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Imine Azaenolates: Synthesis, Reactivity, and Outlook

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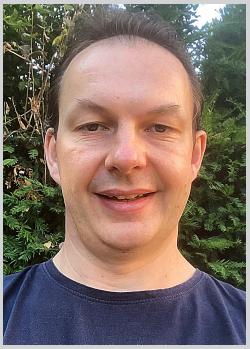
Abstract: Azaenolates are, quite simply, the aza variant of enolates. Compared to their oxygen counterparts, additional control of the reactivity of azaenolates can be achieved by altering the substituent on the nitrogen atom as well as the metal counterion. Since the seminal examples reported in the early 1960s, azaenolates of various metals have been shown to react with a diverse set of electrophilic partners, including challenging electrophiles such as alkyl fluorides, epoxides, and oxetanes. This review describes in detail the current state of the art of the chemistry of azaenolates derived from imines, with a particular focus on the comparison of the reactivity exhibited with different metal counterions.

Keywords: Azaenolates; Imines; Enantioselectivity; Aldol; Enolates

1. Introduction

Azaenolates,[1–4] also referred to as 1-azaallyls,[5] metalloenamines, metallated Schiff bases and imine anions, are the lesser-studied aza analogues of enolates. They offer an alternative strategy to enamines[2,6] and enolates for the α-functionalisation of aldehydes and ketones (Scheme 1a). Azaenolates can be classified by the nature of the nitrogen substituent (Scheme 1b) based on the C=N compound class from which they are derived. Imine azaenolates (N–C) are featured in this review, but hydrazones (*e.g.* RAMP/SAMP auxiliaries),[7–10] oximes,[7,11,12] sulfinyl imines (*e.g.* Ellman auxiliaries)[13–15] as well as oxazolines[16,17] and other heterocycles[4] have also been employed. Imine azaenolates are of particular interest, due to their facile formation and hydrolysis, which potentially opens up opportunities for catalytic (asymmetric) reactions



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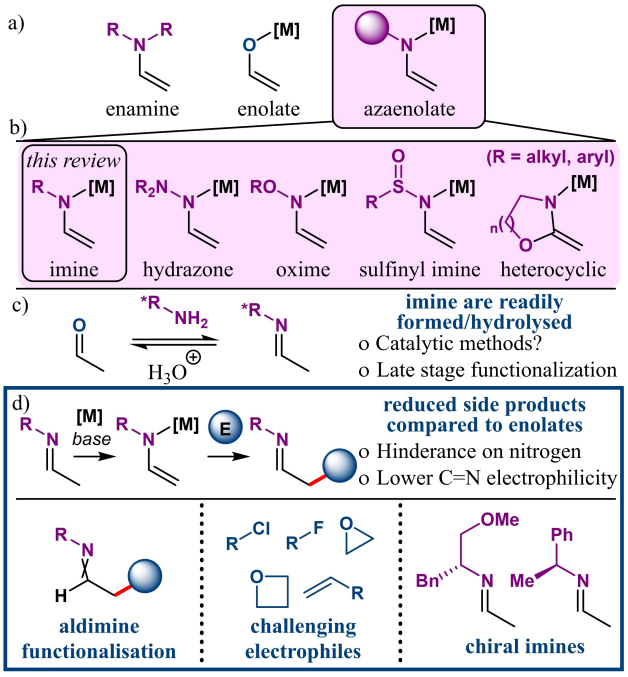


Scheme 1. Azaenolates for the α-functionalisation of imines potential of azaenolate intermediates in asymmetric synthesis merits further investigation.

(Scheme 1c). Given the success of organocatalytic reactions involving related enamine and iminium intermediates, recognised by the award of the 2021 Nobel prize for Chemistry to List & Macmillan, the potential of azaenolate intermediates in asymmetric synthesis merits further investigation.

Catalytic asymmetric induction could potentially be achieved via the use of chiral amines or through chiral ligands bound to the metal counterion. Both of these possibilities can take advantage of a wide range of readily available chiral molecules, but to date catalytic asymmetric azaenolate reactions have yet to be realised.

Imine azaenolates have been formed, for the most part, by deprotonation of imines (Scheme 1d). Strong bases such as lithium diisopropylamide (LDA), butyllithiums and Grignard reagents are typically used, although some examples utilise a Lewis acid, such as boron trichloride[18] or magnesium bromide,[19] coupled with a mild amine base. This latter approach has been somewhat overlooked, but potentially provides exciting opportunities for the development of novel catalytic asymmetric processes. Azaenolates of other metals are usually formed from transmetallation of lithium or magnesium azaenolates. Other methods to generate azaenolate intermediates have been reported, such as addition of nucleophiles into 2-azadienes[20] or α,β-unsaturated imines,[21] oxidation of secondary amines[22,23] and ring opening of 2-methyleneaziridines.[24,25]

α-Functionalisation of carbonyl groups with electrophiles is a familiar and valuable transformation for organic chemists. Enolate intermediates are frequently used as they are highly nucleophilic, but although commonplace, reactions of enolates can suffer significant selectivity problems. Overreaction with electrophiles, functionalisation at O instead of C and unwanted aldol condensations can all be competitive with the desired reaction. Indeed, the high reactivity of aldehydes towards self-condensation under basic conditions limits their use in enolate chemistry.[26] In this context, azaenolates have proven to be an attractive substitute (Scheme 1d). The steric effects of the *N*-substituent and reduced electrophilicity of the C=N bond mean that the formation of side products is less

prevalent with azaenolates.[27] Aldimines are suitable substrates for many transformations, meaning α-functionalised aldehydes can be generated with this approach. By altering the nitrogen substituent and selecting a suitable metal, electrophiles which are typically challenging for enolate functionalisation can be used, including epoxides,[28] alkyl fluorides[29] and even unactivated alkenes.[30] Crucially, imines can be formed from chiral amines, enabling highly enantioselective α-functionalizations.[31,32]

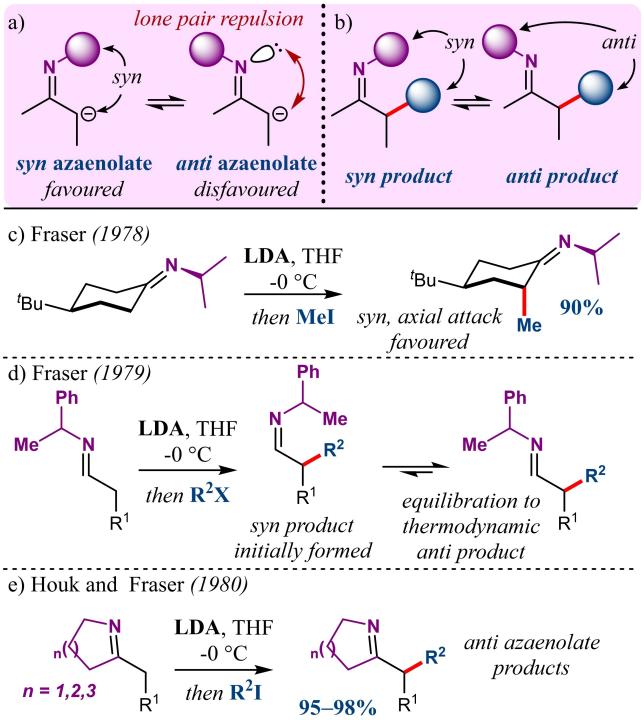
Although most commonly attributed to Stork[33] and Wittig,[22] azaenolates were actually first published in Comptes Rendus de L'académie Bulgare des Sciences in 1960, by Marekov and Petsev.[34] Since these seminal examples, development throughout the 1970's and 1980's unveiled the potential of this chemistry.

The aim of this review is to highlight the bond formations that have currently been achieved through imine azaenolate intermediates, from the original examples to the present day. Following a general discussion on mechanism and selectivity, the reactions of imine azaenolates are categorized by the metal used and further divided by the reactant electrophile. Many of the examples are hydrolyzed with aqueous acid to the aldehyde or ketone prior to isolation of the products, yields are given for the isolated compound (imine or aldehyde/ketone) in each case.

2. Selectivity and Mechanistic Considerations

For reactions of azaenolates, there are many possible confirmations that must be considered to understand the mechanism and selectivity. Firstly, the position of the nitrogen substituent relative to the nucleophilic carbon determines whether the azaenolate is *syn* or *anti* (Scheme 1a). The nomenclature of the functionalised imine products can also be described as *syn* or *anti*, determined by whether the new group is on the same or opposite side as the *N*-substituent (Scheme 1b). Although this stereoinformation is lost on hydrolysis to the ketone or aldehyde, the geometry of the functionalised imine is key to determining the prevalence of *syn* or *anti* azaenolates in the reaction mechanism. The formation, stability, and reactivity of *syn* and *anti* azaenolates has been subject to a number of investigations.[35–37]

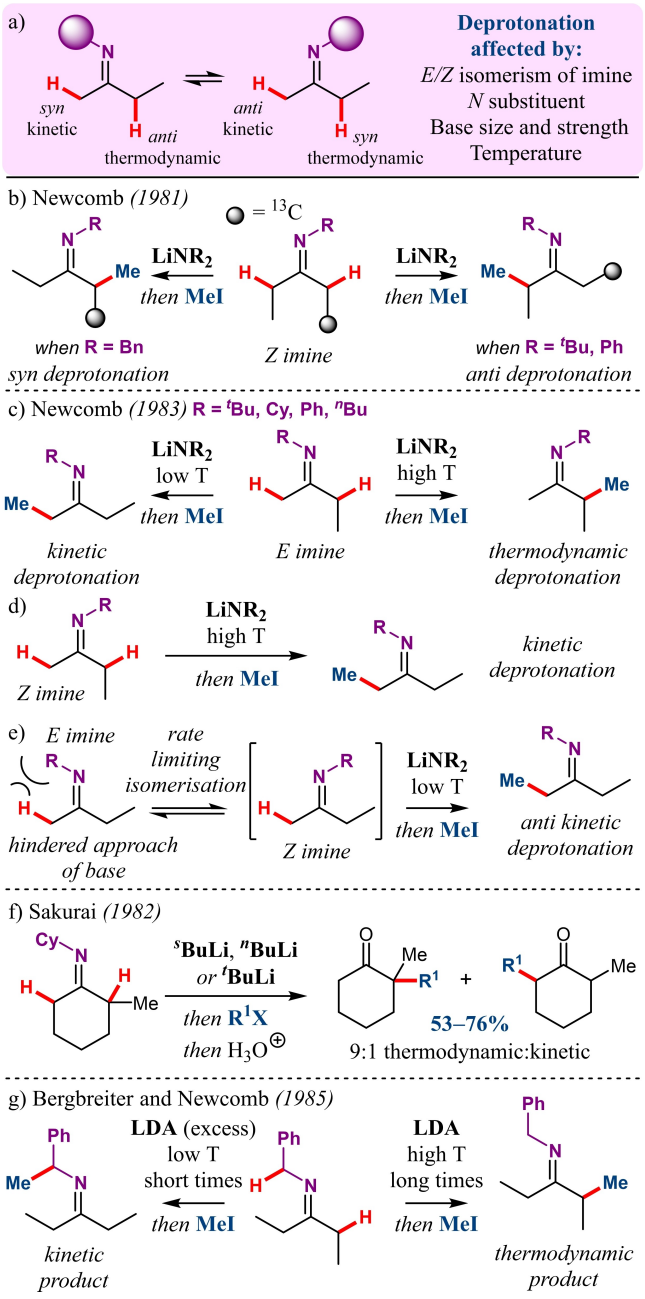
Fraser showed that methylation of a 4-*tert*-butylcyclohexanone imine via a lithium azaenolate was selective towards *syn* alkylation products and axial electrophilic attack, with only small amounts of *anti*-axial (7%) and *syn*-equatorial (3%) methylated products observed (Scheme 2c).[35] Hydrolysis of the monomethylated imine resulted in only a small amount of epimerisation, giving the axial methylated ketone in 83% yield. Monoalkylation of other cyclic ketones



Scheme 2. Studies on *syn/anti* conformations of azaenolates.

with different ring sizes also gave exclusively *syn* imine products. They noted that the reason for the higher stability of the *syn* azaenolate is unclear, but it may be due to a destabilizing repulsion of the nitrogen lone pair with the carbanion in the *anti* geometry, and this was later supported by DFT studies.[37] Fraser investigated this "*syn* stabilisation effect" further, this time with aldimines (Scheme 2d).[36] Upon deprotonation, despite this putting the large *N*-substituent and alkyl groups on the same side, aldimines also favoured formation of the *syn* azaenolate, to give exclusively the *syn* product. The *syn* product imines then equilibrate to the thermodynamic *anti* geometry at temperatures as low as −20 °C. The *syn* stabilisation effect was calculated to be much higher in aldimines (>18 kJmol^{-1}) than ketimines (>7.4 kJmol^{-1}). Endocyclic imines of various ring sizes and R^1 groups however, only gave products from the *anti* azaenolate (Scheme 2e).[37] This was due to ring strain in the *syn* azaenolate, which overcomes the other factors.

As for generating enolates from unsymmetrical ketones, kinetic and thermodynamic deprotonation of imines can be controlled by modifying the reaction conditions. However, there is the additional consideration of *E/Z* isomerism for imines, so that deprotonation can occur on the same side (*syn*) or opposite side (*anti*) to the nitrogen substituent, which is largely influenced by the steric demands of the substrate and base (Scheme 3a).



Scheme 3. Studies on *syn/anti* and thermodynamic/kinetic deprotonation of azaenolates.

To investigate the *syn/anti* deprotonation of imines, Newcomb considered the methylation of 3-pentanone imines, labelled with ^{13}C on one of the methyl groups (Scheme 3b).[38] The imines were formed as exclusively the *Z* isomer, with the labelled carbon on the same side as the R group on nitrogen. The regioselectivity of the deprotonation was determined by trapping the corresponding azaenolates with methyl iodide and observing the ^{13}C NMR shifts. Notably the products observed were all *syn* as expected (with the *N*-substituent and new alkyl group on the same side) but whether the deprotonation, hence alkylation, occurred on the same side (*syn* deprotonation) or opposite side (*anti* deprotonation) as the *N*-substituent on the starting imine varied. *N*-*tert*-butyl and *N*-phenyl imines led to the major products from *anti*-deprotonation, with either LDA or lithium diethylamide (LDEA) as the base (up to 80%). This was as a result of the large groups blocking deprotonation by the hindered base. The benzyl imine favoured the *syn*-deprotonation product and the cyclohexylimine gave a 50:50 mixture. Using ^{13}C NMR, it was shown that none of the observed products arose from isomerisation of the imine starting material prior to deprotonation.

The formation of the kinetic or thermodynamic enolates of aza-analogues is more complicated than for oxygen enolates. This is due to 1) the steric influence of the group on nitrogen and 2) when imines are synthesized, they are generally formed as a mixture of *E*/*Z* isomers. Newcomb considered the regioselectivity of the deprotonation of butanone imines with lithium amide bases, and the influence this had on the outcome of subsequent methylation (Scheme 3c–e).[39] Whether alkylation occurred at either the methyl or methylene group was dependent on the hindrance of the lithium amide base, temperature, and the size of the nitrogen substituent. They found that using thermodynamic mixtures of imines (predominantly the *E* isomer), high temperature (0 °C) favoured the thermodynamic product using both LDA and LDEA as the base and low temperature (−78 °C) favoured the kinetic product, with any substituent on the imine nitrogen (Scheme 3c). *Z*-Imines could be synthesized regioselectively from the methylation of the *N*-*tert*-butyl imine of acetone, and they were investigated as alkylation substrates. Interestingly, the rate of deprotonation of the *Z* imine was faster and dependent on the concentration of base, whereas the rate of deprotonation of the *E* isomer was slower and independent of base concentration. The *Z* imine also only gave the kinetic product (alkylated at the methyl group) even at higher temperatures (Scheme 3d). This was convincing evidence that the *E* isomer must isomerize to the *Z* prior to deprotonation of the methyl group to give the kinetic product, since the group on nitrogen otherwise hinders the approach of the large base (Scheme 3e). With the *E* imines, as the temperature increases, the methylene deprotonation becomes competitive with *E*/*Z* isomerisation, resulting in a mixture of products. Smaller groups on nitrogen are less effective at hindering the approach of the base, this is illustrated when R = ^{n}Bu, where rate of deprotonation has a dependence on base concentration, suggesting it does not have to be isomerised to the *Z* isomer before deprotonation can occur, or that isomerization is no longer rate limiting.

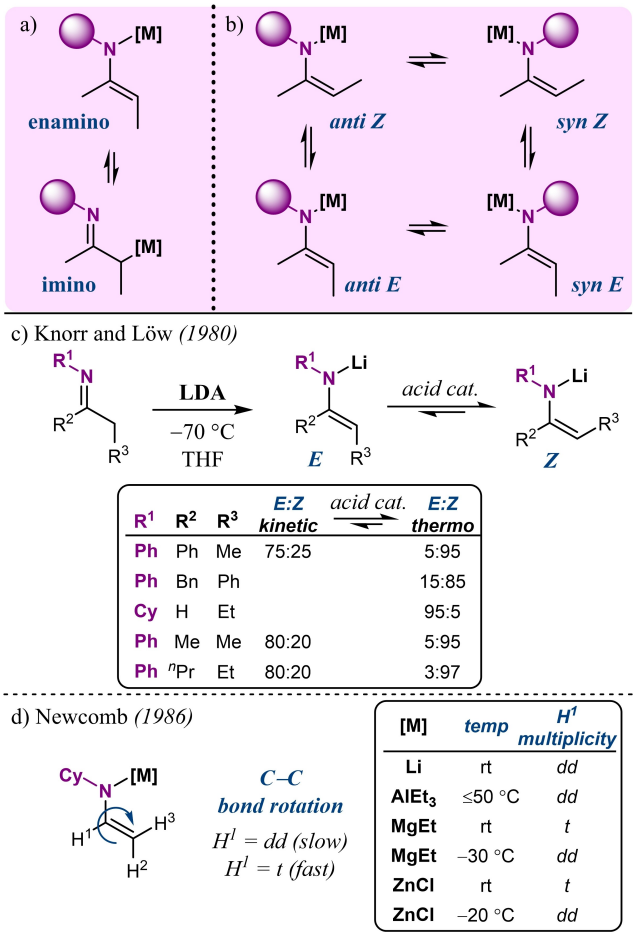
When using butyllithium instead of a lithium amide base for the deprotonation of cyclohexanone imines, Sakurai showed that the selectivity of alkylation

switches from the least substituted to the more substituted carbon (Scheme 3f).[40] They commented that this is the first method of azaenolate alkylation at the most hindered α-carbon where the azaenolate is formed from deprotonation of an imine. Reaction temperature had no impact on the selectivity of the alkylation, however the addition of tetramethylethylenediamine (TMEDA) did give slightly more of the minor kinetic product. The selectivity is proposed to be due to either the increased basicity of the butyllithium bases compared to LDA, or that the *anti*-proton (opposite the large group on nitrogen) is more easily extracted by butyllithium. Interestingly, under the same conditions, the dimethyl hydrazone azaenolate of 2-methylcyclohexanone was completely selective for the kinetic product on alkylation with benzyl chloride, whereas the cyclohexylimine azaenolate favoured the thermodynamic product (90:10 thermodynamic:kinetic). Acyclic *N*-cyclohexyl or *N*-*tert*-butyl ketimines also gave significant amounts of product from alkylation at the most hindered position (up to 56:44 themodynamic:kinetic), but with poorer selectivity compared to 2-methylcyclohexanone. In the presence of hexamethylphosphoramide (HMPA) however, deprotonation of an acyclic ketimine with *sec*-butyllithium, gave exclusively the kinetic product.

On the benzylamine imine of 3-pentanone, deprotonation of the benzylic position is competitive with azaenolate formation (Scheme 3g).[41] In fact, deprotonation occurs initially at the benzylic position which, under certain conditions, can isomerise to the azaenolate to allow alkylation at the α-carbon. Low temperature, short reaction times and higher equivalents of base all favoured methylation on the kinetic benzylic position. The mechanism of isomerisation of the carbanions was proposed to be through a protonation/deprotonation sequence.

Using density functional theory (DFT), Collum calculated that changing the substituent on the nitrogen of cyclohexanone imines resulted in a 60,000 fold range of deprotonation rates.[27] The reactivity of the imines towards deprotonation was found to be related to several factors, including 1) axial or equatorial position of the proton on the cyclohexyl ring, 2) *syn* vs *anti* deprotonation relative to the group on nitrogen, 3) presence of a secondary chelating group on the imine nitrogen, which gave much faster rates, 4) the presence of a 2-methyl group on the ring and 5) branching on the alkyl group of the nitrogen. Using DFT, NMR and kinetic studies, Collum also found that the aggregation characteristics of the lithium azaenolate of cyclohexanone imines changed in different solvents.[42]

Azaenolates can also be described as having "enamino" (N–**[M]**) or "imino" (C–**[M]**) tautomers (Scheme 4a). Which of these is formed, and how easily they equilibrate, is dependent on the size of the substituents and the metal counterion. When considering the enamino tautomer, the stereoselectivity of azaenolate functionalisation is affected by both the *E*/*Z* isomerisation about the C=C bond and the *syn* or *anti* geometry of the *N*-substituent (Scheme 4b).



R¹	R²	R³	E:Z kinetic	acid cat. ⇌	E:Z thermo
Ph	Ph	Me	75:25		5:95
Ph	Bn	Ph			15:85
Cy	H	Et			95:5
Ph	Me	Me	80:20		5:95
Ph	^{n}Pr	Et	80:20		3:97

[M]	temp	H¹ multiplicity
Li	rt	dd
$AlEt_3$	≤50 °C	dd
MgEt	rt	t
MgEt	−30 °C	dd
ZnCl	rt	t
ZnCl	−20 °C	dd

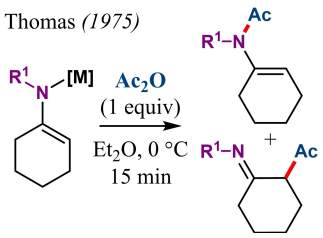
Scheme 4. Studies on the *E*/*Z* isomerism of azaenolates.

Knorr and Löw considered the *E*/*Z* conformation of lithium azaenolates formed from deprotonation of various imines with LDA (Scheme 4c).[43] Three key findings were identified: 1) when R^3 is an alkyl group the azaenolates are conformationally stable; 2) the *E*/*Z* isomers can be equilibrated under mild conditions; and, 3) protonation of the azaenolate with methanol is stereoselective and affords metastable *sec*-enamines,[44] which allows for the assignment of azaenolate geometry. When R^3 was an alkyl group, deprotonation with LDA gave preferentially the kinetically controlled *E* isomer which could be converted to the thermodynamic *Z* isomer with acid catalysis. The exception of this was for the aldimine (R^2 = H) where the *E* isomer formed on kinetic deprotonation was also the thermodynamically favourable species.

Newcomb investigated the effect of the metal on the rate of C–C bond rotation of azaenolates (Scheme 4d).[45] This was measured by observing

changes in the splitting of the formyl (H_1) proton by NMR (triplet when rotation is fast, doublet of doublets when rotation is slow). The lithium azaenolate, formed by deprotonation of the imine by *sec*-butyllithium, gave a doublet of doublets at room temperature, indicating slow rotation. Aluminium, magnesium, and zinc azaenolates were formed by transmetallation of the lithiated species. Although the aluminium species also presented a doublet of doublets for the formyl proton in the ^{1}H NMR spectra at room temperature, both the magnesium and zinc azaenolates were triplets, meaning faster rotation about the C=C bond. Low temperature NMR however did reveal a change in multiplicity for both of these cases, indicating a temperature dependence on the bond rotation. All of the azaenolates were treated with ethyl iodide or benzyl bromide at −78 °C, which with the exception of zinc (3–7% yield), gave high alkylation yields (62–100%).

As with enolates, heteroatom functionalisation can be competitive with reaction at the α-carbon for azaenolates. Thomas explored the impact the metal has on *N* or *C* selectivity of azaenolate acetylation with acetic anhydride as well as solvent and substituent effects (Scheme 5).[46] The main findings were as follows: 1) total acylation yields were consistently lower with cyclohexylamine imine azaenolates than aniline imine azaenolates, but the cyclohexylamine azaenolate favours *C* over *N* acylation, as the electron withdrawing nature of the aromatic amine removes electron density from the nucleophilic carbon, 2) solvent has little effect on product yield and composition and 3) the metal used plays a major role, after transmetalation from magnesium, both zinc and cadmium azaenolates favour *N* over *C* acylation. Higher proportions of carbon acylation were also observed for magnesium azaenolates compared to their oxygen counterparts under the same conditions. They attributed this to the lower electronegativity of nitrogen which leads to a more covalent N–Mg bond and thus an increased negative charge density on the nucleophilic carbon.



R¹	Metallating agent	N:C acylation	total yield
Ph	$MgEt_2$	23:77	65
Cy	$MgEt_2$	0:100	35
Ph	$ZnEt_2.2MgBr_2$	100:0	83
Cy	$ZnEt_2.2MgBr_2$	73:27	5
Ph	$CdEt_2.2MgBr_2$	100:0	89
Cy	$CdEt_2.2MgBr_2$	89:11	6

Scheme 5. *N* vs *C* acylation of azaenolates.

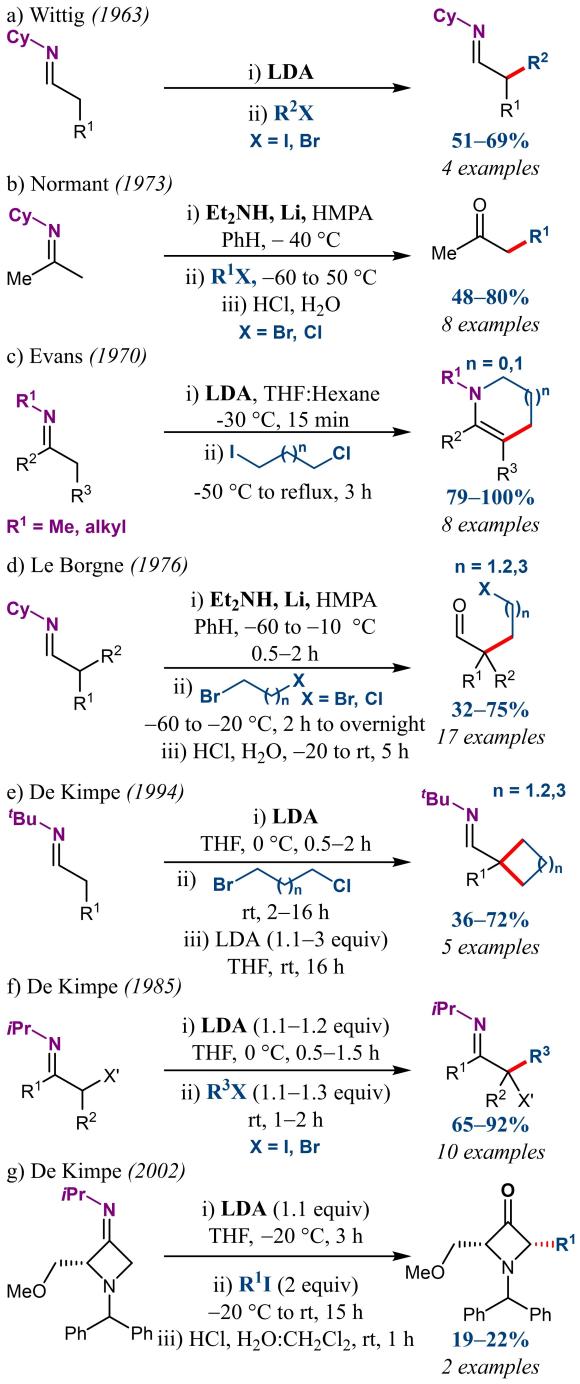
3. Lithium

Lithium is the most commonly used metal in imine azaenolate chemistry. Lithium azaenolates are normally generated from the deprotonation of imines with lithium amide bases or alkyl lithium reagents, but they can also be accessed from oxidation of secondary amines,[22,23] and addition into 2-azadienes.[20] Once formed, lithium azaenolates have been demonstrated to react with a wide range of electrophiles with alkyl halides or aldehydes being most studied; other electrophiles such as esters and chloroformates, imines and imidic acid derivatives can also be used. Lithium azaenolates can even ring-open strained oxygen heterocycles such as epoxides and oxetane which are largely unreactive towards enolates. Enantioselective alkylations have been reported by many researchers using chiral imines.

3.1. Reaction with Alkyl Halides

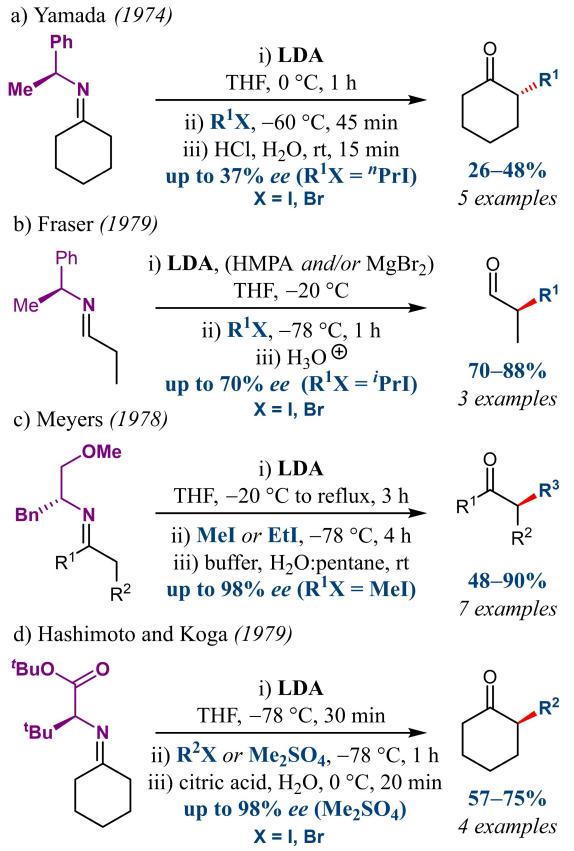
Lithium azaenolates of both aldimines and ketimines (aromatic and aliphatic) have been reacted with various alkyl halide electrophiles. Alkylations have been shown on various substrate classes (Scheme 6, 8, 11) including on α,β-unsaturated systems (Scheme 9). Enantioselective alkylations have also been demonstrated (Scheme 7, 10). In general, harsher conditions such as more basic systems or higher temperatures have been needed for less reactive halides such as unactivated chlorides. The seminal α-alkylation of imines with a lithium azaenolate was shown by Wittig in 1963, who deprotonated the *N*-cyclohexylimine of acetaldehyde with LDA and treated the resultant azaenolate with unactivated alkyl iodides or activated (R^2 = allyl, benzyl) alkyl bromides and chlorides (Scheme 6a).[47,48]

Lithium amide bases ($LiNR_2$), such as LDA, are normally formed by deprotonation of amines by butyllithium. However, Normant observed that the direct formation of lithium amides from metalation of aliphatic amines by lithium metal in HMPA and benzene resulted in a significantly more basic system.[49] These bases were named "activated lithium amides" and they enabled the formation of lithium azaenolates at reduced temperatures and subsequent trapping with less reactive electrophiles. The first of these examples in 1973 involved alkylation of the cyclohexyl ketimine of acetone with unactivated alkyl chlorides and bromides in good yields (Scheme 6b).[50] These conditions were later applied to a broader range of ketimines.[51] Other alkyl halide electrophiles were also used with these highly basic conditions, including bromoacetals,[52] 2,3-dichloroprop-1-ene and 2,3-dibromoroprop-1-ene.[53] Furthermore, aldimine substrates could also be functionalised under similar conditions.[54]

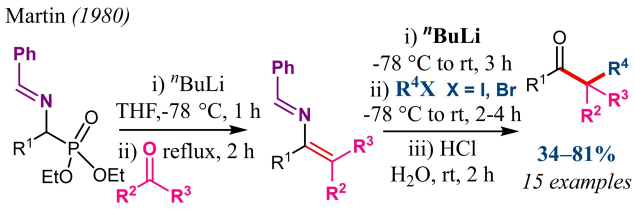


Scheme 6. Alkylation of lithium azaenolates with alkyl halides.

Depending on the reaction and hydrolysis conditions, alkylation of lithium azaenolates with dialkyl halides leads to different products (Scheme 6c–e). Evans's conditions, which involved heating the alkylated imine, resulted in cyclisation via displacement of a pendant chloride by the imine nitrogen to form 5- and 6-membered cyclic enamines in excellent yields (Scheme 6c).[55] *N*-Methyl or endocyclic imines were used, which enabled the generation of bi and tricyclic



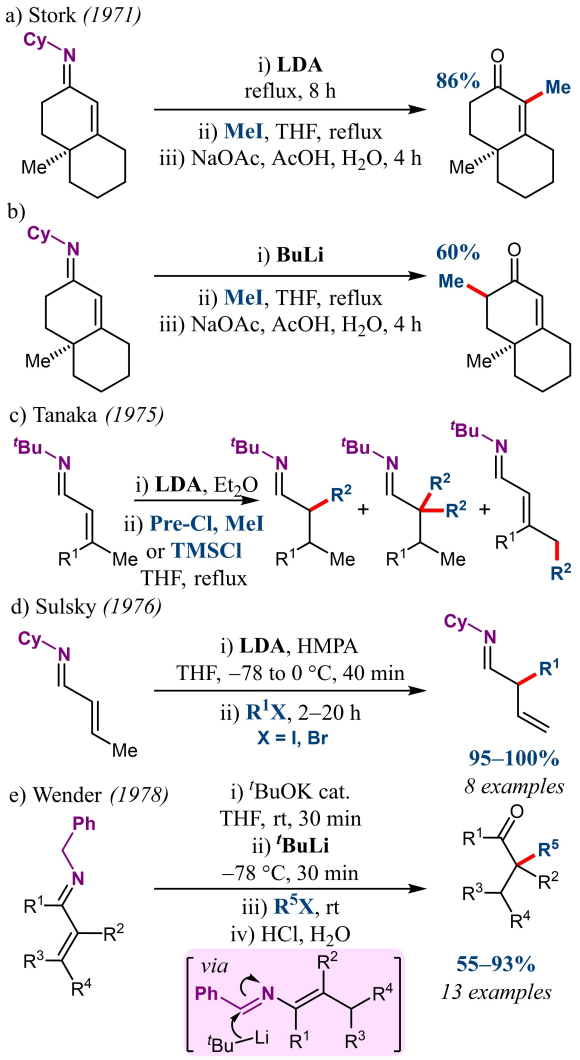
Scheme 7. Enantioselective alkylation of lithium azaenolates with alkyl halides.



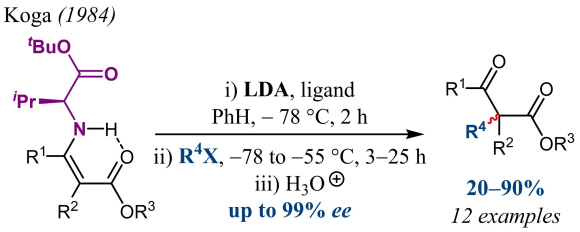
Scheme 8. Formation of a lithium azaenolate from addition of BuLi into a 2-azadiene.

enamines. Cyclisation is prevented in Le Borgne's 1976 example, with an activated lithium amide as the base, where hydrolysis of the imine with aqueous hydrochloric acid affords the alkylated ketone with a further alkyl bromide or chloride group (Scheme 6d).[56] De Kimpe showed that aldimines with α-cyclobutyl, cyclopentyl and cyclohexyl groups could be formed by sequential azaenolate formation and alkylation with bromochloroalkanes, in this case using a hindered *tert*-butyl imine (Scheme 6e).[57]

Some interesting imine substrates have been used with this chemistry, such as those derived from α-halo ketones, which are challenging for α-alkylation reactions using enolates (Scheme 6f).[58] α-Alkylations of

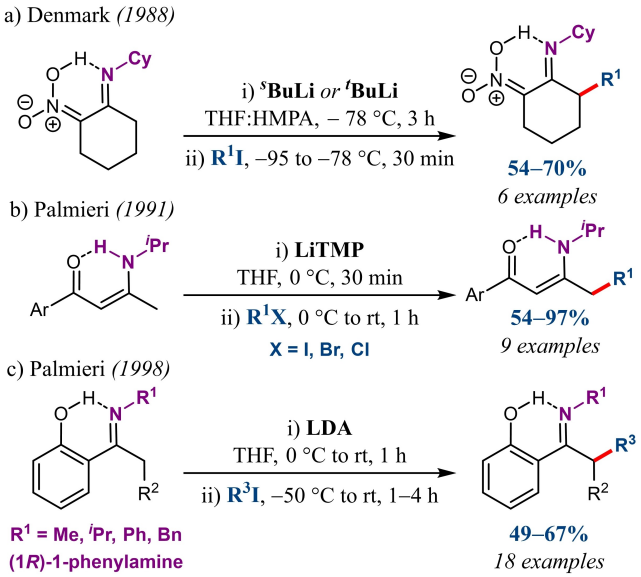


Scheme 9. Alkylation of lithium azaenolates of α,β-unsaturated aldehydes and ketones.



Scheme 10. Alkylation of α-alkyl-β-keto esters via a lithium azaenolate.

ketones with a lithium azaenolate have been used in total synthesis. e.g. Zhang used a cyclohexylimine azaenolate in the early steps towards the atropurpuran A-ring,[59] and De Kimpe successfully used a lithium azaenolate to incorporate an ethyl or propyl group onto an azetidinone scaffold (Scheme 6g).[60]



Scheme 11. Alkylation of dianionic lithium azaenolates.

Enantioselective α-alkylation of azaenolates has been achieved through incorporation of chiral groups on the imine nitrogen. This has also been achieved with magnesium (see Scheme 33) and zinc (see Scheme 46) azaenolates, but reactions with lithium bases have given the best overall yields and enantiomeric excesses to date. The first example of a chiral lithium azaenolate was revealed by Yamada, who showed that an *(S)*-phenylethylamine imine could be used to induce moderate enantioselectivity for the α-alkylation of cyclohexanone (Scheme 7a).[61] Fraser also used this auxillary for the enantioselecive alkylation of aldimines, with the addition of HMPA and/or magnesium bromide depending on the substrate (Scheme 7b). Meyers discovered that using an imine with a secondary binding methoxy group could promote alkylations of cyclohexanone (50% yield, >95% *ee* with ^{n}PrI),[62] other cyclic ketones,[63] linear ketones[64] and aldehydes[65] with improved enantioselectivity compared to Yamada's auxiliary. The superior stereoinduction was a result of the increased rigidity of the azaenolate due to chelation of the lithium atom. With linear ketimines (Scheme 7c), in order to achieve good enantioselectivity, the kinetic mixture of *E* and *Z* azaenolates formed upon deprotonation was heated to reflux affording only the thermodynamic azaenolate which was then treated with the alkyl halide. More recently, Nanda used Meyers'[62] chiral lithium azaenolate in the asymmetric total synthesis of Ioxoprofen and derivatives.[66] Hasimoto and Koga formed a chiral imine of cyclohexanone with the *tert*-butyl ester of *(S)*-*tert*-leucine, which could be deprotonated and alkylated in good yields and high *ee* with either methyl sulfate, unactivated alkyl iodides or allyl bromide (Scheme 7d). When considering a direct comparison of

alkylation of cyclohexanone with ^{n}PrI, this reaction outperformed Yamada's and Meyers protocols in terms of yield and *ee* (70% yield, 97% *ee*). They also showed the *tert*-leucine imines of 2-phenyl cyclohexanone (40% yield, 96% *ee*) and 2-phenyl cyclopentanone (62% yield, 94% *ee*) could be enantioselectively alkylated with iodomethane, with alkylation occurring at the benzylic position.

A new route to lithium azaenolates was demonstrated by Martin and co-workers. The azaenolate was generated by the addition of an alkyl lithium to 2-azadienes, which were formed from a Horner-Wadsworth-Emmons (HWE) reaction of *N*-benzelidenaminophosphonates. The azaenolate was alkylated with MeI, EtI or allyl bromide then hydrolysed to form functionalised aldehydes or ketones (Scheme 8).[20] Methyl disulfide could also be used as the electrophile in the last step, affording the methyl thioether in 40% yield. Similarly, alkyl bromides with a pendant acetal group could be used in this process.[20]

Achieving selective alkylation of the enolates of α,β-unsaturated ketones is challenging as there are multiple potentially nucleophilic sites and the products tend to overreact. In 1971, Stork and co-workers provided a solution to this problem, showing that lithium azaenolates could enable regioselective α-alkylation of α,β-unsaturated ketones with methyl iodide (Scheme 9a).[67] Notably, a slight deficiency of LDA was used, and the act of refluxing this mixture enabled full equilibration to the thermodynamic, conjugated enolate. The kinetic methylation product could also be accessed, by using an excess of butyllithium (Scheme 9b).

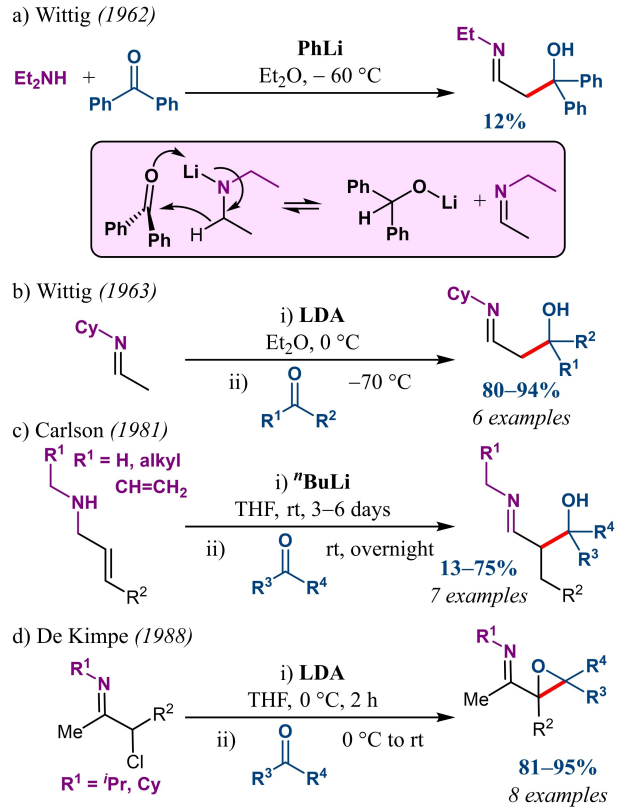
Tanaka studied the effect of temperature and sterics on the alkylation and silylation of α,β-unsaturated aldehydes (Scheme 9c).[68] With a hindered aldimine, using prenyl chloride (1-chloro-3-methyl-2-butene) as a hindered electrophile at a temperature of −15 °C, good yields of monoselective α-alkylation could be achieved. Lowering the temperature to −78 °C however led to a mixture of mono, di and γ-functionalised products when $R^1 = Me$. When the aldimine was less hindered ($R^1 = H$) dialkylation was exclusively observed. With iodomethane as the electrophile a mixture of mono and dialkylated products was obtained. In contrast, a large silylating agent gave 100% yield of the γ-functionalised product in each case. Sulsky developed a high yielding and regioselective method for monoalkylation of crotonaldehyde imines with alkyl halides, using HMPA as a ligand (Scheme 9d).[69] Wender demonstrated an alternative method of forming lithium azaenolates from α,β-unsaturated imines through a one-pot isomerisation, addition sequence (Scheme 9e).[70] Catalytic potassium *tert*-butoxide converted the α,β-unsaturated ketimines into 2-azadienes, which on addition of *tert*-butyllithium formed the azaenolate which could be trapped with alkyl bromides or iodides. The key advantage of this technique is the regioselectivity control, which is determined by the position of the C=C double bond in the starting material, whereas most previous methods lead to azaenolate alkylation at the least hindered α-position.[71]

Koga demonstrated that lithium azaenolates can be used to form enantioenriched quaternary α-centres upon alkylation of α-alkyl β-keto esters via chiral enamines (Scheme 10).[72] Interestingly, it was found that addition of various ligands could give the opposite stereochemistry upon alkylation with alkyl iodides or bromides. HMPA always favoured the product where the new group was installed on the same face as the valine isopropyl group as drawn, whereas THF, trimethylamine and dioxolane gave the opposite enantiomer. The reasoning for this was proposed to be due to the strong coordination of the larger HMPA molecule (compared to smaller, weaker ligands such as THF) which hinders the approach of the electrophile from the bottom face.[73,74]

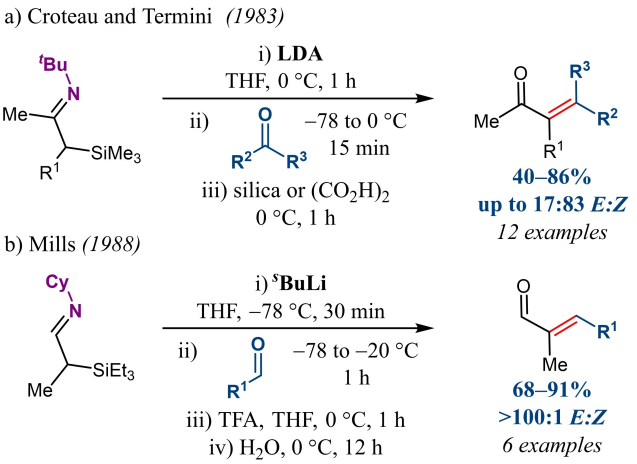
Substrates that form dianions can also be used in α-alkylation reactions of imine azaenolates (Scheme 11). For example, after forming a dianion with excess *sec*- or *tert*-butyllithium in a THF:HMPA solvent mixture, cyclohexylamine imines of 2-nitrocyclohexanones can be alkylated with alkyl iodides in good yield (Scheme 11a).[75] A chiral group on the imine nitrogen enabled this reaction to progress with high diastereoselectivity.[76] Palmieri showed that selective alkylation at the γ-position of linear β-enamino phenyl ketones was feasible using a large excess of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) to form the dianion (Scheme 11b).[77] Similarly, selective γ-alkylation was achieved on β-enamino methyl ketones using MeLi and TMEDA in THF;[78] diastereoselective α-alkylation of β-enamino ketone dianions was also demonstrated.[79,80] 2-(1-Iminoalkyl) phenols could also be doubly deprotonated to make a dianionic azaenolate intermediate, which was alkylated with alkyl iodides (Scheme 11c).[81]

3.2. Reaction with Aldehydes and Ketones

Crossed-aldol reactions with enolate intermediates can suffer significant problems with regioselectivity. By first converting one of the ketone or aldehyde reactants into an imine, selective aldol reactions can be conducted. Aldol reactions of lithium azaenolates have been shown on both aliphatic and aromatic ketimines or aldimines of a number of different substrate classes (Scheme 12, 13, 15, 16). In the majority of examples, both aromatic and aliphatic ketone/aldehyde electrophiles could be used. The first reaction of a lithium azaenolate was serendipitously discovered by Wittig in 1962.[22] In the presence of benzophenone, lithium diethylamide (LDEA, formed from phenyllithium and



Scheme 12. Aldol reactions of lithium azaenolates.



Scheme 13. Aldol reactions of lithium azaenolates of organosilicon compounds to form α,β-unsaturated aldehydes.

diethylamine) was oxidised to an imine, which could add into another equivalent of the ketone (Scheme 12a). Later, using LDA to deprotonate the cyclohexylimine of acetaldehyde, further examples of aldol reactions of lithium azaenolates were established (Scheme 12b)[47,48,82] Interestingly it was found that nucleophilic MeLi could be used in place of LDA with only slightly lower yields and minimal amounts of addition into the imine. Increased steric hindrance on the aldehyde led to much reduced yields in the aldol reaction (92% for acetaldehyde with benzophenone but only 29% for isobutyraldehyde). Using a deuteration study they concluded this was due to reduced deprotonation at the α-carbon.[83] Steam distillation of the aldol products enabled direct access to α,β-unsaturated aldehydes.[84]

Following deprotonation of the amine nitrogen with n-butyllithium, Carson showed that anions of secondary allylic amines could isomerise into azaenolates and subsequently react with ketones (Scheme 12c).[85] With this technique, 1,2,3,6-tetrahydropyridine was converted into its cyclic azaenolate, which was not accessible by other strategies. De Kimpe showed α-chloroketimines react with aldehydes or ketones through a lithium azaenolate in a Darzens-like reaction, with the intermediate alkoxide cyclising to form epoxides in excellent yields (Scheme 12d).[86]

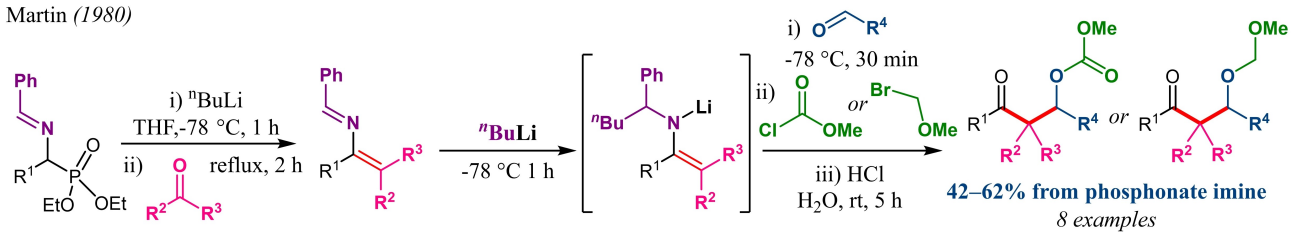
The reaction of lithium imine azaenolates with aldehydes and ketones has been used in several total syntheses.[4] For example, Büchi formed an α,β-unsaturated aldehyde with an azaenolate aldol reaction in the final step of a nuciferal[87] synthesis, as did Dauben in the synthesis of (+/-)-cembrene.[88]

Although not discussed in this review, azaenolate intermediates have also been employed in HWE reactions of α-phosphonoimines using either lithium[89,90] or sodium counterions.[91–94]

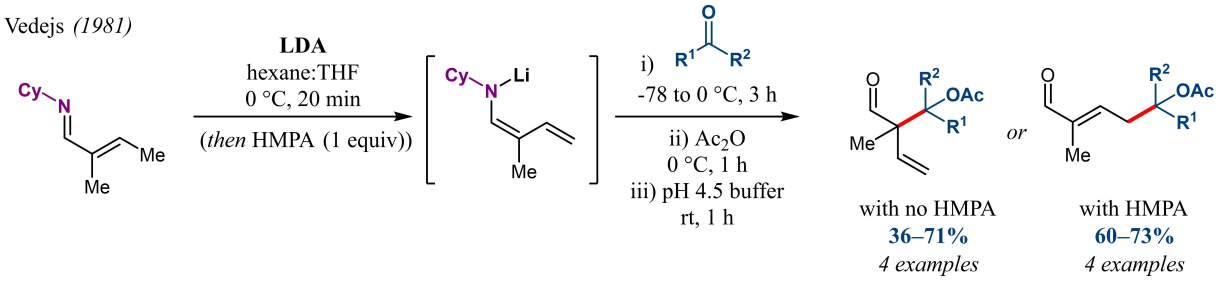
Depending on the reaction conditions, aldol-type reactions of lithium azaenolates of α-silylimines followed by elimination of the silyl group can be used to access either *E* or *Z* α,β-unsaturated ketones and aldehydes (Scheme 13). With this approach, Croteau and Termini were able to synthesize substantial amounts of difficult to form *Z*-isomers of α,β-unsaturated methyl ketones (Scheme 13a).[95] The silyl imine was prepared using Corey's method (see Scheme 18a).[96] Using a TES α-silylated imine[97] Mills used lithium azaenolate aldol chemistry to form *E*-α,β-unsaturated aldehydes, with complete *E* selectivity (Scheme 13b).[98] Hydrolysis using only oxalic acid gave *E:Z* ratios ranging between 1.3:1 to 11:1, whereas a TFA mediated isomerisation followed by hydrolysis gave *E*-selectivity of over 100:1 in every case.

As well as the alkylation previously described (see Scheme 8), Martin also showed that an intermediate azaenolate formed from addition of BuLi into a 2-azadiene could react with an aldehyde (Scheme 14)..[20] The resultant alcohol was then trapped with methyl chloroformate or 2-methoxybromomethane. The 2-azadiene was formed from an initial telescoped HWE reaction.

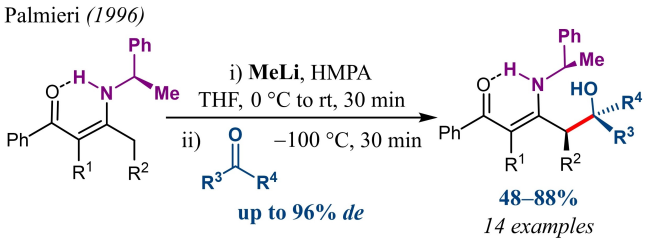
Selective γ or α-functionalization of tiglaldehyde could be achieved using a lithium azaenolate with HMPA as an additive (Scheme 15).[99] Acetic anhydride was used to trap the resultant alcohol and avoid



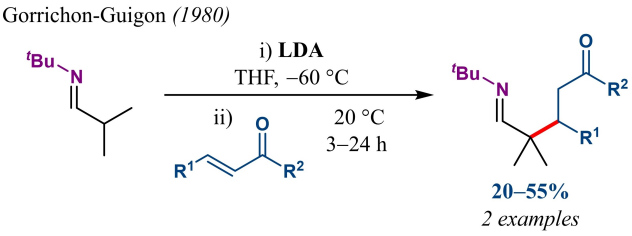
Scheme 14. Formation of a lithium azaenolate from an imine phosphonate through HWE and addition of BuLi.



Scheme 15. Aldol reaction of imine azaenolates of α,β-unsaturated aldehydes.



Scheme 16. Diasteroselective addition of 2-enaminoketone dianions into ketones.



Scheme 17. Reaction of imine azaenolates with α,β-unsaturated ketones.

dehydration. When HMPA was added to the deprotonated imine at 0 °C the γ-functionalised product was formed preferentially. Without HMPA however, the α-functionalised aldehyde was the major product.

2-Enaminoketone dianions have also been shown to add into aldehydes and ketones.[77,100] When using a chiral benzylamine imine, these reactions could be conducted diastereoselectively (Scheme 16).[101]

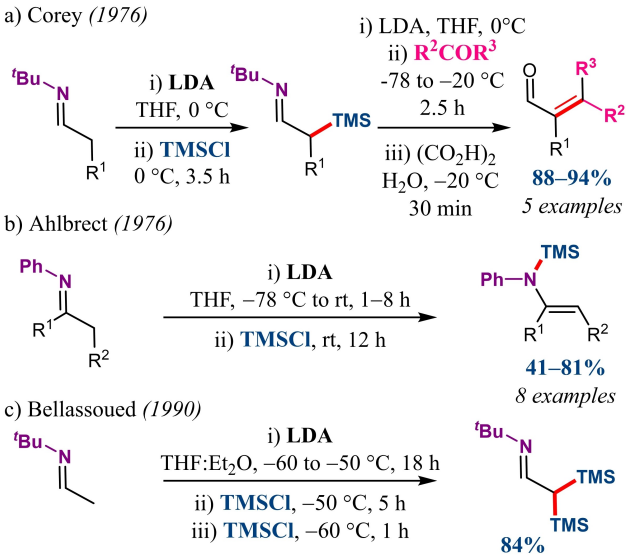
3.3. Reaction with Michael Acceptors

Selective 1,4-addition of a lithium azaenolate into α,β-unsaturated ketones (*trans*-chalcone (R_1, R_2 = Ph) or cyclohexenone) was demonstrated by Gorrichon-Guigon in 1980 (Scheme 17).[102] Notably, improved yields were observed for this reaction when using a magnesium azaenolate instead of lithium, and hydrazone enolates gave a mix of 1,2 and 1,4 addition products. The addition of azaenolates into α,β-unsaturated ketones can also be achieved with copper and zinc counterions (see sections 7.1 and 8.3). Additionally, other Michael acceptors have been shown to react with silicon and tin azaenolates (see sections 6.3 and 9.1).

3.4. Reaction with Silylating Agents

Reaction of lithium azaenolates with silylating agents can be used to access a number of different products (Scheme 18). Corey found that on treatment with trimethylsilyl chloride, lithium azaenolates formed from *N*-*tert*-butylaldimines underwent α-silylation (Scheme 18a). These intermediates were not isolated, instead the silylated imine was deprotonated and reacted with an aldehyde or ketone, followed by acid hydrolysis, to provide a new, high yielding route to α,β-unsaturated aldehydes.[96] Similarly, Schlessinger used TESCl for the α-silylation of lithium azaenolates, which gave a more stable triethylsilane product.[97] Numerous groups have used Corey's methodology in the synthesis of complex natural products.

Ahlbrecht showed that azaenolates of *N*-phenyl ketimines gave selective *N*-silylation products

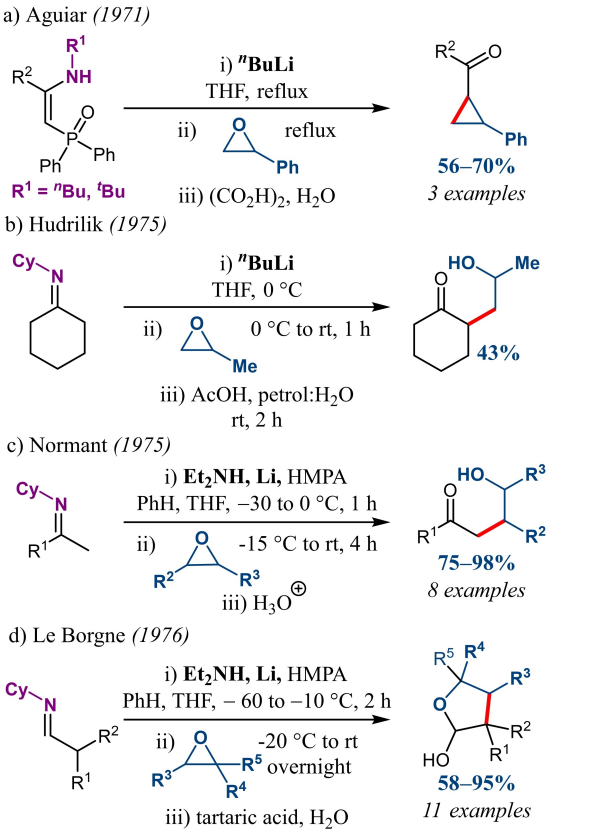


Scheme 18. Reaction of lithium azaenolates with silylating agents.

(Scheme 18b).[132] With excess LDA and then adding two sequential portions of TMSCl Bellassoued achieved disilylation of the *tert*-butylimine of acetaldehyde (Scheme 18c).[103,104]

3.5. Reaction with Epoxides and Oxetanes

Enolates of ketones do not typically react with epoxides,[28] but this problem can be circumvented with azaenolates. The stereoselectivity of most of these reactions was not reported in the original articles however, so remains to be investigated. Aguiar demonstrated that on deprotonation and reaction with 2-phenyloxirane, enamine phosphine oxides undergo a Wadsworth-Emmons cyclopropanation (Scheme 19a).[105] Hudrlik showed that propylene oxide could be ring opened with a lithium azaenolate in moderate yields (Scheme 19b).[106] However, improved yields could be achieved using a magnesium azaenolate (see Scheme 35). Normant increased the scope of this reaction by using an "activated lithium amide" base, formed from Li metal and diethylamine in benzene with HMPA. Under these conditions, lithium azaenolates of *N*-cyclohexyl ketimines reacted with a number of different epoxides (Scheme 19c).[107] This included less reactive electrophiles, such as cyclohexene oxide, which was ring opened in good yield (62–91%). Le Borgne showed the activated lithium amide mediated epoxide ring opening could be used on aldimine substrates (Scheme 19d).[108] After acid hydrolysis, the products cyclised to give 2-hydroxytetrahydrofurans. 2-Aminotetrahydrofurans could also be accessed if the imines were not hydrolysed, by working up with water (not shown). In each example, the

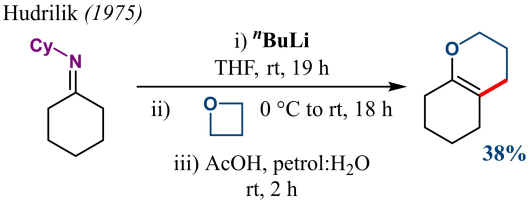


Scheme 19. Reaction of lithium azaenolates with epoxides.

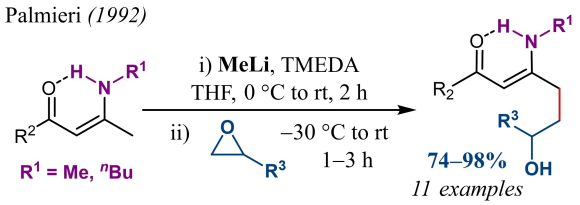
epoxide was opened at the least sterically hindered position.

On reaction with oxetane and acidic hydrolysis, the lithium azaenolate cyclised with loss of water to form a dihydropyran (Scheme 20).[106]

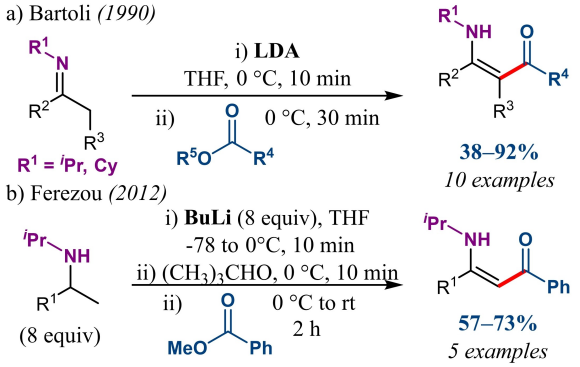
Dianionic lithium azaenolates of 2-enaminoketones undergo regioselective γ-functionalisation on reaction with epoxides (Scheme 21).[109] Two examples of disubstituted epoxides were also given which formed the products in high yield (87–98%).



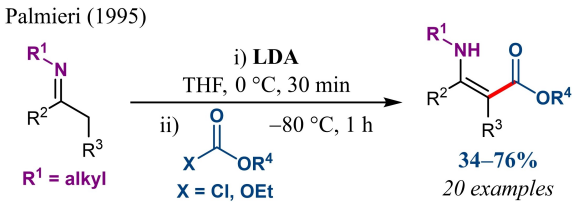
Scheme 20. Reaction of a lithium azaenolate with oxetane.



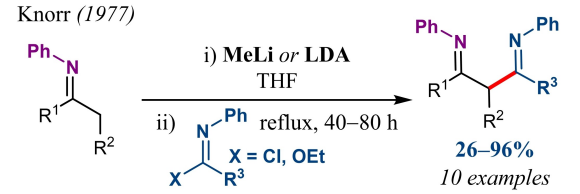
Scheme 21. Reaction of dianionic lithium azaenolates with epoxides.



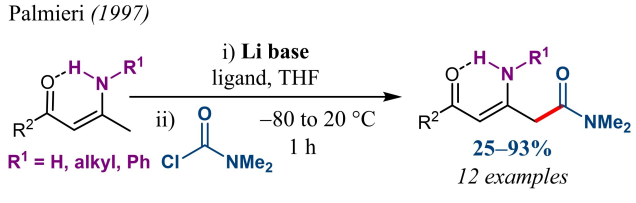
Scheme 22. Reaction of lithium azaenolates with esters.



Scheme 23. Reaction of lithium azaenolates with chloroformates and ethyl carbonate.



Scheme 24. Reaction of lithium azaenolates with imidic acid derivatives.



Scheme 25. Reaction of dianionic lithium azaenolates with dimethylcarbamoyl chloride.

3.6. Reaction with Carbonyl Derivatives containing a Leaving Group

Lithium azaenolate intermediates have enabled the α-functionalisation of aldimines/ketimines with esters (Scheme 22), chloroformates/carbonates (Scheme 23), imidic acid derivatives (Scheme 24), carbamoyl chlorides (Scheme 25) and CDI (Scheme 26).

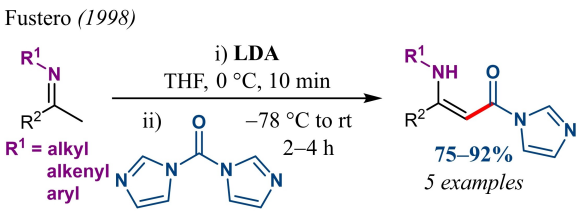
In 1968, Wittig discovered one example of the reaction of a lithium azaenolate with an ester, to form an enamino ketone.[83] Much later, Bartoli provided further examples of this transformation, where isopropyl and cyclohexyl imines of acetone and cyclohexanone respectively were reacted with aromatic and aliphatic esters (Scheme 22a).[110] Ferezou showed that lithium azaenolates, formed *in situ* by α-oxidation of secondary amines, could also react with esters to form enamino ketones (Scheme 22b).[23] These products could also be trapped with hydrazine sulfate to give pyrazoles in one pot.

With the cyclohexylimine of acetone, Wittig demonstrated the ambident nature of lithium azaenolates. On reaction with ethyl chloroformate, a mixture of *C* and *N* functionalisation products was formed; reaction at carbon was favoured however.[83] Palmieri later showed azaenolates of various aldimines and ketimines, including endocyclic examples, could be reacted with benzyl chloroformate or ethyl carbonate (Scheme 23).[111]

Lithium azaenolates were shown to react with imidic acid derivatives to form dianils, which were used as "horseshoe-like" ligands for nickel (Scheme 24).[112]

Palmieri reacted lithium dianions of β-enaminoketones with *N,N*-dimethylcarbamoyl chloride under four distinct sets of conditions, forming *N,N*-dimethylcarbamoylenaminones (Scheme 25).[113] Depending on the substrate, either MeLi, LDA or LiTMP was used as the base coupled with different ligands, times and temperatures. Notably, a chiral enaminone formed from I-α-methylbenzylamine enabled enantioselective preparation of the products in 78–88% isolated yield of the single enantiomers.

On reaction with CDI, lithium azaenolates of aromatic and aliphatic methyl ketimines with various nitrogen substituents can be used to generate β-



Scheme 26. Reaction of lithium azaenolates with CDI.

enamino carbonyl imidazole derivatives in excellent yields (Scheme 26).[114] The products were treated with alcohols or thiols to form β-enamino esters and thioesters respectively in a one pot process from the methyl ketimines (40–90% overall yields).

3.7. Reaction with Imines

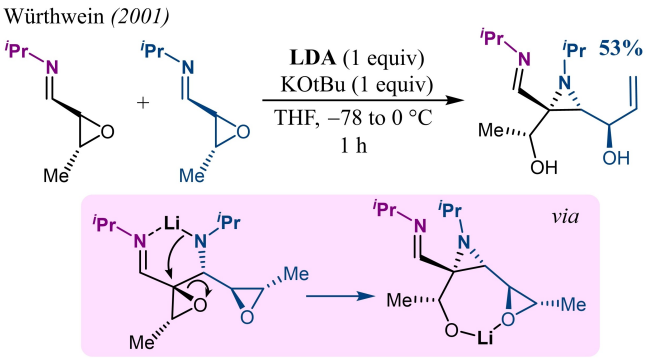
Lithium azaenolates are the only class of azaenolate which have been shown to react with imines, although the more general methods require activated (*N*-sulfonyl) imines. Wurthwein observed that treatment of an oxiranyl carbaldimine with LDA led to dimerization through an aza-Darzens reaction, to form a highly functionalised aziridine (Scheme 27).[115] The mechanism, supported by computational studies, was thought to proceed through formation of a lithium azaenolate which adds into the electrophilic imine carbon. The resultant nitrogen anion then ring opens the proximal epoxide.

Hou showed sulfonyl imines were suitable electrophiles for reaction with lithium azaenolates of aldimines (Scheme 28a).[116] Only aryl sulfonyl imines were shown to work in this reaction, with imines bearing phenyl and diphenyl-phosphinoyl groups on the nitrogen proving unreactive.

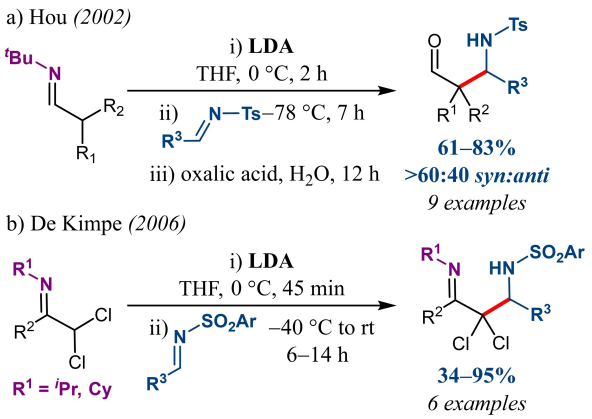
De Kimpe previously showed that α-haloketimines could undergo reaction with aldehydes or ketones via a lithium azaenolate to form epoxides (see Scheme 12d).[86] A similar, aza-variant was also feasible, where lithium azaenolates bearing two α-chlorides were added into sulfonyl imines (Scheme 28b).[117] The imine products could be hydrolysed to gietamineaminted β-amino ketones with aqueous hydrochloric acid (92–99% yield) or treated with potassium hydroxide to give *cis*-3-aryl-2-chloro-2-imidoylaziridines as single diastereomers (81–99% yield).

3.8. Reaction with Other Electrophiles

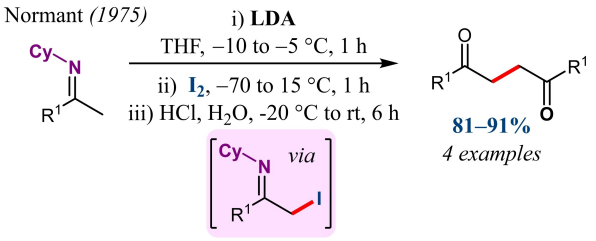
Uniquely, azaenolates of lithium have been shown to react with iodine (Scheme 29), a chlorophosphate (Scheme 30) and nitriles (Scheme 31). Normant showed that iodination of lithium azaenolates with



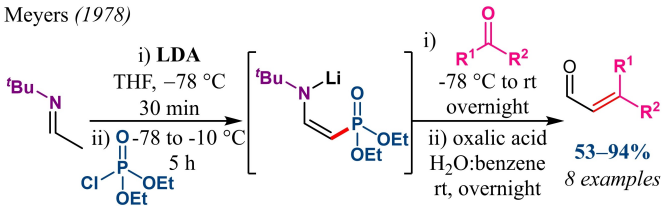
Scheme 27. Dimerisation of an oxiranyl carbaldimine through an azaenolate intermediate.



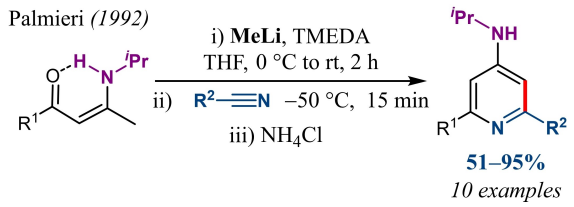
Scheme 28. Addition of lithium azaenolates into sulfonyl imines.



Scheme 29. Reaction of a lithium azaenolate with iodine to form symmetrical 1,4-diketones.



Scheme 30. Formation of α-β-unsaturated aldehydes from simple aldimines.



Scheme 31. Reaction of dianionic lithium azaenolates with nitriles.

iodine was possible, with the α-iodoketone rapidly reacting with remaining lithium azaenolate to form symmetrical aliphatic 1,4-diketones in high yields (Scheme 29).[107]

Meyers developed a new method for preparing α,β-unsaturated aldehydes in 1978.[118] In this reaction a lithium azaenolate is reacted with diethylchlorophosphate to form an organophosphorus compound, which in the presence of excess base goes on to react with an aldehyde or ketone (Scheme 30). Previously Nagata showed sodium azaenolates of organophosphorus compounds react with aldehydes and ketones,[91] but crucially Meyers' method is able to form the α,β-unsaturated aldehyde in one pot from a simple acetaldehyde imine.

Palmieri showed dianionic lithium azaenolates of β-enaminoketones readily react with aromatic and aliphatic nitriles, which upon quenching with ammonium chloride afford 4-aminopyridines (Scheme 31).[119]

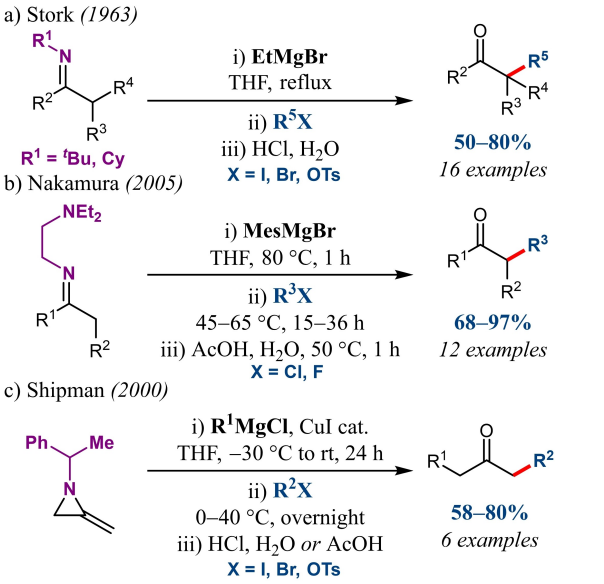
4. Magnesium

Magnesium imine azaenolates have been synthesized from the deprotonation of imines using Grignard reagents or Lewis acidic magnesium bromide wietaminneamineine. Additionally, they have been shown to be formed from copper catalysed ring opening of 2-methyleneaziridines with Grignard reagents.[24] Magnesium azaenolates can be used in alkylation reactions with alkyl halides or tosylates, including enantioselective methylation. When treated with an aldehyde or ketone, magnesium azaenolates form aldol products. Furthermore, these intermediates can be used to ring open strained oxygen heterocycles such as epoxides and oxetane and have also been used for silylation.[120,121]

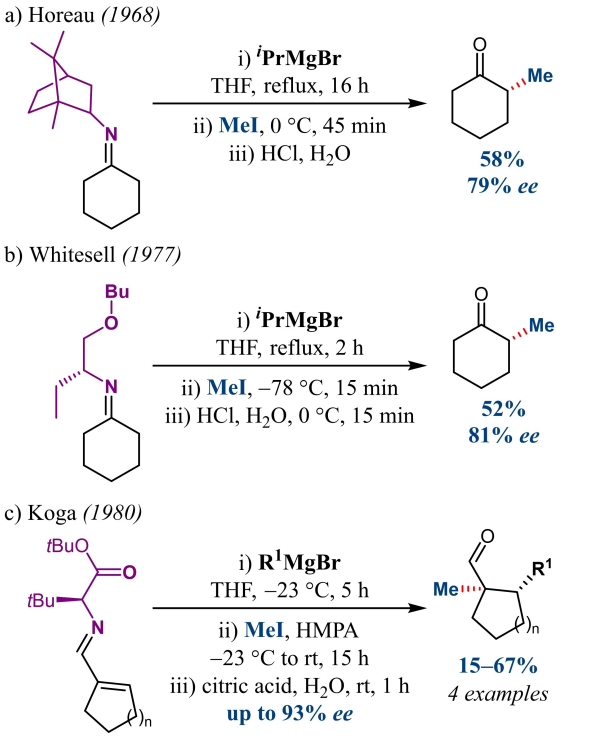
4.1. Reaction with Alkyl Halides

Magnesium azaenolates show comparable reactivity to lithium enolates (see Section 3.1) with alkyl halides (Scheme 32), including in enantioselective variations (Scheme 33). Notably however, magnesium azaenolates have also been used with alkyl tosylates and, with a bidentate imine, even unactivated alkyl chlorides and fluorides can be used.

Stork and co-workers demonstrated the first example of alkylation of a magnesium azaenolate in 1963 (Scheme 32a).[33] Imines formed from either *tert*-butylamine or cyclohexylamine and an enolisable aldehyde or ketone could undergo complete enolization with minimal addition to the electrophilic carbon, when refluxed with ethylmagnesium bromide. The formation of the magnesium azaenolates from the imine could be carried out in the presence of alkyl bromides, which proved useful where the azaenolate formed was



Scheme 32. Alkylation of magnesium azaenolates with alkyl halides and tosylates.



Scheme 33. Enantioselective α-methylation of ketones and aldehydes with a magnesium azaenolate.

reactive with its parent imine, such as for propanal. When using ketones with two possible enolisable positions, alkylation occurred preferentially on the least hindered side of the ketone. Butyl tosylate was also a suitable electrophile, giving a high yield of 2-butylcyclohexanone (80%) from the cyclohexylamine

imine. Gates[122] and Silverstein[123] also showed that alkyl tosylates could be used for alkylation of magnesium azaenolates, in total synthesis.

In 2005, Nakamura demonstrated remarkable reactivity of azaenolates with typically unreactive alkyl halides. They reported that a secondary coordination site, suitably spaced off the imine nitrogen, could facilitate enhanced reactivity of the magnesium azaenolates of aliphatic ketones, enabling alkylation reactions with unactivated alkyl chlorides and fluorides (Scheme 32b).[29,124]

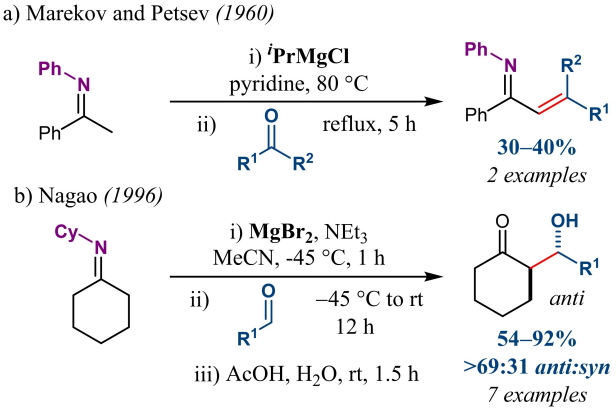
Shipman demonstrated that magnesium azaenolates could be formed from the ring opening of 2-methyleneaziridines with a benzyl or alkyl Grignard reagent and catalytic copper(I) iodide (Scheme 32c).[24] The resulting azaenolate was trapped with various benzyl chlorides, alkyl bromides or an alkyl tosylate in good yields. Similarly, this methodology was used in multicomponent reactions, whereby tetamineine formed on alkylating the azaenolate was trapped with diethylphosphite to form α-amino phosphonates.[25]

Horeau first used an azaenolate formed from a chiral amine, (−)-isobornylamine, to promote enantioselective α-methylation of cyclohexanone (Scheme 33a).[125] With a chelating chiral azaenolate, Whitesell also showed enantioselective α-methylation of cyclohexanone was possible with a magnesium azaenolate (Scheme 33b).[31] Notably in Whitesell's model the *syn* azaenolate is proposed, with the ethyl group able to block the approach of the electrophile resulting in high product enantiopurity. This is contrary to the explanation proposed by Meyers a year earlier.[62]

Stereoselective α,β-difunctionalisation of cyclic α,β-unsaturated cyclopentene and cyclohexenecarboxyaldehyde was achieved by Koga in 1980 (Scheme 33c).[21,126] Conjugate addition of a Grignard reagent resulted in the initial C–C bond formation at the β-position of the aldehyde, which gave a magnesium imine azaenolate intermediate. The azaenolate was then trapped with methyl iodide resulting in the *trans* products in high *ee*, due to the chelation of the *tert*-leucine *tert*-butyl ester group on the imine.

4.2. Reaction with Aldehydes and Ketones

Fewer examples of aldol-type reactions have been reported with magnesium azaenolates compared to lithium (see Section 3.2). Prior to the seminal work of Stork[33] and Wittig,[22] in 1960 the very first example of an azaenolate was reported by Marekov and Petsev.[34] In this study, the aniline imine of acetophenone was converted into a magnesium azaenolate on reaction with isopropylmagnesium chloride (Scheme 34a). Although only low reactivity with electrophiles was achieved in ether, switching the solvent to pyridine prior to adding the imine to the Grignard



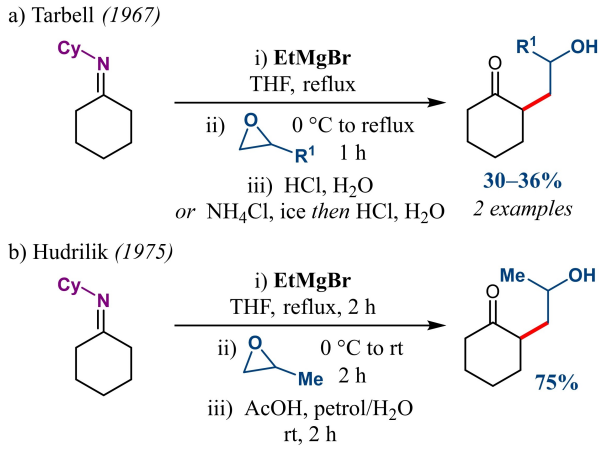
Scheme 34. Reaction of magnesium azaenolates with aldehydes and ketones.

reagent meant the resulting magnesium azaenolate reacted with benzophenone (40% yield) and benzaldehyde (30% yield), to give the dehydrated aldol products.

Although strong lithium or magnesium bases are commonly used, there are some examples of the generation of imine azaenolates using a weak base with a Lewis acid (see also Scheme 38 with BCl_3).[18] In 1996, Nagao demonstrated that a magnesium azaenolate could be formed from activation of the imine with magnesium bromide and deprotonation by triethylamine. The cyclohexylamine-cyclohexanone azaenolate was readily formed at low temperature under these conditions and it was then treated with various benzaldehydes or pivaldehyde (Scheme 34b).[19] *anti* Selectivity was observed in the aldol products under these conditions. Hayashi investigated the *anti/syn* selectivity of this reaction with different magnesium salts in 2007.[127]

4.3. Reaction with Epoxides and Oxetanes

Magnesium azaenolates can be used to ring open strained oxygen heterocycles, with higher yields and a broader reaction scope than lithium azaenolates (see Scheme 19c,d). Tarbell found that the magnesium azaenolate of the cyclohexylamine imine of cyclohexanone reacted with ethylene and propylene oxide at 0 °C (Scheme 35a).[128] In contrast, the enamine *N*-cyclohex-1-enylpyrrolidine was unchanged after heating with ethylene oxide in benzene for 18 h at 80 °C, highlighting the enhanced reactivity of the azaenolate over the corresponding enamine. Hudrlik also demonstrated the ring opening of propylene oxide with a magnesium azaenolate (Scheme 35b).[106] Compared to Tarbell's method[128] an improved yield was obtained, which was attributed solely due to the milder hydrolysis conditions (AcOH instead of HCl).

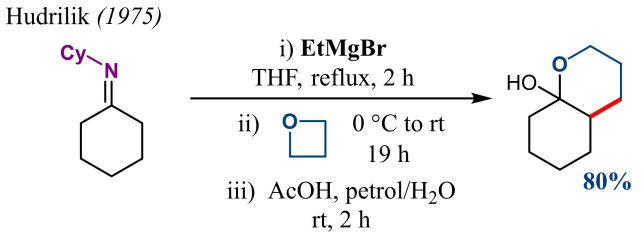


Scheme 35. Reaction of magnesium azaenolates with epoxides.

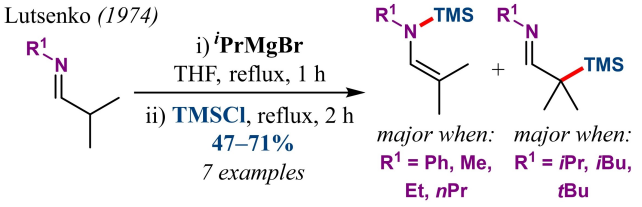
Oxetane was also ring opened under these conditions and the resultant alcohol underwent intramolecular ring closure to form a cyclic hemiacetal (Scheme 36).[106]

4.4. Reaction with Silylating Agents

As for lithium azaenolates(see Scheme 18), the magnesium analogues can be reacted with a silylating agent for *N* or *C* selective functionalisation. Lutsenko and co-workers formed magnesium azaenolates from a selection of butyraldehyde imines and treated them with chlorotrimethylsilane (Scheme 37).[120,121] They found that *N*-phenyl imines and smaller *N*-alkyl imines favoured the *N*-silylated product, whereas larger groups preferentially gave the C–Si isomer. It was found that the C–Si isomers could be converted to the thermodynamic N isomer by heating with bromotrimethylsilane, though this process was very slow and did not occur at all with the more hindered examples.



Scheme 36. Reaction of a magnesium azaenolate with oxetane.



Scheme 37. Reaction of magnesium azaenolates with TMSCl.

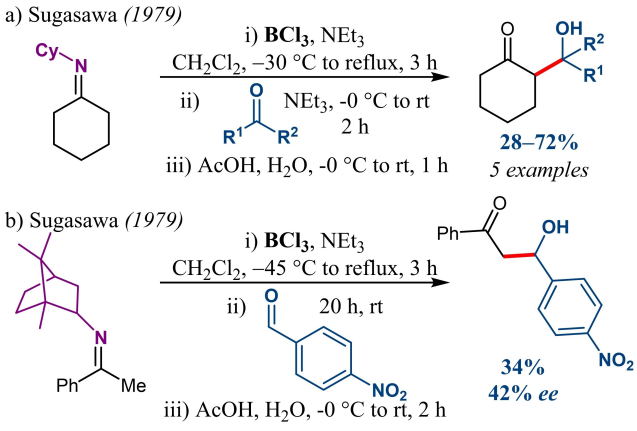
5. Boron

Boron imine azaenolates have been formed from reaction of an imine with a Lewis acidic boron reagent and triethylamine or by reduction of isoquinolines. They have only been used for aldol-type chemistry and this reaction has been studied in detail computationally.

5.1. Reaction with Aldehydes and Ketones

Sugasawa showed that the cyclohexylamine imine of cyclohexanone could be converted into the corresponding boron azaenolate by treatment with Lewis acidic boron trichloride and triethylamine. The boron azaenolate was isolated by distillation then reacted with a variety of aldehydes and ketones, forming aldol products (Scheme 38a).[18] Both aromatic and aliphatic aldehydes were tolerated as electrophiles, however cyclohexanone and acetone gave reduced yields of 28% and 31% respectively. A one-pot process with no isolation of the boron azaenolate was also developed.

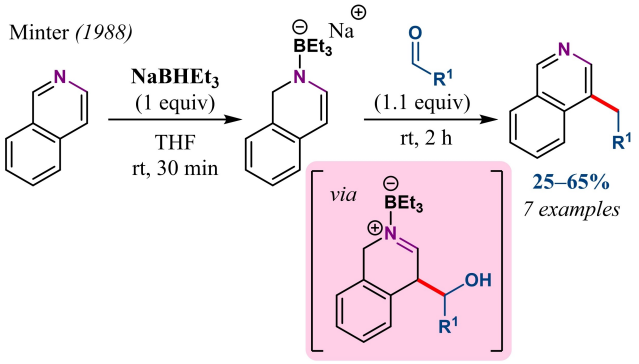
An asymmetric boron azaenolate aldol reaction was also developed by incorporating a chiral group on the imine nitrogen, with the best yield and enantiomeric excesses obtained with a bornylamine imine (Scheme 38b).[129] A lithium or magnesium azaenolate, derived from an α-methylbenzylamine imine, gave a poorer yield and lower enantioselectivity than the boron equivalent. This was rationalised by the more rigid intermediates that are formed with boron, as a result of its stronger coordination to the carbonyl oxygen.



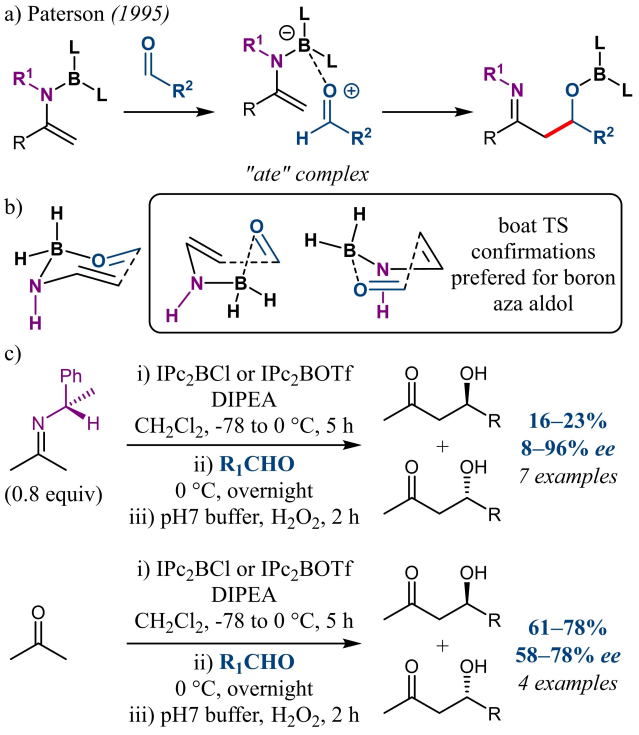
Scheme 38. Reaction of boron azaenolates with aldehydes and ketones.

Minter used a boron azaenolate intermediate in a new route to 4-substituted isoquinolines (Scheme 39).[130] The azaenolate was formed by reduction of isoquinoline with sodium triethylborohydride, which reacted with aldehydes at the 6-position. The alcohol intermediate then undergoes dehydration and rearomatisation to give functionalised isoquinolines. Yields were low for aliphatic aldehydes (25–38%), but good for a selection of aromatic and heteroaromatic aldehydes.

Computational and experimental comparisons between enolate and azaenolate reactions were conducted by Paterson in 1995 (Scheme 40).[131] These studies



Scheme 39. Synthesis of 4-substituted isoquinolines via a boron imine azaenolate.



Scheme 40. Computational and experimental investigations of boron aza-aldol reactions.

suggested that the mechanism of the boron azaenolate aldol reaction, as for a boron enolate, proceeded through an "ate complex" (Scheme 40a). The nitrogen in the azaenolate was found to be almost sp^2 hybridised, with effectively a double bond between N and B, and the C–N bond also had some double bond character. Compared to the oxygen analogue, the barrier for rotation about the C–N bond (conversion to the *syn* or *anti* azaenolate) was much higher (24 vs 8.5 $kJmol^{-1}$). Boron and nitrogen atomic orbitals match in energy and geometry much better than oxygen and boron, meaning that the association between the carbonyl electrophile and the boron is much weaker than for the analogous aldol reaction, resulting in a much longer B–O bond in the ate complex of the azaenolate.

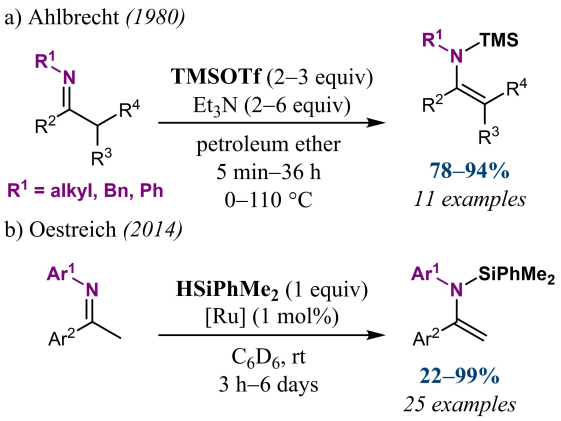
The difference in energies of the possible transition states for the aza-aldol reaction were then considered, and boat confirmations in the TS were found to be much lower in energy than a chair conformation (Scheme 40b). The calculated energies of the enolates, ate complexes and transition states for the aldol and aza-aldol reactions were compared which showed that less energy is gained from forming the ate complex for the aza-aldol reaction relative to the aldol. When forming the C–C bond, the energy barrier was higher for the aza-aldol than the aldol. To support these calculations, the yield and enantioselectivity of boron aldol and aza-aldol reactions were compared experimentally, using a chiral boron Lewis acid (Scheme 40c). Generally low yields in the aza-aldol reaction were observed, and it was unclear if this was due to a problem in the procedure or a fundamental problem of the reaction. The aza-aldol did however sometimes give very good enantioselectivity. For both reactions, the chirality of the boron Lewis acid directed which enantiomer was formed, suggesting both proceed via the same transition state. This was likely to be the lowest energy boat confirmation (middle structure in Scheme 40b). When there was a matched pair on the imine nitrogen and the chiral boron reagent, the *ee* values were highest. The aza-aldol gave a large variation in selectivity when the aldehyde was changed, which was not the case for the aldol. This was proposed to be due to the presence of the large group on nitrogen, clashing sterically with some aldehydes and not others. Diethylketone in place of acetone was unreactive in the aza-aldol, but successful in the aldol. This was explained by the preference of a chair transition state for this substrate, which is too high energy for the aza-aldol case. Due to the higher energy barrier to form the C–C bond in the aza-aldol reaction, the ate complex is longer lived, and therefore more likely to undergo unwanted side reactions. It was suggested this could potentially be avoided by making the nitrogen deactivate the boron to a lesser extent, by reducing the electron density on N.

6. Silicon

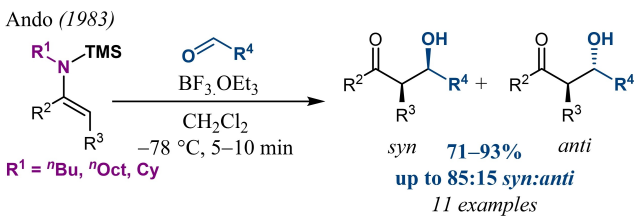
Silicon imine azaenolates (*N*-silylenamines, enaminosilanes), can be considered as the nitrogen analogue of silyl enol ethers. They have been accessed by silylation of lithium (see Scheme 18), and magnesium (see Scheme 37) azaenolates, but significant amounts of *N*-silylation products have only been seen in the case of Albreight's reaction with *N*-phenyl imines (See Scheme 18b).[132] Highly selective formation of *N*-enaminosilanes can be achieved from imines using trimethylsilyltriflate and triethylamine (Scheme 41a).[133] The reactions were selective for *N*-silylation regardless of the steric hindrance at nitrogen (*N*-*tert*-butyl) or when there were no substituents at the α-position. The reaction was also successful with aldimines ($R_2 = H$), and so provides a general route to *N*-silylenamines. More recently, Oestreich synthesized *N*-silylenamines through a ruthenium catalysed base-free dehydrogenative Si–N coupling (Scheme 41b).[134]

6.1. Reaction with Aldehydes and Ketones

In the presence of a Lewis acid, enaminosilanes are highly reactive towards aldehydes and can undergo a *syn* selective aldol reaction (Scheme 42).[135] 2-Pentanone and cyclohexanone enaminosilanes were used as the substrate, and aromatic, alkenyl, α,β-unsaturated as well as aliphatic aldehydes could all be used effectively.



Scheme 41. Synthesis of enaminosilanes.



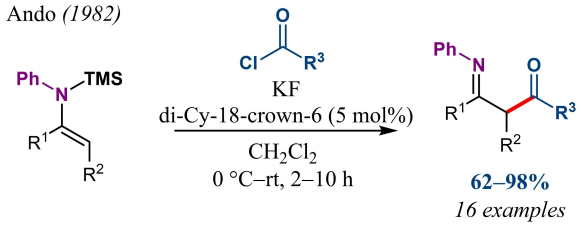
Scheme 42. Aldol reaction of enaminosilanes.

6.2. Reaction with Acid Chlorides

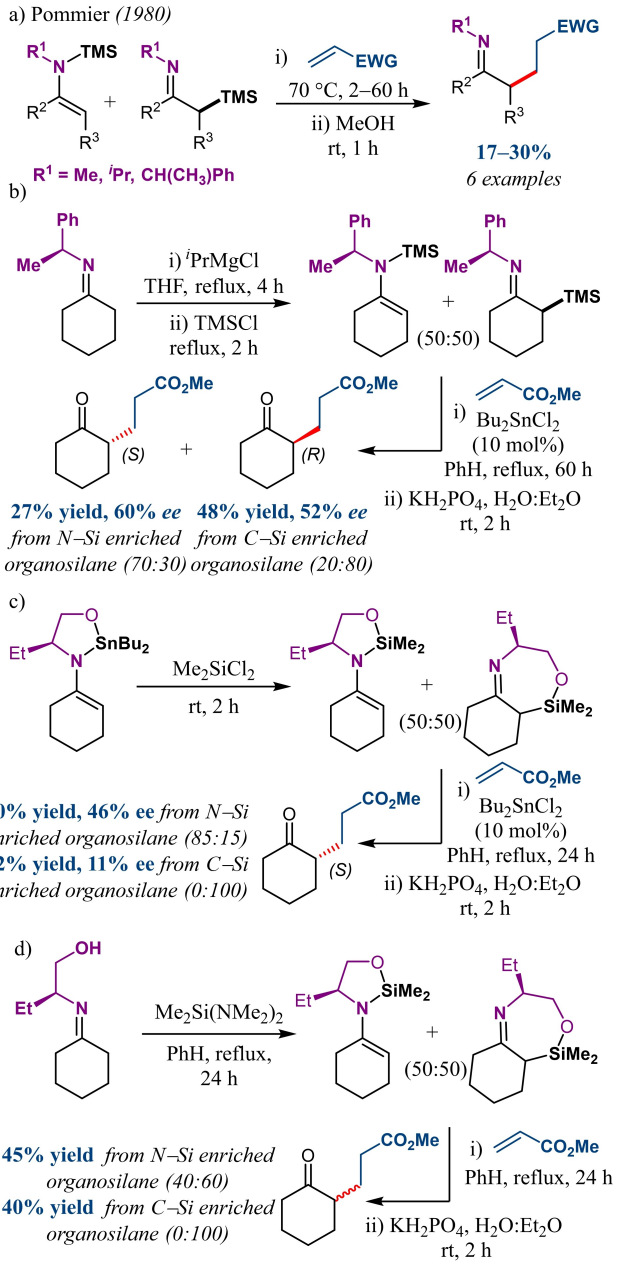
Enaminosilanes of aliphatic ketones can be acylated at the α-position on reaction with acid chlorides (Scheme 43).[136] A fluoride source (KF) was used to activate the silicon, assisted by a catalytic amount of crown ether to solvate the cation. In the absence of these key components, the organosilane reacted at nitrogen. Acylation at the heteroatom instead of the carbon also occurs when a silyl enol ether is used instead of the enaminosilane.

6.3. Reaction with Michael Acceptors

Pommier formed enaminosilanes using various methods, and studied their reaction with α-β-unsaturated esters and nitriles (Scheme 44).[137] In particular, they considered the reactivity of the possible isomers (N–Si vs C–Si). Firstly, they found that although yields were low, enaminosilanes of isobutyraldehyde or cyclohexanone with methyl, isopropyl or phenylethylamine groups on the nitrogen react with methyl acrylate or acrylonitrile to give, after reaction with methanol, α-alkylated products (Scheme 44a). *Either* the C–Si or N–Si isomers gave this product selectively, although the C–Si organosilane isomer from the isopropylimine of isobutyraldehyde reacted significantly slower than the N–Si isomer. This highlighted that interconversion of these isomers was slow, even at 70 °C, and the N–Si "enaminosilane" form was more reactive. To achieve asymmetric synthesis, a chiral imine was synthesized from *(S)*-phenylethylamine and cyclohexanone, the enaminosilane isomers were then generated by reaction of a magnesium azaenolate with chlorotrimethylsilane. This gave a 50:50 mixture of the C–Si and N–Si isomers. Enriched mixtures of either of these isomers was achieved through distillation of the 50:50 mixture (for C–Si) or repeating the reaction under thermodynamic control (for N–Si, 25 h, 150 °C). They found these isomers only isomerised very slowly, taking 200 h in benzene at reflux in the presence of a Lewis acid catalyst. Very interestingly, the mixtures enriched in either isomer favoured different enantiomers upon



Scheme 43. Reaction of enaminosilanes with acid chlorides.



Scheme 44. Reaction of enaminosilanes with Michael acceptors.

alkylation with methyl acrylate in the presence of a catalytic Lewis acid (Scheme 44b). They also investigated bidentate imine groups to induce stereoselectivity, which were formed from transmetallation of a tin azaenolate. Alkylation of this enaminosilane with methyl acrylate gave the same enantiomer of product with either the N–Si or C–Si isomers, with varying degrees of *ee* and low yield (Scheme 44c).

The enaminosilanes could also be synthesized from the imine directly (Scheme 44d). From this tin-free synthesis, the enaminosilane was reacted with the alkene in the absence of the Bu_2SnCl_2 catalyst. Interestingly this gave the product in higher yield but with no stereoinduction, showing chelation of the tin plays a key role in the formation of the chiral centre.

7. Copper

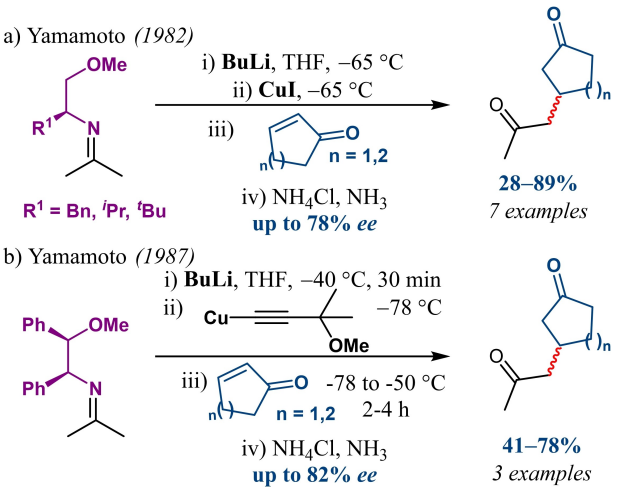
Copper imine azaenolates, formed in each case from transmetalation from a lithium azaenolate, have been used for enantioselective conjugate addition into α,β-unsaturated cyclic ketones. Lithium azaenolates can also be used in a similar reaction (see Scheme 14), but reactions using copper have shown a broader scope and higher yields.

7.1. Reaction with Michael Acceptors

Yamamoto formed a chiral copper azaenolate by transmetallation from a lithiated species with copper(I) iodide. The copper azaenolate could undergo asymmetric conjugate addition into cyclohexenone or cyclopentanone, with enantiomeric excess ranging from 17–78% (Scheme 45a).[138] The stereochemical outcome (*R* or *S*) varied depending on whether cyclohexanone or cyclopentenone was used as well as the size of the R^1 group. Yamamoto used this reaction in the asymmetric synthesis of trans-dihydrindandione.[139] Use of (*1S, 2R*)-2-methoxy-1,2-diphenylethylamine to form the chiral imine, and with a mixed cuprate formed from the lithium azaenolate with a copper acetylide, led to overall improved enantioselectivity in this reaction (Scheme 45b).[140]

8. Zinc

Zinc azaenolates have been synthesized from transmetallation of lithiated species with zinc(II) halides or dimethylzinc. They have been used in aldol-type



Scheme 45. Conjugate addition of copper azaenolates into α,β-unsaturated ketones.

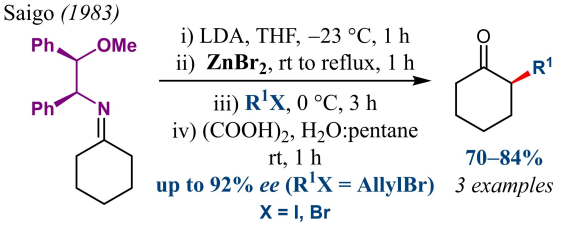
reactions, as well as alkylation with alkyl halides or addition into both unactivated alkenes and Michael acceptors.

8.1. Reaction with Alkyl Halides

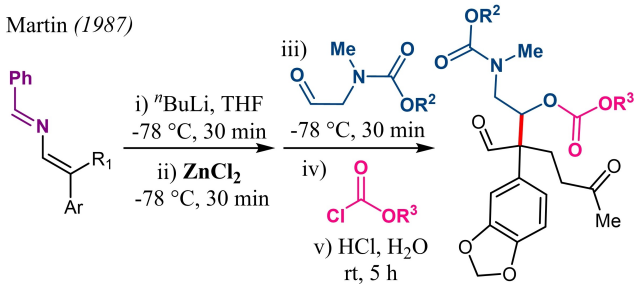
Enantioselective alkylation of cyclohexanone through a chiral zinc azaenolate was achieved by Saigo (Scheme 46).[141] Benzyl bromide, allyl bromide and iodoethane were all used successfully to obtain the alkylated ketones in high yield and enantioselectivity with either enantiomer of the imine.

8.2. Reaction with Aldehydes and Ketones

Martin provided the first example of a zinc azaenolate in 1986, which was formed from addition of n-butyllithium into the C=N bond of a 2-azadiene followed by transmetallation with zinc chloride (Scheme 47).[142] The zinc azaenolate was subsequently reacted with an aldehyde and the resultant alcohol trapped with methyl chloroformate or pivaloyl chloride. The aldehyde products were then treated with acetic acid to effect cycloaldolisation (not shown) with the ketone group, which gave isolated yields ranging from 21–78% over the two steps. This reaction was a key step in the total synthesis of amarllidacae alkyloids.



Scheme 46. Enantioselective alkylation with a zinc imine azaenolate.



Scheme 47. Reaction of a zinc imine azaenolate with an aldehyde.

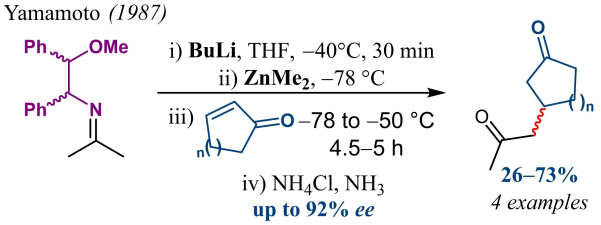
8.3. Reaction with Michael Acceptors

As for copper (see section 7.1), a chiral zinc azaenolate was shown to add to cyclohexenone or cyclopentenone in an asymmetric conjugate addition reaction with variable yields (Scheme 48).[140]

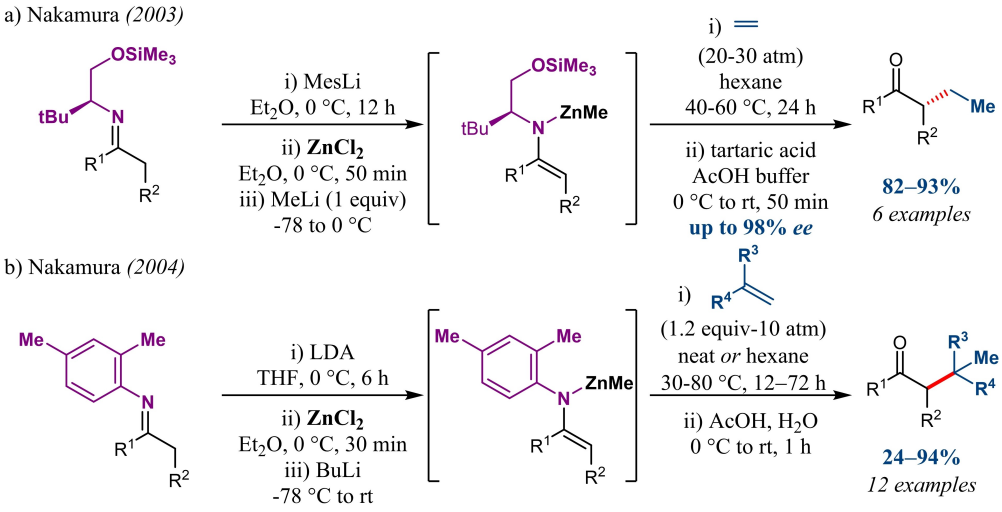
8.4. Reaction with Alkenes

Uniquely, zinc azaenolates have been shown to undergo addition to unactivated alkenes to generate an alkylzinc intermediate. In 2003 Nakamura developed an enantioselective ethylation of zinc azaenolates using ethene as the alkylating agent (Scheme 49a).[30] The zinc azaenolate was formed from deprotonation of an imine with mesityl lithium, followed by transmetallation. Ligand exchange with methyl lithium was required to achieve high reactivity in the alkylation step. The zinc azaenolate formed using this method was reactive towards ethene, which has not been observed with enolates of zinc or other metals. Notably, a zinc azaenolate of a chiral hydrazone can react with ethene but with poor stereoselectivity.[143] The organozinc intermediate formed on addition of the azaenolate into the alkene prior to hydrolysis could be used for various known reactions of organozincs, including copper and palladium catalysed cross-couplings. Interestingly, the observed enantioselectivity of this reaction is opposite to that seen of the same imine reacting with an alkyl iodide through a lithium azaenolate.[63]

A year later, a more general reaction of zinc azaenolates with alkenes was unveiled (Scheme 49b).[144] In this case, the C–C bond is formed at the most substituted carbon of the alkene, with essentially complete regioselectivity. Interestingly, the reaction does not work with electron deficient alkenes such as acrylates and other Michael acceptors. Compared to zinc hydrazone azaenolates,[143] much improved yields on reaction with alkenes were found with the imines, and low equivalents of alkene could be used.



Scheme 48. Conjugate addition of a zinc azaenolate into α,β-unsaturated ketones.



Scheme 49. Reaction of zinc imine azaenolates with alkenes.

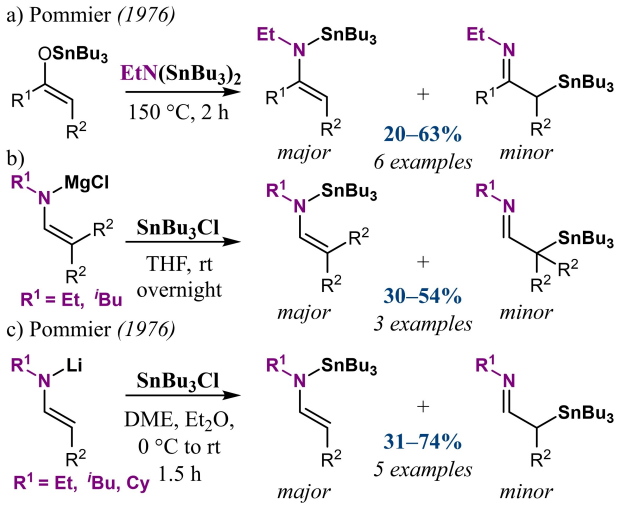
9. Tin

Tin azaenolates have been explored almost exclusively by Pommier. Unlike azaenolates of other metals, tin azaenolates are often isolated before being reacted with electrophiles. The synthesis of these species has been shown through various strategies, and they have been used for addition into electron deficient alkenes or in silylation reactions.

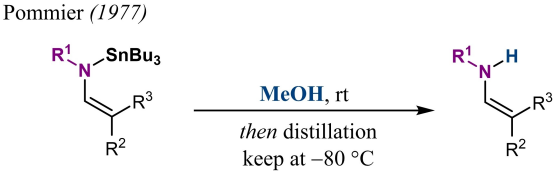
Tin azaenolates were first synthesized using various approaches in 1976 (Scheme 50).[145–147] Firstly, the reaction of a tin enolate with stannazane could provide tin azaenolates of aliphatic aldehydes or ketones in moderate yields (Scheme 50a). Using this method, the major isomer observed was with the tin bound to the nitrogen atom (N–Sn). The tin azaenolate could also be formed by transmetallation of a magnesium azaenolate with tributyltin chloride, again favouring the N–Sn isomer whether R^2 = Me or Et (Scheme 50b). Finally, reaction of a lithium azaenolate with tributyltinchloride gave improved yields of the organotin species (Scheme 50c).[145] In this procedure, the N–Sn isomer was again favoured, except when a large cyclohexyl substituent was present on the imine nitrogen, which gave exclusively the C–Sn species.

Protonolysis of these tin azaenolates with methanol led to reactive secondary enamines, despite their instability compared to the corresponding imine tautomer (Scheme 51).[148] The enamines could be completely equilibrated to the imine at room temperature after one hour, but they were also shown to add into acrylonitrile with much greater reactivity than the corresponding imine.

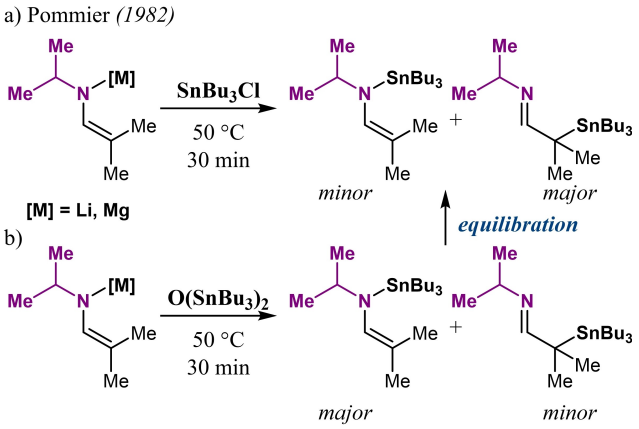
Later studies on tin azaenolates concluded that the ratio between the N–Sn and C–Sn isomers are dependent on the size of the substituents on both the nitrogen and carbon.[149] No matter which method was used to create each azaenolate, the same percentages of *C* and *N* isomers were formed, indicating a thermodynamic equilibrium. There was one exception to this; reacting the lithium or magnesium azaenolate of the isopropylimine of isobutraldehdye with tributyltin chloride gave mostly the C–Sn isomer (Scheme 52a) but reacting with tributyltin oxide gave primarily the N–Sn isomer



Scheme 50. Strategies for the formation of tin azaenolates.



Scheme 51. Protonolysis of tin azaenolates gives reactive secondary enamines.

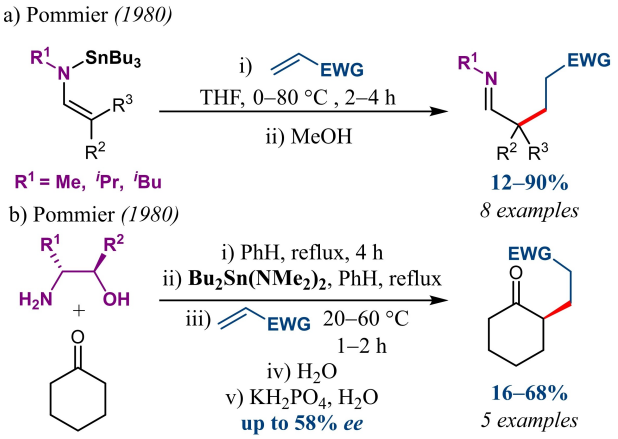


Scheme 52. Formation of different tin azaenolate isomers on transmetallation of Li or Mg azaenolates with tributyltin chloride or oxide.

(Scheme 52b). The C–Sn isomer was found to be thermodynamically favourable however, with the kinetic mixture from tributyltin oxide being equilibrated to favour the C–Sn product upon standing for prolonged periods at room temperature. This only occurred in this more hindered imine out of all the examples given.

9.1. Reaction with Michael Acceptors

Like enaminosilanes (see section 6.3), tin azaenolates, synthesized using the methods outlined above,[145,146] could be used to add into α-β-unsaturated esters and nitriles to form α-alkylated imines (Scheme 53a).[150] Notably, hindered alkenes led to no reaction. The reaction of a tin azaenolate with an activated alkene could also be conducted enantioselectively by incorporating a chiral group on the imine nitrogen (Scheme 53b).[151] In this case, the tin azaenolate is synthesized by formation of the hemiaminal ether



Scheme 53. Reaction of tin azaenolates with alkenes.

followed by reaction with $Bu_2Sn(NMe_2)_2$ and the highest level of *ee* achieved was using the amino alcohol with substituents $R^1 = Et$ and $R^2 = H$. Pommier improved the enantioselective alkylation years later on a variety of cyclic ketones.[152] De Jeso and Pommier applied this methodology to aldimines[153,154] which gave lower yields and *ee*'s than the cyclic ketones.

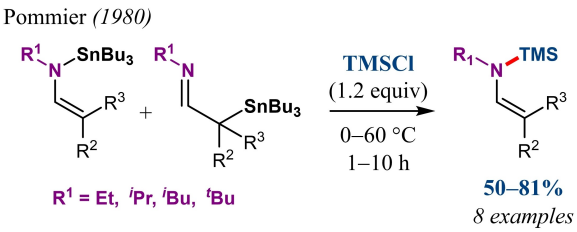
9.2. Reaction with Silylating Agents

Compared to methods using lithium (see Scheme 18) or magnesium (see Scheme 37), tin azaenolates exhibit higher selectivity towards *N*-silylation upon reaction with chlorotrimethylsilane (Scheme 54).[155] The isomer of the tin azaenolate (N–Sn or C–Sn) had no impact on the composition of isomers in the products. Azaenolates derived from the imines of linear, less hindered aldehydes, reacted faster than the branched substrates.

10. Conclusions and Outlook

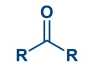
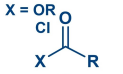
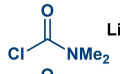
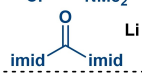
Since the very first example in 1960 by Marekov and Petsev,[34] imine azaenolates of a number of different metals have been synthesized. Although they have largely been formed from imine deprotonation, some alternative syntheses have been shown, such as addition into 2-azadienes,[20] oxidation of secondary amines[22,23] and ring opening of 2-methyleneaziridines..[24,25]

Each class of azaenolate has been shown to have unique reactivity towards electrophiles, and a summary of which metals and bases can be used for a particular electrophile class is given in Table 1. In general, the use of lithium azaenolates from lithium amides or alkyllithium reagents provides a practical, general method for the α-functionalisation of imines with electrophiles. Magnesium azaenolates provide an alternative approach for many reactions, although refluxing the imine with Grignard reagents is often needed for efficient deprotonation, which will reduce functional group compatibility. Azaenolates of other metals have not been extensively studied, so their full reactivity profile is less well understood. Magnesium azaenolates show some unique reactivity, e. g. with alkyl fluorides, and both lithium and magnesium azaenolates have



Scheme 54. Reaction of tin azaenolates with TMSCl.

Table 1. Metal and base selection guide for the α-functionalisation of imines with electrophiles. Examples where the azaenolate was formed by specific *in situ* methods not involving an imine are not included.

E	[M]	Base	Schemes	References
RI	Li	R_2NLi	6a,e,f,g; 7; 9a,c,d, 11	47-48, 57-58, 60-69, 75-81
		RLi	9b	67
	Mg	RMgX	32a; 33	33, 125, 31, 21, 126
	Zn	LDA *then* $ZnBr_2$	46	141
RBr	Li	R_2NLi	6a,e,f,g; 7; 9a,c,d, 11	47-48, 57-58, 60-69, 75-81
		Et_2NH, Li, HMPA	6b,c	50-55
	Mg	RMgX	32a	33
	Zn	LDA *then* $ZnBr_2$	46	141
RCl	Li	R_2NLi	11b	77
		Et_2NH, Li, HMPA	6b,c	50-55
	Mg	RMgX	32b	29, 124
RF	Mg	RMgX	32b	29, 124
	Li	R_2NLi	12b,d, 13a, 15	47-48, 82, 86, 95, 99
		RLi	12c, 13b, 16	85, 98, 77, 100-101
	Mg	RMgX	34a	34
		NEt_3, $MgBr_2$	34b	19
	B	NEt_3, BCl_3	38	18, 129
	Si	*preisolated*	42	135
R_3SiX	Li	LDA	18	96-97, 103-104, 132
	Mg	RMgX	37	120-121
	Sn	*preisolated*	54	155
	Li	Et_2NH, Li, HMPA	19c,d	107-108
		RLi	19a,b, 21	105-106
	Mg	RMgX	35	128,106
	Li	RLi	20	106
	Mg	RMgX	36	106
	Li	LDA	22a	110
	Si	*preisolated*	43	136
	Li	LDA	23	111
	Li	LDA	24	112
		RLi	24	112
	Li	LDA	25	113
	Li	LDA	26	114
	Li	LDA	27, 28	115-117
I_2	Li	LDA	29	107
$ClPO_2(OEt_2)$	Li	LDA	30	118
RCN	Li	LDA	31	119
	Li	R_2NLi	17	102
	Cu	RLi *then* CuX	45	138, 140
	Zn	RLi *then* $ZnMe_2$	48	140
	Si	*preisolated*	44	137
	Sn	*preisolated*	53	150-154
	Zn	RLi *or* R_2NLi *then* $ZnCl_2$	49	30, 144

been shown to ring open strained oxygen heterocycles such as epoxides and oxetane – reactions which are typically impossible with the corresponding enolates. α-Silylation of azaenolates has been successful with lithium, magnesium and tin derivatives, and selectivity for *C* or *N*-silylation can be tuned by the metal used and the steric demands of the substrate. These reactions form silicon azaenolates, which are reactive towards α-functionalisation in their own right. The reaction of imines with Michael acceptors has been achieved with a number of metals. For addition into unactivated alkene electrophiles, zinc azaenolates can be made *in situ* from transmetallation of a lithium azaenolate.

Azaenolates of imines have been known for over 60 years, but despite a lot of early progress, the field has not seen huge amounts of modern development. We believe this presents a gap to be exploited, with immense possibilities for reactivity and selectivity tuning compared to enolate chemistry, brought on by the additional nitrogen substituent. This, and the observed differences in reactivity exhibited by various metals offers an opportunity to enable regio and enantioselective α-functionalisation of aldehydes and ketones with numerous different electrophiles. In addition, the use of "soft enolization" approaches, with a weak base and a Lewis acid, and the reversibility of imine formation, opens up the tantalising possibility of catalytic approaches in the future where a chiral ligand or a chiral amine can be used to obtain enantioselectivity. Improvements in computational analysis since the early mechanistic studies on azaenolates should enable improved understanding of the reaction mechanisms. Of particular interest are the various stereochemical models proposed to explain the observed selectivity, which are often contradictory to one another so have not been discussed here. We hope this review will prove a useful resource for study into this often forgotten field, and potentially spark a renewed interest into further discovery.

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REVIEWS

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