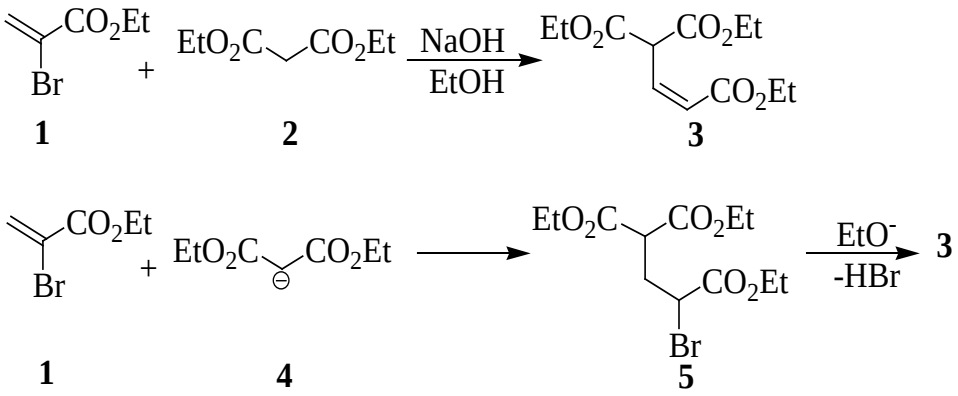
1.1. Introduction

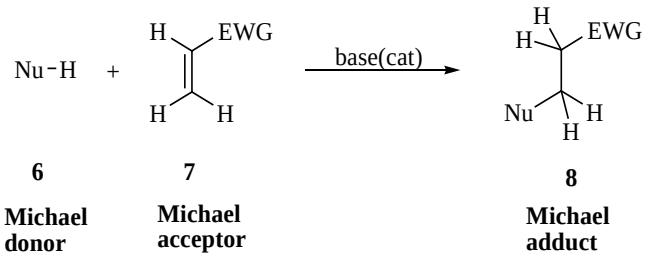
A. Michael[1] for the first time reported a reaction of ethyl α-bromoacrylate (**1**) with diethyl malonate (**2**) in the presence of sodium hydroxide in ethanol to give a product **3**; formation of the latter was interpreted as the addition of the carbanion **4** to **1** to form **5** which underwent dehydrobromination in the presence of a base (EtO^-) to yield **3** (**Scheme 1.1**). The reaction was named as the Michael reaction.



Scheme 1.1. Michael reaction of diethyl malonate with ethyl α-bromoacrylate.

Later, Michael reaction could be accomplished with a host of alkenes and alkynes activated by conjugation with electron-withdrawing groups (EWG), such as aldehyde, keto, carboxy, cyano, nitro, acid derivatives, sulphonyl, etc. The scope of the reaction was further broadened by discovering that not only carbanionic nucleophiles, but a variety of heteroatomic nucleophiles also, such as amines, amides, alcohols, thiols, too could add to the activated alkenes and alkynes affording a number of compounds having pharmaceutical importance and usefulness as building blocks.[2-5] The overall reaction was named as the Michael addition.

Thus, over the years Michael addition has emerged as a powerful and versatile synthetic tool for making a C-C or C-X (X=N, O, P, S) bond (**Scheme 1.2**).[6-14]



6 **7** **8**

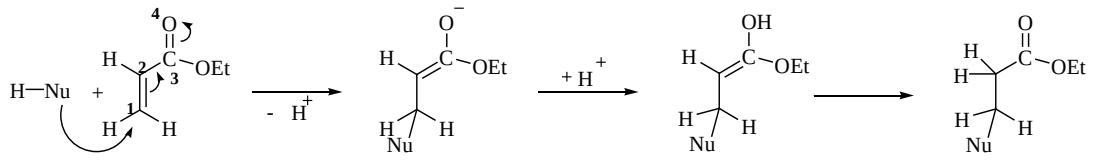
Michael donor **Michael acceptor** **Michael adduct**

EWG = COOR, COR, COH, $CONH_2$, CN, NO_2, etc.

Scheme 1.2. Michael addition reaction.

1.2. Mechanism of Michael Addition

Michael addition occurs in two steps: the first step involves the attack of the nucleophile at the β-carbon atom of the activated alkene or alkyne. The resulting zwitterionic intermediate (**9**) is stabilized by resonance. The second step involves transfer of the proton to the anionic centre producing the species **10**. Thus, Michael addition is overall a "1,4-addition" reaction. It is also called as the "Conjugate Addition". However, the initially formed enolic product (**10)** is stabilized by tautomerization to give **8** as the final product (**Scheme 1.3**).[15]



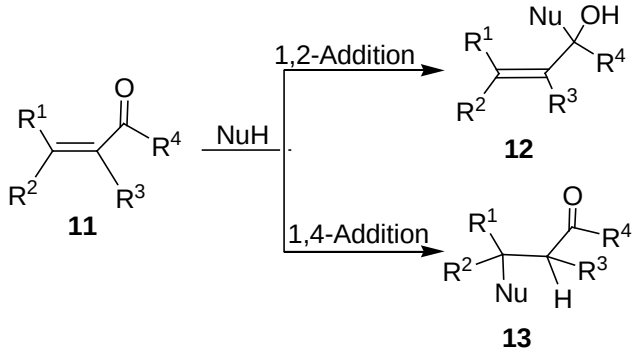
6 **7** **9** **10** **8**

Michael donor **Michael acceptor** **Intermediate** **Enol form of Michael adduct** **Keto form of Michael adduct**

Scheme 1.3. Mechanism of Michael addition.

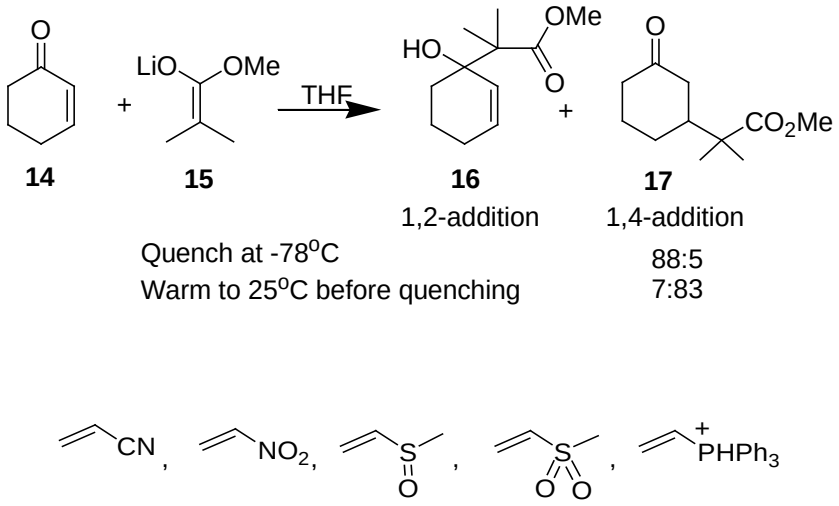
1.3. 1,2- Versus 1,4- Addition

In the reaction with α,β-unsaturated carbonyl compounds, direct addition of the nucleophile across the carbonyl group (1,2-addition) **(12)** often competes with the Michael addition (1,4-addition or conjugate addition) **(13)** (**Scheme 1.4**).



Scheme 1.4. 1,2- Versus 1,4-addition of nucleophile to α,β-unsaturated carbonyl compound.

Schultz and co-workers[16] for the first time studied systematically the factors affecting 1,4-versus 1,2- addition of the stabilized enolates derived from α-substituted methyl propiolates to 2-cyclohexen-1-one (**Scheme 1.5**) and found that 1,2-addition is kinetically preferred and occurs predominantly or exclusively at low temperature i.e. at -78°C, whereas 1,4 –addition is in general thermodynamically selective and the initially formed 1,2-addition product on raising temperature to 25°C changes into the 1,4-addition product (**Figure 1.1**). However, the reaction of the enolate ion derived from the acetonide of lactic acid with 2-cyclohexen-1-one at -78 or 25° over prolonged reaction time gave only 1,2-addition product ruling out reversibility of the latter under reaction conditions. From these results, they concluded that by simple structural modification and careful reaction temperature, it was possible to direct the reaction of enolates to cyclohexenone either to 1,2- or 1,4-addition.



Scheme 1.5. 1,2- Versus 1,4-addition of α-substituted methyl propiolates to 2-cyclohexen-1-one.

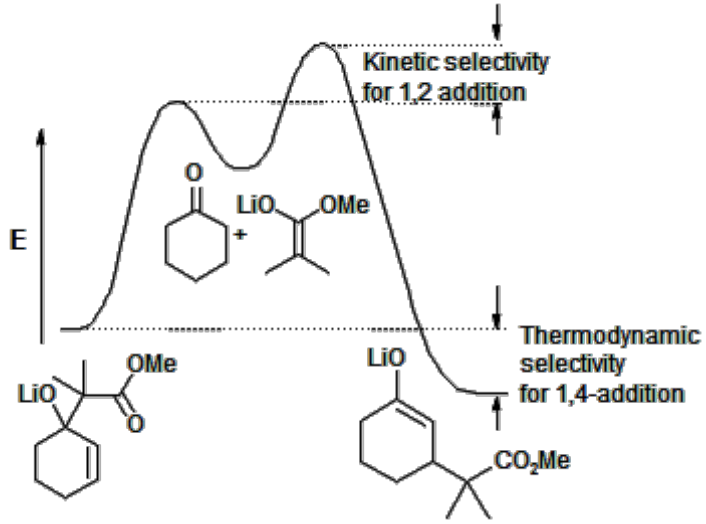


Figure 1.1. 1,2- Versus 1,4-addition of enolates of methyl propiolate with 2-cyclohexen-1-one.

In a similar study, Reich et al.[17] investigated role of the solvent in the reaction of sulphur-substituted carbanionic lithium reagents with 2-cyclohexen-1-one and concluded that under contact ion pairs (CIP) conditions (in the presence of THF or Et_2O), 1,2-addition product is favoured exclusively, whereas under solvent–separated ion pair (SIP) conditions (in the presence of hexamethylphosphoramide), 1,4-addition occurs predominantly.

In contrast to the intensive kinetic studies of the reactions of enolates with α,β-unsaturated carbonyl compounds, only one report[18] could be found about these aspects of the reaction of primary amines with α,β-unsaturated aldehydes and ketones although aza-Michael reaction has been extensively used for obtaining important synthons, such as β-amino carbonyl compounds and heterocyclic scaffolds.[19-23] Whiting, Carbo and co-workers[24] investigated the addition of primary amines to α,β-unsaturated aldehydes and ketones (1,2- vs 1,4-addition) byusing a combination of *in situ* IR, ^{1}H NMR and DFT calculations and concluded that formation of the α,β-unsaturated imines (through 1,2-addition to the C=O group) is kinetically controlled for all enols and most enones with the exception of methyl vinyl ketone, which gave 1,4-addition exclusively. Furthermore, DFT calculations indicated that selectivities are governed by conformational and stereo-electronic effects.

1.4. Aza-Michael Addition

As mentioned earlier, aza-Michael addition involves conjugate addition of the nitrogen-containing nucleophiles as Michael donor. The aza-Michael addition acquires much importance due to its ability to make β-aminocarbonyl derivatives[25-30] accessible, which are useful synthons for the preparation of several nitrogen containing bioactive natural products,[3] antibiotics[4] and chiral auxiliaries.[5]

The use of various N-nucleophiles (aliphatic amines,[31] aromatic amines,[32] amides,[33] carbamates,[34] azides[35]) and Michael-acceptors (enones,[36] acrylates,[37] unsaturated nitriles,[38] amides,[39] sulphones,[40] phosphonates,[41] trifluoromethylalkenes,[42] and nitroalkenes[43]) have been reported in literature.

As the present thesis incorporates the work done on the reactions of amines with α,β-unsaturated carbonyl compounds, the research work on aza-Michael addition of nitrogen containing nucleophiles with different Michael acceptors reported during the last 10 years has been reviewed below. As the 4th chapter deals with asymmetric Michael addition of chiral benzyl amines, the literature concerning asymmetric aza-Michael additions will be presented there.

In the following review, reactions have been classified on the basis of the nature of the Michael donors.

1.4.1. Addition of amines

1.4.1.1. Aza-Michael addition of amines without the use of a catalyst

1.4.1.2. Aza-Michael addition of amines in the presence of a catalyst

1.4.1.2.1. Metal and metal salts as catalyst

1.4.1.2.2. Organocatalysts

1.4.1.2.3. Ionic liquids as catalysts

1.4.1.2.4. Heterogeneous catalysts

1.4.2. Addition of amides and carbamates

1.4.3. Addition of azides

1.4.4. Addition of hydrazines/hydrazones

1.4.5. Addition of Aromatic aza heterocycles

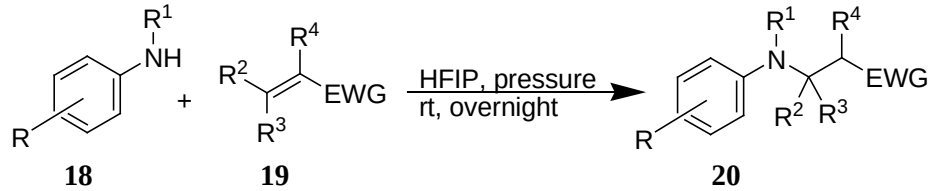
1.4.1. Addition ofamines

As amines can behave both as nucleophiles and bases, additional base is not required during the reaction. The reactions tend to follow second order kinetics as the rate coefficient depends on the concentration of Michael acceptor as well as amine. In some cases, tertiary amines are afforded via the addition of primary

amines to two equivalents of Michael acceptors. However, the second addition can alter the observed kinetics.[44] In spite of this, secondary amines being stronger nucleophiles than the primary amines exhibit greater reactivity in Michael additions. It has been found that the Michael acceptors should have a very active double bond for the reaction with primary and secondary aromatic amines.[45]

1.4.1.1. Aza-Michael addition of amines without the use of a catalyst

Uncatalyzed aza-Michael additions have been carried out under varying conditions of solvents, temperature and pressure. The 1,4-addition of poor nucleophiles such as aromatic amines (i.e. primary and secondary anilines) (**18**) to activated Michael acceptors (**19**) has been reported by Fedatova et al.[46] under hyperbaric conditions (10-15kbar) using different combinations of solvents (**Scheme 1.6**). Under high pressure, using hexafluoroisopropanol (HFIP) as the solvent, the reaction with amines yielded 100% productsin 17 hours. However, while using aprotic solvents, no reaction was observed even at 10 kbar pressure.



18 **19** **20**

R, R^1 = H,H; H,Me; *p*-Cl,H; *p*-Cl,Me; H,Cy
EWG=CO_2Me, CO_2Et, CN

R^2	R^3	R^4
H	H	H
H	H	Cl
H	H	Me
H	Me	H
H	CF3	H
Me	H	H
Me	Me	H

Scheme 1.6. Solvent-promoted Aza-Michael addition of anilines under hyperbaric conditions.

The explanation for the occurrence of reaction under high pressure has been given on the basis of the kinetic effects that are induced by high pressure which in turn is directly related to the negative activated volume $\Delta V^{\pm}$ characterizing the reactions that go through a compact transition state (**Figure 1.2**).[47]

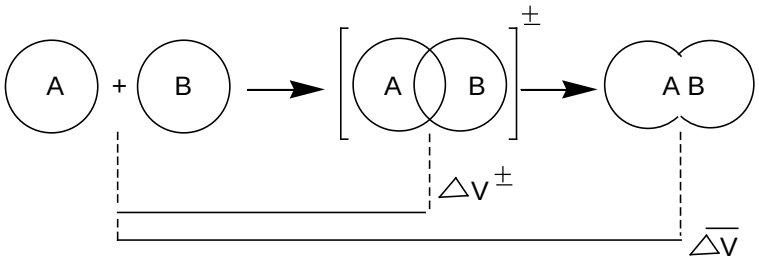
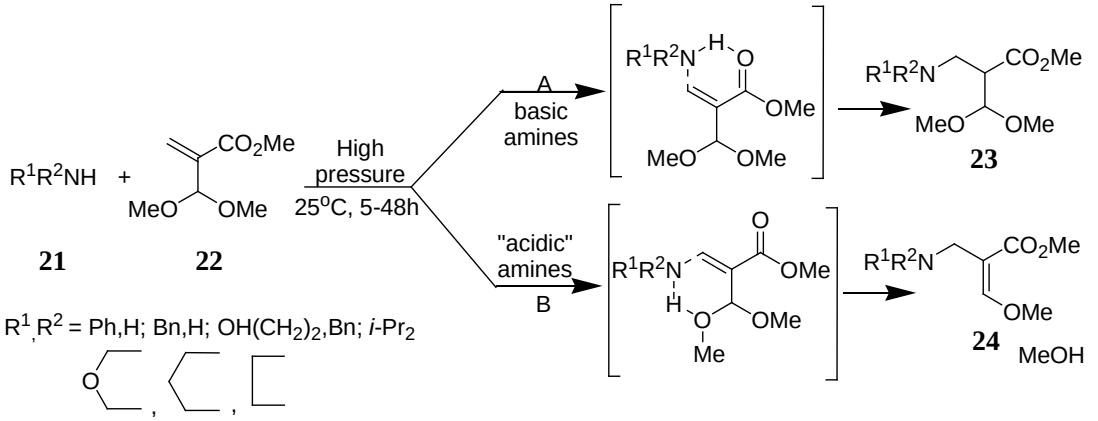


Figure 1.2. Kinetic effect induced by high pressure through a compact transition state.

Analogous studies of the accelerated conjugate addition of nitrogen nucleophiles (primary and secondary amines) (**21**) on to α,β-unsaturated carbonyl compounds specifically, α-methylacrylates (**22**) under high pressure reaction conditions have been reported by Rulev et al.[48] The results indicate that sluggish electrophiles also undergo hetero-Michael addition easily under 15 kbar pressure.

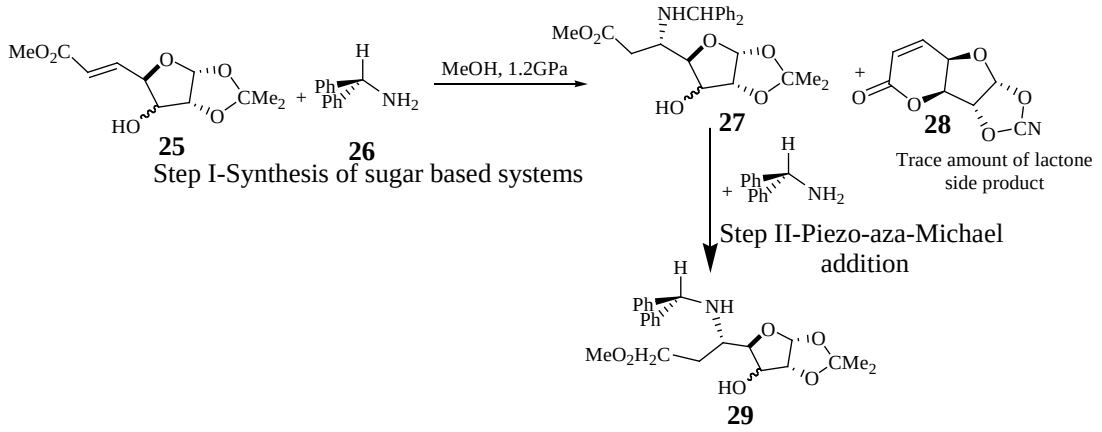
These procedures are eco-friendly and high yielding. Besides, the formation of a simple aza-Michael adduct (**23**), anaddition-elimination product (**24**) featuring aza-Baylis-Hillman type reaction is reported (**Scheme 1.7**).



Scheme 1.7. Aza-Michael addition of amines onto ester in THF.

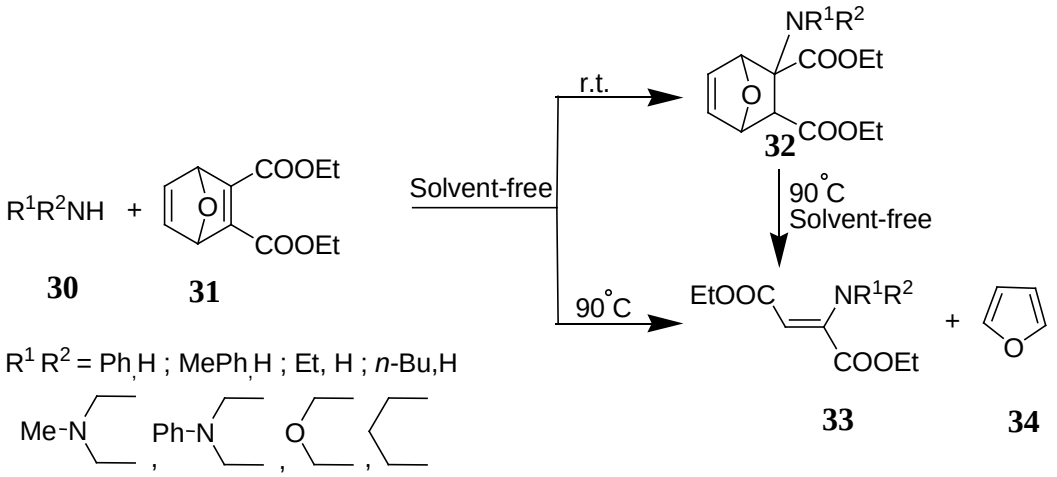
However, the preferential formation of **23** over **24** depends on the structure of amines or acidity of the NH proton. The poorly acidic proton of strongly basic amine interacts selectively with the best Lewis base, i.e. the carbonyl oxygen atom, favouring the formation of **23**. With the decrease in the amine basicity, the acidity of the NH proton increases and the Lewis basicity of the ethereal oxygen atom becomes sufficient to compete with that of the carbonyl oxygen atom, thus the parallel formation of the esters **23** and **24** is observed.

Under high pressure conditions, chiral amines were synthesized in good yields with excellent stereoselectivity from the reaction of unsaturated methyl ester of sugar (**25**) with different amines (**Scheme 1.8**). Asymmetric Piezo-aza-Michael addition is the key step in the transformation.[49]



Scheme 1.8. Aza-Michael addition of diphenylmethanamine.

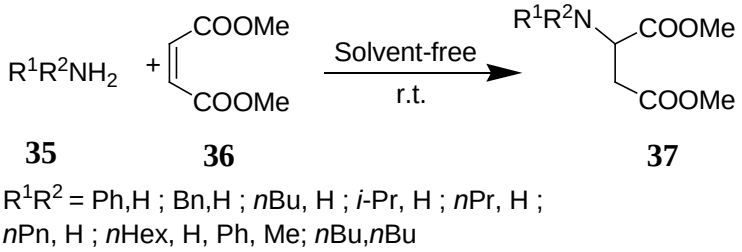
Yang and co-workers developed an eco-friendly protocol to synthesize β-amino carbonyl compounds through solvent free aza-Michael addition reaction of oxanobornene (**31**) with a variety of amines (**30**) (**Scheme 1.9**). The tuning of the reaction temperature yielded two types of β-amino esters, namely oxanorbornene β-amino esters (**32**) and β-enamine esters (**33**).[50]



Scheme 1.9. Synthesis of β-amino carbonyl compounds under solvent free conditions.

The compound **32** was formed at room temperature while compound **33** is a thermodynamic product formed at higher temperature. In fact, **33** resulted from retro-Diels-Alder reaction of **32** at higher temperature.

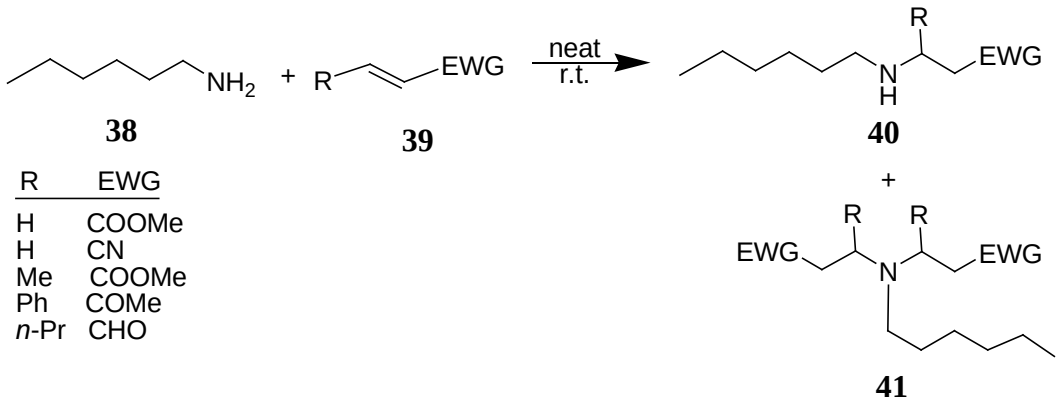
Bosica et al.[51] reported uncatalyzed green aza-Michael addition of aminesto dimethylmaleate (**36**) (**Scheme 1.10**).



Scheme 1.10. Aza-Michael reaction of various amines to dimethyl maleate.

It was shown that catalysts, solvents and heating had no effect on the addition of 1-pentylamine to **36**. The use of DBU, potassium carbonate, alumina, amberlyst resins and ionic liquid [DBU][Ac] did not improve the yield or reaction time when screened as catalysts (**Scheme 1.10**).[51]

In the aforesaid investigation, synthesis of several novel aza-Michael mono- and bis adducts could be accomplished, avoiding hazardous organic solvents and excess of reagents, with 100% atom economy (**Scheme 1.11**).[51]

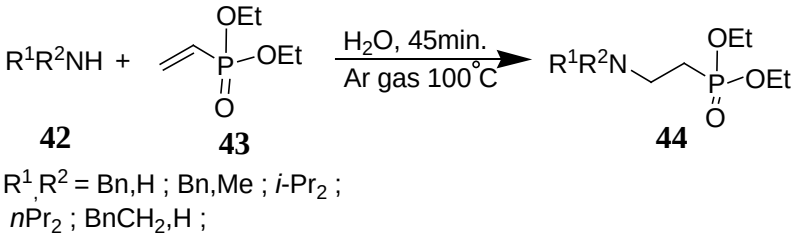


R	EWG
H	COOMe
H	CN
Me	COOMe
Ph	COMe
n-Pr	CHO

Scheme 1.11. Aza-Michael reaction between 1-hexylamine and Michael acceptors.

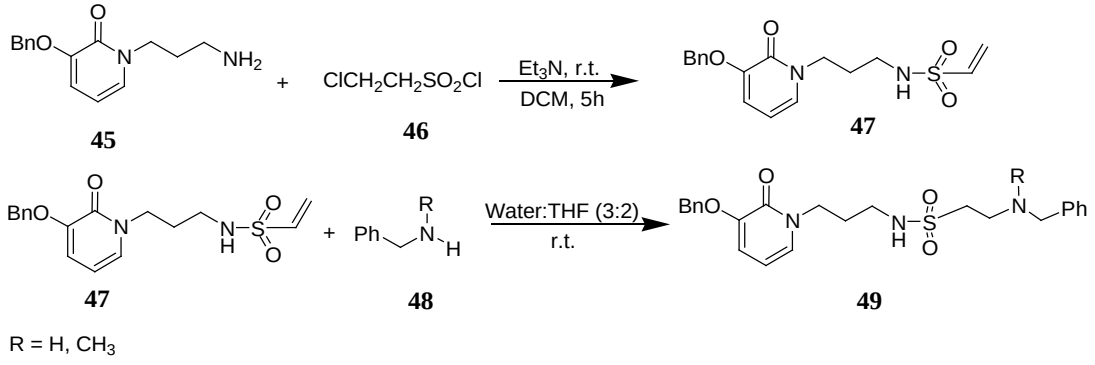
The use of diethylvinylphosphonate **(43)** as a coupling partner in the aza-Michael addition has been reported in literature under a variety of reaction

conditions and with a number of different amines.[52-62] The aromatic amines, which normally do not undergo Michael addition due to weak nucleophilic nature and steric hindrance, react with **43** successfully in the presence of water to afford 2-(arylamino)ethyl phosphonic ester (**44**), the compounds of biological significance (**Scheme 1.12**).[63]



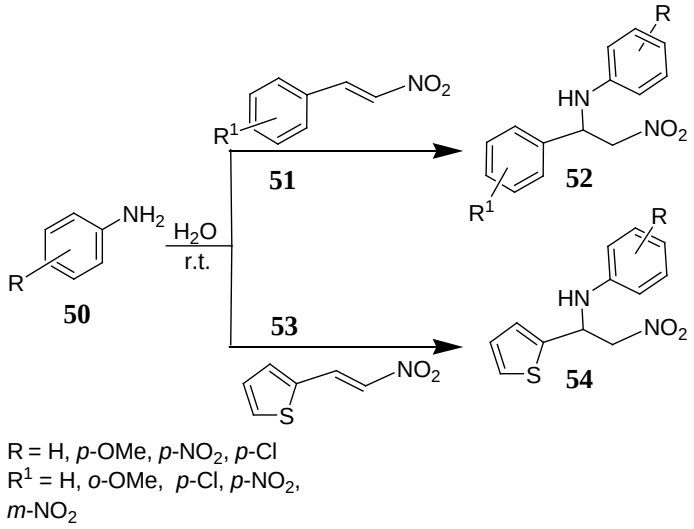
Scheme 1.12. Aza-Michael addition of diethylvinylphosphonate with amines in degassed water.

Analogously, the aza-Michael addition of 3-(3-benzyloxy2-pyridinon-1-yl)propylvinylsulfonamide (**47**) with benzylamine (**48**, R=H) and benzyl methyl amine (**48,** R=Me) were accomplished using a mixture of water and THF as solvent (**Scheme 1.13**).[64]



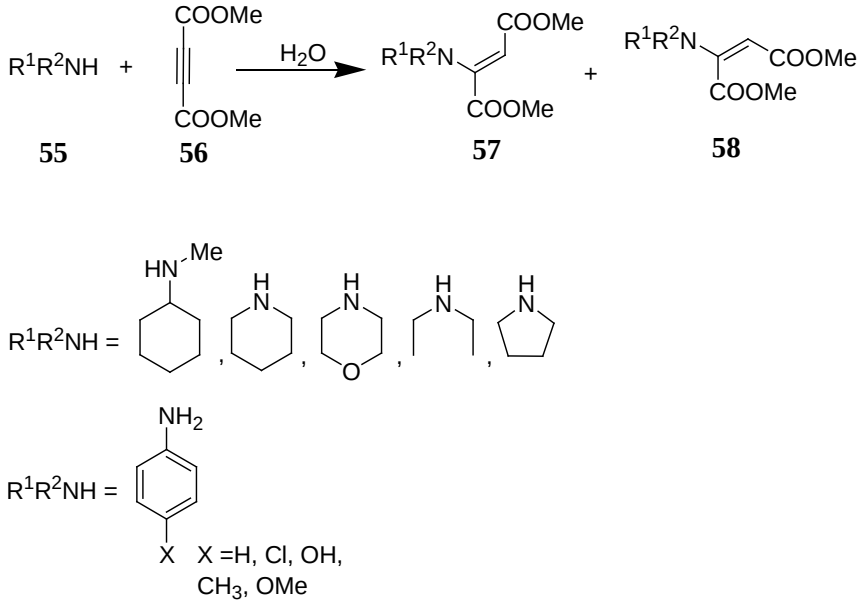
Scheme 1.13. Michael addition of 3-(3-benzyloxy2-pyridinon-1-yl)propylvinylsulfonamide with benzylamines.

Likewise, water was found to be the solvent of choice for the Michael addition of various amines with nitrostyrenes (**51**) and its 2-thienyl analogue (**53**) (**Scheme 1.14**).[65]



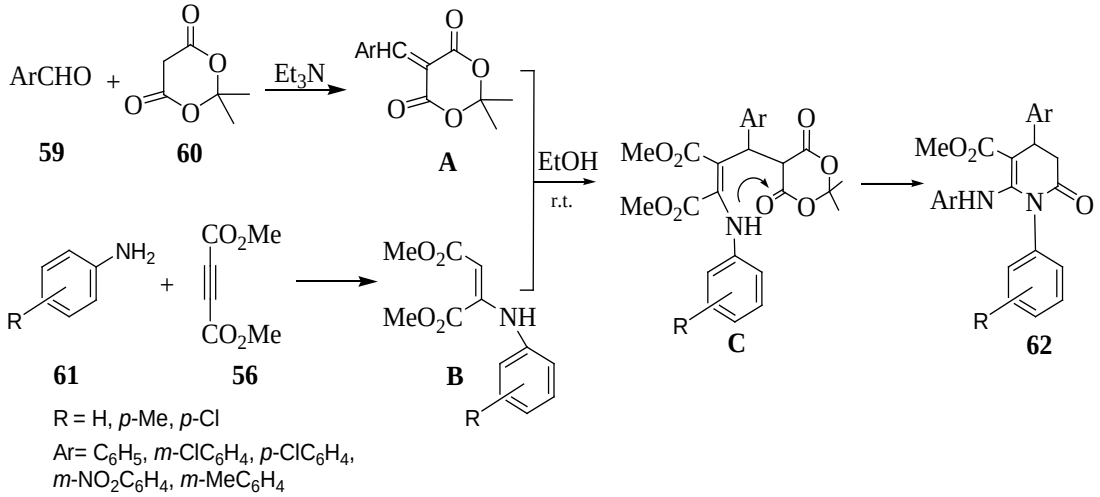
Scheme 1.14. Michael addition of amines with nitroolefins in water.

The aforesaid studies were also carried out using DMAD (**56**) as the Michael acceptor resulting into the formation of the corresponding enamines (**57, 58**) in less than 2 hrs (**Scheme 1.15**).[65]



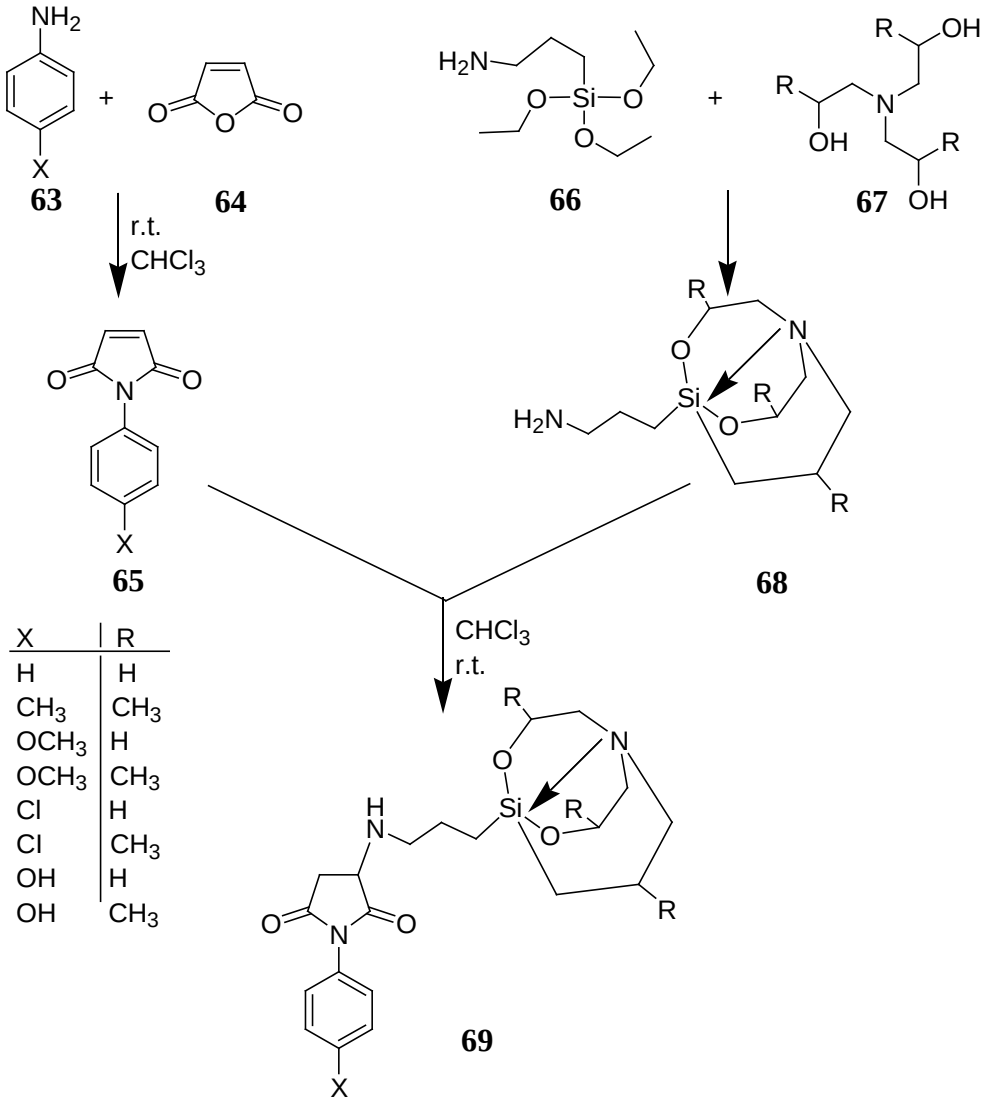
Scheme 1.15. Reaction of aliphatic and aromatic amines with DMAD in water.

In one of the reports, structurally diverse 3,4-dihydropyridine-2-(1*H*)-ones (**62**) and 3,4-dihydro-2*H*-pyrans were obtained via four component reaction of arylamines (**61**), acetylenedicarboxylate (**56**), aromatic aldehydes (**59**) and cyclic 1,3-diketones (**60**).[66] The mechanistic study revealed that the key step involved the Michael-addition of the enamino ester formed in situ from the reaction of aryl amine with DMAD (**56**) to arylidene cyclic 1,3-diketone (**Scheme 1.16**).



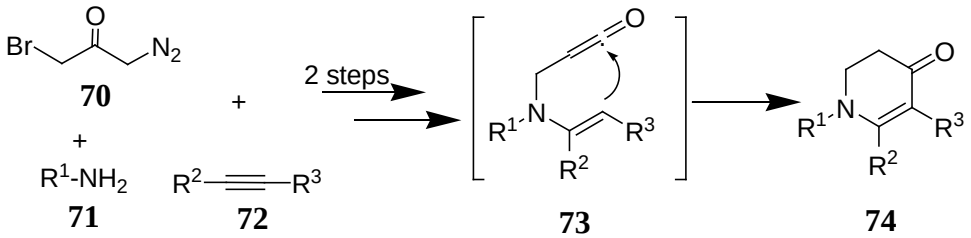
Scheme 1.16. Four component reaction involving Michael addition of arylamines and DMAD.

Literature survey reveals designing of the new receptors for amines in order to synthesize many biologically active molecules.[67,68] One such interesting biomimetic studyinvolved use of N-phenylmaleimide (**65**) a receptor for γ-aminopropylsilatranes via the aza-Michael reaction to synthesize substituted N-phenylsuccinimide possessing silatranes without any catalysts (**Scheme 1.17**). The compounds so obtained (**69**) exhibited modest activity against the tested organisms. In terms of the reaction time and yield, the reaction conditions were optimized for one compound using different solvents and the best yielding solvent was found to be chloroform.[69]



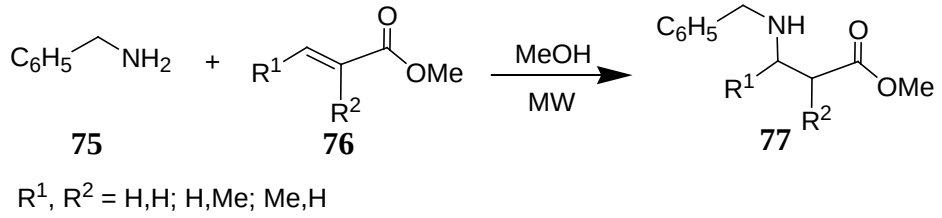
Scheme 1.17. Synthesis of aminosuccinimide substituted silatranes.

One pot synthesis of an enaminone library (**74**) has been reported via sequential occurrence of aza-Michael addition, Wolff rearrangement and nucleophilic ketene cyclazitation (**Scheme 1.18**).[70] The first step involved the synthesis of amino diazoketones from the reaction of bromo diazoacetone (**70**) with primary amine (**71**) in 1,2-dichloroethane. Resulting enaminones are well known for the synthesis of alkaloids.[71]



Scheme 1.18. Synthesis of enaminone library via successive aza-Michael addition, Wolff rearrangement, and ketene cyclization.

Catalysts have been avoided by the use of microwave irradiation in some Michael additions.[72] A series of β-amino esters (**77**) was obtained from 1,4-addition of benzylamine (**75**) and (s)-(-)-α-methylbenzylamine to methyl crotonate, methyl methacrylate, and methyl acrylate (**76**) under microwave irradiation (**Scheme 1.19**).



Scheme 1.19. 1,4-Addition of amines to α,β-unsaturated compounds under microwave irradiation.

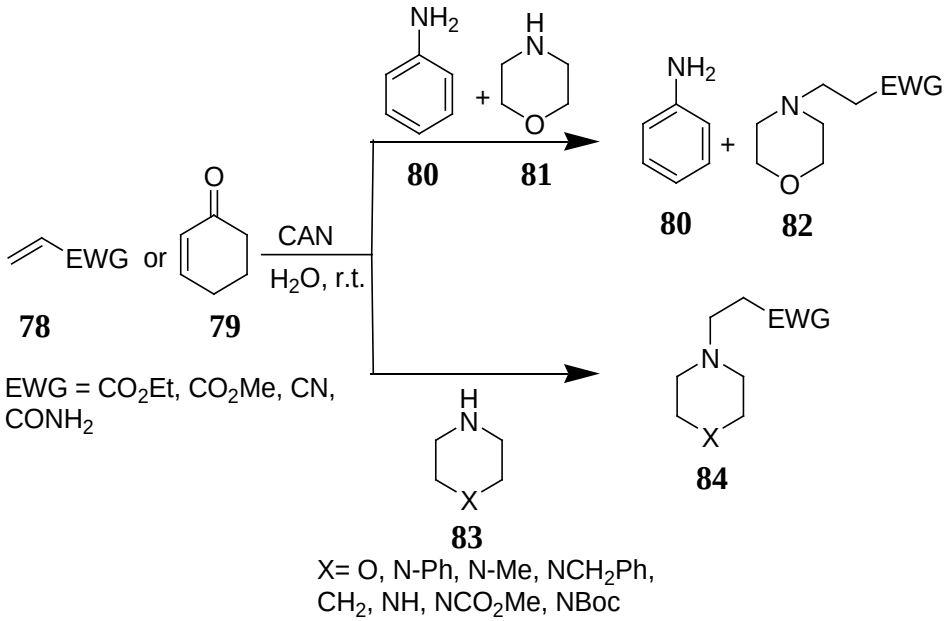
1.4.1.2. Aza-Michael addition of amines in the presence of a catalyst

1.4.1.2.1. Metal and metal salts as catalyst

Though the use of Lewis acid and base catalysts is found predominantly, a good number of alternative procedures include the use of metal catalysts such as $Yb(OTf)_3$, $InCl_3$, $CeCl_3.7H_2O/NaI$, $Bi(NO)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, $FeCl_3.7H_2O/Co(OAc)_2$, $LiClO_4$.[73a-h]

Ceric ammonium nitrate (CAN) is one such reagent, which has emerged as a powerful single electron transfer reagent in many carbon-nitrogen bond forming reactions.[74]

A variety of electronically divergent secondary acyclic amines were made to react with ethylenic compounds (**78, 79**) in the presence of catalytic amount of CAN and water as solvent at ambient temperature to give Michael adducts (**82, 84**) (**Scheme 1.20**).[75] These conditions were standardized in terms of solvent and temperature for efficient product yield.

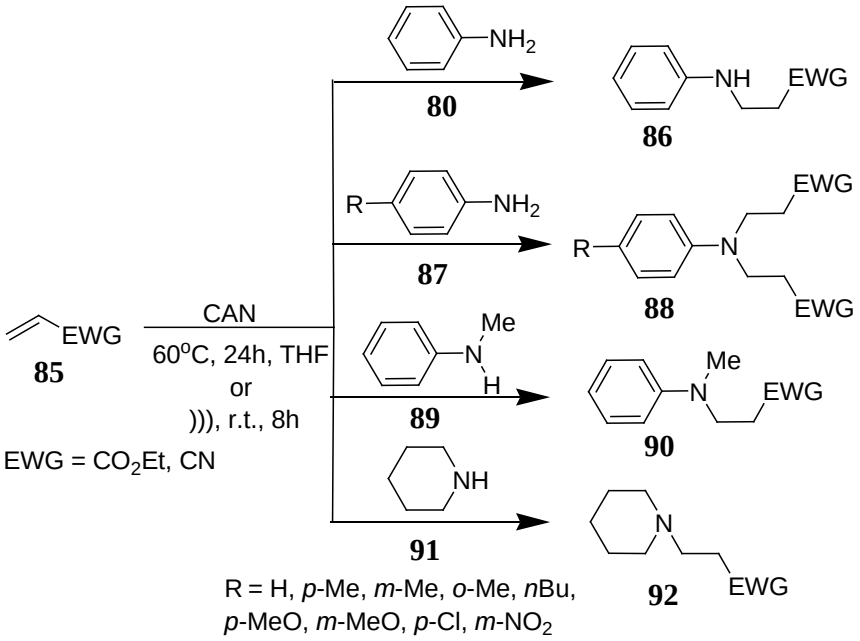


Scheme 1.20. CAN-Catalyzed aza-Michael reaction of amines with ethylenic compounds.

It can be noted here that the secondary amines reacted very well under these conditions to furnish Michael adducts while the primary amines remained unchanged.[75]

In the same year, an intermolecular aza-Michael addition of primary and secondary amines with α,β-unsaturated carbonyl compounds using CAN as a catalyst and varying conditions of temperature and solvent was reported by Z. Duan et al.[76] (**Scheme 1.21**).

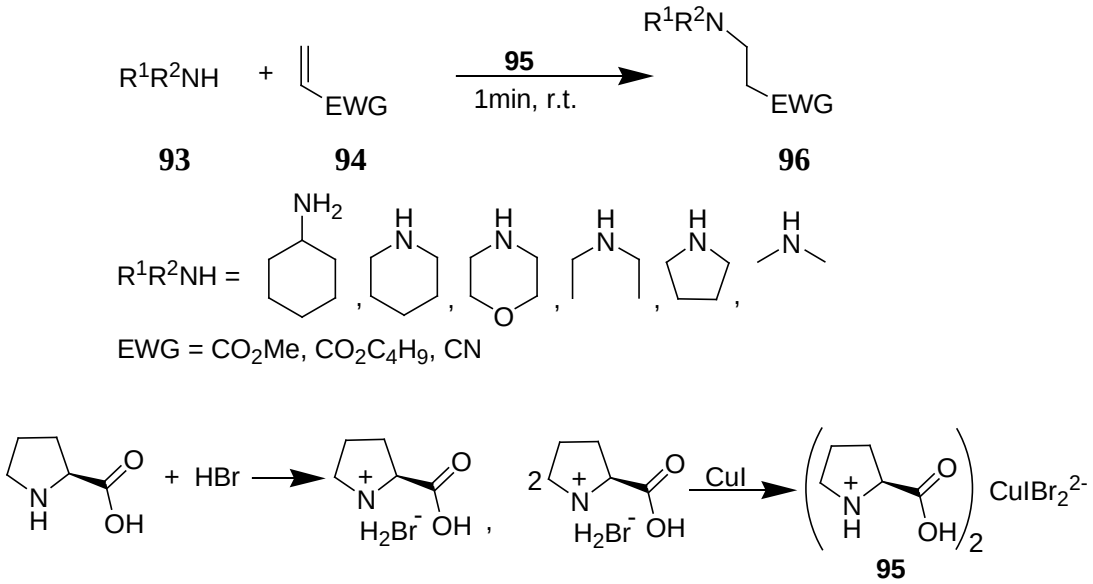
It is reported that the reaction yielded good results for primary aromatic amines in different solvents like THF, EtOH and CH_3CN at 60˚C. However, it failed in case of secondary aromatic amines, which was further attempted under ultrasound irradiation in the absence of any solvent when the desired product was obtained in good yield. Subsequently, all reactions were carried out under ultrasonication and the results were compared. In most of the cases, mono adducts were formed (**86, 90, 92**), while in some of the reactions with primary amines, formation of bis-alkylation (**88**) has been reported.



Scheme 1.21. CAN-catalyzed aza-Michael reaction of aromatic and alicyclic amines.

The use of Cu salts as catalysts is also reported in literature owing to its ease of handling, environmentally benign nature, low cost and mild reaction conditions required in its presence.

A proline cuprous iodide complex catalyst (**95**) containing Lewis acid and a BrØnsted acid sites was used for the aza-Michael addition of amines (**Scheme 1.22**).[77]

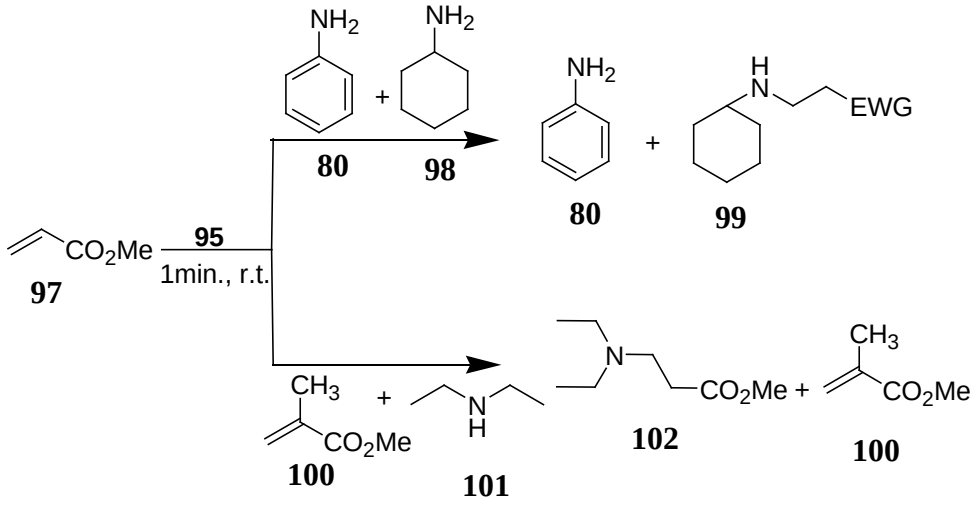


Synthesis of proline cuprous iodide complex catalyst

Scheme 1.22. Proline cuprous iodide complex catalysed aza-Michael addition of amines.

The catalyst functions selectively and transforms only aliphatic amines and not aromatic amines (**Scheme 1.23**). With regard to the alkene, the reactivity is affected by the electron withdrawing group and the steric hindrance around the double bond. The primary amines undergo single substitution reaction (**99**) as the reaction conditions are mild and not sufficient enough to cause double substitution. The multi substitution could only be achieved when more alkene and high

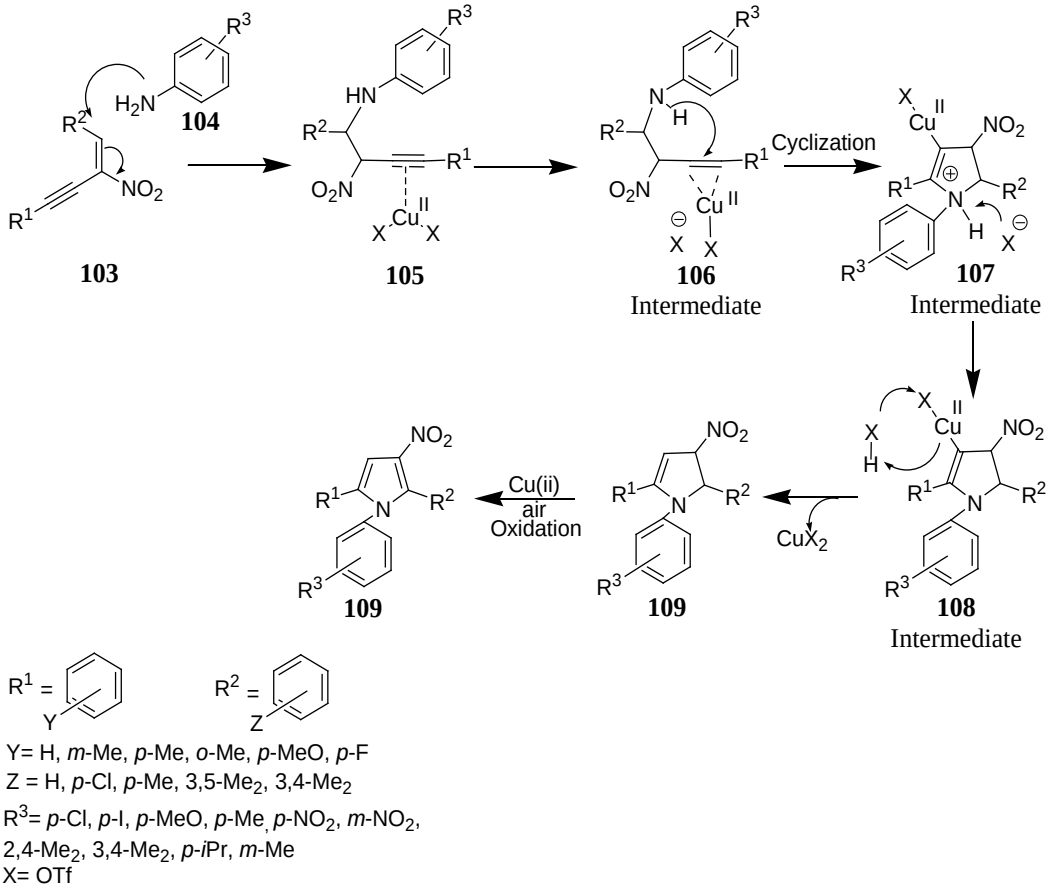
temperature (80°C) were applied; however, aromatic amines (**80**) could not be transformed to the corresponding products under these reaction conditions.[77]



Scheme 1.23. Selectivity of proline cuprous iodide complex catalyst.

Some of the salts of copper, such as CuCl, CuBr, CuI, $Cu(OAc)_2$ and $Cu(OTf)_2$ have been used for expedient synthesis of tetra-substituted pyrroles and pyrazoles. The reaction occurs via cascade aza-Michael addition, cyclization and aromatization at room temperature.[78]

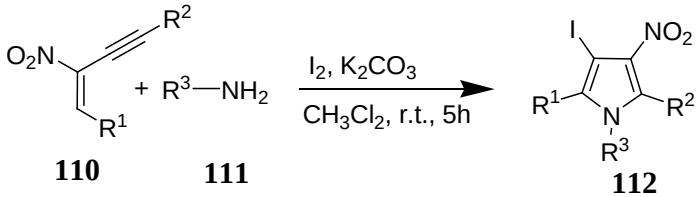
On screening a variety of copper catalysts, $Cu(OTf)_2$ exhibited superior results. In terms of the solvents, THF was found to give better yields. The use of $Cu(OTf)_2$ as a Lewis acid catalyst activates the alkene by increasing its electrophilicity and brings about easy transformation. A plausible mechanism for the formation of pyrroles (**109**) given by the investigators is shown below (**Scheme 1.24**).[78]



103 **104** **105** **106** **107** **108** **109** **109**

Scheme 1.24. Mechanism for the formation of pyrroles.

Later, molecular iodine was used as a catalyst for the reaction of 1,3-enyns (**110**) with amines (**111**) to obtain pyrroles (**112**) via a sequential tandem aza-Michael addition, iodocyclization, and oxidative aromatization (**Scheme 1.25**).[79]

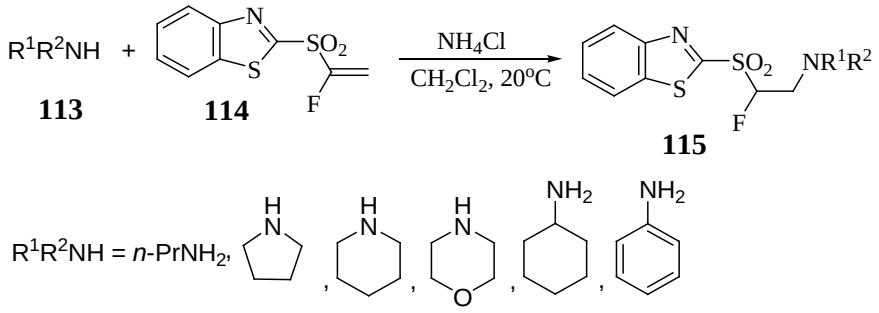


110 **111** **112**

R^1 = C_6H_5, *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-FC_6H_4
R^2 = C_6H_5, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-ClC_6H_4, 3,5-$Me_2C_6H_3$, 3,4-$Me_2C_6H_3$
R^3 = *o*-BrC_6H_5, *o*-ClC_6H_5, *p*-$NO_2C_6H_4$, *p*-MeC_6H_5, *p*-CF_3, 2,5-$Me_2C_6H_3$, Bn, *i*Pr, *n*-Bu

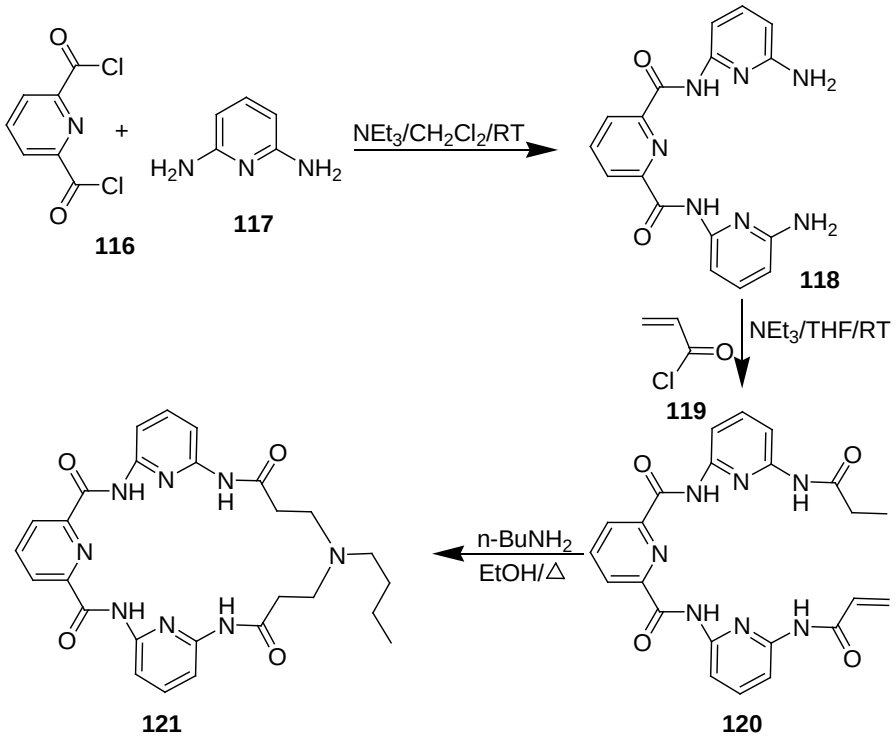
Scheme 1.25. Iodine-mediated electrophilic cyclization of various 1,3-enynes with amines.

Various vinyl sulfones (**114**) were prepared and reacted with different amines (**113**) to yield amino sulfones (**115**). All reactions were carried out in the presence of a base and dichloromethane as solvent (**Scheme 1.26**).[80]



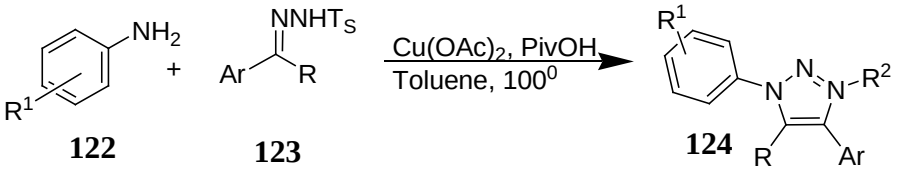
Scheme 1.26. Michael addition of primary or secondary amines to α-fluorovinylsulfones.

The 22 ring atom macromolecule ligand (**121**) has been synthesized via double aza-Michael addition of n-butyl amine (**117**) with 2-acrylamide groups (**116**) (**Scheme 1.27**).[81]



Scheme 1.27. Synthesis of macrocycles.

Chen et al.[82] reported the occurrence of copper mediated ($Cu(OAc)_2$) Michael addition, between anilines (**122**) and *N*-tosylhydrazone substrates (**123**) in the presence of pivalic acid (PivOH) to afford 1,4-disubstituted and 1,4,5-trisubstituted triazoles (**124**) (**Scheme 1.28**).

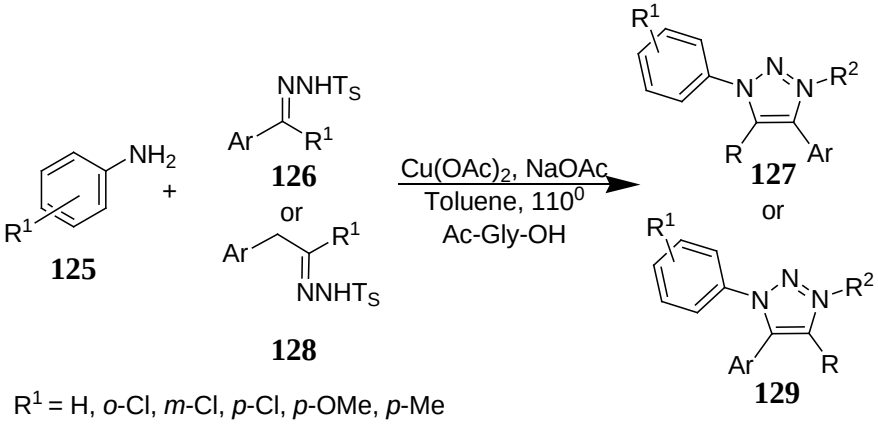


122 **123** **124**

R^1 = H, *o*-Cl, *m*-Cl, *p*-Cl, *p*-OMe, *p*-Me

Scheme 1.28. Cu catalyzed synthesis of triazoles from *N*-tosylhydrazones.

In order to overcome the limitation of the above reaction in terms of its application to only aromatic amines, the same research group further extended their work using the same catalyst but changing the reaction conditions from acid to a base system (**Scheme 1.29**). A variety of copper salts and bases were tested for best and improved results.[83]



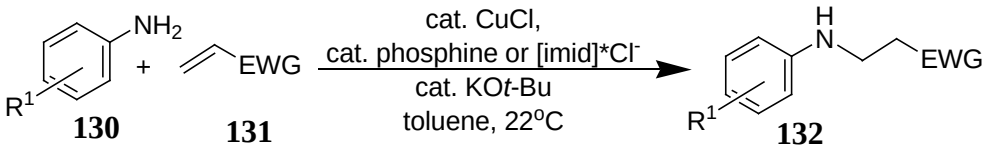
125 **126** **128** **127** **129**

R^1 = H, *o*-Cl, *m*-Cl, *p*-Cl, *p*-OMe, *p*-Me

Scheme 1.29. Synthesis of triazoles from *N*-tosylhydrazones.

Further, a variety of amino acids were also screened for their use as catalysts. In this case overall, the transformation exhibited high regioselectivity and good functional group tolerance.[83]

The nucleophilicity of aromatic amines (**130**) or aza heterocycles has been enhanced by the use of complexed Cu salts (complexed with an electron donating phosphine or NHC-based ligand). The catalytic Michael addition enabled the synthesis of a broad range of new β-amino sulfone, β-amino nitrile and β-amino carbonyl compounds including aniline, indole, carbazole, pyrrole, imidazole, pyrazole, and triazole derivatives in high yields (**Scheme 1.30**).[84]

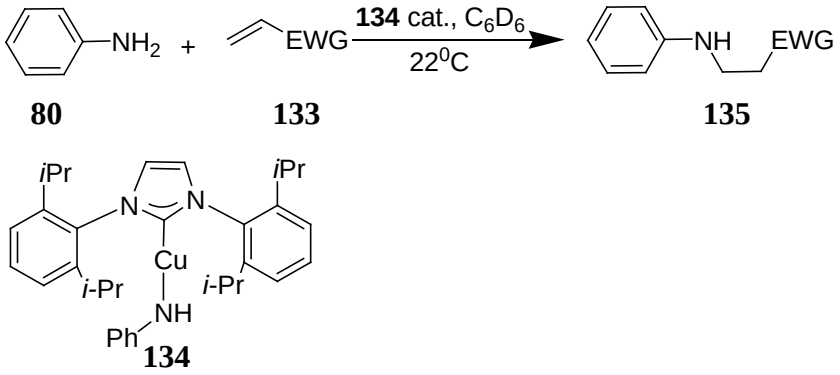


130 **131** **132**

R^1 = H, *o*-Me, *p*-Br, *p*-MeO, *p*-F, *p*-CF_3, *o*-Cl, *o*-OMe, *o*-COOMe, 3,5-Me_2, 3,4-Me_2
EWG= CN, CO_2Me, COEt, SO_2Ph

Scheme 1.30. Cu-catalyzed aza-Michael addition of aromatic amines.

This study was an attempt to overcome the limitations of earlier work reported by Gunnoe and coworkers (**Scheme 1.31**). [85]



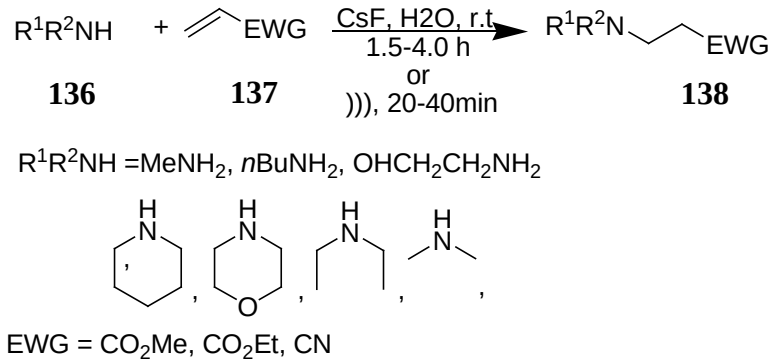
80 **133** **135**

134

Scheme 1.31. Cu-catalyzed aza-Michael addition of aromatic amines.

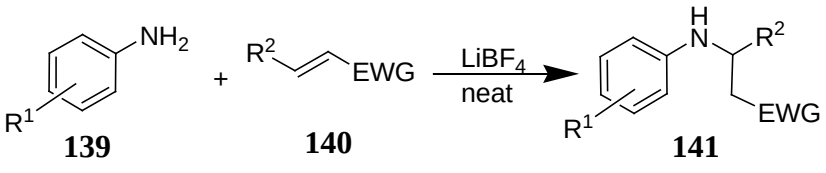
As an attempt to develop better synthetic protocol for the aza-Michael reaction in terms of operational simplicity, economic viability, etc., the use of cesium fluoride (CsF) as a catalyst in aqueous media at ambient temperature and

using non-conventional energy source i.e. ultrasound irradiation is reported in literature.[86] The reactions were also investigated by the conventional method and the results compared (**Scheme 1.32**). The use of ultrasonication requires milder reaction condition and lower reaction time. The reaction mechanism enumerates the enhancement of nucleophilicity of amine, eventually accelerating the rate of reaction enormously.



Scheme 1.32. CsF catalyzed aza-Michael addition.

For the first time, use of lithium tetrafluoroborate ($LiBF_4$) for the inter (**Scheme 1.33**) and intra-molecular (**Scheme 1.34**) aza-Michael addition was reported by Lad et al.[87]

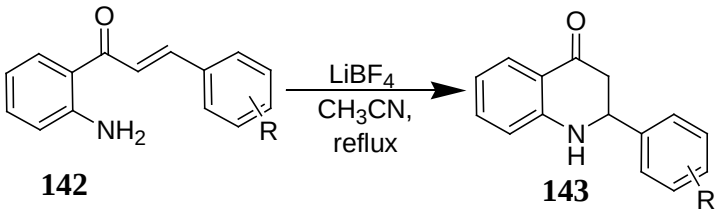


R^1 = Me, OMe, Br, NO_2

R^2	EWG
H	COMe
Me	COEt
Ph	COPh
H	COOMe
Me	COOMe
H	CN
H	$CONH_2$

Scheme 1.33. Lithium tetrafluoroborate catalyzed intermolecular Aza-Michael addition.

$LiBF_4$ is a well-known mild Lewis acid catalyst, available commercially and unlike lithium perchlorate, it is non-explosive, non-oxidizing as well as a non-nucleophilic agent. It acts as a slow release source of boron-trifluoride and provides a convenient route to effect organic transformations under neutral conditions. In this study, a variety of substituted anilines (**139**) were reacted with methyl methacrylate, acrylonitrile, and acryloamine (**140**) in solvent free conditions in the presence of $LiBF_4$. The intramolecular addition was explored using amino chalcone (**142**) as a model substrate.[87]

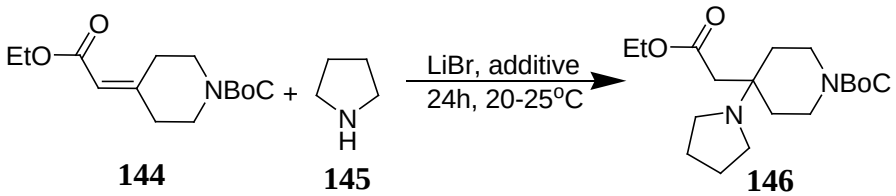


142 **143**

R = H, *p*-OMe, *p*-Me, *p*-*i*Pr, *p*-Cl
m-NO_2, 2,5-Me_2, 4,5-OMe

Scheme 1.34. Lithium tetrafluoroborate catalyzed intramolecular aza-Michael addition.

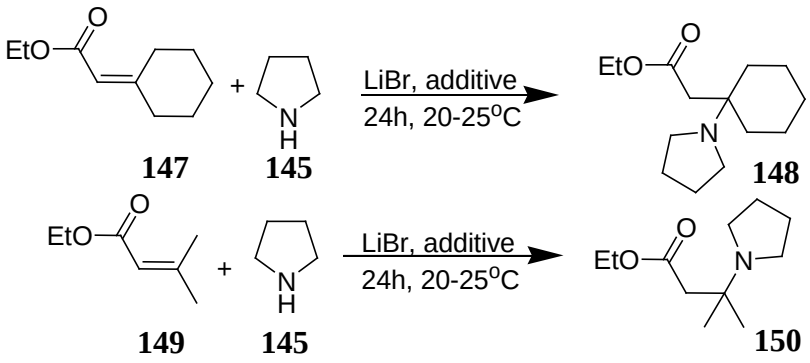
The aza-Michael addition of β,β-dialkylated unsaturated ester (**144**) and pyrrolidine (**145**) in the presence of a variety of lithium salts has been reported.[88] The selection of lithium salt was done after screening about 38 metal salt additives. Lithium bromide (LiBr) gives effective results, in fact as effective as lithium perchlorate (**Scheme 1.35**).



144 **145** **146**

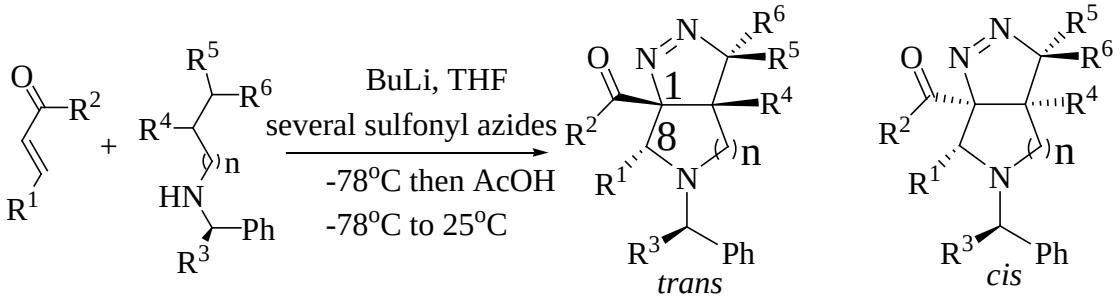
Scheme 1.35. LiBr catalyzed aza-Michael addition.

The substrate generality of the reaction was also investigated using cycloalkylidenic ester (**147**) and β,β-dialkylated ester (**149**). The compound (**147**) gave poor yield due to the generation of by products (**Scheme 1.36**).[88]



Scheme 1.36. LiBr catalyzed aza-Michael addition reaction of pyrrolidine.

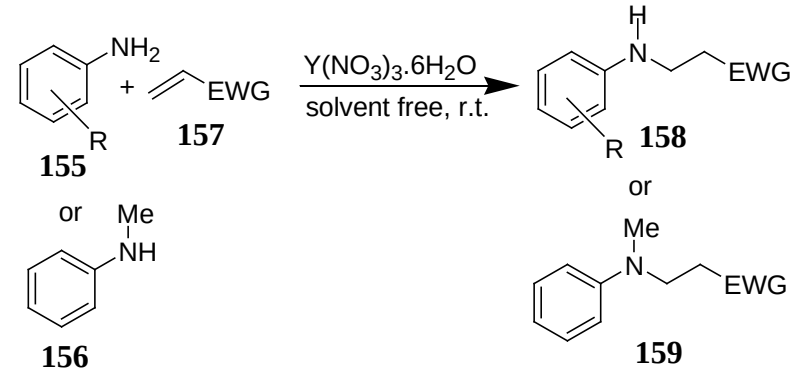
The use of lithium catalysts in a combination of asymmetric Domino aza-Michael addition and [3+2] cycloaddition reaction for the generation of α,β,γ-triamino acid derivatives (**153, 154**) was reported (**Scheme 1.37**).[89]



R_1	Me	Me	Ph	Me	Me	Me	Me	Me	Ph	Me	Me
R_2	OtBu	OMe	OtBu	OMe	OtBu	OtBu	OtBu	OtBu	OtBu	NMe_2	OtBu
R_3	H	H	H	Me	Me	Me	Me	H	Me	Me	Me
R_4	H	H	H	H	Me	H	H	H	H	H	H
R_5	H	H	H	H	H	Me	H	Me	H	H	H
R_6	H	H	H	H	H	H	Me	Me	H		H

Scheme 1.37. Michael addition of α-alkylbenzylamines to α,β-unsaturated ester and amide.

The coordinating ability of yttrium nitrate along with its commercial availability motivated Bhanushali et al.[90] to further investigate its activity for aza-Michael reaction. The weakly nucleophilic amines like substituted anilines (**155**) reacted with α,β-unsaturated compounds such as butyl acrylate, acrylonitrile and acrylamide (**157**) effectively in the presence of this catalyst under solvent free conditions (**Scheme 1.38**).



R = H, *p*-Me, *m*-Me, *o*-Me, *n*Bu,
p-OMe, *m*-MeO, *p*-Cl, *m*-CF_3,*m*-Br, *o*-NH_2
EWG=CO_2Me, CN, CO_2Bu, $CONH_2$

Scheme 1.38. Aza-Michael addition of aromatic amines using $Y(NO_3)_3.6H_2O$ as catalyst under solvent free conditions.

The catalytic application and the efficacy of palladacycle (**Figure 1.2**) in a tandem Heck-intramolecular aza-Michael reaction sequence for one pot synthesis of isoindolines, incorporating an ester substituent at the 1-position (**166**) was investigated (**Scheme 1.39**). The protocol afforded a wide range of isoindolines which were hitherto not possible.[91]

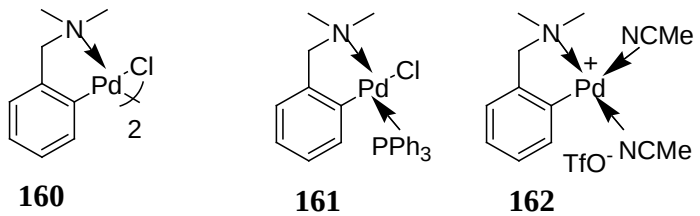
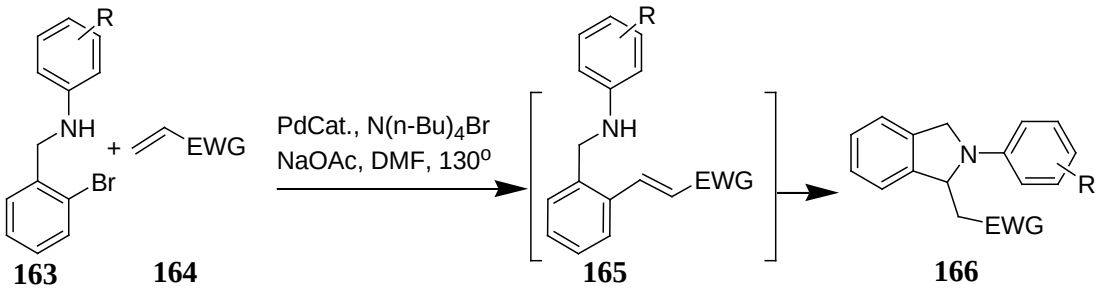


Figure 1.2. Structure of Palladacycles.

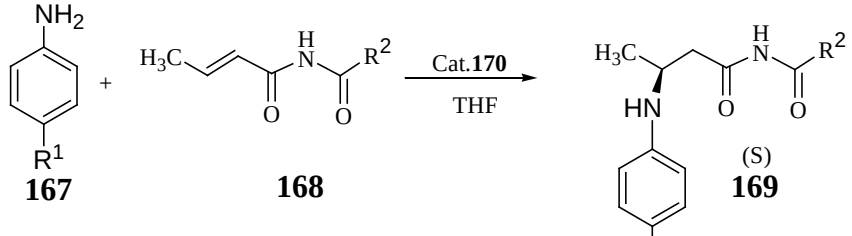


163 **164** **165** **166**

R = *p*-Me, H, *p*-OMe, *m*-Me,
m-OMe, *p*-OPh, *p*-CN, *p*-NO_2
EWG=CO_2Me, CO_2Et, CO_2Bu,
CO_2Bu^t, $CONMe_2$

Scheme 1.39. Palladacycle-catalsed one-pot tandem Heck-intramolecular aza-Michael reaction.

A new reaction protocol, affording a significant enhancement in reaction yield and enantioselectivity was developed by Phou et al.[92] wherein the reaction was carried out in the presence of a palladium catalyst (**Scheme 1.40**).

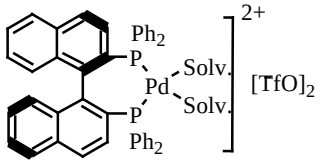


167 **168** **169**

R^1 = OMe, H, Cl
R^2 = Ph, OMe

Scheme 1.40. Aza-Michael addition of aniline to α,β-unsaturated-*N*-imide.

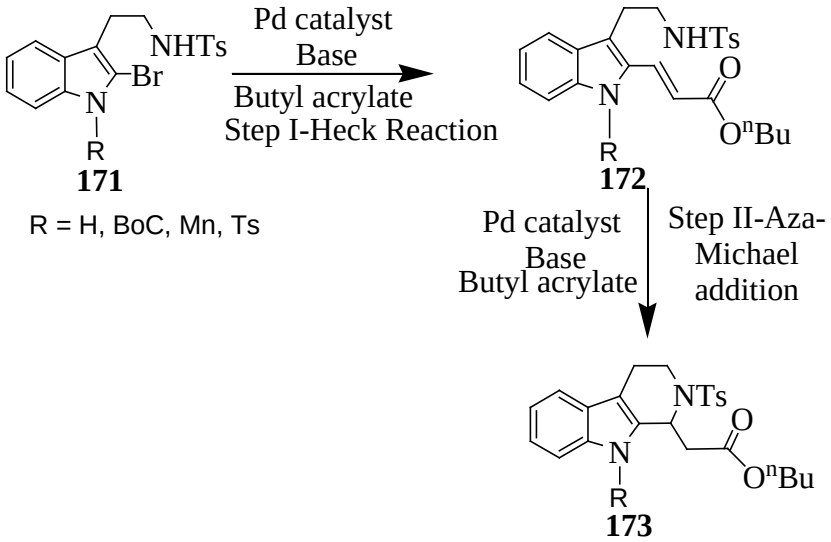
In this reaction a number of cationic palladium catalysts were screened and eventually one containing diphosphine ligands (**170**) furnished improved yields and highest enantioselectivities. The results also varied with the change in the mole percent of **170** (**Figure 1.3**).[92]



170

Figure 1.3. Palladium catalyst.

Another simple and efficient palladium-catalyzed Domino process involving Heck reaction at the indole-2-position of a halogenated tryptamine precursor (**171**), followed by intramolecular aza-Michael addition was reported for the synthesis of a series of tetrahydro-β-carbolines (**173**) (**Scheme 1.41**). The reaction conditions were optimized in terms of the palladium catalyst, base and the solvent and the best results were found when $Pd(PPh_3)_4$ was used.[93]



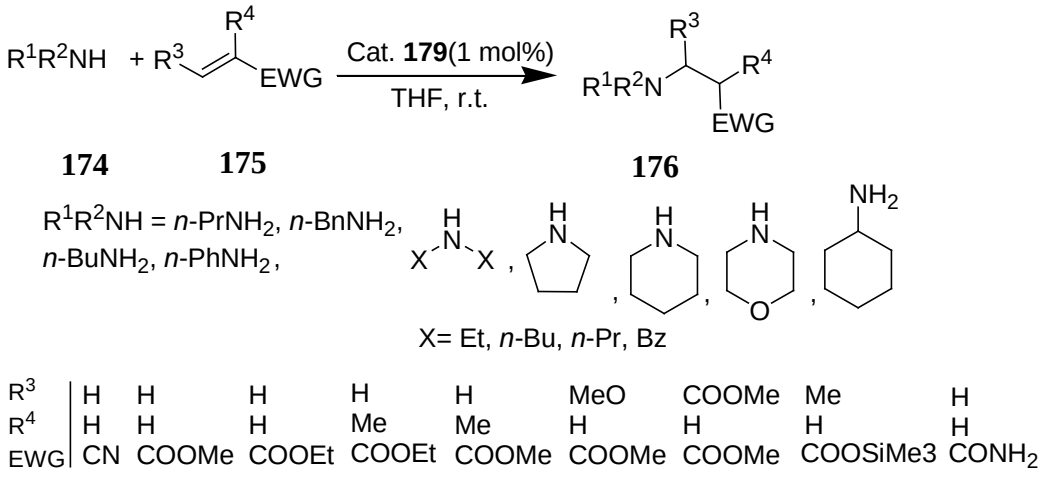
Scheme 1.41. Intramolecular aza-Michael addition of 2-(2-bromoindol-3yl)ethyl aminederivative.

1.4.1.2.2. Organocatalysts

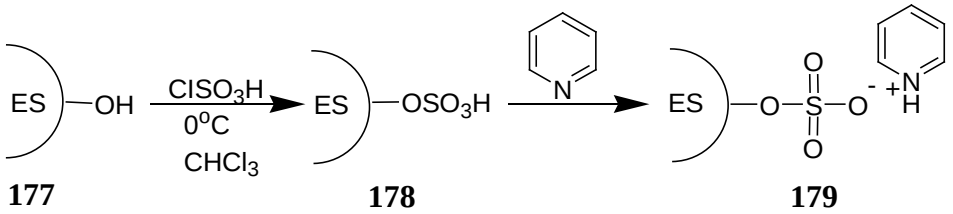
Organic catalysis, involving the use of small organic molecules has evolved as an innovative synthetic approach towards developing greener and environmental

friendly chemical synthesis protocols. Their easy availability, greater stability to air and water, less toxic nature, facile recovery after use and easy handling approach make them catalysts of choice in various C-N forming reactions. Further advantage due to which it is gaining ever increasing interest in the current years is that these catalysts can promote an organic reaction by several activation modes.

Verma and co workers[94] synthesized about 27 β-amino carbonyls (**176**) from the reaction of amines (**174**) with electron deficient alkenes (**175**) (**Scheme 1.42**). The reaction yields were excellent within 20-25 mins. The catalyst is reported to act via dual activation (**Figure 1.4**). A remarkable enhancement in the reaction rate was observed on using the bifunctional organocatalyst (**179**) in comparison to starch grafted sulfonic acid and the corresponding homogeneous pyridinium *p*-toluenesulfonate.



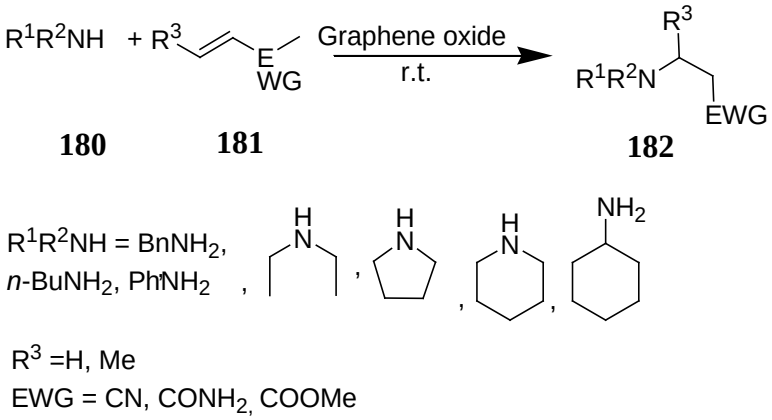
Scheme 1.42. Use of organocatalyst in aza-Michael addition.



177 **178** **179**

Figure 1.4. Preparation of catalyst.

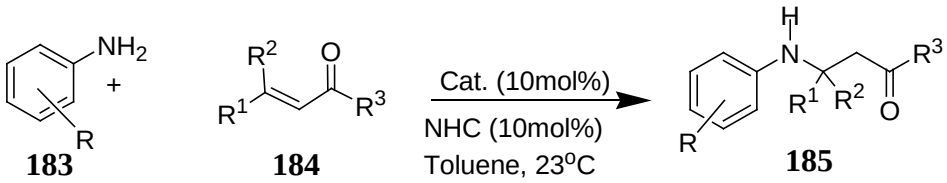
The same research group[95] developed graphene oxide as an efficient organocatalyst for the aza-Michael addition of amines (**180**) to activated alkenes (**181**) to furnish various β-amino compounds (**182**) (**Scheme 1.43**).



180 **181** **182**

Scheme 1.43. Graphene oxide catalyzed aza-Michael addition.

Recently, N-heterocyclic carbenes (NHC) have emerged as powerful organocatalysts for C-N bond formation. Catalyst optimization using different imidazolium and imidazolinium salts indicated that sterically more demanding imidazolium salt provided best results in terms of yield. Further, other reaction conditions were also optimized with respect to the base, solvent and temperature. Both aromatic and aliphatic amines yielded β-amino ketones (**185**) with up to 98% yield (**Scheme 1.44**).[96]

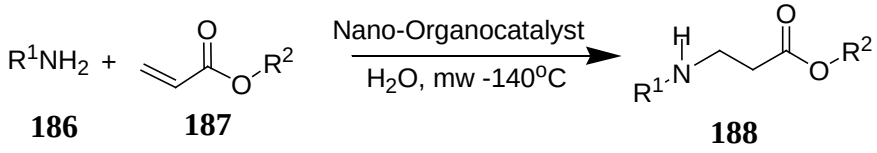


R = H, Ph, *p*-OMe, *p*-Cl, 3,5-$(Me)_2$

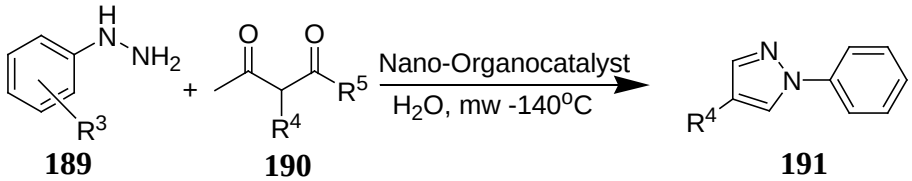
R^1	R^2	R^3
H	H	Me
H	H	C_6H_5
H	Me	OBn
Me	Me	C_6H_5
H	C_6H_5	C_6H_5
H	COOEt	C_6H_5
H	$CH_3(CH_2)_3$	Et
H	$CH_3(CH_2)_3$	C_6H_5

Scheme 1.44. N-Heterocyclic carbene catalyzed aza-Michael addition.

Nano organocatalyst, synthesized using glutathione, has been effectively used with high selectivity in the microwave assisted aza-Michael reaction of various amines (**186, 189**) with methyl and butyl acrylate (**187, 190**) in aqueous media (**Scheme 1.45**).[97]



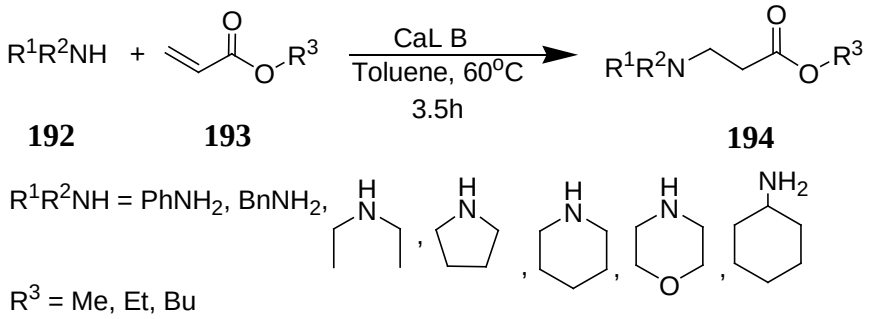
R^1 = Ph, Bn, Cy, 4-ClC_6H_4
R^2 = Me, *n*-Bu



R^3 = H, 4-Cl
R^4 =H, Et, Cl
R^5 =Me, OEt

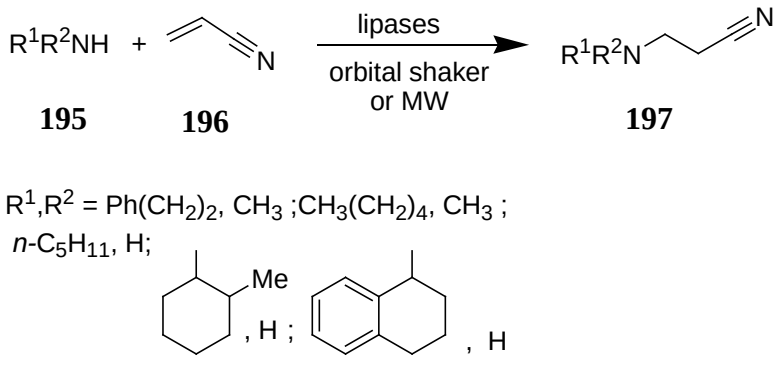
Scheme 1.45. Nano-organocatalyst promoted aza-Michael addition.

The enzymelipase has been used for the catalyzed aza-Michael addition. In one of the studies, an efficient enzymatic protocol using, *Candida Antarctica* lipase B as a biocatalyst was developed to generate β-amino esters (**194**) via aza-Michael addition of the primary and secondary amines (**192**) to acrylates (**193**) (**Scheme 1.46**).[98]



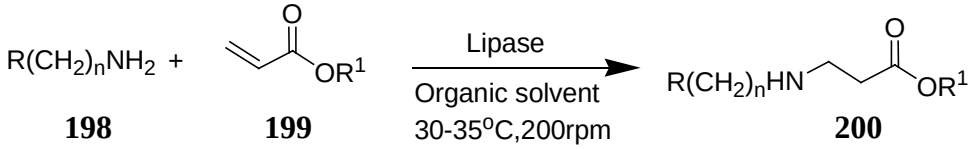
Scheme 1.46. Lipase catalyzed aza-Michael addition of amines to acrylates.

The same biocatalyst was employed to synthesize propanenitrile derivatives (**197**) under microwave irradiation, using water as a protic solvent and hexane as an aprotic solvent. The results reveal that microwave irradiation yields the desired products in shorter duration in comparison to the conventional orbital shaking method (**Scheme 1.47**). [99]



Scheme 1.47. Aza-Michael addition of amines and acrylonitrile under orbital shaking and MW irradiation.

Likewise, *Rhizomucor miehei* lipase was used to catalyze aza-Michael addition. It enhanced high selectivities and high substrate specificity. Mono adducts (**200**) were produced in high yields. On using diamines (**198**), the reaction led to only one monoadduct (**Scheme 1.48**).[100]

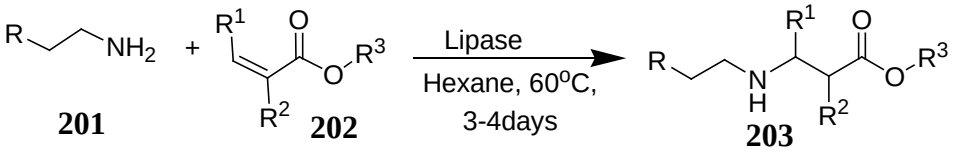


198 **199** **200**

n = 2-12
R = Ph, NH_2, OH
R^1 = Et, C_5H_{11}, *n*-Bu, *n*-Pr, $HO(CH_2)_2$, $Ph(CH_2)_2$

Scheme 1.48. Lipase catalyzed synthesis of *N*-substituted β-amino esters.

Recently, a number of lipases were screened for chemoselective aza-Michael addition by Steunenberg et al.[101] It is reported that *Pseudomonas stutzeri* lipase and *Chromobacterium viscosum* lipase showed the highest selectivity for the aza-Michael addition to substituted alkyl acrylates (**203**) (**Scheme 1.49**). The selective Michael addition of diamines (**201**) to these substituted acrylates (**202**) was also achieved.



201 **202** **203**

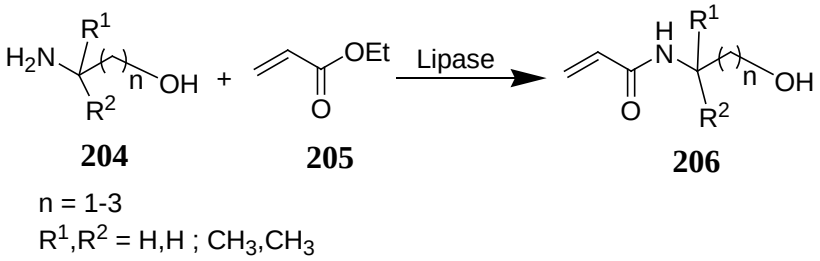
R = OH, NH_2

R^1	R^2	R^3
Me	H	Et
H	Me	Me
Me	H	Et

Scheme 1.49. Lipase catalyzed aza-Michael addition of amines to acrylates.

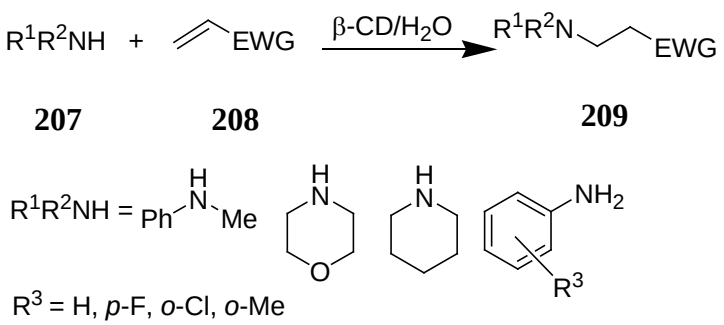
Another use of lipase in catalytic transformation has been reported for the enzymatic preparation of *N*-hydroxyalkylacrylamides (**206**). This procedure

provides a simple and mild alternative method for the synthesis of substituted acrylamides from linear alkanolamines (**204**) of variable chain length and also branched ones. The most interesting products are N-(2-hydroxxyethyl)-acrylamide (HEA), the monomer used in the synthesis of polymeric matrices with application in capillary electrophoresis and *N*-(2-amino-2-methyl-1-propyl)acrylamide, precursor of 2-acrylamido-2-methylpropansulfonic acid (AMPS). Following a biocatalytic approach, all the products were obtained in high yields and purity under environmentally friendly reaction conditions (**Scheme 1.50**).[102]



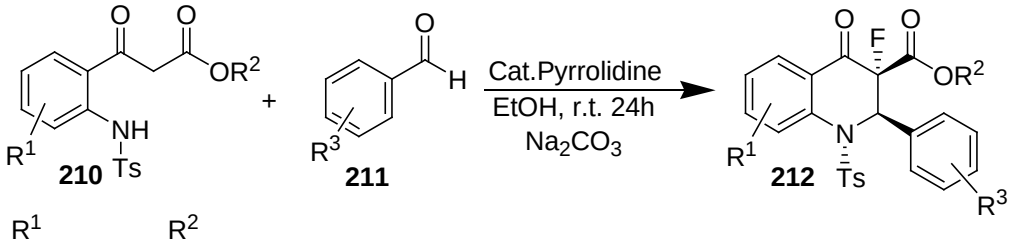
Scheme 1.50. Enzyme catalyzed synthesis of acrylamides via aza-Michael addition.

Supra molecular catalysis involving use of cyclodextrin as calatysts for aza-Michael addition is also reported. The reaction of primary and secondary aliphatic and aromatic amines (**207**) with α,β-unsaturated ketones, esters, and nitriles (**208**) was carried out under biomimetic conditions with water as a solvent at room temperature. The environmentally benign reaction in these cases exhibits high selectivity. CDs are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. Hydrogen bonding of amines with CD hydroxyl make the N-H bond weaker, enhancing the nucleophilicity of nitrogen for the addition; thus in the case of primary amines, only monomers were formed (**Scheme 1.51**).[103]



Scheme 1.51. Cyclodextrin promoted aza-Michael addition of amines.

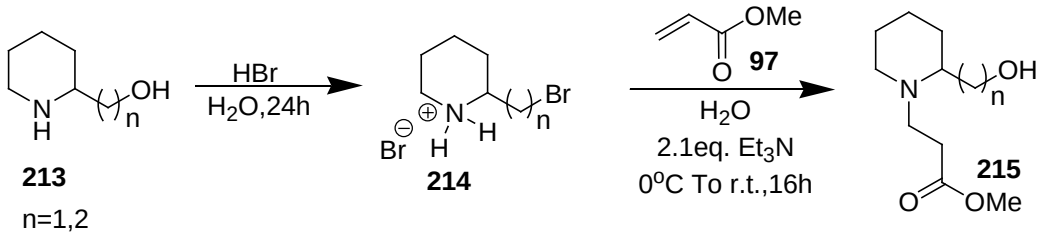
Some amines like pyrrolidine[104] (**Scheme 1.52**), triethylamine[105] (**Scheme 1.53**), proline[106] (**Scheme 1.54**) were also used as organocatalysts in aza-Michael addition, when high yields and diastereoselectivities were reported.



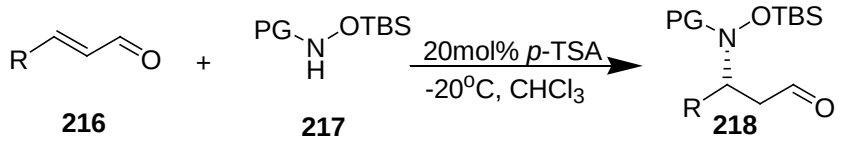
R^1	R^2
H	^{t}Bu
5-F	^{t}Bu
4-Cl	^{t}Bu
4,5-$(MeO)_2$	^{t}Bu

R^3 = H, Et, *n*Pr, 4-Me, 4-F, 2-Cl, 4-Cl, 2-Br, 4-Br, 2-MeO, 3-MeO, 3-PhO, 3,4-OCH_2O, 2,4,6-$(MeO)_3$, 4-NO_2, 4-CF_3, 3,4-Cl_2, 3,5-$(CF_3)_2$

Scheme 1.52. Pyrrolidine catalyzed one pot multistep transformation.



Scheme 1.53. Triethylamine catalyzed aza-Michael addition.



216 **217** **218**

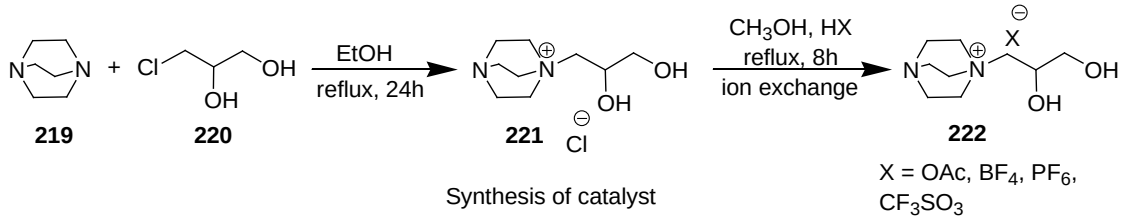
R = Me, *n*-Pr, $BnOCH_2$, Bn, CO_2Me,
PG = Cbz, Boc, Fmoc

Scheme 1.54. Amine catalyzed aza-Michael addition.

1.4.1.2.3. Ionic liquids as catalysts

Over the past two decades, ionic liquids have been extensively used in Michael additions. These have been termed as the green solvents as well as catalysts or promoters.

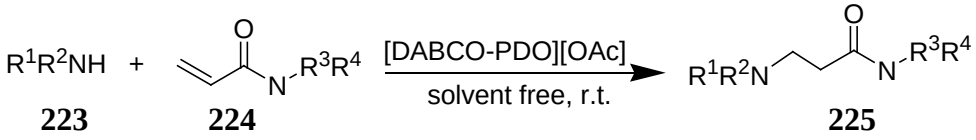
Ying et al.[107] synthesized an array of 1,4-diazobicyclo[2.2.2]octane (DABCO) based ionic liquids (**222**) and used them as recyclable catalyst without any organic solvents (**Scheme 1.55**).



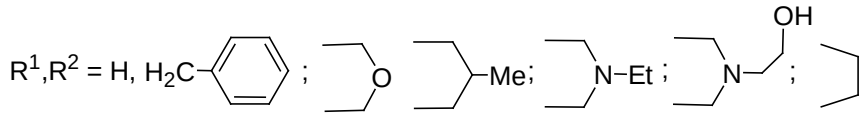
219 **220** **221** **222**

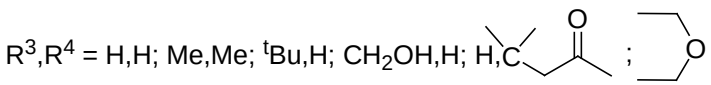
Synthesis of catalyst

X = OAc, BF_4, PF_6, CF_3SO_3



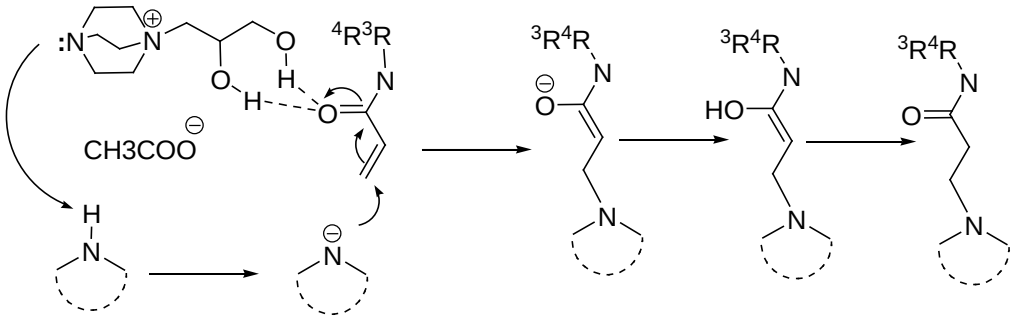
223 **224** **225**





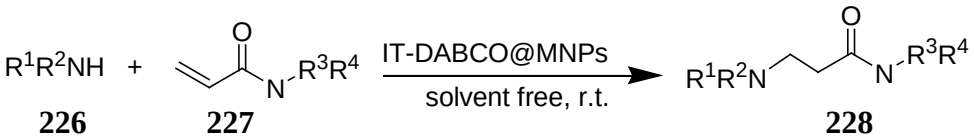
Scheme 1.55. [DABCO-PDO][OAc] catalyzed aza-Michael addition of amines with α,β-unsaturated amides.

The aza-Michael addition of amines (**223**) with α,β-unsaturated amides (**224**) afforded the adducts (**225**) in good to excellent yields and a plausible mechanism was proposed (**Scheme 1.56**). The charges on atoms of acrylamide and acrylamide-[DABCO-PDO][OAc] mixture were computationally calculated using Gaussian 03 employing the B3LYP/3-21G-optimized geometry. It is reported that the presence of hydrogen bonding interactions between the hydroxyl groups of the catalyst and the carbonyl group of acrylamide is the key element and facilitates these reactions.[107]



Scheme 1.56. Mechanism for the [DABCO-PDO][OAc] catalyzed aza-Michael addition of amines with α,β-unsaturated amides.

The same research group[108] employed ionic tagged DABCO, grafted on magnetic nanoparticles (NP) as a catalyst for aqueous aza-Michael addition of amines (**226**) to α,β-unsaturated amides (**227**) (**Scheme 1.57**). The use of magnetic NPs as catalyst made them readily dispersed in solution and provided high surface area rendering the efficient accessibility of the substrates to bind to the active catalytic sites. Besides, being super-paramagnetic, can be easily recovered from the reaction mixture using an external magnet.

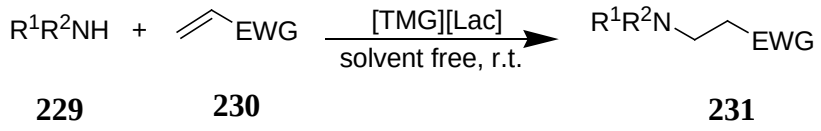


226 **227** **228**

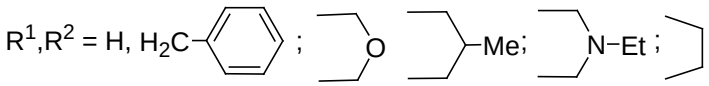
R^1,R^2,R^3,R^4 as in Scheme 1.55

Scheme 1.57. IT-DABCO@MNPs catalyzed aza-Michael addition of amines with α,β-unsaturated amides.

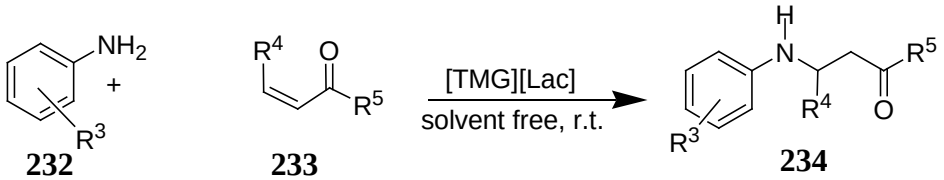
Earlier this group[109] reported the aza-Michael addition of amines to electron deficient alkenes using 1,1,3,3-tetramethylguanidine (TMG)-derived ionic liquids, prepared by simple neutralization reaction of TMG and acids. The results revealed that the aromatic amines (**232**) also reacted well in the presence of a catalytic amount of [TMG][Lac] (**Scheme 1.58**).



229 **230** **231**



EWG = CN, CO_2Me, CO_2Et, CO_2Bu^n, $CONH_2$



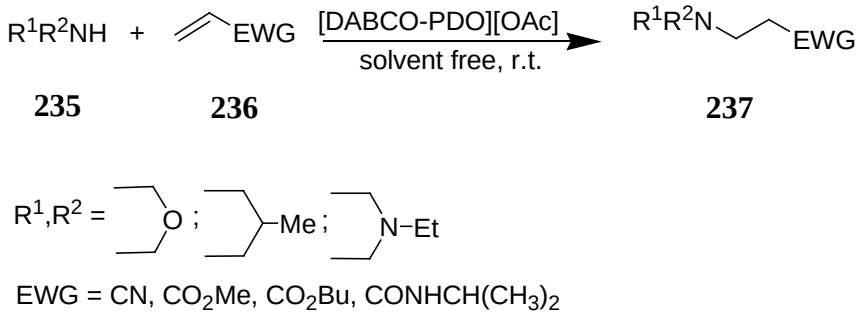
232 **233** **234**

R^3 = H, *p*-OMe,*p*-Me, *o*-NO_2, *p*-Cl, *o*-Br, *o*-Me

R^4, R^5 = H, Et ; $CH_3(CH_2)_2$-, $CH_3(CH_2)_2$-; Ph, Ph ; H, CN

Scheme 1.58. [TMG][Lac] catalyzed aza-Michael addition of amines with electron-deficient alkenes.

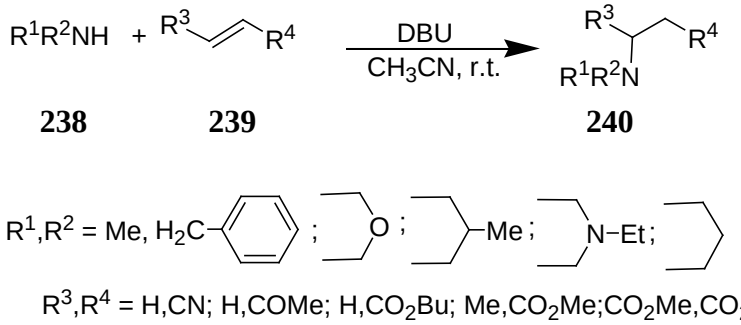
Analogous to the above work, the use of DABCO based ionic liquids as green and efficient catalyst for a different set of Michael acceptors (**236**) and donors (**235**) was reported.[110] (**Scheme 1.59**) The proposed mechanism involved H-bonding interactions between the carbonyl group of the methyl acrylate and the hydroxyl groups of the [DABCO-PDO][OAc]. Further, Gaussian charges were also calculatedto support it.



Scheme 1.59. [DABCO-PDO][OAc] catalyzed aza-Michael addition of secondary amines to α,β-unsaturated compounds.

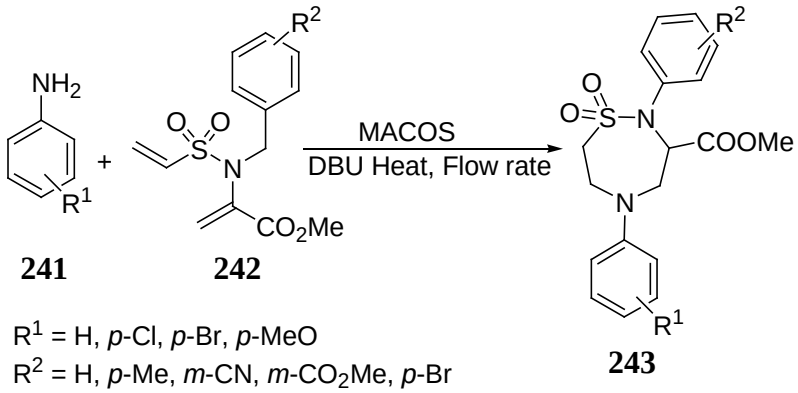
Yeom et al.[111] employed 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst. Various amines (**238**) efficiently afforded Michael adducts (**240**) with unsubstituted and α- or β-methylsubstituted acrylates and their analogues (**Scheme 1.60**). In the case of a primary amine, side product formation could be minimized by controlling the amount of the Michael acceptor. Less reactive amines such as 1,2-diazole, imidazole, 2-oxazolidinone, sulfonamide, phthalimide and indole could also be applied successfully without additional modification of experimental procedure. Reaction of aniline, however, was sluggish. Reactions of substituted Michael acceptors such as maleate ester and α- or β-methyl-substituted acrylates also proceeded smoothly with all the secondary amines that were examined, sometimes

assisted by moderate heating. This method is versatile, high yielding, and operationally very simple.



Scheme 1.60. DBU-catalyzed aza-Michael addition of amines with α,β-unsaturated compounds.

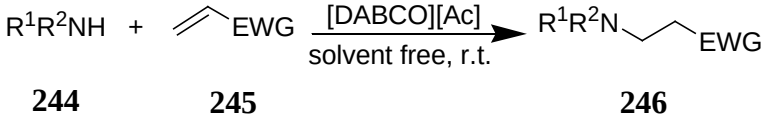
A microwave-assisted continuous-flow organic synthesis (MACOS) protocol for the generation of functionalized 1,2,5-thiadiazepane-1,1-dioxide library (**243**) utilizing a one-pot elimination and inter-/intramolecular double aza-Michael addition strategy has been reported (**Scheme 1.61**).[112]



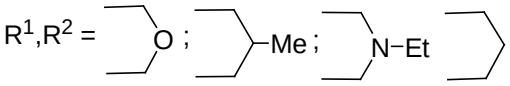
Scheme 1.61. Aza-Michael addition using DBU and MACOS protocol.

A new ionic liquid developed from neutralization of DBU with acetic acid was used as a catalyst in the solvent less addition of amines (**244**, **247**) to electron-deficient olefins (**245**, **248**) (**Scheme 1.62**). It was reported that 1,8-

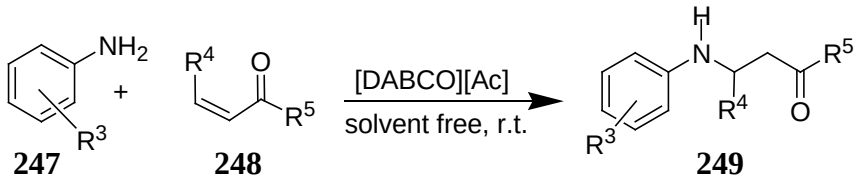
diazabicyclo[5.4.0]-undec-7-en-8ium acetate (DBU(Ac)) exhibited improved catalytic property over DBU.[113]



244 **245** **246**



EWG = CN, CO_2Me, CO_2OBu^n, CO_2NH_2, CO_2Et,



247 **248** **249**

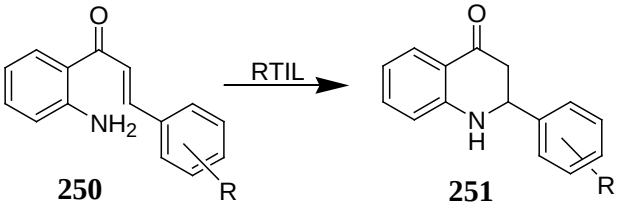
R^3 = H, *p*-OMe,*p*-Me, *p*-Cl, *o*-Cl

R^4,R^5 = H,MeO ; $CH_3(CH_2)_2$-, $CH_3(CH_2)_2$- ; Me, OMe ; Ph, Ph ; H,CN

Scheme 1.62. [DBU][Ac] catalyzed aza-Michael addition of amines with α,β-unsaturated compounds.

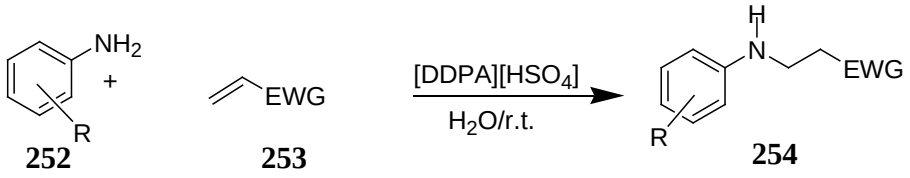
The other functionalized Ionic liquids (ILs) that have been used as catalysts for the aza-Michael reactions include 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (Room temperature ionic liquids-RTIL)[114] (**Scheme 1.63**) and 3-(N,N-dimethyldodecylammonium) propansulfonic acid hydrogen sulphate ([DDPA][HSO_4])[115] (**Scheme 1.64**).

The use of [DDPA][HSO_4] (**Scheme 1.64**)[115] afforded good results with aromatic amines, while 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (**Scheme 1.63**)[114] was found suitable for intramolecular aza-Michael addition.



R = H, *p*-OMe,*p*-Me, *p*-Cl, *p*-Br, *m*-NO_2, *o*-OMe, *o*-Cl

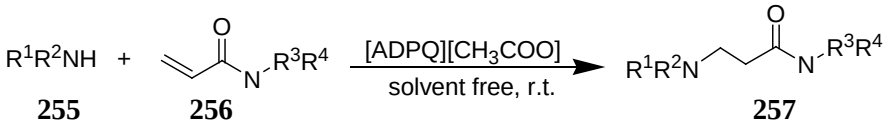
Scheme 1.63. RTIL -catalyzed aza-Michael addition of 2'-aminochalcones.

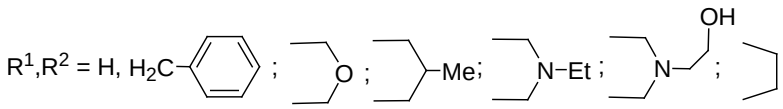


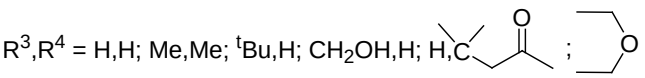
R = H, *p*-Me, *o*-Me, *m*-Me, *p*-OMe, *p*-Cl, *p*-Br, *m*-NO_2,
EWG = COMe, CN, CO_2Me, $C_2H_4CO_2Me$, C_2H_4CN

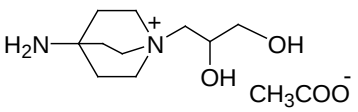
Scheme 1.64. [DDPA][HSO_4]-catalyzed aza-Michael addition of amines with α,β-unsaturated compounds.

X.Gao et al.[116] developed a new IL: [ADPQ][CH_3COO]. The scope of the procedure was investigated for a wide range of additions of amines (**255**) to α,β-unsaturated amides (**256**) (**Scheme 1.65**).







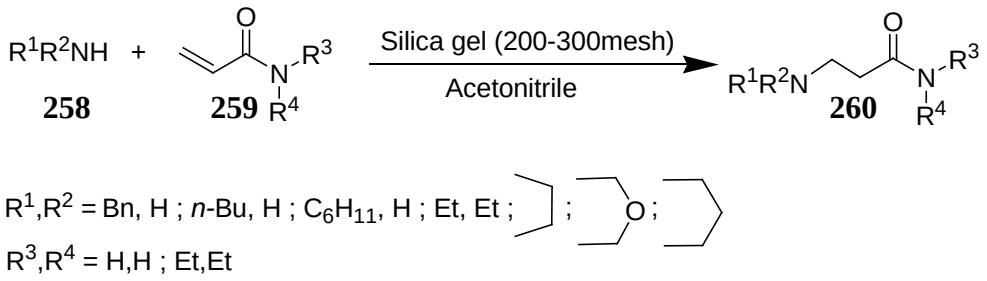


Structure of [ADPQ][CH_3COO]

Scheme 1.65. [ADPQ][CH_3COO] catalyzed aza-Michael addition of amines with α,β-unsaturated amides.

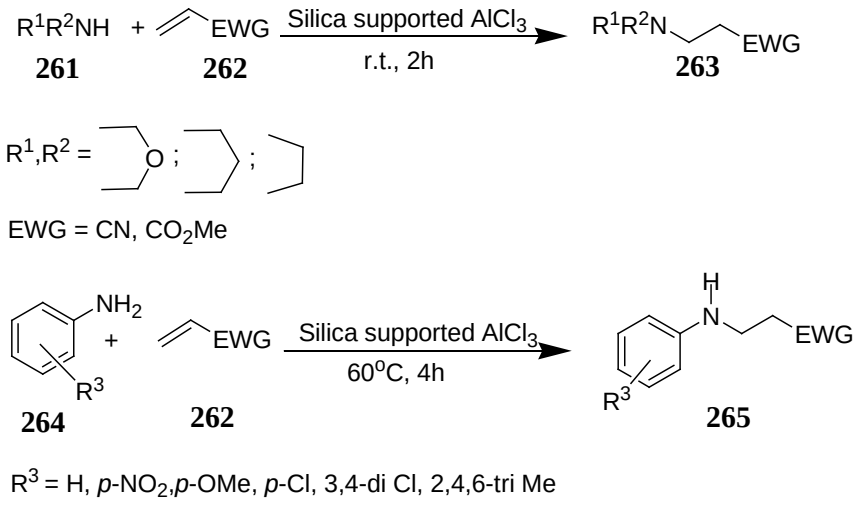
1.4.1.2.4. Heterogeneous catalysts

Over the last few years, several groups have reported use of sub-stoichiometric amount of a few Lewis acids, such as $Yb(OTf)_3$, $Bi(OTf)_3$, $Bi(OTF)_3$, $Bi(NO_3)_3$, hydrated $CeCl_3$-NaI supported on silica gel or clay as catalyst.[117] Michael additions have also been promoted on the surface of silica gel. In a typical experiment, a mixture of amines (**258**) (aromatic or aliphatic) and α,β-unsaturated amide (**259**) in a ratio of 1.1:1.0, was mixed with silica gel (0.1g GF 254, 200-300 mesh) to afford the Michael adducts (**260**) in good yields. The reaction was reported to proceed smoothly both in the presence of a solvent or in its absence (**Scheme 1.66**).[118]



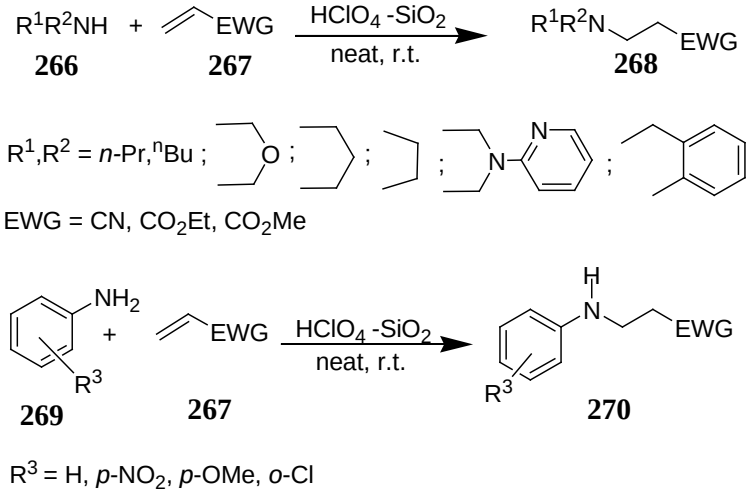
Scheme 1.66. Silica gel accelerated Michael addition of amines with α,β-unsaturated amides.

Besides, silica gel is also an important choice as an impregnating agent. Silica-supported aluminum chloride is a strong Bronsted Lewis acid presumably arising from the formation of $SiOAlCl_2$ on the site surface. Aliphatic and aromatic amines (**261**, **264**) were reported to undergo smooth Michael addition to α,β-unsaturated compounds (**262**) in the presence of a catalytic amount of silica supported aluminum chloride at 60°C under solvent free conditions to produce the corresponding β-amino compounds (**263**) in excellent yields. The catalyst could be reused at least three times (**Scheme 1.67**).[119]



Scheme 1.67. Silica-supported aluminum chloride catalyzed aza-Michael addition of various amines with α,β-unsaturated compounds.

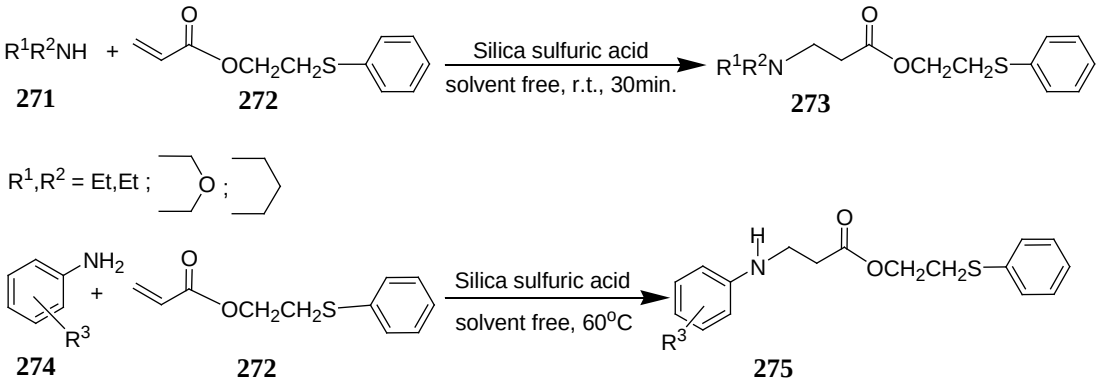
Another example of the use of a heterogeneous catalyst is perchloric acid supported over silica gel which efficiently activates the Michael acceptors (**267**) affording the products (**268**) without any side products in a short reaction time under solvent free conditions (**Scheme 1.68**). A comparison of the catalytic activity of silica supported $HClO_4.SiO_2$ over ordinary silica was carried out on a model reaction of morpholine with methyl vinyl ketone, when aza-Michael addition product could not be obtained even after 24 h of refluxing while using silica alone.



Scheme 1.68. Silica-supported perchloric acid catalyzed aza-Michael addition of amines with activated alkenes.

Interestingly, later You et al.[118] in 2008 reported occurrence of the same reaction by using silica (200-300 Mesh) under solvent free conditions.

In the series of solid supported Bronsted acid catalysts, yet another catalyst, namely silica sulfuric acid was used as an inexpensive, more stable, nontoxic, catalyst to catalyze Michael addition with greater selectivity under solvent free condition. However, this catalyst showed poor reactivity with aromatic amines (**274**) in comparison to the aliphatic amines (**271**). The chemoselectivity of thiols, phenone and aniline was investigated in the presence of silica sulfuric acid (SSA) at room temperature and it was found that amines and phenols are less reactive than thiols (**Scheme 1.69**).[121]

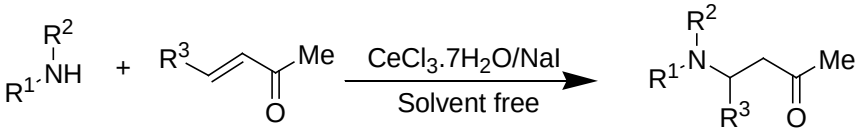


Scheme 1.69. Silica sulfuric acid catalyzed aza-Michael addition.

Furthermore, they compared a model reaction of morpholine with acrylic acid 2-phenylsulfanyl-ethyl ester (PTEA) in the presence of ordinary silica and SiO_2H-SO_3H, and found that reaction did not occur in the presence of silica at room temperature.[121]

A mixture of $CeCl_3.7H_2O$ and NaI deposited on an inorganic support proved to be a good catalyst in Michael addition of secondary amines (**276**) to α,β-

unsaturated enones (**277**). Surprisingly, cerium chloride alone failed to promote this reaction (**Scheme 1.70**).[122]

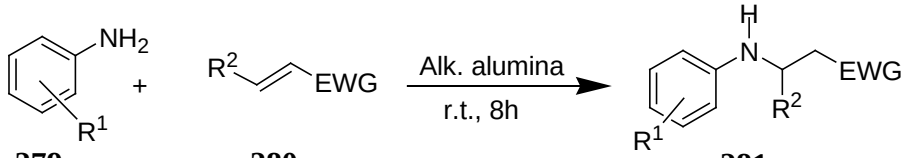


276 **277** **278**

R^1	R^2	R^3
Bn	Bn	H
Bn	H	H
Me	Ph	H
Bn	Bn	$-(CH_2)_4-CH_3$

Scheme 1.70. Michael addition to α,β-unsaturated enones promoted by alumina supported $CeCl_3.7H_2O$ and NaI.

An alkaline Al_2O_3 was reported to be an efficient catalyst and even the aromatic amines, (**279**) which are reported to be sluggish Michael donor, reacted in the presence of this catalyst (**Scheme 1.71**). The results demonstrated that the mono- or bis aza-Michael adducts could be controlled by adjusting the relative mole ratio of the reactants.[123]



279 **280** **281**

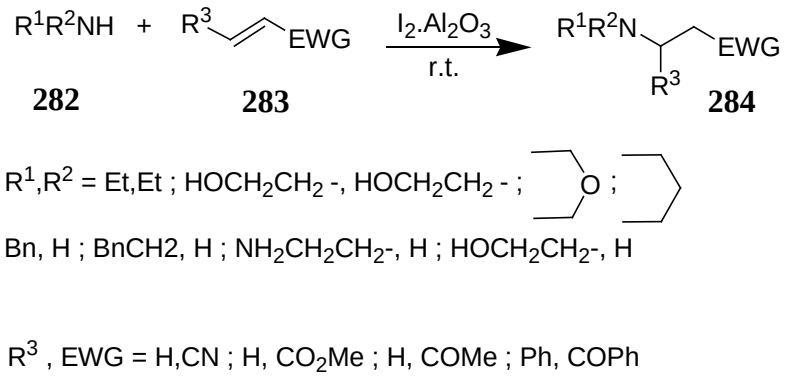
R^1 = H, *m*-NO_2, *o*-Me,*m*-Me,*p*-Me, *o*-Cl, *m*-Cl, *p*-Cl, *p*-Br

R^2 , EWG = H,CN ; H, CO_2Me ; H, $CHCHNO_2$; Ph, COPh

Scheme 1.71. Michael addition of various amines using alkaline Al_2O_3as catalyst.

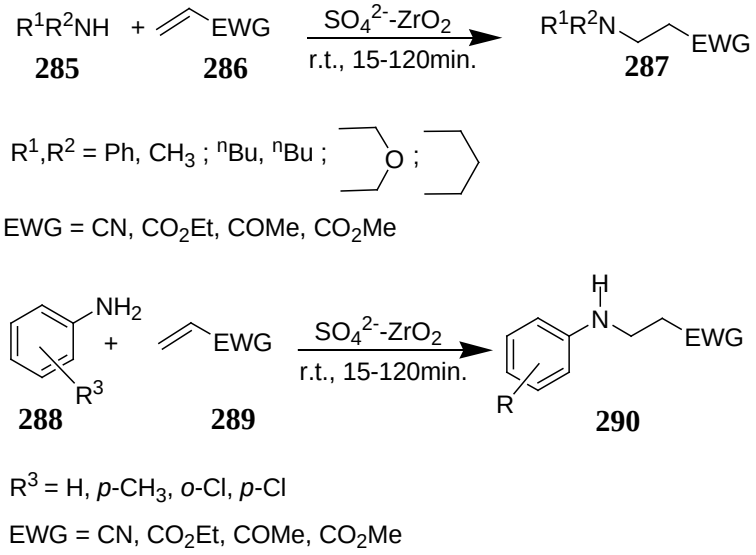
Iodine impregnated alumina (acidic) is also an effective catalyst and brings about efficient aza-Michael addition of amines (**282**) to a variety of activated olefins (**283**) at room temperature or under microwave irradiation (in case of solid) and solvent free conditions (**Scheme 1.72**). The choice of I_2-Al_2O_3 (acidic) was based on

a set of preliminary experiments carried out using I_2, Al_2O_3 (neutral), Al_2O_3 (acidic), Al_2O_3 (basic), I_2-Al_2O_3 (neutral), I_2-Al_2O_3 (acidic), I_2-Al_2O_3 (basic) and without any catalyst.[124]



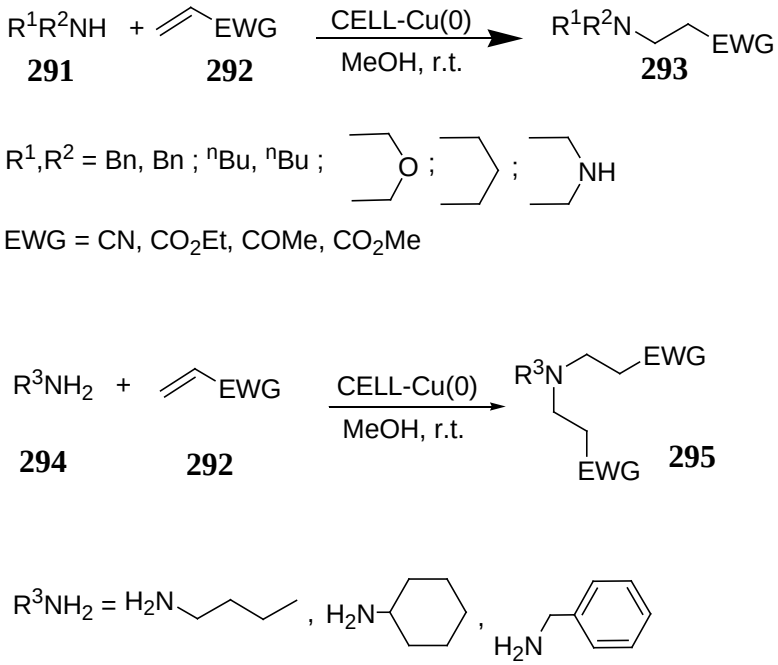
Scheme 1.72. I_2-Al_2O_3 catalyzed aza-Michael addition of amines with α,β-unsaturated compounds.

Sulfated-zirconia is another solid acid catalyst used as a heterogeneous catalyst in Michael addition reactions under solvent free conditions. As a mild Lewis acid, moisture and air sensitive zirconium oxychloride adds as a new catalyst for the aza-Michael addition of primary and secondary amines (**285**, **288**) (**Scheme 1.73**).[125]



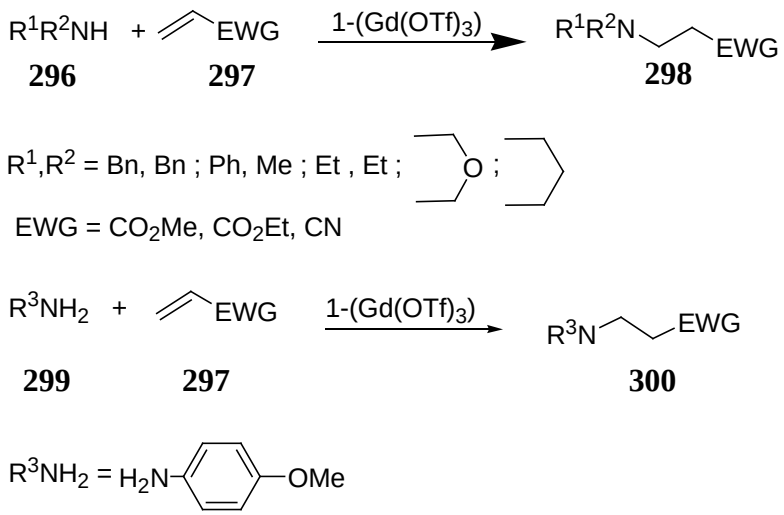
Scheme 1.73. Sulfated zirconia catalyzed aza-Michael addition with α,β-unsaturated compounds.

Same research group[126] reported cellulose supported Cu(O) catalyzed aza-Michael addition of amines (**291**, **294**) and imidazoles with α,β-unsaturated carbonyl compounds (**292**) (**Scheme 1.74**). The reactions are facile and the recovered catalyst could be used for several cycles with consistent activity.



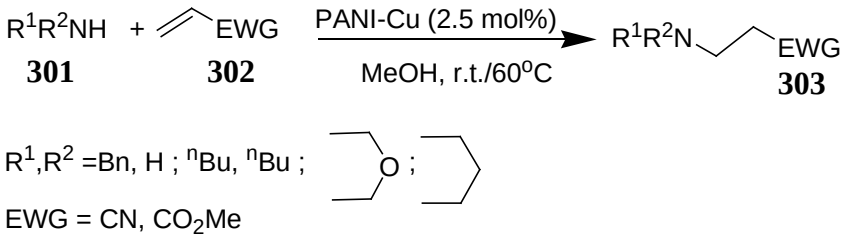
Scheme 1.74. Sulfated zirconia catalyzed aza-Michael addition of amines with α,β-unsaturated compounds.

Reddy and co-workers[127] developed another heterogeneous catalyst, namely polymer supported aza-phosphatrane nitrate by incorporating gadolinium triflate on poly[styrene-*co*-(1-((4-vinylphenyl)methyl)-3-methylimidazolium) tetrafluoroborate for the reaction of secondary amines (**296**, **299**) with α,β-unsaturated esters and acrylonitrile (**297**) (**Scheme 1.75**). The reactions proceeded under mild conditions affording high yields.



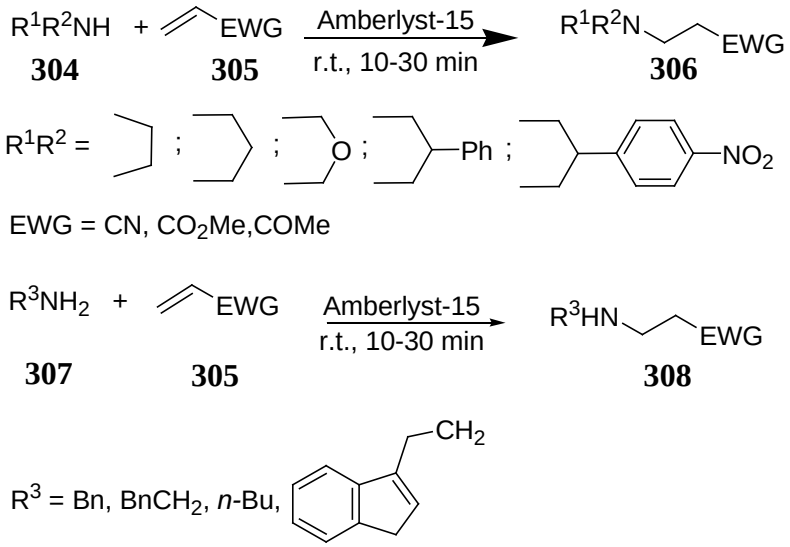
Scheme 1.75. 1-($Gd(OTf)_3$)-catalyzed aza-Michael addition of amines with α,β-unsaturated esters and acrylonitrile.

Kantam et al.[128] prepared polyaniline (PANI) impregnated CuI heterogeneous catalyst and used it for the aza-Michael addition of amines (**301**) with activated alkenes (**302**) (**Scheme 1.76**). The catalyst could be recovered and reused for several cycles with consistent activity. The activity of this catalyst was compared with the other reported heterogeneous catalysts. It was noted that the activity of PANI-Cu is more or less similar to other reported systems such as cellulose-Cu(0), Cu-FAP, SiO_2-Py-$Cu(OAc)_2$, Cu-Y zeolite, Cu_2O, nano CuO etc.

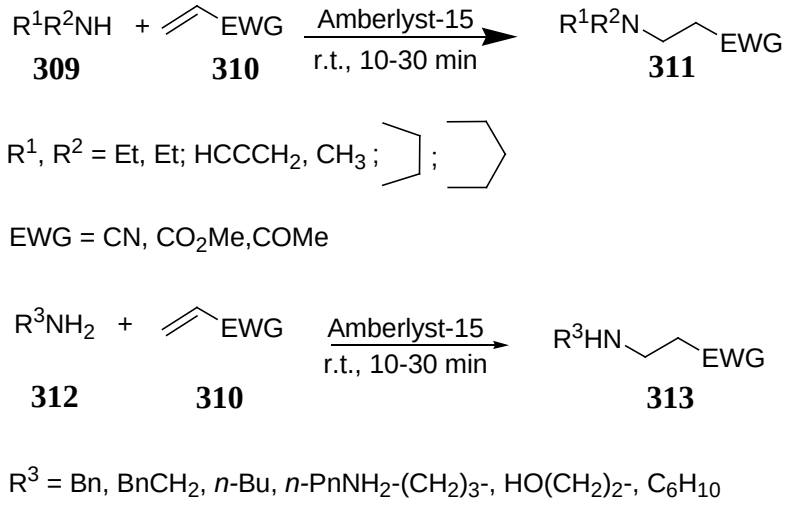


Scheme 1.76. Aza-Michael addition of amines using PANI-Cu.

The use of Amberlyst-15 for aza-Michael additions was reported (**Scheme 1.77**) (**Scheme 1.78)**.[129, 130]



Scheme 1.77. Amberlyst-15 catalyzed aza-Michael addition of amines to vinyl sulfones.

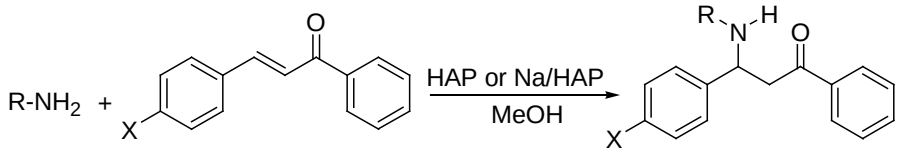


Scheme 1.78. Aza-Michael addition of amines using PANI-Cu.

By using this catalyst a series of β-amino carbonyl and nitrile compounds (**306**, **308**) were prepared.[129] Esteves et al. synthesized several amines, containing the vinyl sulfone moiety (**311**, **313**) by aza-Michael approach.[130]

It is reported that doping with mineral salts increases the activity of solid catalysts. One such example is hydroxyapatite modified with sodium nitrate, which

was used as a heterogeneous catalyst to catalyze Michael addition of aliphatic and aromatic amines (**314**) to α,β-unsaturated carbonyl compounds (**315**) (**Scheme 1.79)**.[131]

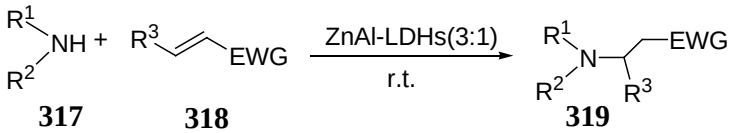


314 **315** **316**

R = Ph, Bn, *p*-$OMeC_6H_4$
X = H, Cl, Me, OMe

Scheme 1.79. HAP AND Na/HAP-catalyzed aza-Michael addition of amines with α,β-unsaturated carbonyl compounds.

The novel efficient procedure has been developed for the conjugate addition of amines to electron deficient alkenes. A series of hydrotalcite-like materials were synthesized as catalysts for the aza-Michael addition of amines with alkenes. After optimizing the reaction conditions, ZnAl-LDHs (3:1) was chosen as the best catalyst for the reaction. The results showed that the catalyst worked very well for the addition of amines (**317**) to electron deficient alkenes (**318**) giving excellent yields in several minutes. Operational simplicity, no solvent, low cost of the catalyst, high yields, reusability, excellent chemoselectivity, wide applicability are the key features of this method (**Scheme 1.80**).[132]



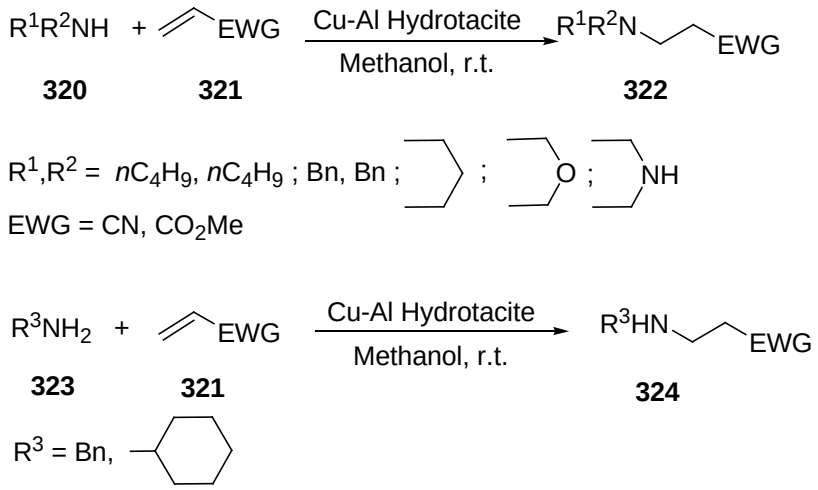
317 **318** **319**

R^1,R^2 = Me, Me ; Et, Et ;
Et, H ; ^{n}Bu, H ; C_6H_{10}, H ; Ph, H

R^3	EWG
H	CO_2Me
H	CO_2Et
CO_2Me	CO_2Me
$CO_2C_4H_9$	$CO_2C_4H_9$

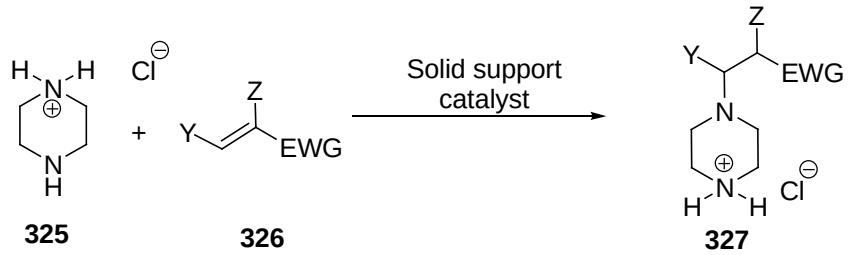
Scheme 1.80. Aza-Michael addition of amines with alkenes catalyzed by hydrotalcite-like materials.

Kantam et al.[133] described a simple, convenient, and efficient protocol for the conjugate addition of amines (**320**, **323**) to α,β-unsaturated compounds (**321**) using Cu-Al hydrotalcite catalyst at room temperature affording very good yields. The Cu-Al hydrotalcite showed enhanced activity over the other solid catalysts tested and it could be reused for several cycles with consistent activity and selectivity (**Scheme 1.81**).



Scheme 1.81. Aza-Michael addition of amines with α,β-unsaturated compounds catalyzed by Cu-Al hydrotacite.

Herova et al.[134] reported mono-aza-Michael addition of piperazine to compounds with activated multiple C-C bond (functional derivatives of acrylic, propiolic, and acetylenedicarboxylic acid) using piperazin-1-ium cation (**325**) under catalysis by various metal ions supported on weakly acidic cation-exchanger resin (**Scheme 1.82**).

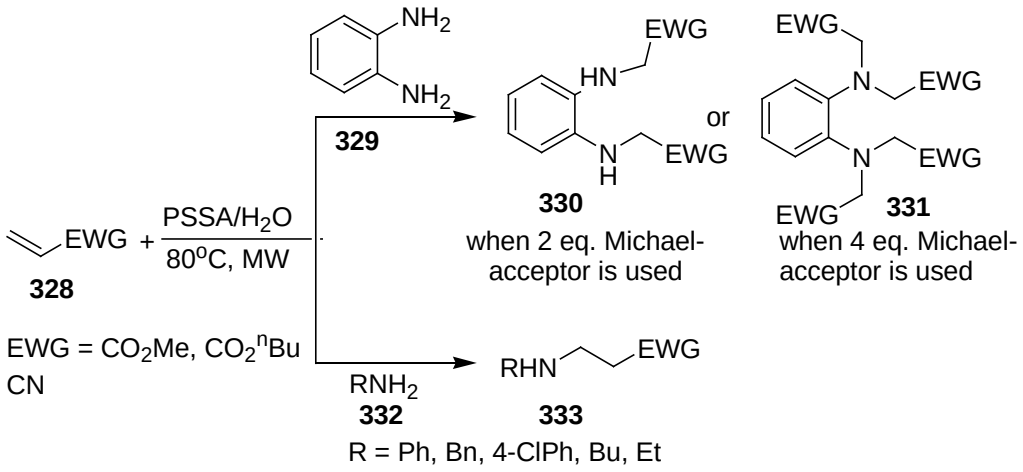


325 **326** **327**

Y	Z	EWG
CO_2Me	H	CO_2Me
H	H	CO_2Me
H	H	CN
H	Me	CO_2Me

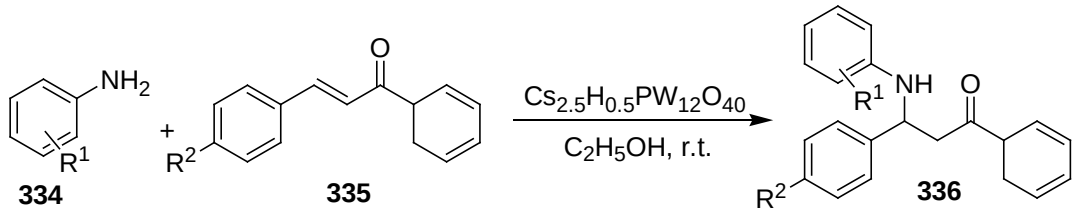
Scheme 1.82. Solid support catalyzed aza-Michael addition of piperazin-1-ium cation with α,β-unsaturated compounds.

Another greener, ecofriendly method involves the use of polymer supported, relatively low toxic and inexpensive polystyrenesulfonic acid (PSSA) as a catalyst. The microwave assisted, PSSA catalyzed tandem aza-Michael addition of aromatic amine (**332**) and aliphatic diamines (**329**) to alkyl acrylates (**328**) yields disubstituted diamines (**330**) or tetra substituted diamines (**331**). The formation of the type of reaction product depends on the relative mole ratio of the reactants (**Scheme 1.83**).[135]



Scheme 1.83. PSSA-catalyzed aza-Michael addition of amines with α,β-unsaturated compounds.

The heterogeneous nano-catalyst $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, with an average particle size of 22.2 nm and surface area of 49.16m^2g^{-1} was prepared and applied to synthesize some β-amino ketone derivatives (**336**) in good yields at room temperature. The formation of the products of undesirable side reactions could be avoided by the use of this heterogeneous nano-catalyst (**Scheme 1.84**).[136]



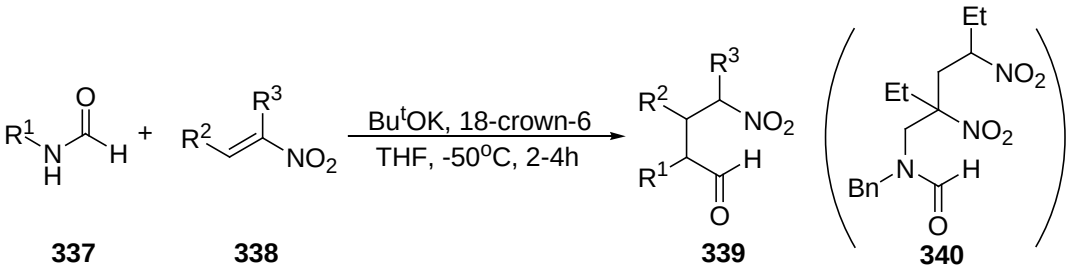
R^1	H	*p*-Me	*p*-OMe	*p*-Br	*p*-NO_2	*p*-Me	*p*-Br	H	H	*p*-Me	*p*-Br	*p*-OMe	*p*-NO_2
R^2	H	H	H	H	H	H	H	Me	Cl	Cl	Cl	Cl	Cl

Scheme 1.84. Nano CsPW-catalyzed aza-Michael addition of amines to chalcone derivatives.

The use of animal bone meal (ABM) and potassium fluoride or sodium nitrate doped ABMs as heterogeneous catalyst was reported by Lazar and co-workers[137]. A series of chalcones were synthesized using this catalyst, which were subsequently reacted with various aromatic amines under this catalytic system and mild reaction conditions.

1.4.2. Addition of amides and carbamates

Though the amide nitrogen atom exhibits reduced nucleophilicity, these compounds have also been reported to undergo aza-Michael addition with enones, acrylates and other Michael acceptors. Formamides undergo additions with a variety of nitroalkenes in the presence of 18-crown-6 and Bu^tOK, in THF at -50^oC (**Scheme 1.85**).[138]

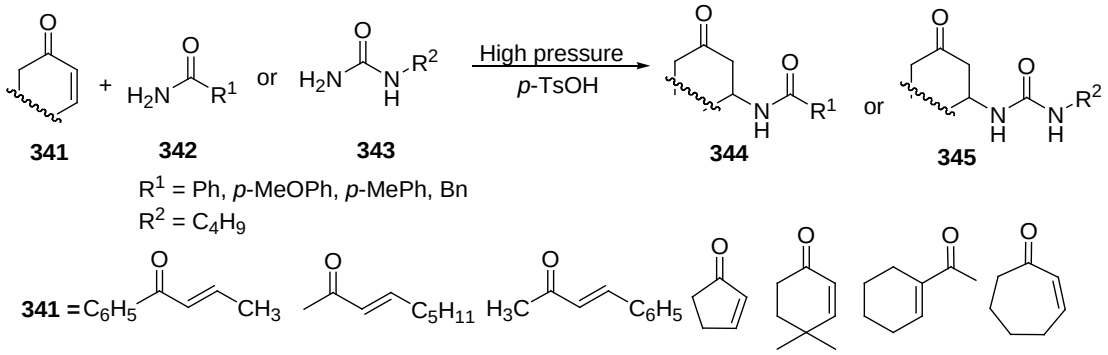


337 **338** **339** **340**

R^1	R^2	R^3
Bn	*i*-Pr	H
Bn	H	Et
CH2=CHCH2-	*i*-Pr	H
CH2=CHCH2-	Ph	H
CH2=CHCH2-	*i*-Pr	H
CH2=CHCH2-	*i*-Pr	Me
CH2=CHCH2CH2-	*i*-Pr	H

Scheme 1.85. Aza-Michael addition of amides to nitroalkenes.

The aza-Michael addition of amides (**342**) and ureas (**343**) with α,β-unsaturated enones (**341**) was carried out under a combination of BrØnsted acid catalysis and high pressure technique to yield **344** and **345** respectively . Among several acid catalysts, *p*-toluenesulfonic acid (*p*-TsOH) gave the best results. It was emphasized that high pressure was the necessary condition for the reaction to occur. However, acrylic and cinnamic acid esters did not react with benzamide. Furthermore, the addition was limited to enones (**Scheme 1.86**).[139]



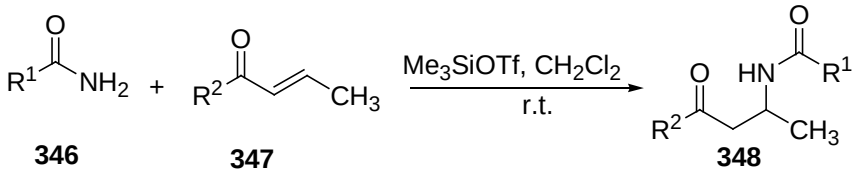
341 **342** **343** **344** **345**

R^1 = Ph, *p*-MeOPh, *p*-MePh, Bn

R^2 = C_4H_9

Scheme 1.86. High pressure promoted aza-Michael addition of amides and ureas with enones.

Lewis acid, Me_3SiOTf was found to be a promising promoter for the aza-Michael reaction of relatively acidic primary amides (**346**) with α,β-unsaturated ketone (**347**) at room temperature in THF. In fact, Me_3SiOTf showed best catalytic activity among other Lewis-acids such as, $AlCl_3$, $BF_3.OEt_2$, $ZnCl_2$, Et_3SiOTf (**Scheme 1.87**).[140]



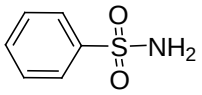
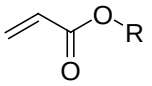
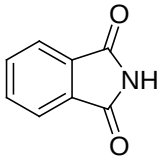
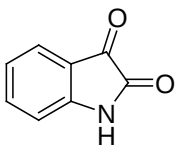
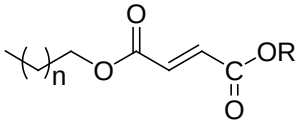
346 **347** **348**

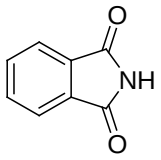
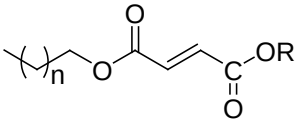
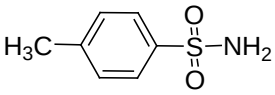
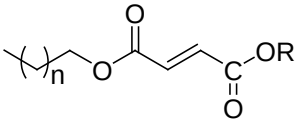
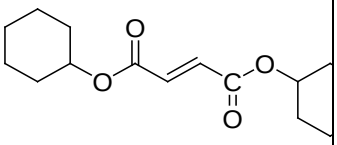
R^1 = Ph, Me, $ClCH_2$-, CH_2-CH-
R^2 = *n*-Bu, Ph, *p*-MeOPh, Bn

Scheme 1.87. Aza-Michael addition of amides with α,β-unsaturated ketones.

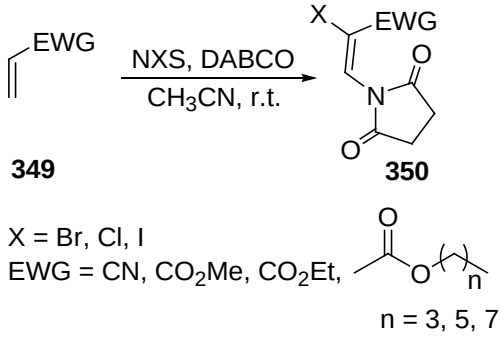
Imanzadeh et al. investigated the aza-Michael addition of amides with a variety of Michael acceptors which are summarized in Table1.1.[141-144]

Table 1.1. Aza-Michael addition of amides with a variety of Michael acceptors.

Michael donor	**Michael acceptor**	**Reaction conditions**	**Ref.**
	 R = Et, ^{n}Bu, Bn	K_2CO_3, TBAB, M.W.(300W)	141
 or 	 n = 0-10	DABCO ionic liquid	142

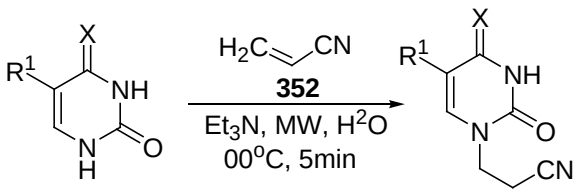
Michael donor	Michael acceptor	Reaction conditions	Ref.
	 n = 0-10	DABCO, TBAB	143
	 n = 0-10 And 	K_2CO_3, U.S., Solvent free	144

Ionic liquids have also been used to catalyze the reaction of amides. An efficient DABCO ionic liquid mediated synthesis of functionalized enamide (**350**) from amide and alkene (**349**) reported by Bhat and coworkers[145] (**Scheme 1.88**). The reaction proceeded through an unprecedented cascade involving an aza-Michael addition/α-bromination/elimination and a Morita-Baylis-Hillman type reaction to generate an array of α-halo-β-amidoalkenes in a regio- and stereoselective fashion. The plausible mechanism for the reaction was proposed.



Scheme 1.88. Synthesis of a range of α-halo-β-amidoalkenes.

Pyrimidine and purine bases have been successfully used as Michael donors in the reaction with acrylates and acrylonitrile in the presence of base catalysts (**Scheme 1.89**)[146], (**Scheme 1.90**)[147] or bio-catalysts[148,149] (**Scheme 1.91**)[149]. Triethylamine has proved to be the mildest and most efficient base. Acyclic nucleosides can be synthesized rapidly and in high yield if the reaction is performed in water and assisted by microwave irradiation. The addition of dihydropyrimidinones to ethyl acrylates and acrylonitrile occurred regioselectively to afford 3-substituted derivatives exclusively in the presence of KF/Al_2O_3 (**Scheme 1.92**).[150]

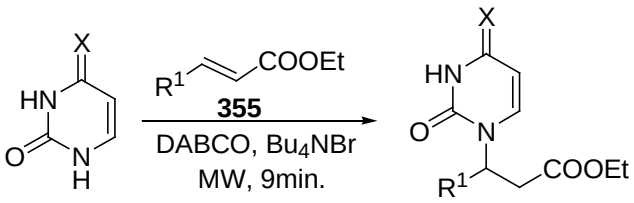


351

R^1	X
H	O
I	O
Me	O
H	S

353

Scheme 1.89. Base catalyzed synthesis of acyclic nucleosides.

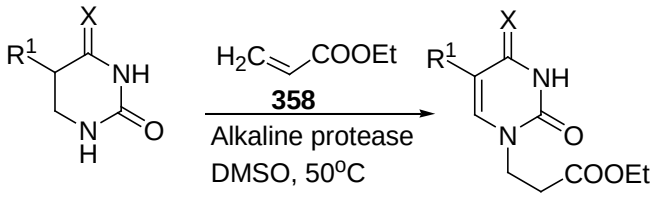


354

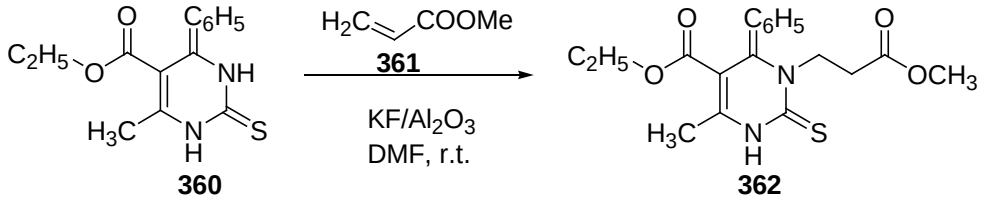
R^1 = Ph, Me

356

Scheme 1.90. DABCO base catalyzed synthesis of acyclic nucleosides.



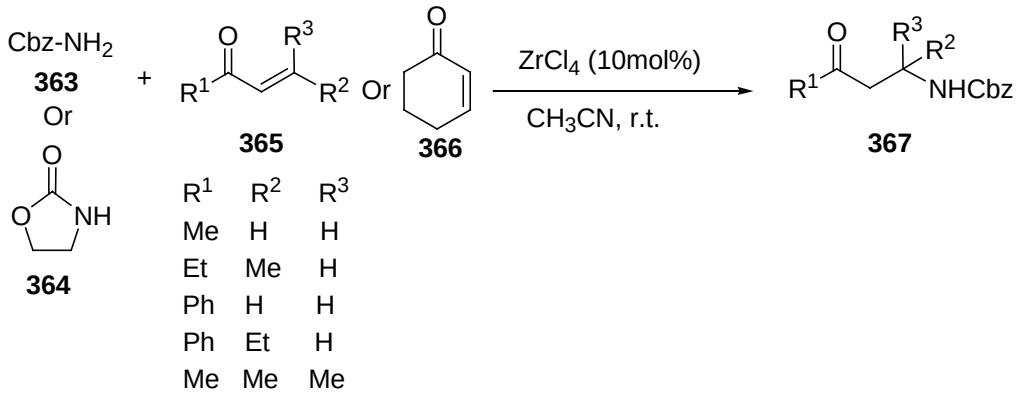
Scheme 1.91. Lipase catalyzed aza-Michael addition of pyrimidine derivatives to ethylenic compounds.



Scheme 1.92. KF/Al_2O_3 catalyzed synthesis of *N*3-substituted 3,4-dihydropyrimidinones.

The catalysts that worked well with the conjugate addition of amines were found to be inactive or poorly active in the reactions with carbamates. For example, copper, iron, indium and lanthanum halides and triflates failed to catalyze the reaction of ethyl and benzyl carbamates with enones.[151]

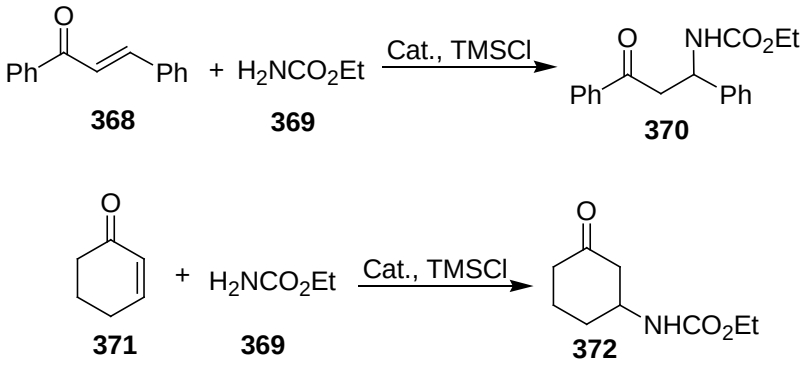
These obstacles were overcome with the use of strong BrØnsted and Lewis acids as catalysts. Zirconium chloride ($ZrCl_4$) turned out to be an efficient catalyst in the aza-Michael reaction of carbamates (**363**, **364**) with enones (**365**, **366**) (**Scheme 1.93**).[152]



Scheme 1.93. $ZrCl_4$ catalyzed aza-Michael addition of carbamates with enones.

The conjugate addition of carbamates easily occurred in the presence of $RhCl_3.3H_2O$, $AuCl_3.3H_2O$,[153] $Vo(OTf)_2$[154] and zeolite supported $SnCl_4$[155].

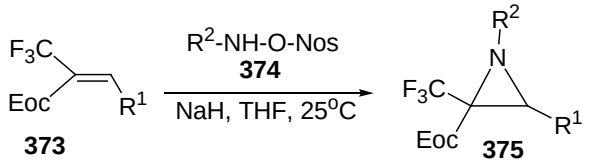
The efficiency of Lewis acids as catalysts for the aza-michael addition of carbamates increased substantially in the presence of Me_3SiCl (TMSCl) (**Scheme 1.94**).[156]

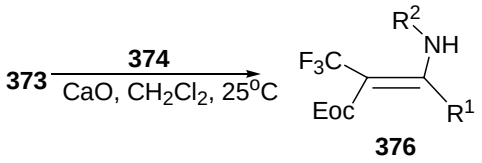


Scheme 1.94. Me_3SiCl and acid catalyzed aza-Michael addition of carbamate with enones.

Tardella and co-workers[157] reported an interesting observation about the aza-Michael addition of aziridine versus vinyl carbamates. Treatment of trifluoromethyl enoates (**373**) with nosylcarbamates (**374**) gave aziridines (**375**) and/or vinyl

carbamates (**376**) depending on the conditions and position of the trifluoromethyl group (**Scheme 1.95**).

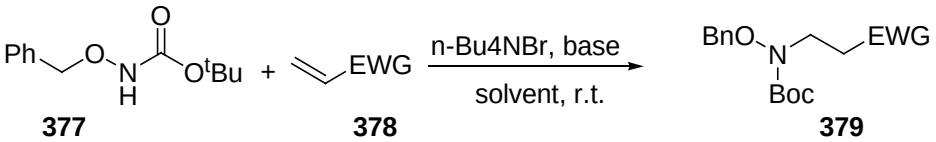




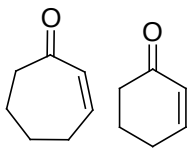
R^1	COMe	COMe	COMe	COMe	Eoc	Eoc	Eoc	CN	CN	CN
R^2	Eoc	Boc	Cbz	Fmoc	Eoc	Boc	Cbz	Eoc	Boc	Cbz

Scheme 1.95. Aza-Michael addition of trifluoromethyl enoates with nosylcarbamates.

Lee and coworkers[158] reported a highly efficient phase-transfer catalyzed aza-Michael addition of *ter*-butyl benzyloxycarbamate (**377**) to a wide range of electron deficient olefins (**378**) (**Scheme 1.96**).

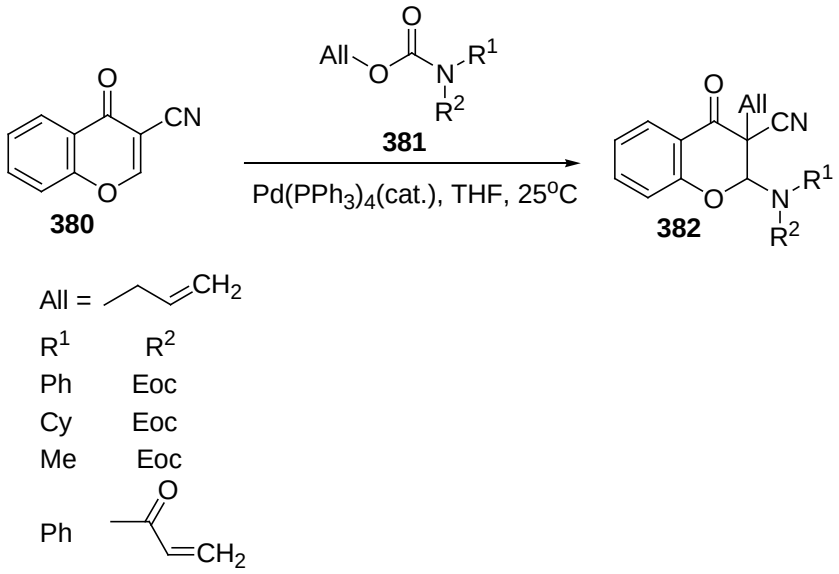


EWG = COMe, COPh, COEt, COOEt, COOMe, $CONH_2$, CN, SOPh, SOOPh



Scheme 1.96. Phase-transfer catalytic aza-Michael addition of *ter*-butyl benzyloxycarbamate to electron deficient olefins.

It could be possible to generate a quaternary carbon adjacent to the secondary amine carbon center through aza-Michael addition of allyl carbamates (**381**) to activated olefins (**380**), using palladium as catalyst. (**Scheme 1.97**).[159]

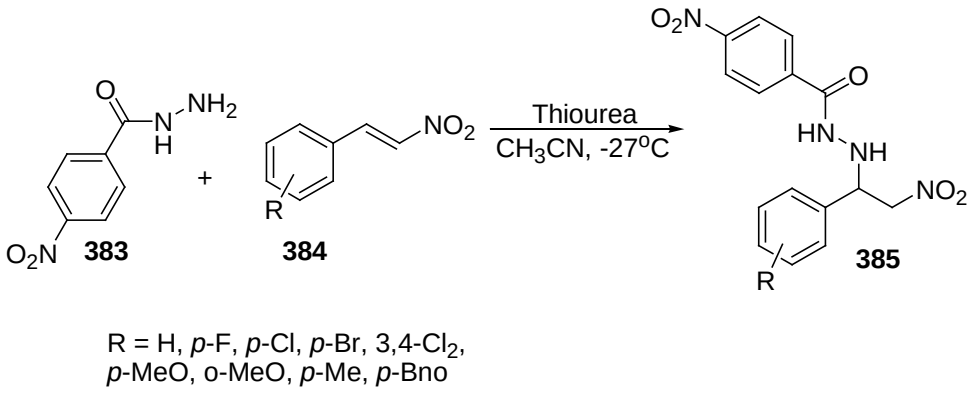


Scheme 1.97. Aza-Michael addition of allyl carbamates to activated olefins using palladium as catalyst.

The addition of carbamates to enones occurred efficiently in the presence of strong Bronsted acids[160] including polymer-supported acids.[161]

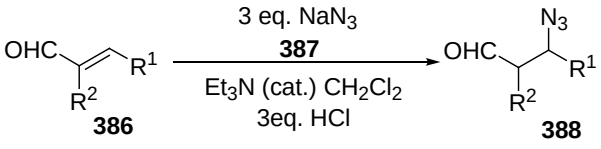
1.4.3. Addition of hydrazides

The thiourea catalyzed aza-Michael addition of hydrazide (**383**) with nitroalkenes (**384**) afforded β-nitrohydrazides which were found to exhibit antimicrobial activity (**Scheme 1.98**).[162]



Scheme 1.98. Thiourea catalyzed aza-Michael addition reaction of hydrazide with nitroalkenes.

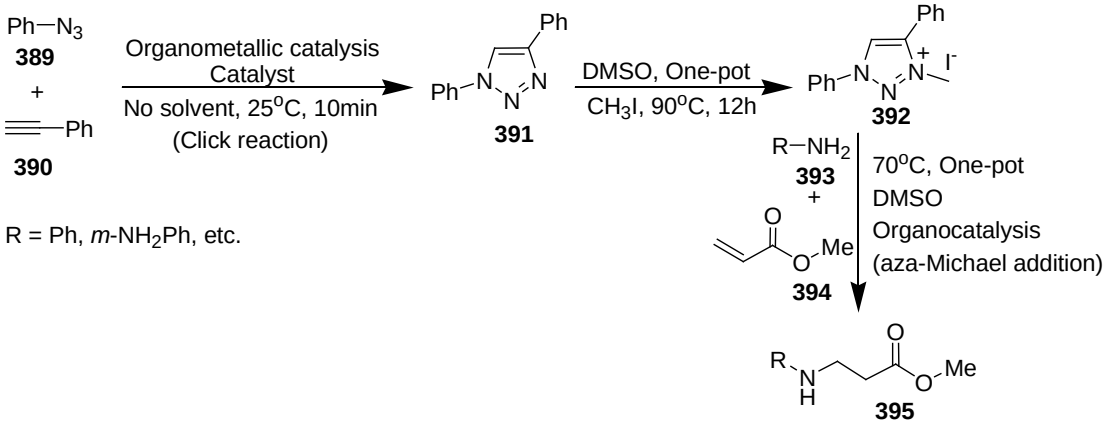
Aza-Michael addition of azide ion to α,β-unsaturated aldehydes (**386**) was achieved successfully by Kim et al. using triethylamine as organocatalyst (**Scheme 1.99**).[163]



R^1	R^2
*n*Pr	H
*i*Pr	H
-CH_2-O-Bz	H
-CH_2-O-Bz	H
Cy	H
-CO-O-Me	H
Ph	H
H	Me

Scheme 1.99. Aza-Michael addition of azide ion to α,β-unsaturated aldehydes.

A catalytic array of reactions in which the product of the first step acts as a catalyst for the next step is reported in literature (**Figure 1.5**). This study integrated two types of catalysis, namely, organometallic catalysis and organocatalysis in one reaction pot. In this process, N-heterocyclic carbene-copper based organometallic catalyst acted efficiently for different organic transformations, for example, aza-Michael addition and multi component reactions, in a consecutive fashion in the same reaction pot (**Scheme 1.100**).[164]



Scheme 1.100. Integration of organometallic catalysis (click reaction) with organocatalysis (aza-Michael addition).

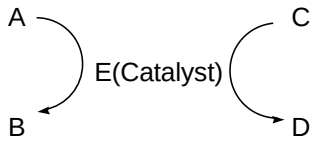


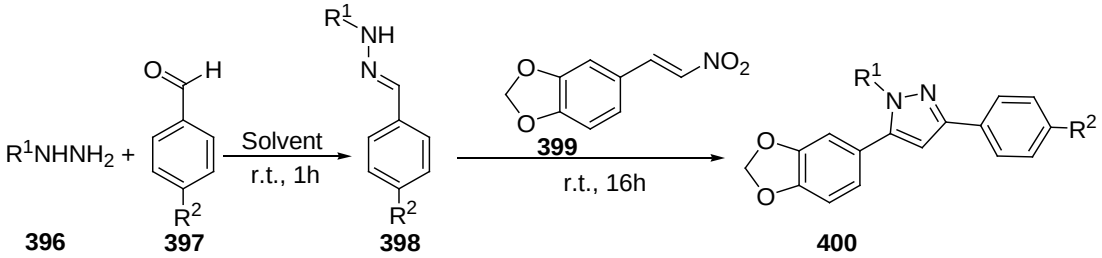
Figure 1.5. Dual catalysis.

Another one pot aza-Michael addition of azides using Cu catalyst in dichloromethane solvent was reported by Attanasi et al.[165] which yielded Michael adducts in good yields.

1.4.4 Addition of hydrazines/hydrazones

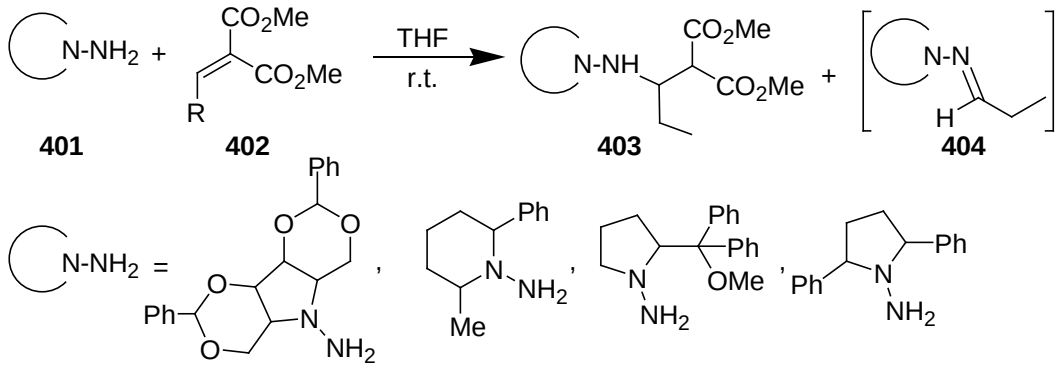
Hydrazines, as well as hydrazones containing at least one free amino group, are involved in the aza-Michael reaction with various activated alkenes. If the electrophilicity of the β-carbon atom in the Michael acceptor is relatively high (for example, in nitroalkenes[166] or alkylidene malonates[167]), the addition occurs easily and in the absence of a catalyst. In other cases, the reaction is catalyzed by bases.[168,169]

Though hydrazone is an ambident nucleophile and can react with electrophiles on both C and N positions, the reaction (in all cases) is highly regioselective and is exclusively on the N position. The scope of the reaction is quite broad and generates a diverse range of pyrazole derivatives in moderate to excellent yields. With the isolation and characterization of nitropyrazolidine intermediate, plausible mechanism of the reaction was proposed (**Scheme 1.101**).[166]



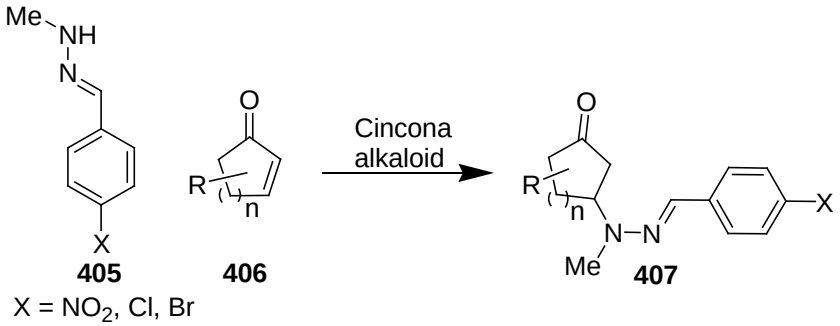
Scheme 1.101. Three component aza-Michael reaction for pyrazole synthesis.

The high electrophilicity of alkylidine/arylidene malonates affords β-hydrazino esters (**404**) in the absence of a catalyst, as reported by Prieto et al. (**Scheme 1.102**).[167]



Scheme 1.102. Aza-Michael addition of hydrazine to alkylidene malonates.

Most of the reactions of hydrazones with electrophiles are stereoselective in nature and will be covered under introduction in the 4th chapter (**Scheme 1.103**).[168]

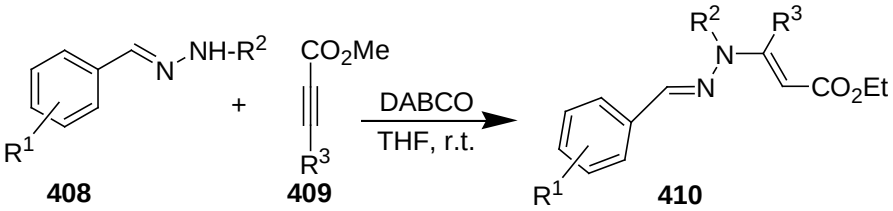


405 **406** **407**

X = NO_2, Cl, Br

Scheme 1.103. Aza-Michael addition of hydrazones to enones.

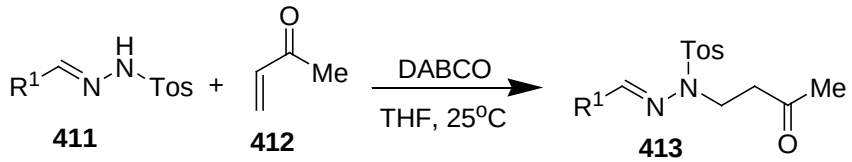
Several highly efficient DABCO catalysts have been used to catalyze the reaction of hydrazones and hydroxy hydrazones with activated alkynes (**Scheme 1.104**)[170] (**Scheme 1.105**)[171]. It is reported that, other nitrogen containing bases such as DBU, DMAP and pyridine are not as efficient as DABCO under optimized conditions. DABCO acts as a Bronsted base in these reactions. Through this synthesis route, interesting adducts were obtained in good to excellent yields. Moreover, in the case of hydroxyl substituted substrates, unexpected products were obtained in which, both NH and OH groups reacted with the acetylenic bond.[170]



408 **409** **410**

R^1	R^2	R^3
H	Ts	CO_2Me
H	Bz	H
o-Cl	Bz	CO_2Me
m-Cl	Bz	CO_2Me
p-Cl	Bz	CO_2Me
p-Br	Bz	CO_2Me
p-Me	Bz	CO_2Me
o-MeO	Bz	CO_2Me
p-MeO	Bz	CO_2Me
1-naph	Bz	CO_2Me
2-furan	Bz	CO_2Me

Scheme 1.104. Aza-Michael addition of hydrazone in the presence of DABCO.

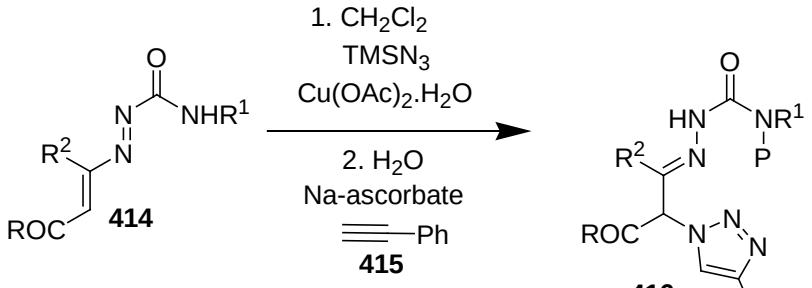


411 **412** **413**

R^1 = Tol, Ph, ^{i}Pr, 4-Cl C_6H_4, 4-$NO_2C_6H_4$

Scheme 1.105. DABCO catalyzed aza-Michael addition of hydrazones.

In the same year, Attansi et al.[172] reported a one pot Cu(II) catalyzed aza-Michael addition of in situ generated α-azidohydrazones with alkynes. However, disubstituted acetylene, such as diphenylacetylene and dimethyl acetylenedicarboxylate did not react under these conditions. These studies showed that a single inexpensive Cu catalyst ($Cu(OAc)_2.H_2O$) sequentially enabled two catalytic transformations, aza-Michael addition followed by [3+2] cycloaddition to furnish α-triazolehydrazone derivatives (**414)** (**Scheme 1.106**).



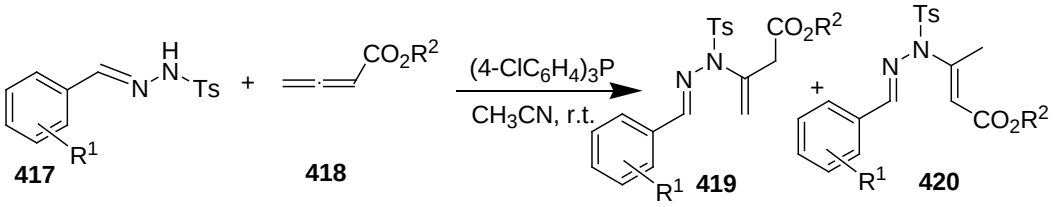
414 **415** **416**

R	R^1	R^2
t-BuO	H	Me
EtO	H	Me
Me_2N	H	Me
MeO	H	Et
$MeO(CH_2)_2O$	Ph	Me
EtO	Ph	Me
MeO	*m*-F-C6H4	Me

Scheme 1.106. One pot synthesis of triazolehydrazones.

Huang and co-workers[173] reported a phosphine catalyzed aza-Michael addition of hydrazones (**417**) to allenoates (**418**) (**Scheme 1.107**). It was found that acidity of the N-H proton in hydrazones played a key role in this phosphine-

catalyzed addition. This atom economic reaction is operationally simple and different adducts can be produced in excellent yields by using different phosphine catalysts.



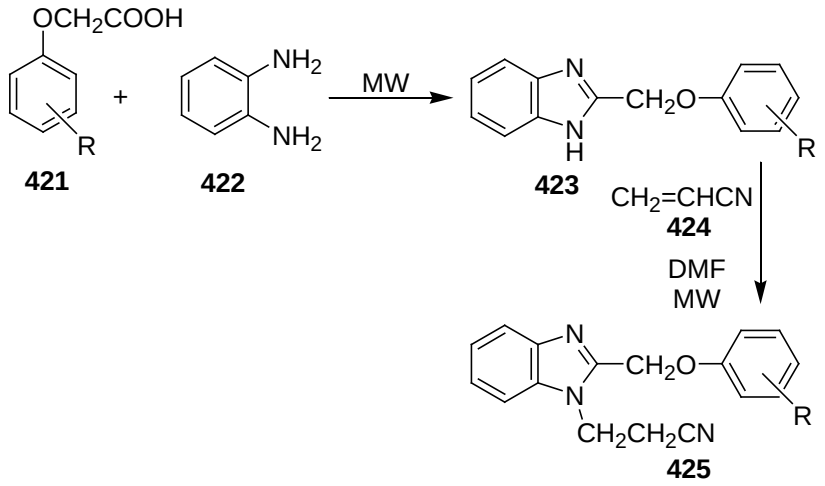
R^1	*p*-Cl	*p*-Me	*p*-F	*p*-Br	*p*-NO_2	*p*-MeO	*m*-Cl	*m*-Br	*m*-Me	*o*-Me	*o*-Br	H	*p*-Cl	*p*-Cl	*o*-furyl
R^2	Et	Et	Et	Et	Et	Et	Et	Et	Et	Et	Et	Et	Me	Bn	Et

Scheme 1.107. Phosphine catalyzed aza-Michael addition of hydrazones.

1.4.4. Addition of aromatic aza-heterocycles

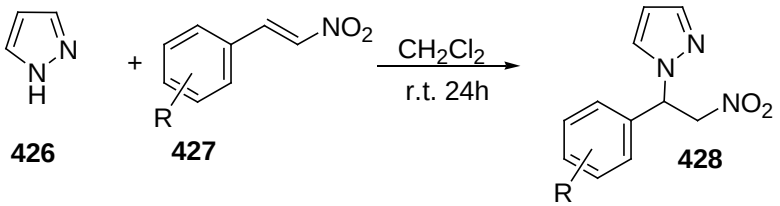
β-Amino ketones and β-amino acid derivatives having an aromatic N-heterocycle are important constituents of drugs. For this reason, the Michael addition of imidazoles, pyrazoles, pyrroles, triazoles and indoles to enones and acrylates has attracted much attention of the chemists. In spite of the fact that all these heterocycles are weak nucleophiles, their aza-Michael addition has been achieved under varying reaction conditions to afford adducts in high yields.

2-Aryl-oxymethylbenzimidazole derivatives (**423**) have been reported to react with acrylonitrile (**424**) in highly aprotic DMF solvent (**Scheme 1.108**).[174]



Scheme 1.108. Aza-Michael addition of 2-aryloxymethylbenzimidazole with acrylonitrile.

Likewise, Michael addition of pyrazole (**426**) with nitroalkenes (**427**) could be achieved under catalyst free conditions using methylene chloride as solvent (**Scheme 1.109**). Likewise, reaction between pyrazole and β-nitrostyrene proceeded smoothly with excellent yields without any catalyst. Further, it is stated that reaction medium also has an impact on the reaction. No more than 50% of conversion was obtained when reaction was carried out in THF, Et_2O and EtOAc, MeOH, etc. Best result leading to 99% of conversion was obtained in CH_2Cl_2.[175]

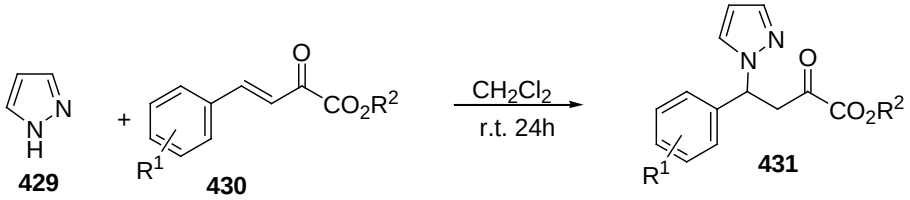


R = H, *p*-Me, *p*-MeO, *p*-F, *o*-F, *o*-Cl, *p*-Br, *p*-CF_3O, 2,3-$(MeO)_2$, *o*-BnO, *p*-BnO

Scheme 1.109. Aza-Michael addition of pyrazole to nitroalkenes.

The same research group reported the addition of azoles (**429**) to β,γ-unsaturated-α-keto esters (**430**) using CH_2Cl_2 as solvent under catalyst free conditions at r.t. only (**Scheme 1.110**). It is reported that pyrrolidine and imidazole

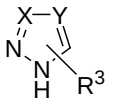
did not afford the Michael adduct, while pyrazole reacted to afford the corresponding product in good to excellent yields.[176]



429 **430** **431**

R^1	R2
H	Me
H	Et
H	*i*-Pr
o-Br	Et
m-Br	Et
p-Br	Et
m-Cl	Et
p-Cl	Et
m-NO_2	Et
m-NO_2	Me
p-NO_2	Et
p-NO_2	Me
m-Me	Et
p-Me	Et
m-MeO	Et
p-MeO	Et
p-F	Et

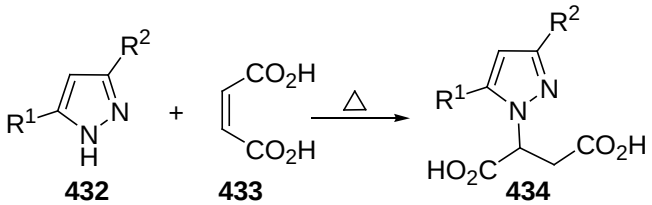
scope of azoles in reaction with methyl 2-oxo-4-phenyl-but-3-enoate



X	Y	R^3
CH	CH	3,5-Di-Me
N	CH	H
CH	N	H

Scheme 1.110. Aza-Michael addition of pyrazole to β,γ-unsaturated-α-keto esters.

Hasratyan and co-workers[177] reported catalyst free aza-Michael addition of pyrazoles (**432**) to maleic acid (**433**) at higher temperature (**Scheme 1.111**).

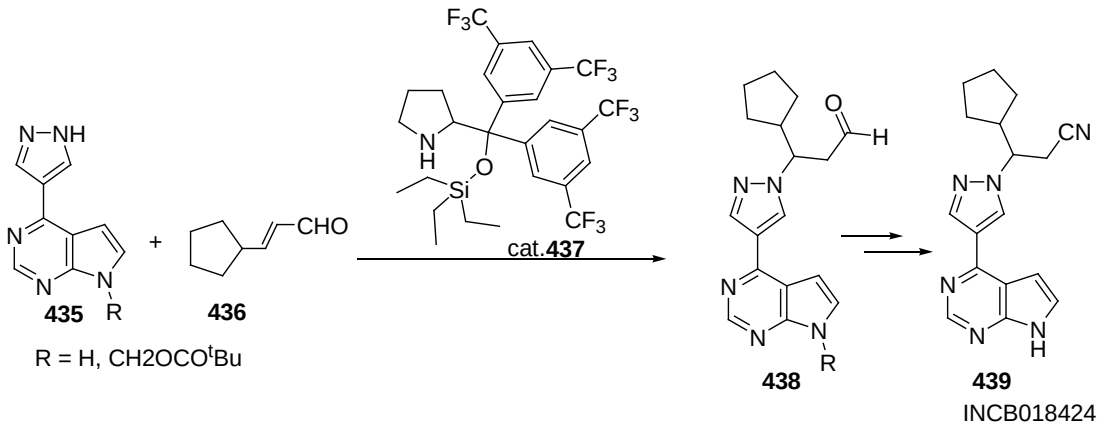


432 **433** **434**

R^1	R^2
H	H
CH_3	H
H	CH_3
CH_3	CH3

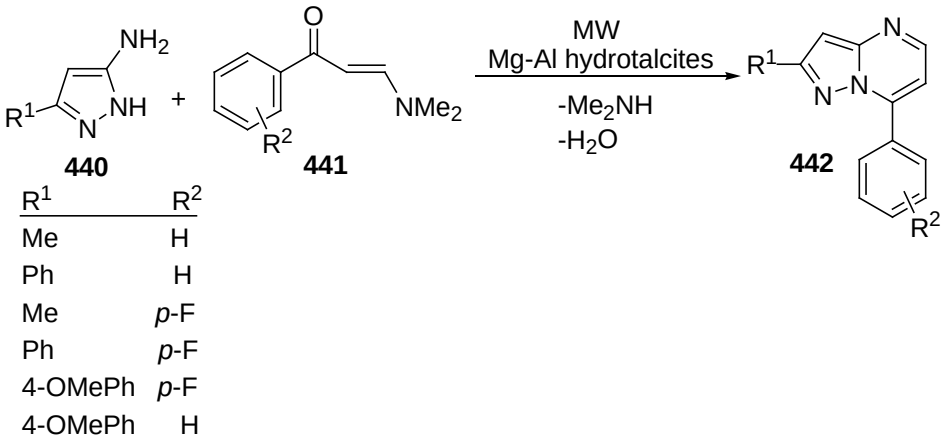
Scheme 1.111. Aza-Michael addition of pyrazoles to maleic acid.

Organocatalytic aza-Michael addition of substituted pyrazoles (**435**) to cyclopentylaldehyde (**436**) using diarylprolinol silyl ether (**437**) as catalyst was reported. Michael adducts (**438**) were isolated and further converted to INCB018424 (kinase inhibitor) (**439**) (**Scheme 1.112**). Moreover, the use of benzoic acid or 4-nitrobenzoic acid as an additive increased the reaction rate.[178]



Scheme 1.112. Organocatalytic aza-Michael addition of substituted pyrazoles.

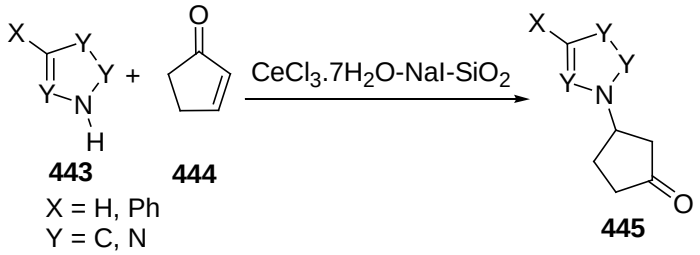
Use of solid base, Mg-Al hydrotalcites as catalyst was reported for the aza-Michael addition of amino pyrazoles (**440**) to enaminone derivatives (**441**). The synthesized as-Mg-Al-hydrotalcite catalyst was found to be the most efficient catalyst in comparison to the other activated solid catalysts tested for this conversion. The high performance of this catalyst was attributed to the co-operative contribution of its acidic and basic sites (**Scheme 1.113**).[179]



R^1	R^2
Me	H
Ph	H
Me	*p*-F
Ph	*p*-F
4-OMePh	*p*-F
4-OMePh	H

Scheme 1.113. Hydrotalcite catalyzed synthesis of pyrazolopyrimidine derivatives from aza-Machael addition.

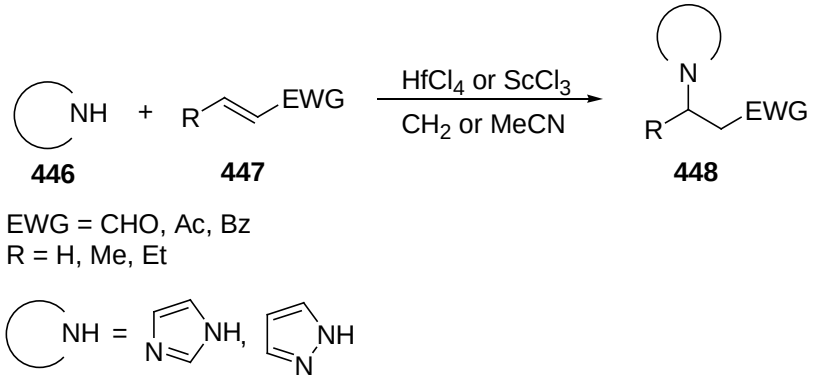
Lee et al.[180] investigated solvent-free, $CeCl_3.7H_2O$-NaI-SiO_2 catalyzed Michael addition of pyrazoles (**443**) and some other heterocycles with α,β-unsaturated ketones (**444**). Both cyclic and acyclic α,β-unsaturated ketones underwent the conversion smoothly under optimized conditions (**Scheme 1.114**).



X = H, Ph
Y = C, N

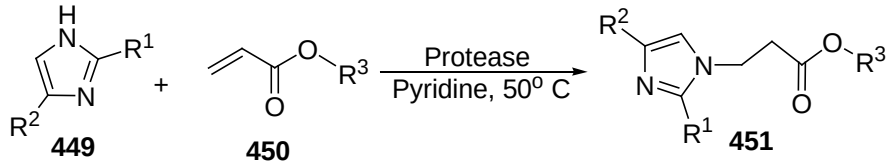
Scheme 1.114. $CeCl_3.7H_2O$-NaI-SiO_2 catalyzed aza-Michael addition of pyrazoles to enones.

The action of some catalytic systems is selective and depends on the nature of the Michael donor and the Michael acceptor. For example, hafnium and scandium chlorides efficiently catalyzed the addition of imidazole and pyrazole (**446**) to enals and enones (**447**)[181]. In contrast, no reaction occurred of imidazole with methyl vinyl ketone in the presence of any of these salts (**Scheme 1.115**).



Scheme 1.115. Hafnium and scandium chlorides catalyzed aza-Michael addition of imidazole and pyrazole to enals and enones.

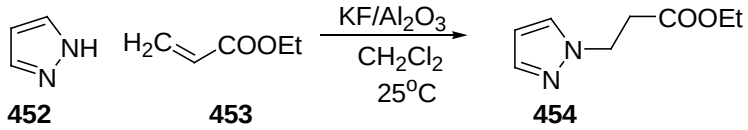
Some alkaloids[182,183] and enzymes[184-186] proved to be efficient biocatalyst for the conjugate addition of N-heterocycles to alkyl acrylates and chalcones. For examples, Lin and co-workers[184] reported a new activity of alkaline protease from *Bacillus subtilis* for the aza-Michael addition of imidazole, 4-nitro-1H-imidazole and 2-methyl-4-nitro1H-imidazole (**449**) with acrylates and acrylic acid (**450**). The reactions were carried out in pyridine at 50^{o}C for 72h. It was also reported that lipase from hog pancreas has lower catalytic activity than the protease in this process (**Scheme 1.116**).



R^1	R^2	R^3
H	H	CH_3
H	H	C_2H_5
H	H	C_4H_9
H	NO_2	CH_3
CH_3	NO_2	CH_3

Scheme 1.116. Protease-catalyzed aza-Michael addition of imidazole with acrylates and acrylic acid.

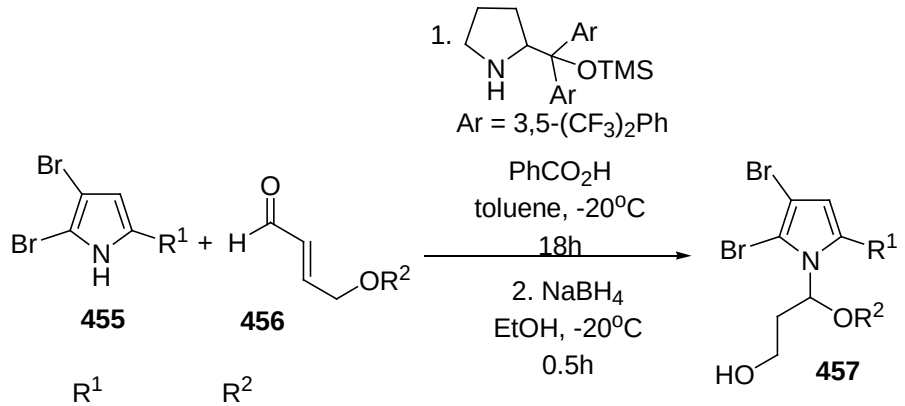
As mentioned earlier, potassium fluoride supported on some metal oxide activates the addition of aliphatic amines to acrylates.[187] It was reported that KF/Al_2O_3 can catalyze the addition of much less nucleophilic imidazole, pyrazole and pyrrole to the same substrates, pyrrole acting as the N-nucleophile.[188] The yields of the reaction products were up to 42%-98%, but lower on using enones act as Michael acceptors (**Scheme 1.117**).



452 **453** **454**

Scheme1.117. KF/Al_2O_3 catalyzed aza-Michael addition reaction.

Aza-Michael addition of pyrrole (**455**) using organocatalyst was reported by Lee and co-workers[189]. Alkaloids were synthesized in excellent yield using this methodology (**Scheme 1.118**).



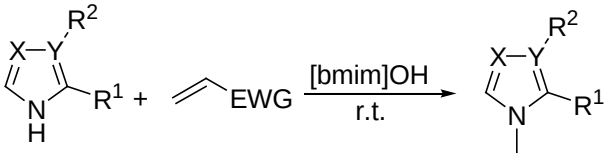
455 **456** **457**

R^1	R^2
CN	Bz
CO_2Me	Bz
CN	TBS
CN	TBDPS

Scheme 1.118. Aza-Michael addition of pyrrole using organocatalyst.

Analogous to aliphatic and aromatic amines, the aza-Michael reaction with aromatic N-heterocycles efficiently occurs in ionic liquids.[190-192] The best results

were noted with the use of basic ionic liquids. The efficiency of this method was so high that the reactions easily occurred even with imidazoles containing strong electron-withdrawing groups. For example, the reaction of 4-nitroimidazole with methyl acrylate in conventional organic solvents (THF, DMSO) at room temperature afforded the Michael adduct in low yield (5%) after 48h, whereas the reaction in the ionic liquid [bmim]OH was complete in one hourgiving the target compound in 95% yield. The advantages of [bmim]OH as the catalyst and the medium are clearly manifested in the conjugate addition of imidazole to methyl acrylate (**Scheme 1.119**).[190]



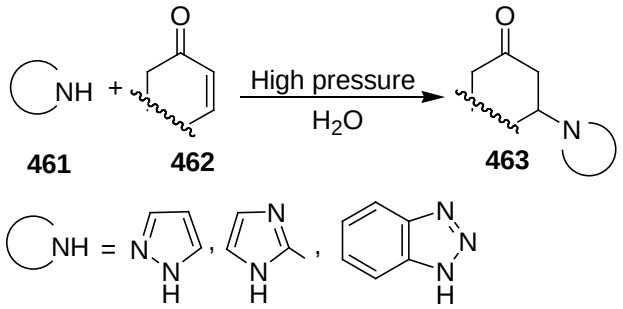
458 **459** **460**

X	Y	R^1	R^2
N	C	H	NO_2
C	N	H	-
C	N	Me	-

EWG = CN, CO_2Me, COMe, CO_2Et

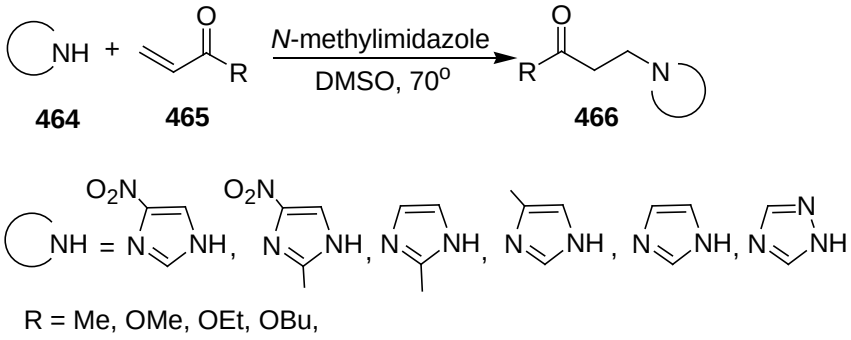
Scheme 1.119. Aza-Michael addition of imidazoles to vinyl esters promoted by [bmim]OH.

Some catalyst free methods have been reported for the aza-Michael reaction of triazole and other aromatic heterocycles with enones. The reaction was carried out in water in the absence of a catalyst at a pressure of 0.6-0.8 GPa and temperature 60^oC-80^oC when it was complete in 20-40 h. The reactions of less reactive acyclic enones proceeded under more drastic conditions and required longer time to achieve satisfactory yields of Michael adducts (**Scheme 1.120**).[193]



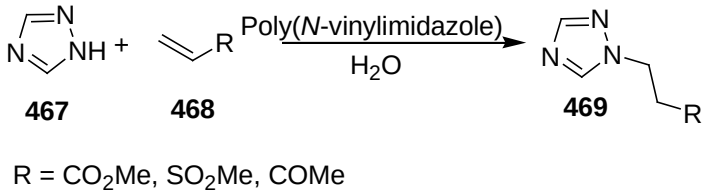
Scheme1.120. High pressure promoted aza-Michael reaction of heterocycles with enones.

Taking into account the evident structural similarities of N-methylimidazole and cation of alkylimidazolium ionic liquids, Liu et al. suggested that this compound could be used for the catalysis of the aza-Michael addition. The attempt was successful; in the presence of 5 mol% of this catalyst, the reaction of 4-nitroimidazole with methyl acrylate upon heating in DMSO for one hour afforded the adduct in quantitative yield. In the absence of the catalyst, the yield of the target product was at most 4%. The reactions of 2-and 4-methyl imidazoles with alkyl acrylates and methyl vinyl ketone were also successful. The reactions with α-or β-substituted acrylates were much more difficult to perform, and they were completed in 12 h (**Scheme 1.121**).[194]



Scheme 1.121. Aza-Michael addition of azoles to methyl vinyl ketones.

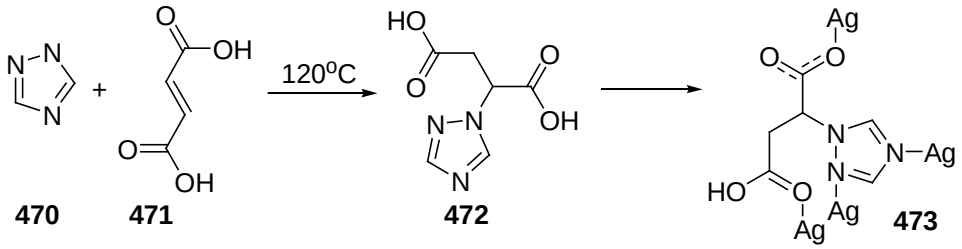
It was found that poly(N-vinyl imidazole) showed high catalytic activity. The addition reaction of 1,2,4-triazole (water, 20-25^{o}C, 2-48h) with terminal alkenes (methyl vinyl ketone, methyl vinyl sulfone, methyl acrylate) (**468**) occurred readily to give aza-Michael adducts in high yields (**Scheme 1.122**).[195]



467 **468** **469**

Scheme 1.122. Poly(N-vinyl imidazole) catalyzed aza-Michael addition of 1,2,4-triazole with terminal alkenes.

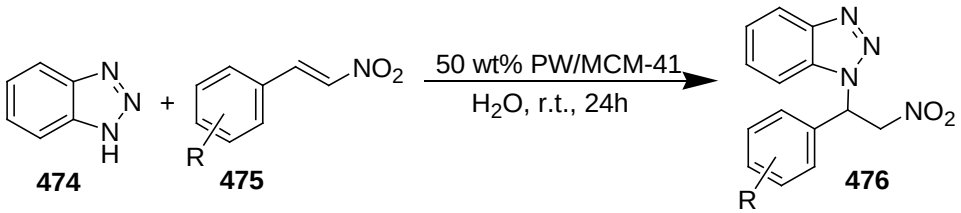
Zhao et al. reported the synthesis of a 2-D Ag(I) coordination polymer incorporating a ligand through *in situ* aza-Michael addition of 1H-1,2,4-triazole (**470**) with fumaric acid (**471**) using hydrothermal treatment (**Scheme 1.123**).[196]



470 **471** **472** **473**

Scheme 1.123. *In situ* aza-Michael addition reaction.

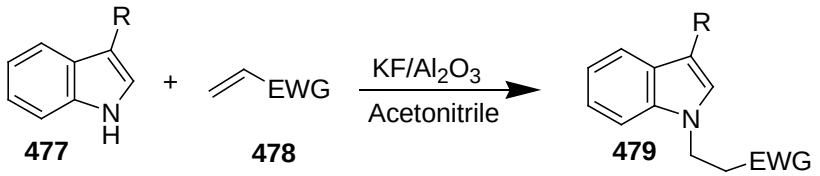
Heterogeneous catalysts have also been employed in the aza-Michael addition of triazoles. Xie et al. prepared MCM-41 supported heteropoly acid catalysts and evaluated their catalytic activity. The reaction of benzotriazole with nitroolefins proceeded at room temperature in water in the presence of a catalyst. The catalysts could be reused up to 6 times without significant loss in the activity (**Scheme 1.124**).[197]



Scheme 1.124. Aza-Michael addition of benzotriazole to nitroolefines catalyzed by PW/MCM-41.

Indoles and their derivatives exhibit a wide range of biological activities. Several methods have been developed for the reaction of indoles with carbonyl compounds using catalysts such as silica sulfuric acid,[198] Ru(III),[199] $H_3PMo_{12}O_{40}.xH_2O$,[200] P_2O_5/SiO_2,[201] silica chloride,[202] $ZrOCl_2.8H_2O$,[203] PPh3-HClO4(TPP),[204] AlPW12O40,[205] In(OTf)3,[206] Dy(OTf)3,[207] and La(PFO)3[208].

Indoles are involved in the aza-Michael addition with methyl vinyl ketone and acrylic acid derivatives in the presence of base catalyst such as KF/Al_2O_3[209-211] and DBU[212]. KF/Al_2O_3 efficiently catalyzed the aza-Michael addition of indole and 3-methyl indole to a variety of electron-deficient conjugate alkenes such as α,β-unsaturated ketones, amides and nitriles. However, reaction was not found to be successful with unsaturated esters and aldehydes (**Scheme 1.125**).[212,213]



Scheme 1.125. Aza-Michael addition of indoles with electron-deficient conjugated alkenes.

1.5. Problem Statement

After careful analysis of the review, following gaps could be located:

1. No studies have been carried out so far of the reactions of secondary amines with maleic anhydride.
2. Only one reference could be found about the studies of aza-Michael addition under kinetic and thermodynamic controls. However, the reaction of secondary amines with maleic anhydride has not been investigated so far under kinetic and thermodynamic controls.
3. No studies could be found about correlation of the site selectivity in the attack of the amine on different position of α,β-unsaturated carbonyl compounds with condensed Fukui Functions.
4. We could not find any reference about the reactions involving amines namely, 1-methylpiperazine, morpholine, pyrrolidine, diethylamine, benzylamine, 2-methylpiperidine, 2,6-dimethylpiperidine and 1-amino-4-methylpiperazine with methyl propiolate.
5. No theoretical studies about the reaction mechanism of the reaction of secondary amine with methyl propiolate were found.
6. As regards the reaction of benzylamine with methyl propiolate, only speculative propositions have been made about the mechanism of *trans*-*cis* isomerisation and no theoretical studies have been undertaken so far.
7. We could not find study of diastereoselectivity in asymmetric Michael addition of R, and S-α-methylbenzylamines with cinnamaldehyde, crotonaldehyde, 4-nitrocinnamic acid, 4-nitrocinnamaldehyde, methyl *trans*-cinnnamate and *trans*-2-methyl-2-butenal.
8. No tin complexes have been prepared with maleamic acids.

1.6. Technology Available

A well-equipped laboratory for organic synthesis is available in the Chemistry Department at The IIS University.

The facilities for screening the organic compounds for their bioactivities, namely antibacterial are available at the Department of Biotechnology at The IIS University. The facilities for getting elemental analysis and spectral studies, namely IR, NMR and HRMS can be availed at the local institutes, Malviya National Institute of Technology and Thera Chem Pvt. Ltd. on payment basis.

After taking into account the gaps in the literature and facilities available locally, following objectives were set for the research work.

1.7. Objectives

1. To investigate the reaction of some secondary amines with maleic anhydride experimentally and theoretically.
2. To study these reactions under kinetic and thermodynamic control.
3. To correlate the site selectivity in the attack of the amine on different positions of maleic anhydride with condensed Fukui Functions and its comparison with the corresponding amines with acrolein.
4. To undertake experimental and theoretical investigation of aza-Michael addition of amines, namely 1-methylpiperazine, morpholine, pyrrolidine, diethylamine, benzylamine, 2-methylpiperidine, 2,6-dimethylpiperidine and 1-amino-4-methylpiperazine with methyl propiolate.
5. To investigate mechanism of the reaction of secondary amine with methyl propiolate theoretically at the DFT level.

6. To investigate the mechanism of *trans-cis* isomerisation in the reaction of benzylamine with methyl propiolate theoretically at the DFT level.
7. To determine experimentally diastereoselectivity in asymmetric Michael addition of R, and S-α-methylbenzylamines with some α,β-unsaturated carbonyl compounds and rationalize the results by computational calculations.
8. To synthesize and characterize tin complexes with maleamic acids.
9. To screen the newly formed complexes for their anti-bacterial activity against Gram positive and Gram negative bacteria.