Scheme 9). Different Lewis acids



Scheme 9

combined with different aryl sulfinyl moieties gave differing ratios of the epimers about the α-ester position (from 30 : 70 to 87 : 13).[67]

Isocyanoacetamide reacts with *N*-sulfonylimines to give 4-disubstituted-5-amino-1,3-oxazole products in 60–94% yields by a novel double addition process.[68]

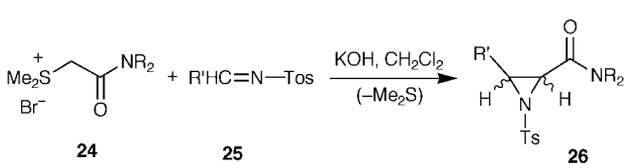
Asymmetric aza-Diels–Alder reactions of imines derived from ethyl glyoxylate with Danishefsky's diene in the presence of various Lewis acids give 4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylates in 42–90% yields with a wide variance of enantioselectivities (0% ee when $RuSbF_6$ was used, up to 80% ee when $CuClO_4$·4MeCN was used). Higher ee's can be obtained for more substituted dienes.[69]

2.5 Conversion of imines to aziridines

A review covering the formation of reactive intermediates from *N*-aziridinylimines has been published.[70]

Tungsten(II) methylene carbene complexes catalyse aziridine formation from imines and ethyl diazoacetate in 68–88% yields as predominantly the *cis* product. Enamines are formed as by-products.[71,72] Another example of carbenoid transfer to imines utilises a rhodium(III) or manganese(III) exchanged Montmorillonite K10 clay as a catalyst with methyl diazoacetate. The resultant aziridines are formed in 32–75% yields.[73]

cis-Vinyl and *cis*-ethynyl aziridines are furnished in 67–93% yields and with *cis* : *trans* ratios of 50 : 50 to 100 : 0 by conducting aziridinations of unactivated imines with sulfur ylides in the presence of Lewis acids.[74] This methodology was modified and used to conduct asymmetric aziridination of *N*-sulfonylimines by using a chiral sulfonium species to provide *cis*-acetylenyl-*N*-sulfonylaziridines in 58–95% yields and with 14–99% ee.[75] Similarly *N*-sulfonylimines **25** react with *N*,*N*-dialkylcarbamoylmethyl dimethylsulfonium bromides **24** in the presence of solid potassium hydroxide to give aziridinyl carboxamides **26** in 75–98% yields, predominantly as the *trans* isomer (Scheme 10).[76]



Scheme 10

The metal catalysed aziridination of imines with ethyl diazoacetate as the carbene fragment donor using various Lewis acids gives mainly *cis*-aziridines but selectivity is dependent upon substrate, catalyst and solvent. Zinc triflate and ytterbium triflate are general catalysts for aziridine formation with this methodology.[77] The tin(IV) catalysed aziridination of imines using ethyl diazoacetate has been investigated from a synthetic and mechanistic perspective. The *cis* isomers are the major products. The mechanism is discussed in terms of Lewis acid activation of the imine for nucleophilic attack of ethyl diazoacetate.[78] The iron Lewis acid $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]^+BF_4^-$ is an effective catalyst for the preparation of aziridines from *N*-benzylimines using diazo compounds in 38–95% yields.[79]

Monocarbonyl iodonium ylides, generated *in situ* from (*Z*)-(2-acetoxyvinyl)iodonium salts *via* ester exchange with lithium ethoxide, undergo alkylidene transfer reactions to activated imines to yield α,β-aziridino ketones in 36–89% yields.[80]

The sodium salt of (*S*)-*N*-tosyl-*S*-methyl(4-tolyl)sulfimide reacts with imines to give aziridines in 73–79% yields and 6–38% ee.[81]

2-Aza-1,4-dienes based on *N*-benzaldimine undergo a novel photorearrangement to produce *N*-vinylaziridines in 3–24% yields.[82]

Phosphinoyl imines react with allylsulfonium ylide to give *trans*-aziridines at room temperature (86–95% yields) and *cis*-aziridines at low temperature (72–94% yields).[83]

2.6 Conversion of imines to β-lactams

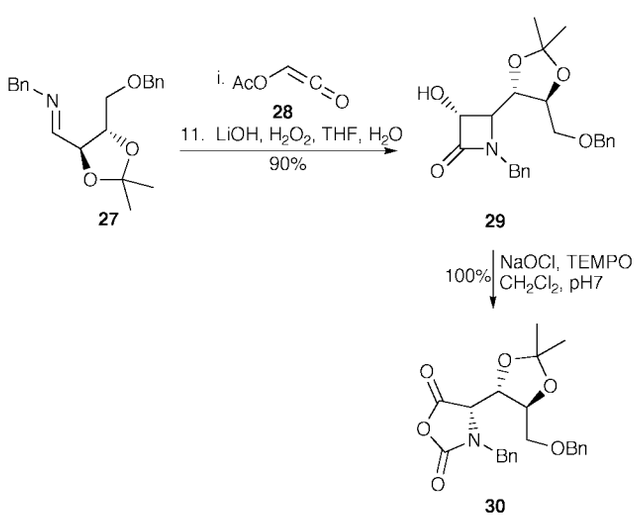
An efficient methodology for the preparation of 1,3-disubstituted β-lactams using the reaction of imines with acid chlorides in the presence of triethylamine proceeds in 50–75% yields.[84] A diastereoselective synthesis of racemic *cis*-β-lactam *via* cycloaddition of *N*-1-(α-thiophenyl)benzaldimines with acid chlorides in the presence of triethylamine proceeds in 50–79% yields.[85] A [2 + 2] cycloaddition of alkoxyketenes with imines derived from chiral α-amino aldehydes or chiral β-amino aldehydes to give 3-alkoxy-β-lactams has been used in a concise synthesis of piperazine-2-carboxylic acid derivatives.[86]

A one-pot synthesis of (3*R*)-hydroxy-β-lactams *via* enolates of 2-*tert*-butyl-1,3-dioxolan-4-ones and their reaction with *N*-phenylbenzaldimine proceeds in 51–99% ee with low *exo* : *endo* selectivity.[87]

Ethyl 3-hydroxybutanoate reacts with *N*-(4-methoxyphenyl)-benzaldimine in the presence of LDA in THF to give the β-lactam product in 40% yield.[88]

Esterification of 2-methylpropanoyl chloride with the chiral auxiliary (1′*S*,4*S*)-2-phenyl-4-(1′-hydroxybenzyl)-4,5-dihydrooxazole leads to a chiral ester which when treated with a benzaldimine in the presence of base results in the formation of β-lactams *via* an imine–ester enolate condensation. The enantioselectivity obtained at the 4-position of the β-lactam is dependent upon the nature of the metal additives in the reaction mixture.[89]

The reaction of the Mukaiyama's aldehyde-derived *N*-benzylimine **27** with a hydroxyketene equivalent **28** followed by saponification results in the formation of the 3-hydroxy-β-lactam **29**. Exposure of the resultant 3-hydroxy-β-lactam **29** to NaOCl and TEMPO provides a novel α-amino acid *N*-carboxyanhydride **30** (formally derived from polyoxamic acid) (Scheme 11).[90]



Scheme 11

N,*N*-Dibenzyloxycarbonylaminoazetidin-2-ones have been prepared from imines and *N*,*N*-dibenzyloxycarbonylglycyl chloride, which acts as a ketene equivalent, in 40–80% yields.[91]

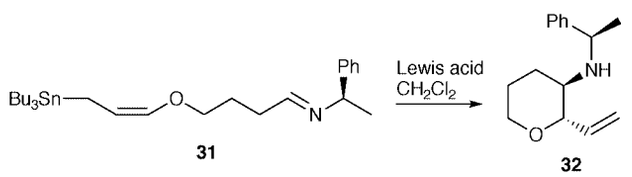
The first synthesis of β-lactams bound to a polyethylene glycol monomethylether polymeric matrix has been conducted on immobilised imines using ketenes.[92]

N-Methylidene[bis(trimethylsilyl)methyl]amine acts as a stable methanimine synthon (CH_2=NH) in [2 + 2] cycloadditions with ketenes to provide 4-unsubstituted β-lactams in 62–75% yields.[93]

Varying the size of the alkoxy moiety of lithium ester enolates in a chiral ligand mediated reaction with imines improved the enantioselectivity of β-lactam products to 75–93% ee. The asymmetric induction step was indicated to be the addition step and not the cyclisation step.[94]

2.7 Imine cyclisations

The Lewis acid mediated cyclisation of γ-oxygen substituted allylic stannanes **31** possessing a chiral imine group afforded the *trans* β-amino cyclic ether **32** with 92% de and 100% *trans* selectivity (Scheme 12). The analogous five and seven membered cyclic ethers were similarly prepared in 90% and 62% yields respectively, also with *trans* selectivity.[95]

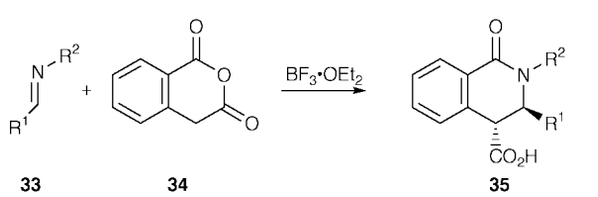


31 **32**

Scheme 12

1-Amino-3,4-dihydroisoquinolines substituted at the 3-position are prepared by lithiation of the *ortho*-methyl aromatic nitriles and addition to *N*-trimethylsilylimines with concomitant cyclisation in 11–77% yields.[96]

Cycloaddition of imines **33** with homophthalic anhydride **34** in the presence of boron trifluoride–diethyl ether leads to the *trans* isomers of isoquinolonic acids **35** in 41–96% yields (Scheme 13).[97]

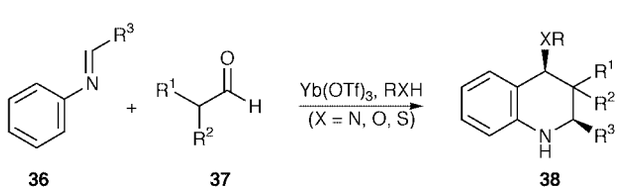


33 **34** **35**

Scheme 13

A procedure to prepare *threo*-(2*S*,3*R*)-3-aryl-2,3-diamino acids is based around the ability of chiral stabilised ylides derived from the reaction of (5*S*)-phenylmorpholin-2-one with aromatic imines to undergo a diastereocontrolled cycloaddition with a second equivalent of imine.[98]

A three component reaction involving an *N*-aryl imine **36**, a branched and enolisable aldehyde **37** and a nucleophile leads to 1,2,3,4-tetrahydroquinolines **38** in 13–93% yields (Scheme 14).[99]



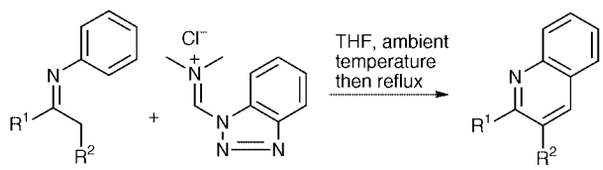
36 **37** **38**

Scheme 14

Chiral α-chloro imines are transformed to 2-aminoallylcations, in the presence of silver tetrafluoroborate, which then undergo an asymmetric [4 + 3] cycloaddition with furan or pyrrole systems to give bicyclic imine products.[100]

The *N*-benzylimine derived from 2,3-di-*O*-benzyl-D-glyceraldehyde undergoes a hetero-Diels–Alder reaction with Danishefsky's diene to give the 5-substituted 4-azacyclohexenone product in 65% yield and 80% de.[101] The aza-Diels–Alder reaction of *N*-(*p*-anisidino)methylglyoximine with Danishefsky's diene is conducted in 64% yield with 97% ee using (1*S*,2*S*)-1,2-diphenylethylenediamine and magnesium iodide in acetonitrile.[102] Microwave irradiation under solvent free conditions of pyrazoyl 2-azadienes with nitroalkenes induces Diels–Alder reactions to occur in 32–84% yields within 5–10 minutes.[103]

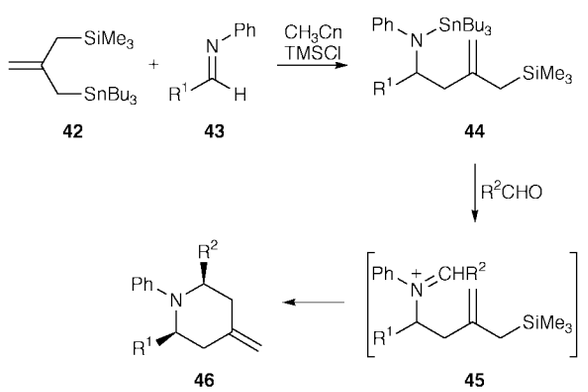
Quinolines **41** are prepared in 65–89% yields by the addition of the Vilsmeier type reagent *N*,*N*-dimethylbenzotriazol-1-yl-formiminium chloride **40**, to imines **39** (Scheme 15).[104]



39 **40** **41**

Scheme 15

2,6-Disubstituted 4-methylenepiperidines **46** are prepared in 12–69% yields in one-pot by the reaction of trimethylsilyl chloride, or boron trifluoride, on activated aldimines **43** with 3-tributylstannyl-2-(trimethylsilylmethyl)propene **42** to give the *N*-stannyl intermediate **44**. Treatment of the *N*-stannyl intermediate **44** with aldehydes gives the desired 2,6-disubstituted 4-methylenepiperidines **46** (Scheme 16).[105]



42 **43** **44** **46** **45**

Scheme 16

A photochemically induced cyclisation reaction of 3-aryl-3-aminoalk-2-ene imines in an acidic medium proceeds in 21–45% yield to give aminoazapolycyclic compounds.[106]

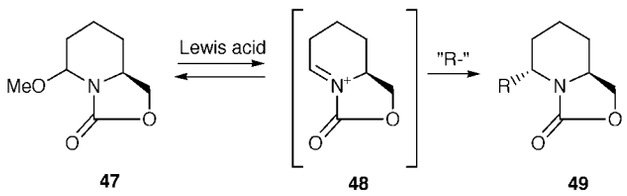
2.8 Iminium compounds

A review on iminium salt formation using silane reagents has been published.[107]

Treatment of the aminoether **47** with Lewis acids leads to the generation of the bicyclic *N*-acyliminium ion **48** which reacts in turn with π-nucleophiles to give *trans* adducts **49** in 56–95% yields (Scheme 17).[108]

An intramolecular cyclisation of a γ-alkyne onto an *N*-acyliminium ion is the key step in a projected synthesis of Roseophilin.[109] A novel allene-terminated *N*-acyliminium ion cyclisation is used to prepare a 7-azabicyclo[4.2.1]nonane-4,8-dione skeleton, an intermediate used in studies towards the total synthesis of the oxindole alkaloid Gelsedine.[110]

Treatment of a variety of α-methoxy amides prepared from 2-acyl-3,4-dihydroisoquinolone with 1-*tert*-butoxy-1-*tert*-butyldimethylsiloxyethene in the presence of boron trifluoride–



Scheme 17

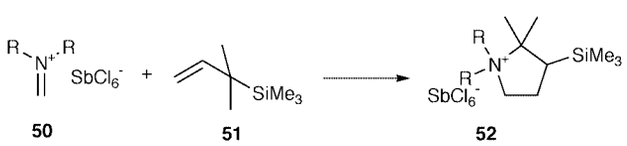
diethyl ether leads to β-substituted isoquinoline propionates (*via* an acyliminium ion approach) in 45–78% yields.[111]

2,3-Disubstituted chloropropeniminium salts react with glycinate esters to give unsymmetrical 2,3,4-trisubstituted pyrrole systems in 11–69% yields.[112]

3,3-Dichloroprop-2-ene iminium salts (vinylogous Viehe salts) display different regioselectivities at the 1- or 3-positions with various nucleophiles. Chloro substitution to afford new propene iminium salts occurs with thiols, amines and some activated arenes and heteroarenes. Attack at the 1-position to provide allyl or allylidene structures occurs with water, alcohols, activated methylene compounds and Grignard reagents. Thioamides give reactions at both the 1- and 3-positions with heterocyclisation.[113]

Amidoalkyl zinc–copper reagents have been shown to undergo conjugate additions to propyne iminium salts.[114]

Preformed iminium salts **50** with $SbCl_6^-$ as the counter-ion react with (1,1-dimethylallyl)trimethylsilane **51** in dichloromethane to give pyrrolidinium salts **52** in 85–95% yields (Scheme 18).[115]



Scheme 18

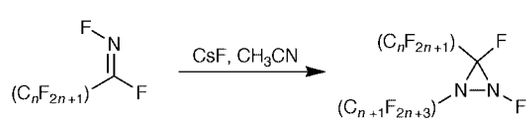
Cyclic iminium salts (fluoroborate or bisulfate adducts) have been treated with an iridium catalyst incorporating chiral amidophosphine–phosphinites in a hydrogen atmosphere such that an asymmetric hydrogenation occurred to give the corresponding cyclic secondary amines in up to 86% ee.[116]

Phosgeniminium salts react with chiral diamines to give chiral guanidinium salts in 53–100% yields.[117]

Enamines are aminoalkylated with preformed ternary iminium salts to give quaternary iminium salts, which are then reduced *in situ* with sodium borohydride to provide access to diastereomerically pure 1,3-diamines in 42–85% yields in this one-pot procedure.[118]

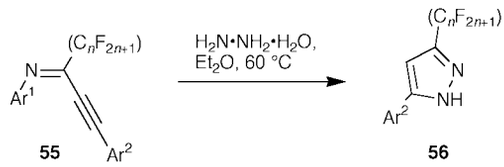
2.9 Miscellaneous

Perfluorinated *N*-fluoroalkanimines **53** undergo fluoride catalysed dimerisation and rearrangement to give diaziridines **54** in 86–90% yields (Scheme 19). *N*-Fluoroimines react with antimony(v) fluoride to give aza-alkenes as a result of Beckmann rearrangement.[119]



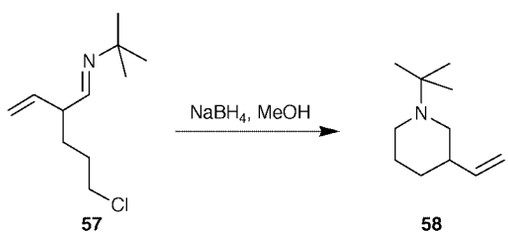
Scheme 19

N-Aryl-1-per(poly)fluoroalkylacetylenic imines **55**, prepared from the corresponding imidosyl iodides and acetylenes *via* a Sonogashira coupling, are novel precursors for the synthesis of fluorinated heterocycles such as pyrazoles **56** (59–99%) and pyrimidines (70–89%) (Scheme 20).[120]



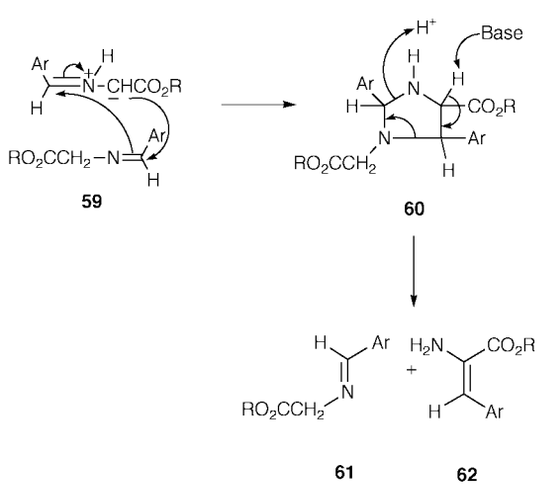
Scheme 20

N-(*tert*-Butyl)-5-chloro-2-ethenylpentanimine **57** is converted to the corresponding 3-vinylpiperidine **58** by treatment with sodium borohydride in methanol (Scheme 21). The aldimine can be functionalised and allowed to undergo similar cyclisations to give 3-ethylidenepiperidines, 5-vinyl-1,2,3,4-tetrahydropyridines and 5-(2-cyanoethyl)-1,2,3,4-tetrahydropyridines.[121]



Scheme 21

A new synthesis of didehydroamino acid (DDAA) esters **62** from aldimines **59** has been devised utilising a [3 + 2] cycloaddition of an azomethine ylide to an aldimine. The imidazoline intermediate **60** then undergoes a base-catalysed ring opening to give the DDAA esters **62** (Scheme 22).[122]



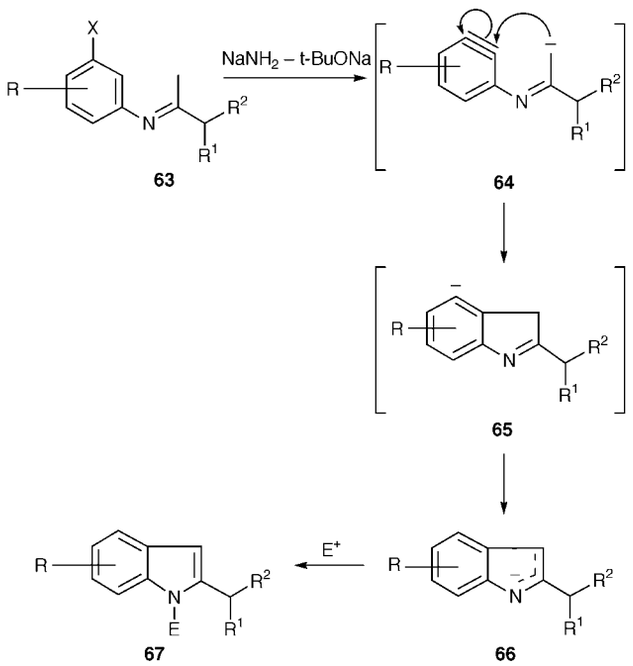
Scheme 22

Chloroimines react with an excess of lithium and 4 mol% naphthalene to give imidoyllithium species at −78 °C. Treatment of these imidoyllithium species with electrophiles (*e.g.* ketones, aldehydes, ethyl chloroformate) followed by hydrolysis with water affords functionalised imines in 26–80% yields.[123]

2-Substituted indoles **67** are obtained in 27–55% yields by selective arynic cyclisation of halogenated *N*-aryl methylketimines **63** in the presence of the complex base $NaNH_2$–^{t}BuONa (Scheme 23).[124]

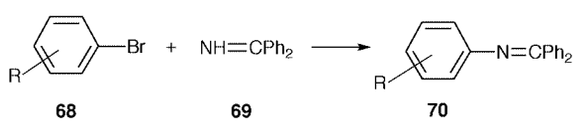
Imines (and ketones) undergo a titanium(IV) chloride–zinc induced reductive (Pinacol) coupling in the absence of solvent in 26–60% yields.[125]

Benzophenone imines act as an ammonia equivalent in the palladium catalysed amination of aryl halides and triflates. The



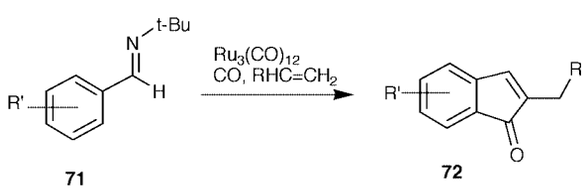
Scheme 23

N-arylimine intermediates undergo cleavage of the N=C bond by hydrogenation or treatment with hydroxylamine hydrochloride or HCl in wet THF.[126] The palladium catalysed C–N bond formation to give *N*-arylimines **70** occurs *via* *N*-arylation of benzophenone imines **69** (or aromatic nitrogen compounds) using sodium butoxide as base (Scheme 24).[127]



Scheme 24

Aromatic benzaldimines **71** are converted into indenones **72** *via* a $Ru_3(CO)_{12}$ catalysed carbonylation, in the presence of an olefin, at an *ortho* C–H bond in 13–85% yields (Scheme 25).[128]



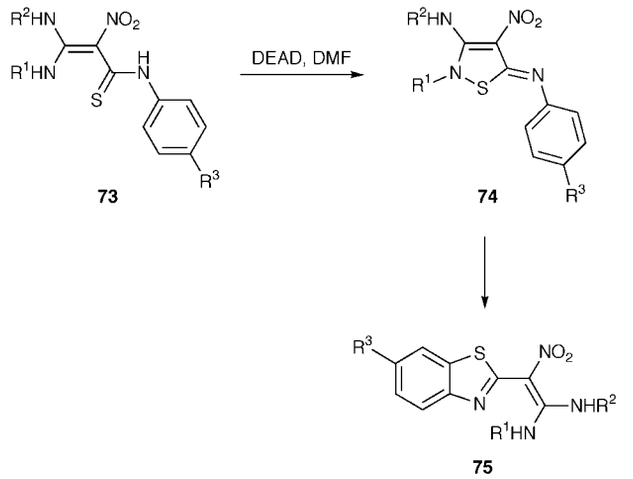
Scheme 25

An expeditious route to vicinal diamino based moieties from aldimines is effected *via* titanium(III) chloride–lithium mediated imino–pinacol coupling. The vicinal diamino products are formed in 62–83% yields with no formation of unimolecular reduced amines.[129]

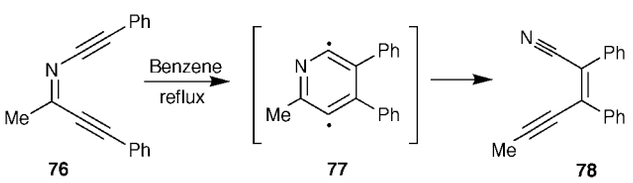
3,3-Diamino-2-nitrothioacrylamides **73** are cyclised to *N*-aryl-3-amino-4-nitroisothiazol-5(*2H*)-imines **74** using DEAD in 44–97% yields. In polar solvents a spontaneous isomerisation to benzothiazoles **75** occurred, although some of the isothiazol-5(*2H*)-imines (Scheme 26) required heating.[130]

A thermal rearrangement of the *C*,*N*-dialkynylimine **76**, a proposed aza-Bergman rearrangement occurring *via* the intermediacy of **77**, has been observed to give the olefin **78** in 88% yield with *Z*:*E* ratio of >95:5 (Scheme 27).[131]

Isomerisation of ketimines to aldimines can be achieved if *N*-benzylimines are treated with ruthenium hydride complexes



Scheme 26



Scheme 27

$[RuH_2(N_2)(PPh_3)_3$ or $RuH_2(PPh_3)_4]$ in toluene or dioxane under a hydrogen atmosphere.[132]

C_2 Symmetrical diamines are obtained by the reductive coupling of imines with a mixture of zinc and trimethylsilyl chloride in acetonitrile.[133]

Imines react with ethyl *p*-nitrophenylsulfonyloxycarbamate at room temperature to give spirodiaziridines in 31–46% yields.[134]

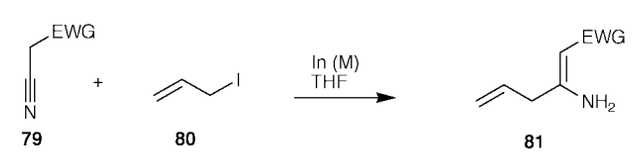
Decarboxylation of α-iminoacids to the corresponding imines is achieved under mild conditions *via* the use of a catalytic amount of tributylphosphine in 52–100% yields.[135]

3 Enamines

3.1 Formation of enamines

β-Nitroenamines have been prepared *via* the amination of nitroolefins with methoxyamines in the presence of a base in 30–94% yields.[136] Polyfunctionalised nitroenamines can also be prepared by the nucleophilic ring opening of 4-nitrooxazoles in 96–99% yields.[137]

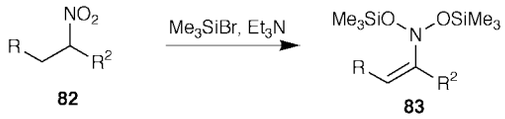
Allylindium reagents, prepared from the corresponding allyl iodide **80** and indium, react with nitriles **79** possessing an α-electron withdrawing group to provide allylenamines **81** in 55–93% yields (Scheme 28).[138]



Scheme 28

Simply treating ethyl α-methylpropionylacetate with (*S*)-α-methylbenzylamine and toluene-*p*-sulfonic acid in toluene results in the formation of the corresponding enamine in 92% yield. The enamine provides a suitable starting material for the synthesis of (+)-cassiol (which shows anti-ulcer activity).[139]

Primary and secondary aliphatic nitro compounds **82** react with two equivalents of bromotrimethylsilane in the presence of triethylamine to give *N*,*N*-bis(trimethylsiloxy)enamines **83** in 71–97% yields (Scheme 29).[140]



82 83

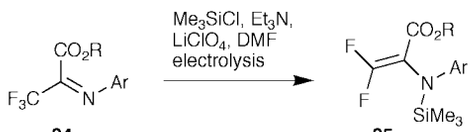
Scheme 29

2-Nitroalkenyl-1-amines are prepared *via* condensation of nitromethanes with (*S*)-methyl methaneimidothiolates in the absence of solvents in 38–100% yields.[141]

A practical method for the synthesis of α-chloro- and α-bromo-enamines involves treatment of a tertiary amide with phosphorus oxychloride or phosphorus oxybromide, followed by addition of triethylamine. The α-haloenamines are prepared in 24–95% yields.[142]

1-Perfluoroalkylenamines are formed by the action of *N*-lithiated amines to perfluoroalkyl and chlorofluoroalkyl enol ethers in 70–87% yields. The resultant enamines can be further functionalised *via* treatment with butyllithium to form vinylic anions followed by quenching with aldehydes or ethyl chloroformate.[143]

N-Trimethylsilylated β,β-difluoroenamines **85** have been prepared from the corresponding trifluoromethyl imines **84** by an electrochemical reduction in 47–78% yields (Scheme 30).[144]



84 85

Scheme 30

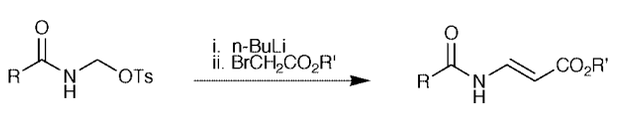
Enaminones, enaminonitriles and enamine esters have been prepared in 35–92% yields by the action of secondary cyclic amines in the presence of trimethylsilyltrifluoromethanesulfonate on β-diketones, β-ketonitriles or β-ketoesters respectively.[145]

Ketones react with secondary amines in the presence of *N*,*O*-bis(trimethylsilyl)acetamide and methyl iodide to form enamines in 80–93% yields.[146]

γ,δ-Unsaturated diformamides undergo Wittig alkenylation to provide γ,δ-unsaturated *N*-formylenamines in 5–94% yields.[147]

(*E*)-Enamines can be prepared by the action of secondary amines on alk-1-enylacetates in 74–88% yields.[148]

Deprotonation of α-amidosulfones **86** with *n*-butyllithium at −90 °C followed by treatment with α-bromoesters gives the desired enamides **87** in 33–62% yields (Scheme 31).[149]

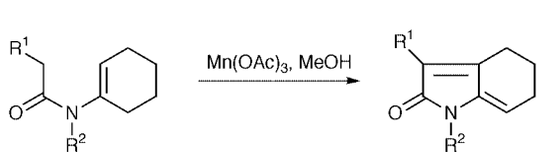


86 87

Scheme 31

3.2 Cyclisation of enamines

N-Acylenamines **88** react with manganese(III) acetate in boiling methanol to produce functionalised pyrrolidines **89** in 23–57% yields *via* an unusual (disfavoured) 5-*endo*-*trig* radical cyclisation (Scheme 32).[150]

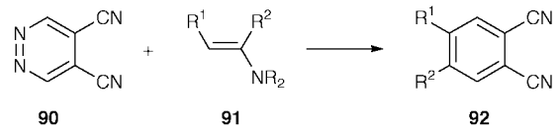


88 89

Scheme 32

A modified Hanztsch reaction between enamines and 3-bromo-1,1,1-trifluoropropan-2-one produces 5-trifluoromethylpyrroles in 60–70% yields, by heating the two components in diglyme at 140 °C.[151]

4,5-Dicyanopyridazine **90** undergoes a [4 + 2] cycloaddition with enamines **91** to furnish 1,2-dicyanobenzenes **92** in 11–96% yields (Scheme 33).[152]

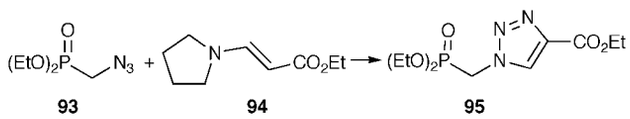


90 91 92

Scheme 33

Primary enamines have been used to prepare isothiazoles. Methyl 3-aminocrotonate will react with 4,5-dichloro-1,2,3-dithiazolium chloride to give methyl 5-cyano-3-methylisothiazole-4-carboxylate in 78% yield.[153]

Azidomethyl phosphonate **93** undergoes a cycloaddition reaction with enamines **94** to form β-functionalised alkyltriazoles **95** under solvent free conditions in 70–86% yields (Scheme 34).[154]

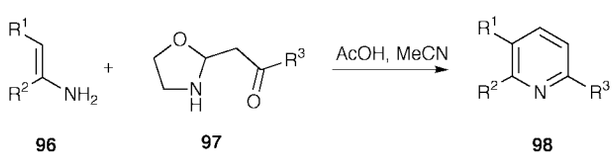


93 94 95

Scheme 34

Trifluoromethyl substituted β-diketones react regioselectively with primary enamines to provide 4-trifluoromethylpyridines in 35–82% yields.[155]

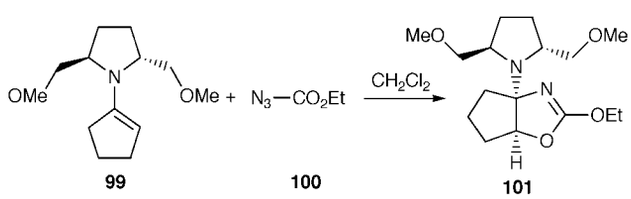
The enamine tautomers of oxazolidines **97** substituted at C-2 with a CH_2 attached to an electron withdrawing group react with enamine derivatives **96** to provide substituted pyridines **98** in 57–82% yields (Scheme 35).[156]



96 97 98

Scheme 35

The chiral cyclopentanone enamine **99** undergoes a stereoselective azide cycloaddition with ethyl azidoformate **100** to give the desired oxazoline **101** in 40% yield with >95% de (Scheme 36).[157]

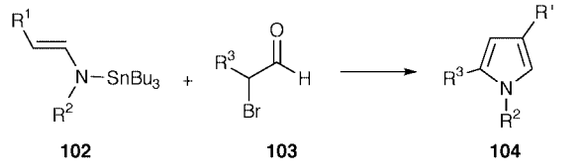


99 100 101

Scheme 36

1-Azaazulene derivatives are conveniently prepared by the reaction of enamines with troponimine derivatives, bearing hydroxy, methoxy, mesyl or tosyl groups on the *N*-atom, in 40–100% yields.[158]

Organotin(IV) enamines **102** undergo effective coupling with α-haloaldehydes **103** to give 2,4-disubstituted pyrroles **104** in 56–99% yields at room temperature under organic or aqueous conditions (Scheme 37).[159]



102 **103** **104**

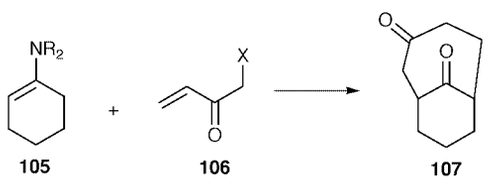
Scheme 37

An intramolecular radical cyclisation approach to 7-, 8- and 9-membered rings proceeds by trapping a radical formed by the action of tributyltin hydride with AIBN on an aryl iodide with an enamine to give the bicyclic products in 52–79% yields.[160]

Intramolecular radical and palladium-mediated (Heck) cyclisations of *ortho*-iodobenzyl enamines were compared to determine the respective methodologies potential for the production of libraries of compounds *via* solid phase synthesis.[161]

Functionalised phenolic derivatives are obtained *via* a [4 + 2] cycloaddition reaction of vinylketenes (prepared by the rhodium acetate catalysed Wolff rearrangement of diazo compounds) with enamines in 47–84% yields.[162]

A series of enamines **105** have been shown to undergo reactions with chloromethyl and iodomethyl vinyl ketone **106** to give bridged ring diketones **107** in 21–60% yields (Scheme 38).[163]



105 **106** **107**

Scheme 38

Enamines undergo a reaction with 2-hydroxynaphtho-1,4-quinones in toluene at reflux to afford the corresponding 2,3-disubstituted naphtho[2,3-*b*]furan-4,9-dione in one pot in 30–70% yields.[164]

The key step in a three stage process to synthesise bicyclo-[3.3.1]nonan-9-one utilised a cyclocondensation between an enamine and acrolein to give 1-hydroxybicyclo[3.3.1]nonan-9-one.[165]

3.3 Cleavage of enamines to carbonyl compounds

Ketones and formamides are the products from the oxidative cleavage of β,β-disubstituted enamines using potassium permanganate on alumina under solvent free conditions using microwave irradiation. Classical heating was compared to the results obtained with a domestic and with a focussed microwave oven.[166] Similarly, treatment of β,β-disubstituted enamines with potassium permanganate on neutral alumina selectively and preferentially oxidises an enamine carbon–carbon double bond in the presence of a distal carbon–carbon double bond. Ketones are isolated in 75–92% yields using this methodology.[167] Potassium permanganate has also been used when supported on Y-zeolite using 1,2-dichloroethane as solvent and conducting the reaction at room temperature.[168]

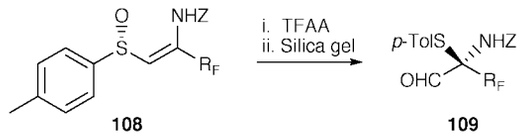
3.4 Miscellaneous

Manganese-mediated aziridination of the *N*-tosyl-2-pyrroline followed by addition of methanol provides a route to a separable mixture of racemic *cis*- and *trans*-2-methoxy-3-*N*-(trifluoroacetyl)aminopyrrolidine derivatives *via* the intermediacy of an aziridine.[169]

Stork enamine reactions of mono-fluorinated enamines, derived from α-fluoroacetophenones and pyrrolidine, with Michael acceptors generates a variety of substituted α-fluoroketones in 40–60% yields.[170]

Trifluoroacetaldehyde ethyl hemiacetal reacts with enamines in hexane at room temperature to give β-hydroxy-β-trifluoromethyl ketones in 25–88% yields.[171]

(*R*)-Fluoropyruvaldehyde *N*,*S*-ketals **109** are prepared *via* a Pummerer-type rearrangement of enantiopure (*R*)-α-fluoroalkyl-β-sulfinylenamines **108** (Scheme 39). The reaction has been optimised using statistical experimental design and multivariate modelling.[172]



108 **109**

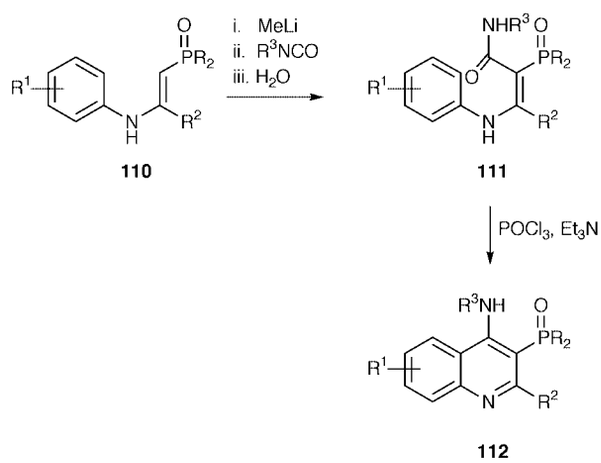
Scheme 39

Cyclohexanone enamines undergo regioselective and stereoselective amination using *N*-[(4-methylphenylsulfonyl)oxy]-carbamate to give mainly the *C*-amination products, *i.e.* 2-oxocyclohexanecarbamic esters.[173]

Enamines react with allyl bromide and metallic indium in THF to afford homoallylamines in 49–88% yields. This reaction is greatly accelerated by the addition of one equivalent of a carboxylic acid. The likely mechanism involves nucleophilic addition of an indium sesquihalide to the iminium salt formed by protonation of the enamine.[174]

Transdithioacetalisation of enamines (as well as acetals, ketals, oximes and tosylhydrazones) using ethane-1,2-dithiol in the presence of natural kaolinitic clay as catalyst produces the corresponding dithiolane in 75–80% yields.[175]

An efficient synthesis of 3-phosphorylated-4-aminoquinolines **112** utilises a regioselective addition of lithiated β-enamino phosphine oxides or phosphonates to isocyanates or isothiocyanates to give functionalised amides **111** or thioamides respectively in 71–83% yields (Scheme 40). Subsequent cyclisation *via* phosphorus oxychloride and triethylamine affords the 4-aminoquinolines.[176]



110 **111** **112**

Scheme 40

4 Oximes

4.1 Formation of oximes

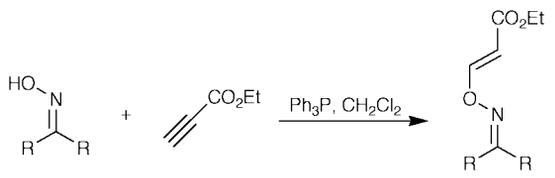
Treatment of ketones with hydroxylamine hydrochloride and an ion-exchange resin (Amberlyst A-21) as catalyst in ethanol leads to oximes in 70–100% yields at room temperature and with a simple work-up procedure.[177]

Ketoxime *O*-ethers are readily prepared in 15–92% yields from the corresponding ketoximes and alkyl iodides, prepared *in situ* from the alkyl chloride and potassium iodide. Phase transfer catalysis conditions are employed using either potassium carbonate or potassium hydroxide and 18-crown-6.[178]

Oximes are prepared in 61–84% yields *via* attack of alkyl radicals on alkyl nitrites. The radicals are generated *in situ* by

the action of hexabutyltin and light on alkyl bromides or aryl iodides.[179]

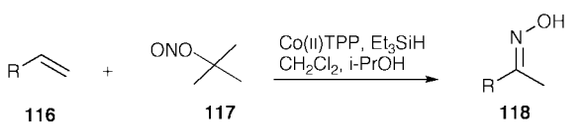
O-Vinyl oximes **115** are prepared in 68–83% yields by the conjugate addition of oximes **113** to ethyl propiolate **114** using triphenylphosphine as catalyst (Scheme 41).[180]



113 114 115

Scheme 41

Oximes **118** are prepared in 61–93% yields from olefins **116** in conjugation to aryl or carbonyl groups by a reduction–nitrosation procedure with *tert*-butyl nitrite **117** and triethylsilane in the presence of cobalt(II) porphyrin as a catalyst (Scheme 42).[181]



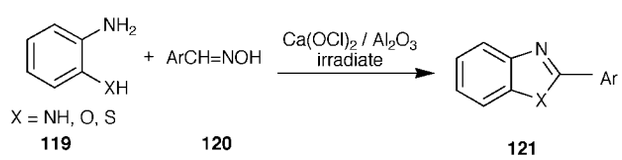
116 117 118

Scheme 42

2,2-Dinitrocyclopentanone oxime can be prepared from cyclopentenecarbaldehyde in 22% yield by the use of ceric ammonium nitrate and sodium nitrite in acetonitrile.[182]

4.2 Cyclisation of oximes

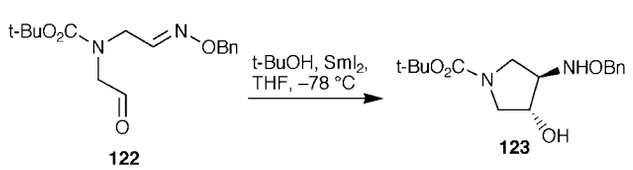
1,3-Azole derivatives **121** are prepared in 86–94% yields by the action of benzaldoximes **120** on 1,2-diaminoaromatics, 1-amino-2-hydroxyaromatics or 1-amino-2-thioaromatics **119** adsorbed onto alumina and treating the mixture to microwave irradiation for 4 minutes (Scheme 43).[183]



119 120 121

Scheme 43

Stereodefined alkoxy aminocyclopentanes have been derived in 68–78% yields from acyclic carbohydrate precursors using a samarium diiodide promoted intramolecular trapping of a radical by an oxime ether.[184] Samarium(II) iodide is also used to induce a 5-*exo*-*trig* cyclisation of an *O*-benzyl oxime **122** connected to a formyl group in an effective method for the preparation of predominantly the cyclic *trans*-amino alcohol **123** (63%) (Scheme 44) with some of the cyclic *cis*-amino alcohol (7%).[185]



122 123

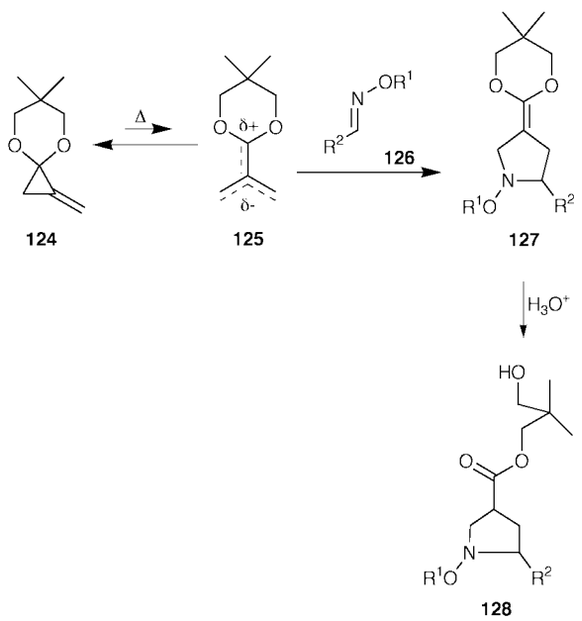
Scheme 44

2-(Arylimino)-1,2-diphenylethanone oximes, prepared from (*E*)-benzil monoxime and anilines, undergo an oxidative cyclisation with lead tetraacetate to 2,3-diphenylquinoxaline 1-oxides in 27–71% yields.[186]

Treatment of benzo-*p*-quinone oximes with sulfur dichloride in the presence of *N*-chlorosuccinimide and Hunigs base in THF provides 6*H*-1,2,3-benzodithiazol-6-ones in 10–45% yields. Some ring chlorination is observed, but 2,6-substituents are retained except for *tert*-butyl groups which are, in some cases, replaced by chlorine.[187]

Arylhydroximoyl chlorides undergo a nucleophilic addition of ethylenediamine in 40–85% yields to give 2-arylimidazolines.[188]

Heating a mixture of an alkylidenecyclopropane **124** to give an incipient dipolar trimethylenemethine species **125** with *O*-alkyloximes **126** proceeds through a hetero [3 + 2] cycloaddition to give pyrrolidines **127** substituted in the 3-position by a ketene acetal group, which upon hydrolysis provides 3-alkoxycarbonylpyrrolidine **128** (Scheme 45).[189]



124 125 127 128

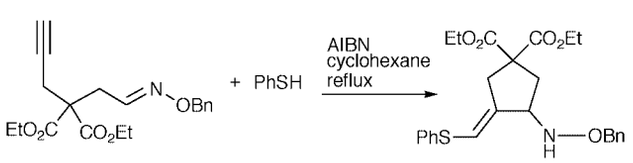
Scheme 45

5-Aminoisoxazoles are readily prepared by the action of isocyanides with α-bromoketone oximes in 52–93% yields.[190]

1-Aryl-2,2-dihaloethanone oximes can be treated with tetrasulfur tetranitride in refluxing dioxane to prepare 3-aryl-4-halogeno-1,2,5-thiadiazoles in 32–99% yields.[191]

1,2-Benzoxazoles have been prepared in 37–95% yields by intramolecular Mitsunobu reactions on salicylaldoximes and *o*-hydroxyphenylketoximes.[192]

Thiophenol **130** radical induced cyclisation of ethylenic and acetylenic tethered oxime ethers **129** give rise to polyfunctionalised 5-membered ring systems **131** (Scheme 46).[193]

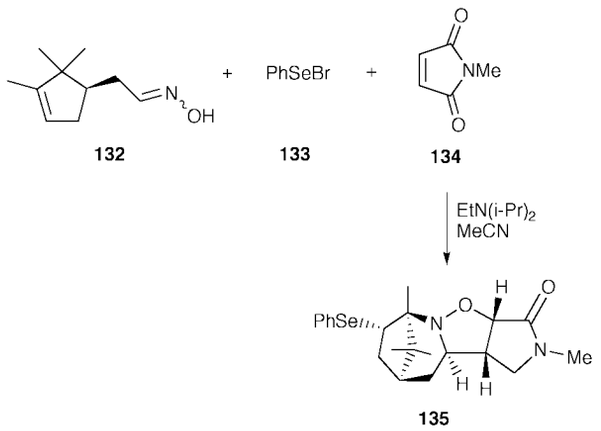


129 130 131

Scheme 46

Perimidine-2-formaldoxime has been prepared in a one-pot procedure from *anti*-monochloroglyoxime and 1,8-diaminonaphthalene in 47% yield. 2,2′-Biperimidine has also been prepared using (*E*,*E*)-dichloroglyoxime.[194]

Electrophile induced 6-*exo*-*trig* spirocyclisation of oximes onto 5-, 6- or 7-membered cycloalkenes occurs stereo- and regio-selectively. Chiral bridged ring systems **135** have been synthesised in 59–72% yields using this chemistry (Scheme 47) to



132 133 134 135

Scheme 47

induce a multiplication of stereogenic centres from one chiral centre to six or seven in one pot.[195]

Ethyl 3,3-diethoxyacrylate reacts with substituted ethanone oximes and LDA to prepare 3-substituted and 3,4-disubstituted isoxazole-5-acetic acids in 23–66% yields.[196]

Highly functionalised 3-oxa-2-azabicyclo[3.3.0]hexanes are prepared in 70–100% yield with diastereomeric ratios from 1:0 to 6:1 from carbohydrate derived oxime precursors using an intramolecular oxime olefin cycloaddition.[197]

3,4-Dihydro-*2H*-pyrroles and 2,3,4,5-tetrahydropyridines are prepared by the intramolecular cyclisation of (*E*)-*O*-methylsulfonyloximes having an active methine group at γ- and δ-positions respectively by treatment with DBU in 71–99% yields.[198]

4.3 Cleavage of oximes to aldehydes and ketones

Oximes and *p*-nitrophenylhydrazones are converted to carbonyl compounds by non-aqueous oxidative cleavage using dimethylammonium chlorochromate adsorbed on alumina in 44–82% yields.[199] Oxidative cleavage of oximes to aldehydes and ketones can also be conducted with ammonium chlorochromate adsorbed onto silica in 20–85% yields.[200]

Trimethylaluminium chlorochromate adsorbed onto alumina also oxidatively cleaves oximes in 58–83% yields.[201]

Ferric perchlorate adsorbed onto silica gel is an effective reagent for the cleavage of the carbon–nitrogen bond of oximes. The adsorbed ferric perchlorate and oxime are ground together as solids using a mortar and pestle.[202]

Ammonium persulfate adsorbed onto silica gel rapidly regenerates carbonyl compounds from their parent oximes under solvent free conditions using microwave irradiation in 59–83% yields.[203] The treatment of ketoximes with sodium bismuthate supported on wet silica using microwave irradiation provides a fast, solvent free method for regenerating ketones in 72–94% yields.[204] Bismuth trichloride in tetrahydrofuran cleaves oximes to give carbonyl compounds in 45–96% yields using microwave irradiation.[205] Silica supported chromium trioxide oxidatively cleaves oximes under microwave irradiation in 57–95% yields.[206] The regeneration of carbonyls from their oximes using clay supported ammonium nitrate "clayan" using microwave irradiation and solvent free conditions proceeds in 64–83% yields.[207]

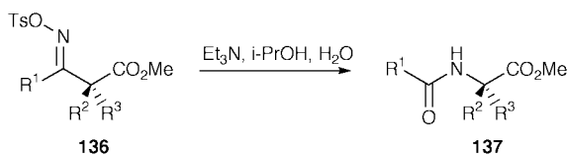
Among a host of other cleavage conditions 1-hydroxy-1,2-benzodioxol-3(*1H*)-one 1-oxide is effective for oxidative cleavage of oximes at room temperature in 85–95% yields.[208] *N*-Bromosuccinimide in aqueous acetone achieves the cleavage in 48–95% yields.[209] Manganese triacetate is effective for the conversion of oximes to carbonyl compounds in 86–96% yields.[210] Oximes are converted into aldehydes and ketones using cheap and non-toxic Oxone in acetic acid and water in 70–85% yields.[211] Benzyltriphenylphosphonium persulfate can be used under aprotic and non-aqueous conditions in organic solvents to oxidise oximes to carbonyl compounds in 75–98% yields.[212] The reagent 70% *tert*-butylhydroperoxide readily regenerates carbonyl compounds from oximes under neutral conditions in 30–100% yields.[213] *n*-Butyltriphenylphosphonium dichromate oxidises benzylic and allylic oximes to their corresponding carbonyl compounds in the presence of aluminium chloride in 70–86% yield.[214]

In a total synthesis of (+)-agelasimine α and (+)-agelasimine β, a substituted cyclohexanone oxime was treated with 4-oxopentanoic acid and hydrochloric acid to give the corresponding cyclohexanone derivative in 91% yield.[215]

Deoximation can be achieved using *N*-bromosuccinimide or *N*-chlorosuccinimide in carbon tetrachloride in 80–96% yields.[216]

4.4 Beckmann rearrangements

A Beckmann rearrangement of the tosyl oxime **136** is the key step in a synthesis of protected, chiral α,α-disubstituted α-amino acids **137** and proceeds in 51–70% yields and 95–99% ee (Scheme 48).[217]



136 137

Scheme 48

Beckmann rearrangement of *O*-pent-4-enyl oxime derivatives proceeds through the formation of a cationic tetrahydrofuranium intermediate in a halocyclisation reaction with *N*-bromosuccinimide in 12–88% yields.[218]

4.5 Reduction of oximes

The reducing behaviour of dihydrobis(1-pyrazoyl)borate and pyrazabole have been studied and shown to reduce oximes to hydroxylamines in 80–84% yields.[219]

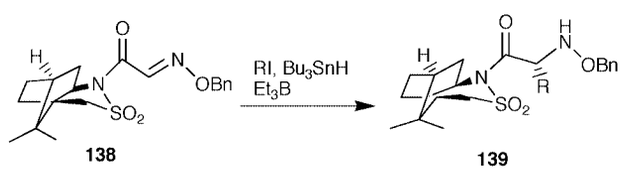
β-Functionalised allyl oximes are converted to (*E*)-allylamines *via* the use of diphenylphosphorus chloride to give *N*-diphenylphosphanylimines which are subsequently reduced with sodium borohydride in ethanol. The resultant *N*-diphenylphosphanylimines are hydrolysed to give the desired (*E*)-allylamines in 67–92% yields. The three steps can be conducted in a one-pot procedure.[220]

Asymmetric reduction of α-oxoketoxime ethers using reagents prepared *in situ* from trimethylborate and chiral amino alcohols derived from α-pinene or L-proline result in stereoselective syntheses of 1,2-aminoalcohols. The 1,2-aminoalcohols are obtained in 31–94% yields as predominantly the *anti*-products and with 31–98% ee.[221]

4.6 Radical addition to oximes

A high degree of stereochemical control (72–96% de) in the alkyl free radical addition to Oppolzer's camphor sultam derivative of glyoxylic oxime ether **138** is achieved in 25–86% yields. The resultant hydroxylamine *O*-ethers **139** are intermediates for enantiomerically pure α-amino acids (Scheme 49).[222]

Intermolecular carbon radical addition to unactivated *O*-benzyl aldoximes in the presence of boron trifluoride–diethyl



138 139

Scheme 49

ether provides an efficient carbon–carbon bond forming method in 41–98% yields for the synthesis of *O*-benzyl hydroxylamines as intermediates for amines.[223]

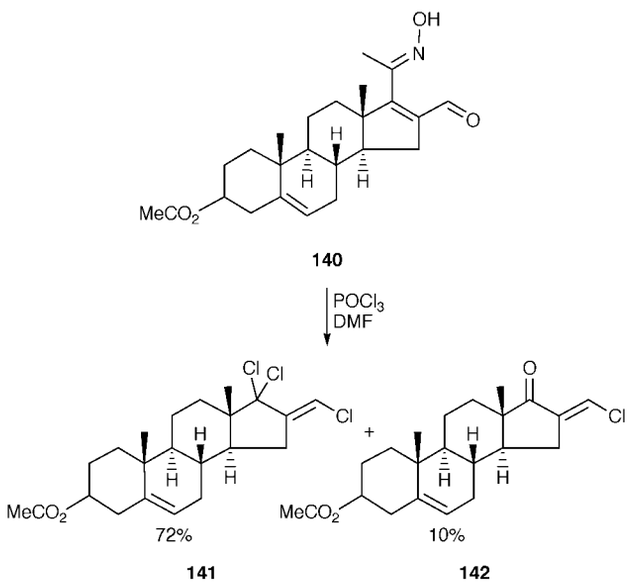
4.7 Oxidation of oximes to nitro compounds

Oximes are conveniently converted into nitroalkanes using Oxone in acetonitrile, buffered at pH 7.5. The nitroalkanes are obtained in 52–75% yields.[224] If oximes are oxidised by Oxone in the presence of sodium chloride then *gem*-chloro-nitro derivatives are obtained in 66–84% yields. The procedure is also effective for the transformation of sterically hindered substrates.[225]

4.8 Miscellaneous

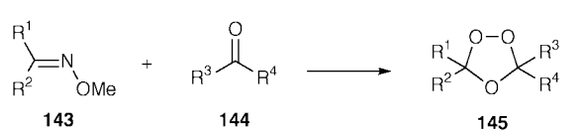
Various iron porphyrin systems are able to catalyse the dehydration of aldoximines to their corresponding nitriles under very mild conditions (pH neutral or slightly acidic at 20 °C).[226]

γ-Formyl conjugated steroidal oximes **140** react under Vilsmeier conditions to afford (*E*)-chloromethylenes **141** and **142** (Scheme 50).[227]



Scheme 50

Ozonolysis of *O*-methyl oximes **143** of ketones in the presence of ketones **144** results in the formation of the corresponding tetrasubstituted cross-ozonides **145** in 11–73% yields (Scheme 51). When the *O*-methylated monoximes of 1,4-, 1,5- and 1,6-dicarbonyl compounds are used the corresponding bicyclic ozonides are obtained.[228]

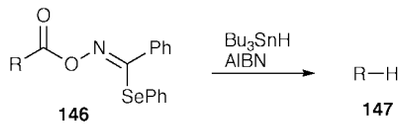


Scheme 51

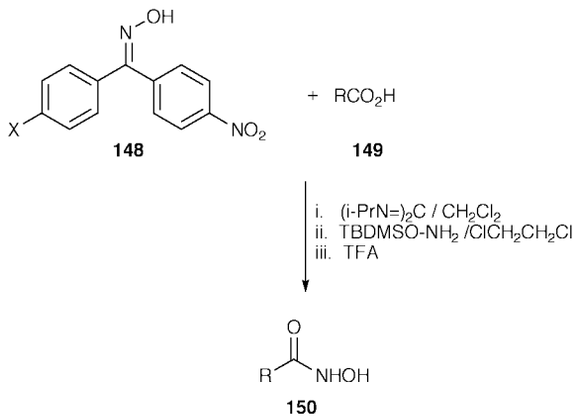
Ozonolysis of *O*-methyloximes of cyclic ketones in the presence of cyclohexa-1,4-dione or butanedione results in the formation of diozonides in 18–48% yields.[229]

Se-Phenyl benzoselenohydroximate derivatives **146** can act as radical precursors for the generation of alkyl **147** (70–94%) (Scheme 52), aminyl (80–93%) and alkoxy (87–97%) radicals. The *Se*-phenyl benzoselenohydroximate compounds are readily available from *Se*-phenyl benzoselenohydroximate.[230]

A three step approach to the solid supported synthesis of hydroxamic acids **150** in 27–96% overall yields has been developed using a resin bound aryl oxime **148** (Scheme 53).[231]



Scheme 52



Scheme 53

5 Acknowledgements

I wish to thank Rachel Lawson for much of the typing and drawing of diagrams in this review.

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Review a808142e