RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Adv.*, 2024, **14**, 30758

Recent advances in the synthesis of highly substituted imidazolidines

Abolfazl Olyaei *[a] and Mahdieh Sadeghpour [b]

Received 19th August 2024
Accepted 20th September 2024

DOI: 10.1039/d4ra06010e

rsc.li/rsc-advances

Imidazolidine is a saturated heterocycle with a cyclic aminal core that can be found in natural products and biologically active molecules. Additionally, these heterocyclic compounds have been utilized as chiral ligands, N-heterocyclic carbene precursors, and catalysts in organic synthesis. This review is an attempt to compile the literature of various synthetic procedures of highly substituted imidazolidines, chiral imidazolidines with high diastereoselectivities and enantioselectivities, bis-imidazolidines, and spiro-imidazolidines, as well as their pharmacological properties during the period from 1949 to 2023.

1 Introduction

Heterocyclic compounds are important structural motifs commonly found in natural products and biologically active molecules, playing a significant role in medicinal chemistry due to their diverse applications and potent effects. Among these heterocyclic compounds, imidazolidine, tetrahydroimidazole, frameworks are prevalent in numerous natural alkaloids (*e.g.*, (−)-chaetominine)[1] and an intrinsic part of various naturally occurring bioactive substances such as chaetominine, fumiquinazolines A, tryptoquivalin G, and kifunensine.[2–7] They serve as chiral ligands, auxiliaries, and N-heterocyclic carbene (NHC) precursors and catalysts in organic catalysis (*e.g.*, MacMillan's catalyst).[8–11] They also form essential structural motifs in synthetic biologically active compounds[12] and hold significant potential in drug discovery, including applications as antipyretic agents and cannabinoid CB2 receptor agonists.[13,14] Moreover, they have shown fungicidal, antiparasitic, antibacterial, antiamebic, and antiviral activities.[15,16] Due to their unique structural characteristics and impressive applications, a number of synthetic strategies have been devoted to the preparation of diversely substituted imidazolidines. In 1954,

[a] *Department of Chemistry, Faculty of Science, Imam Khomeini International University, Qazvin, Iran. E-mail: olyaei_a@sci.ikiu.ac.ir*

[b] *Department of Chemistry, Qazvin Branch, Islamic Azad University, Qazvin, Iran*

Abolfazl Olyaei

Associate professor Dr Abolfazl Olyaei was born in Tabriz, Iran in 1975. He received the BSc degree in pure chemistry from Tabriz University, Tabriz, Iran in 1999 and the MSc degree in organic chemistry from Tehran University, Tehran, Iran under the supervision of professor Mohammad Raouf Darvich in 2001. He obtained PhD degree in organic chemistry from Tehran University, Tehran, Iran under the supervision of professor Mehdi Ghandi, in 2007. He is as an associate professor in Imam Khomeini International University, Qazvin, Iran. His research interests include organic synthesis, synthesis of heterocyclic compounds, multi-component reactions, green chemistry, catalysis and organocatalysis and applications of materials and organomaterials in different sciences.

Mahdieh Sadeghpour

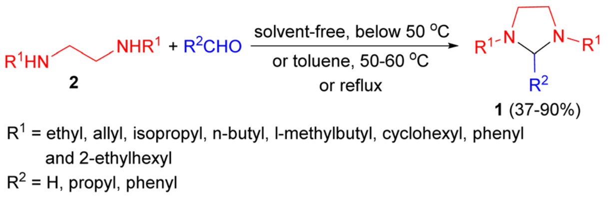
Associate professor Dr Mahdieh Sadeghpour was born in Qazvin, Iran in 1978. She received the BSc degree in pure chemistry from Alzahra University, Tehran, Iran in 2001 and the MSc degree in organic chemistry from Tehran University, Tehran, Iran under the supervision of assistance professor Nikoo Sedighi in 2004. She obtained PhD degree in organic chemistry from Kharazmi University, Tehran, Iran under the supervision of professor Abbas Shokravi and associate professor Abolfazl Olyaei, in 2009. She is as an associate professor in Islamic Azad University of Qazvin, Iran. Her research field is on the synthesis of organic compounds, multi-component reactions, synthetic methodology, green chemistry and applications of materials and nanomaterials in different sciences.

the first review article on the chemistry of 2-imidazolines and imidazolidines was published.[17] Since then, no separate review article on the synthesis of imidazolidine derivatives has been published. In this review, we aim to describe the synthesis strategies of imidazolidine derivatives, including poly substituted imidazolidines, chiral imidazolidines with high diastereoselectivities and enantioselectivities, bis-imidazolidines, and spiro-imidazolidines, as well as their pharmacological properties from 1949 to 2023.

2 Synthesis of imidazolidines

2.1. Synthesis of highly substituted imidazolidines

In 1949, Donia and co-workers reported the first synthesis of 1,3-dialkylimidazolidines **1** in 37–90% yields by the condensation reaction of aldehydes (formaldehyde, butyraldehyde, and benzaldehyde) with *N*,*N*′-disubstituted ethylenediamines **2** in which the substituents were ethyl, allyl, isopropyl, *n*-butyl, *l*-methylbutyl, cyclohexyl, phenyl and 2-ethylhexyl. This condensation proceeded most readily with formaldehyde, with or without a solvent at temperature below 50 °C, afforded the corresponding 1,3-imidazolidines. With butyraldehyde and benzaldehyde, the reactions producing 2-substituted imidazolidines proceeded more slowly, and were aided by warming in the presence of toluene (50–60 °C or reflux conditions) and separation of the water formed (Scheme 1).[18]



Scheme 1 Solvent-free synthesis of 1,3-dialkylimidazolidines **1**.

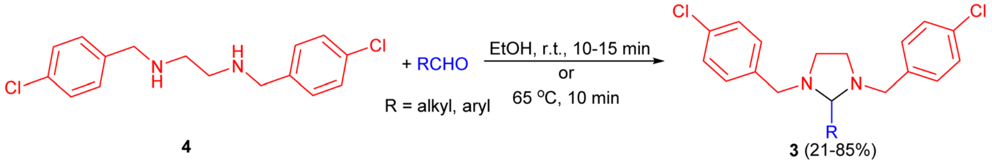
In 1957, Billman described synthesis a series of 2-substituted-1,3-bis (*p*-chlorobenzy1)imidazolidines **3** in 21–85% yields from 1,2-bis(*p*-chlorobenzylamino)ethane **4** and numerous aldehydes in absolute alcohol under shaken occasionally at room temperature for 10 to 15 minutes or 65 °C for 10 minutes. Treatment of the imidazolidines with acid regenerates the diamine and aldehyde in nearly quantitative yields. However, compound **4** did not react with ketones under the experimental conditions used. From this evidence, it appears that compound **4** can be used as a specific reagent for aldehydes in the presence of ketones (Scheme 2).[19]

In 1959, Jaenlcke and Erode developed synthesis of 1,3-diarylimidazolidine derivatives **5** in 75–91% yields by the reaction of substituted *N*,*N*′-diphenylethylenediamines **6** with formaldehyde (30%) in CH_3OH or ethyl acetate in the presence of acetic acid (Scheme 3).[20]

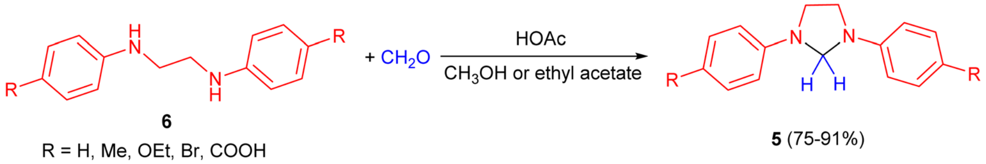
In 1967, the Joullie group described the reaction of 1,2-ethylenediamine (**7**) with ethyl trifluoroacetoacetate (**8**) in xylene refluxing in a flask equipped with a Dean–Stark trap. The solution was refluxed for 1 hour, after the separation of water was completed and left standing overnight. During this procedure, the products, namely 1,2,3,4-tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one (**9**) and ethyl 2-(trifluoromethyl)-2-imidazolidineacetate (**10**) were obtained with yields of 16% and 25%, respectively. Moreover, l,4-diazaspiro[4,5]decan (**11**) synthesized by the same group in 37% yield *via* the reaction of cyclohexanone with **1** in benzene under reflux condition in a flask with a Dean–Stark trap (Scheme 4).[21]

In 1969, Lown and co-workers explored the synthesis of 1-alkyl-2,4-diaryl-5-aroyl-3-(*N*-arylsulfonyl)-imidazolidines **12** in 14.5–94% yields through the reaction of 3-aroylaziridines **13** with aryl-*N*-sulfonylimines **14** in refluxing benzene. The orientation of the [2 + 3] cycloaddition of the intermediate azomethine ylids to the C=N double bond was proven by synthesis of specifically 5-deuterated imidazolidines (Scheme 5).[22]

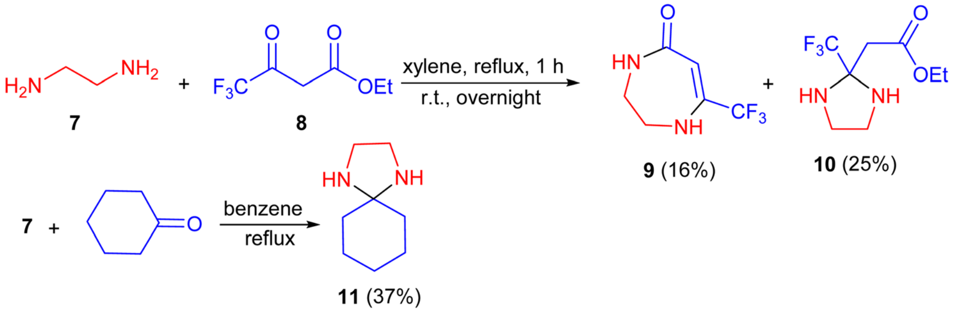
In 1973, Birch and Dastu demonstrated a method for the synthesis of dihydroimidazolidine. In this process, at first, the reaction of 4-isopropylbenzaldehyde with *N*,*N*′-dimethylethylenediamine (**15**) in benzene at 60 °C for 2 hours resulted 1,3-dimethyl-2-(4′-isopropylphenyl)imidazolidine **16** in 69% yield followed by the reduction of **16** with lithium/ammonia in dry tetrahydrofuran and *t*-butyl alcohol under reflux with stirring for 2 hours afforded the desired imidazolidine **17** (Scheme 6).[23]



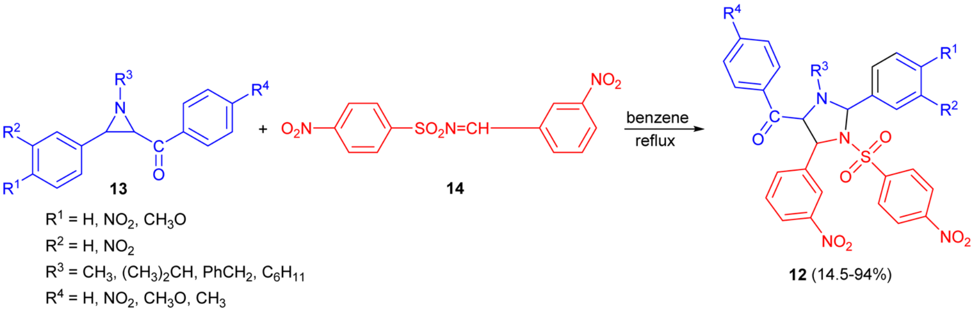
Scheme 2 Synthesis of 2-substituted-1,3-bis(*p*-chlorobenzy1)imidazolidines **3**.



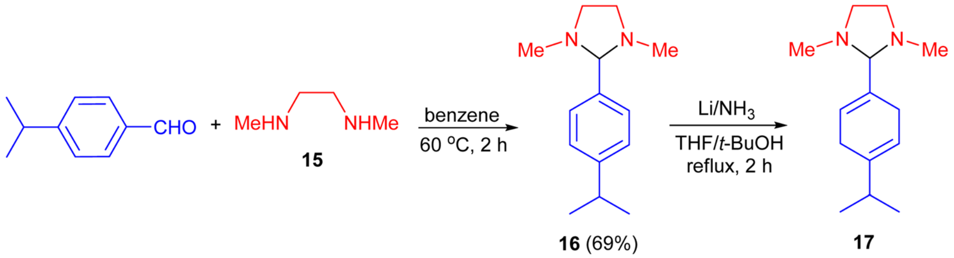
Scheme 3 HOAc catalyzed synthesis of 1,3-diarylimidazolidine derivatives **5**.



Scheme 4 Synthesis of imidazolidine derivatives **10** and **11**.



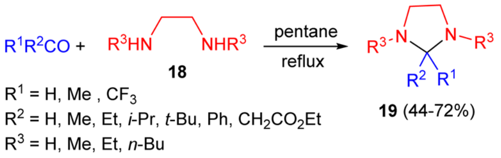
Scheme 5 Synthesis of 1-alkyl-2,4-diaryl-5-aroyl-3-(*N*-arylsulfonyl)-imidazolidines **12**.



Scheme 6 Synthesis of dihydroimidazolidines **16** and **17**.

Next, Hine and his group reported the reaction of carbonyl compounds with *N*,*N*′-dialkylethylenediamine **18** in pentane under reflux conditions gave imidazolidine derivatives **19** in 44–72% yields as depicted in Scheme 7.[24]

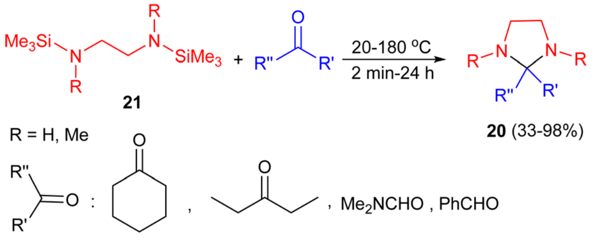
In 1975, Itoh group synthesized imidazolidine derivatives **20** in 33–98% yields by condensation reaction of *N*,*N*′-bis(trimethylsilyl)1,2-diamines **21** with carbonyl compounds *via* the elimination of hexamethyldisiloxane. The reactions were conducted with cyclohexanone and benzaldehyde at 20 °C for 2 minutes, and with diethyl ketone and DMF at 120–180 °C for 1–24 hours (Scheme 8).[25]



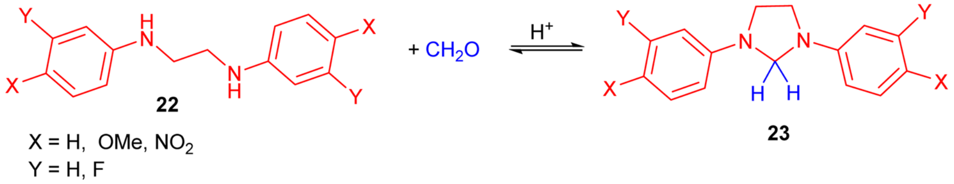
Scheme 7 Preparation of imidazolidine derivatives **19**.

The downward deviations in the pH-rate profiles between 4–6 for the reactions of a series of symmetrically *meta*- or *para*-substituted *N*,*N*′-diphenylethylenediamines **22** with formaldehyde in dioxane–water afforded the imidazolidines **23** (Scheme 9). In this process, kinetic studies of the reactions were investigated.[26]

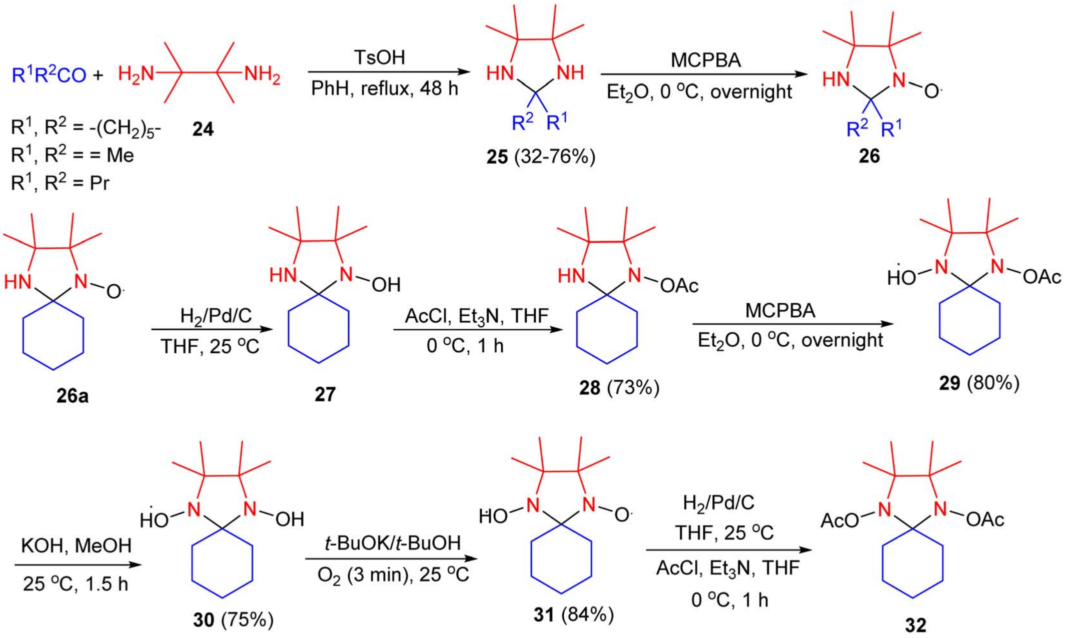
In 1978, Keana and co-workers described a new series of mono- and dinitroxide spin labels derived by oxidation of



Scheme 8 Synthesis of imidazolidine derivatives **20**.



Scheme 9 Acid catalyzed preparation of imidazolidines **23**.



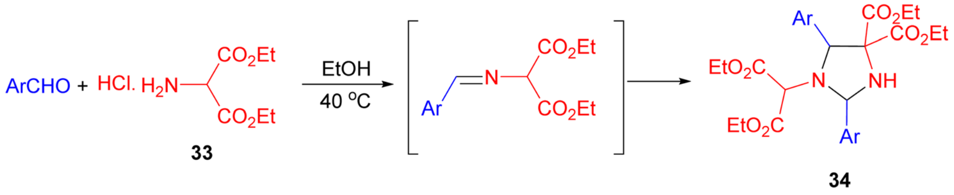
Scheme 10 Synthesis of imidazolidine derivatives **25–32**.

2,2,4,4,5,5-hexasubstituted imidazolidines. Condensation of 2,3-diamino-2,3-dimethylbutane **24** with ketones in the presence of TsOH in benzene under reflux conditions for 48 hours, led to the corresponding imidazolidines **25** in 32–76% yields. Oxidation with 1.5 equiv. of *m*-chloroperoxybenzoic acid (MCPA) in ether at 0 °C for overnight gave the corresponding mononitroxides **26.** Catalytic hydrogenation (Pd/C, THF) of **26a** at 25 °C gave **27** which, without isolation, was acetylated (AcCl, Et_3N, THF) to give **28** in 73% yield. Oxidation of **28** with MCPA in ether gave nitroxide **29** in 80% yield. Hydrolysis in the presence of KOH in MeOH yielded **30** in 75% yield. Oxidation of **30** in the presence of KO-*t*-Bu in *t*-BuOH gave dinitroxide **31** in 84% yield. Using a procedure analogous to the preparation of **27** and **28**, compound **31** gave diacetate **32** (Scheme 10).[27]

In 1980, Amornraksa and Grigg demonstrated the reaction of arylaldehydes with diethyl aminomalonate hydrochloride **33** in the presence of 1 equiv. of sodium ethoxide in ethanol at 40 °C gave the imidazolidines **34** (Scheme 11).[28]

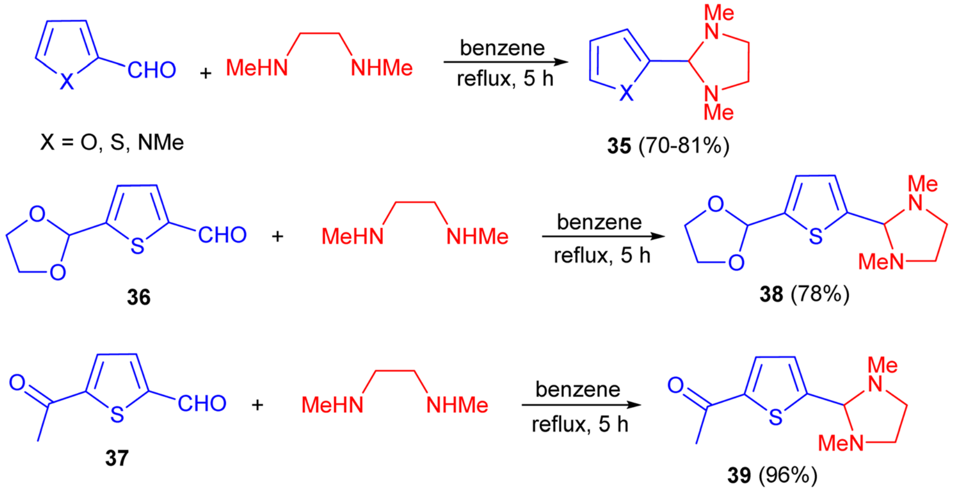
In 1985, Chadwick and his group developed synthesis of imidazolidine derivatives **35** in 70–81% yields by the reaction of thiophene-2-carboxaldehyde/furan-2-carboxaldehyde/1-methylpyrrole-2-carboxaldehyde with *N*,*N*′-dimethylethylenediamine in benzene under reflux for 5 hours with azeotropic removal of water. Also, treatment of **36** and **37** with *N*,*N*′-dimethylethylenediamine in the same reaction conditions afforded imidazolidines **38** and **39** in 78 and 96% yields, respectively (Scheme 12).[29]

In 1993, a one-step synthesis of 1,3-bis[2′-hydroxy-5′-substituted-benzyl]imidazolidines **40** in 21.4–28.1% yields



Ar = 5-(2-phenylthiazoyl), Ph, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 2-furyl, 2-thienyl, 2-pyridyl

Scheme 11 Synthesis of imidazolidines **34** in the presence of sodium ethoxide in ethanol.

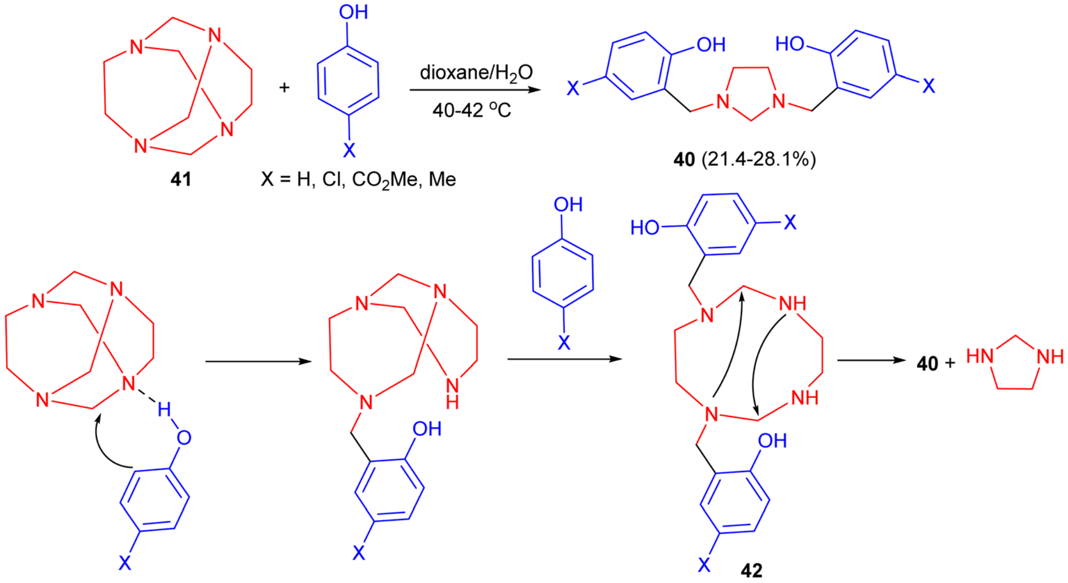


Scheme 12 Synthesis of imidazolidine derivatives **35**, **38** and **39**.

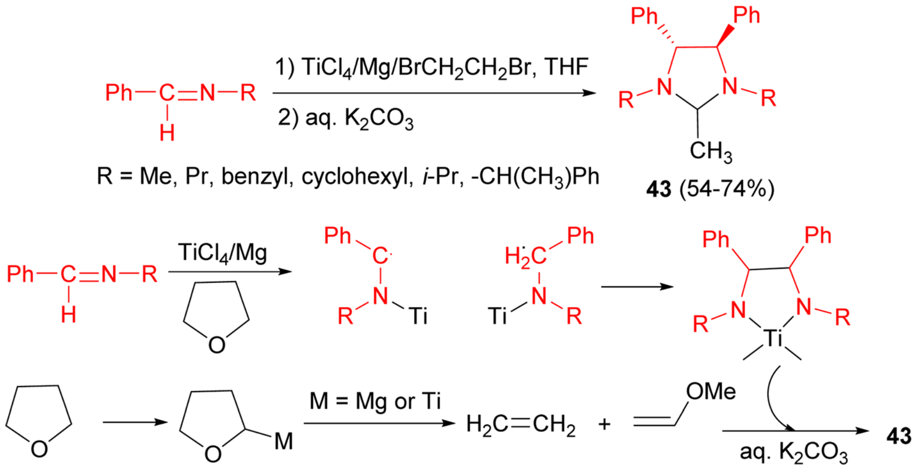
using a Mannich type reaction in basic media was described by Rivera and his group. The reaction was carried out by condensation of tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) (**41**) with a number of *p*-substituted phenols by heating the reactants in aqueous dioxane solution at 40–42 °C. A plausible mechanism is illustrated in Scheme 13. First, when phenol is added to TATD the initially formed hydrogen bond could undergo mono protonation of any of the four nitrogen atoms. Introduction of a proton between nitrogens leads to polarization of the adjacent methylene (aminalic) groups. In agreement with known electrophilic substitution to aromatic rings, the reaction involves the successive attack of two molecules of the phenol. The possible intermediate **42**, not yet isolated, undergoes intramolecular condensation to gain stability.[30]

In 1996, Perisamy and co-workers revealed the reaction of low valent titanium reagent, prepared *in situ* in THF by the reduction of $TiCl_4$ by Mg powder, with certain imines in the presence of 1,2-dibromoethane at 25 °C led to the formation of imidazolidine derivatives **43** in 54–74% yields after 10 hours. The 1,2-dibromoethane was utilized in order to activate Mg. A tentative mechanism is shown in Scheme 14. A possibility is that the $TiCl_4$/Mg system may generate certain reactive species of titanium and/or Mg–X species which might metallate THF leading to cleavage of THF.[31]

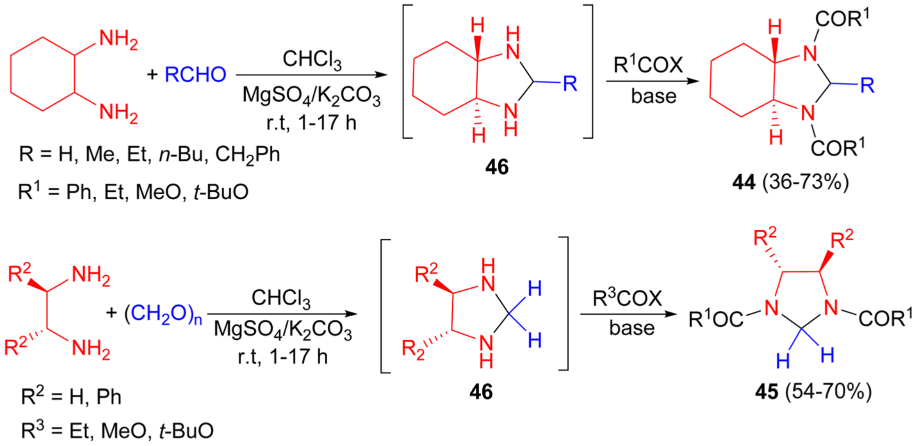
The Coldham group developed a one-pot, two stage process for the preparation of imidazolidines **44** and **45** in 36–73% yields bearing acyl groups on the nitrogen atoms. 1,2-Diamines were condensed with a variety of aldehydes in $CHCl_3$ in the presence of K_2CO_3/$MgSO_4$ at room temperature for 1–17 hours and the subsequent *N*,*N*′-bisunsubstituted imidazolidines **46** were acylated with a selection of acid chlorides at room temperature in the presence of pyridine or Et_3N for 1–2 hours or acid anhydrides in the absence of base for 17–20 hours (Scheme 15).[32]



Scheme 13 Synthesis of 1,3-bis[2′-hydroxy-5′-substituted-benzyl]imidazolidines **40**.



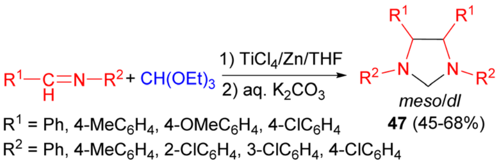
Scheme 14 $TiCl_4$/Mg promoted synthesis of imidazolidine derivatives **43**.



Scheme 15 Preparation of imidazolidines **44** and **45** in the presence of K_2CO_3/$MgSO_4$.

In 1999, Chen and co-workers revealed under the action of a low-valent titanium/Zn reagent, imidazolidine derivatives **47** were synthesized in 45–68% yields from imines and triethyl orthoformate in THF for 50 hours. During this procedure, two isomers (*meso* and *dl*) were obtained in different ratios (Scheme 16). The pure isomer can be obtained by recrystallization.[33]

After that, μ-bis (tetradentate)hydroxybenzamidoimidazolidine ligand **48** synthesized in 65% yield by the reaction of ligand H_4L **49** with salicylaldehyde in methanol in ice-bath for 1 hour, then another period of 0.5 hours at ambient temperature (Scheme 17).[34]



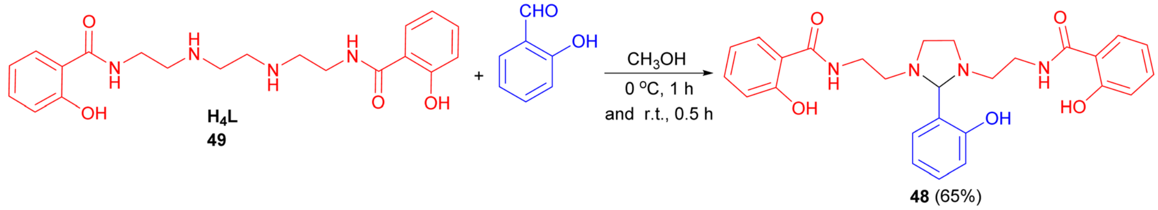
Scheme 16 Preparation of imidazolidine derivatives **47** in the presence of $TiCl_4$/Zn.

Further, starting from glyoxal, 1,3-diarylimidazolinium chlorides **50** were obtained in a three-step sequence *via* the diimines **51** and ethylene diamine dihydrochlorides **52**. Reduction of 1,3-diarylimidazolinium chlorides **50** with lithium aluminium hydride in ether at 23 °C for 2 hours furnished the 1,3-diarylimidazolidines **53** in 52–74% yields (Scheme 18).[35]

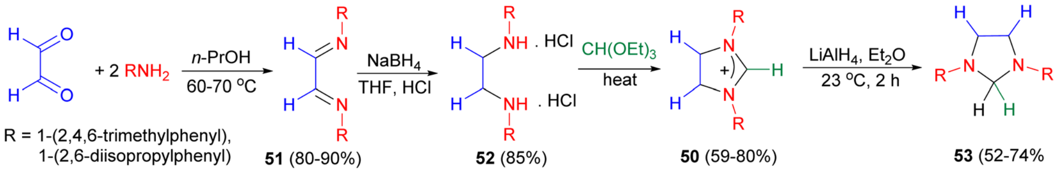
Next, the Sosnovskikh group explored the reactions of aromatic and heteroaromatic β-amino-β-polyfluoroalkylvinyl ketones **54** with ethylenediamine at 20 °C for 1–3 hours resulted in the formation of *N*,*N*′-unsubstituted imidazolidines **55** in 65–95% yields; on refluxing in ethanol for 3 hours. These products were converted into thermodynamically more stable dihydrodiazepines **56** with liberation of water (Scheme 19).[36]

In 2000, Tanaka *et al.* developed a simple and green procedure for the synthesis of various kinds of tetrahydroimidazoles **57** in 86–95% yields by condensation reactions of aldehydes with *N*,*N*′-disubstituted ethylenediamines in a water suspension medium at room temperature for 0.5–4 hours (Scheme 20).[37]

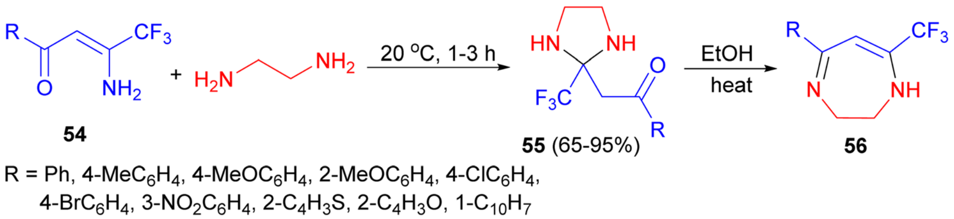
The Lyapova group demonstrated the quantitative reduction of compounds **58**, achieved by utilizing $LiAlH_4$ in diethyl ether



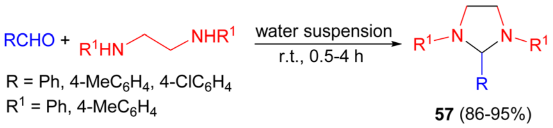
Scheme 17 Synthesis of µ-bis (tetradentate)hydroxybenzamidoimidazolidine ligand **48**.



Scheme 18 Synthesis of 1,3-diarylimidazolidines **53** starting from glyoxal.



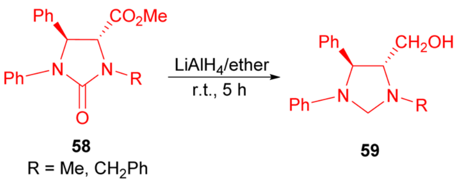
Scheme 19 Synthesis of *N*,*N*′-unsubstituted imidazolidines **55**.



Scheme 20 Water suspension medium synthesis of tetrahydroimidazoles **57**.

and benzene at room temperature for 5 hours. This process led to the formation of *trans*-imidazolidines **59** (Scheme 21).[38]

A one-step synthesis of imidazolidines **60** from 1,3-bis(2′-hydroxy-5′-substituted benzy1)imidazolidines **61** and aromatic aldehydes has been reported by Rivera and coworkers. The reaction was carried out in 1,4-dioxane at 60–101 °C for 50–72 hours, led to the formation of the desired products in 18–40% yields (Scheme 22). The relative stereochemistry of the five-membered ring was evident from ^{1}H-NMR measurements combined with MMX calculations.[39]

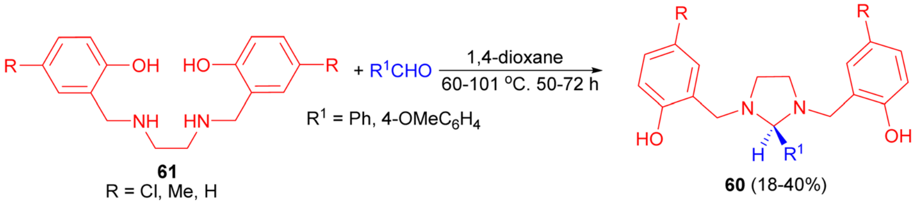


Scheme 21 Synthesis of *trans*-imidazolidines **59**.

Next, a method for the synthesis of 2-substituted *N*,*N*′-diacylimidazolidines **62** in 10–85% yields was developed. The method based on the reactions of acylating reagents (carboxylic acid chlorides and anhydrides, sulfonic acid chlorides, a carbamic acid chloride and ethyl chlorocarbonate) with Schiff bases **63** in the presence of Et_3N in CH_3CN at room temperature for 1–6 hours (Scheme 23).[40]

In 2001, the Sharma and Khan reported synthesis of tetrahydroimidazoles **64** from ethylenediamine and aromatic aldehydes. In this reaction, initially, ethylenediamine was reacted with suitable aromatic aldehydes in order to prepare their respective bis-Schiff bases **65**. Then, these compounds were reduced to give the corresponding tetrahydro bis-Schiff bases **66**. Finally, these derivatives were condensed with different aromatic aldehydes to give the desired tetrahydroimidazoles **64** in 62–79% yields (Scheme 24). These tetrahydroimidazoles showed promising anti-inflammatory, anti-bacterial property against *Staphylococcus aureus* and *Escherichia coli* and analgesic activities.[41]

Next, Coldham *et al.* demonstrated synthesis of imidazolidine **67** in one step from *N*-iso-propylethylenediamine, paraformaldehyde, $MgSO_4$ and K_2CO_3, followed by addition of Boc_2O. Then, imidazolidine **67** converted to imidazolidine **68** at −78 °C by using the standard conditions for asymmetric deprotonation, with *sec*-BuLi in Et_2O and (−)-sparteine after 4–48 hours with high optical purity. Hydrolysis of imidazolidine **68** (carried out for R = $SiMe_3$, $SiMePh_2$, Me, allyl) using malonic



Scheme 22 Preparation of imidazolidines **60**.

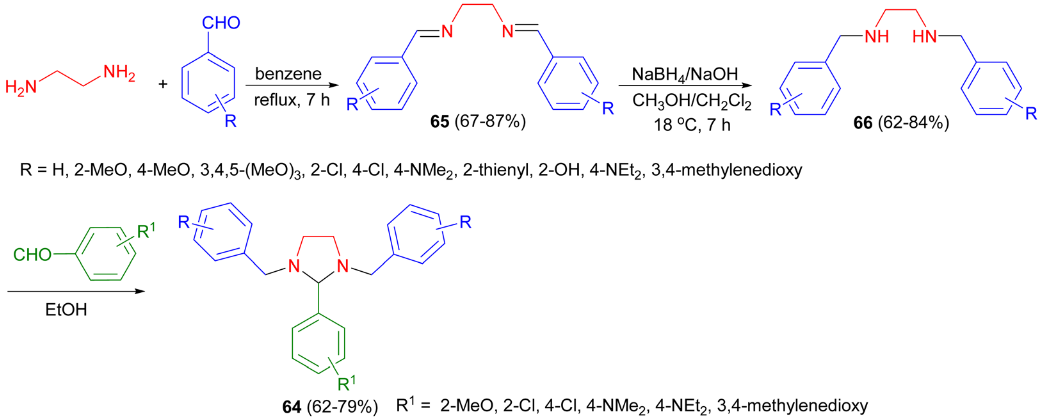
Scheme 23 Synthesis of 2-substituted *N*,*N*′-diacylimidazolidines **62**.

acid resulted in the selective formation of the amino-carbamate **69**, without loss of the *N*-Boc group (Scheme 25).[42]

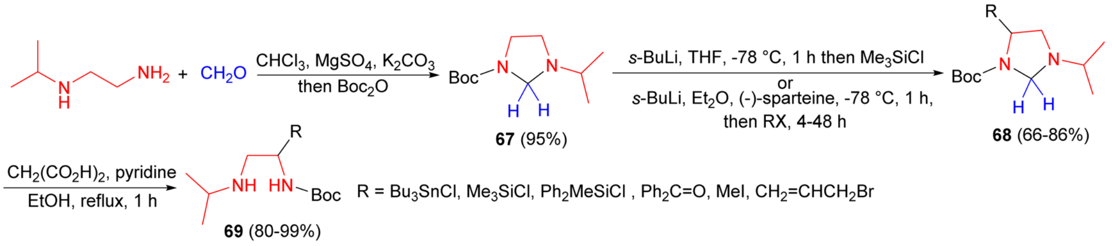
After that, the cross-coupling reaction of Schiff bases **70** with methylene diiodide in the presence of $TiCl_4$/Sm in THF at room temperature for 10–14 hours to give imidazolidine derivatives **71** in 60–75% yields (Scheme 26).[43]

In addition, phase-transfer catalyzed reaction of *N*-(benzylidene)benzylamine with arylmethyleneanilines **72** using NaOH afforded the stereoisomeric 1,2,4,5-tetraarylimidazolidines **73** and **74** *via* a two-step addition–cyclisation mechanism. In all cases formation of both **73** and **74** was observed, but further crystallisation of the mixtures yielded pure **73** or **74** (Scheme 27).[44]

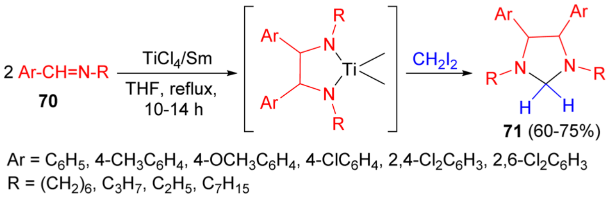
In 2002, Katritzky and co-workers developed synthesis of unsymmetrical imidazolidines **75** in 90–96% yields by Mannich reaction of 1,2-ethanediamines **76** with benzotriazole and formaldehyde in CH_3OH/H_2O for 4 hours at 20 °C. Then, the other imidazolidines **77** synthesized from **75** under various conditions as depicted in Scheme 28. Also, the same group reported optically active imidazolidines **78–81** in 66–99% yields. At first, reaction of diamines with benzotriazole and formaldehyde generated benzotriazol-1-yl intermediates **78** in 85–93% yields. Then, nucleophilic substitutions of **78** by Grignard



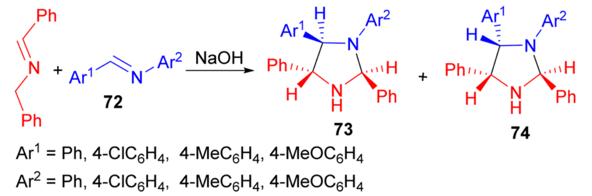
Scheme 24 Synthesis of tetrahydroimidazoles **64** starting from ethylenediamine.



Scheme 25 Preparation of imidazolidines **67** and **68**.



Scheme 26 TiCl$_4$/Sm catalyzed synthesis of imidazolidines **71**.



Scheme 27 NaOH catalyzed synthesis of tetraarylimidazolidines **73** and **74**.

reagents, triethyl phosphite, or sodium cyanide gave the desired product **79–81** (Scheme 28).[45]

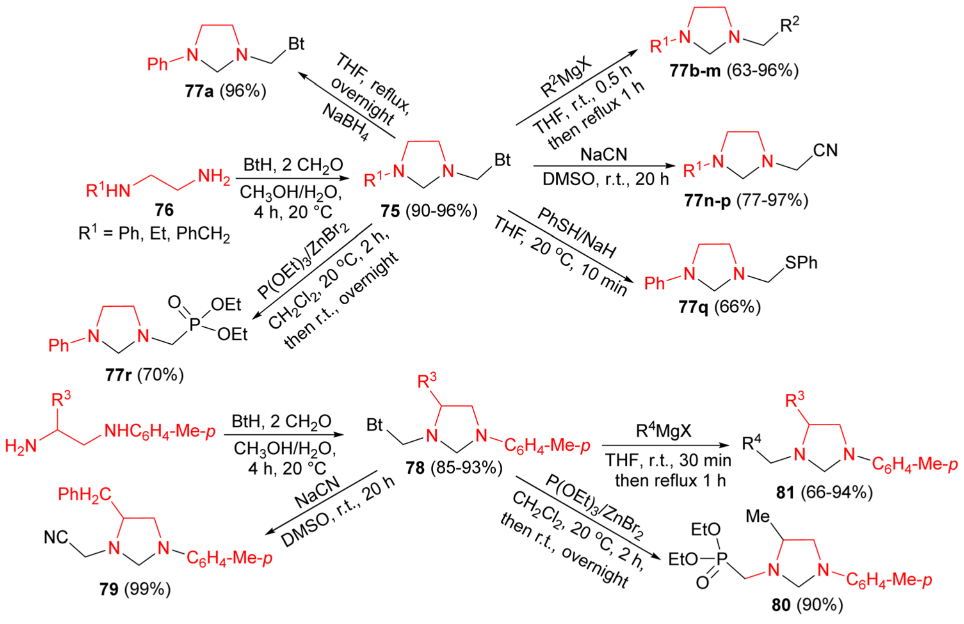
In addition, several 1,2,3-trisubstituted tetrahydroimidazoles **82** in 25–79% yields were synthesized by Khan and Chawla. Synthesis of these compounds is based on formation of di-Schiff bases **83** formed by condensing two moles of aromatic aldehydes with ethylene diamine in dry benzene under reflux conditions. These Schiff bases on reduction with NaBH$_4$ in methanol and methylene chloride under ice-cold condition for 7 hours gave substituted *N*,*N′*-dibenzyl ethylene diamines **84** which on subsequent condensation with various aromatic aldehydes in ethanol for 5–10 hours at room temperature gave tetrahydroimidazoles **82** (Scheme 29). These compounds showed excellent and far superior anti-inflammatory activity as compared to indomethacin.[46]

Next, Katritzky group described synthesis of unsymmetrical imidazolidines **85** in 85–96% yields by Mannich reactions of 1,2-ethanediamines **86** with benzotriazole **87** and formaldehyde in MeOH/H$_2$O at room temperature for 4 hours. Nucleophilic substitutions of **85** with NaBH$_4$, Grignard reagents, sodium cyanide, benzenethiol, and triethyl phosphite afforded unsymmetrical imidazolidines **88–92** in 63–97% yields. Also, the reaction of diamines **93** with benzotriazole and formaldehyde generated benzotriazol-1-yl intermediates **94** in 85–93% yields. Nucleophilic substitutions of **94** by Grignard reagents, triethyl phosphite, or sodium cyanide gave optically active imidazolidines **95–97** in 66–99% yields (Scheme 30).[47]

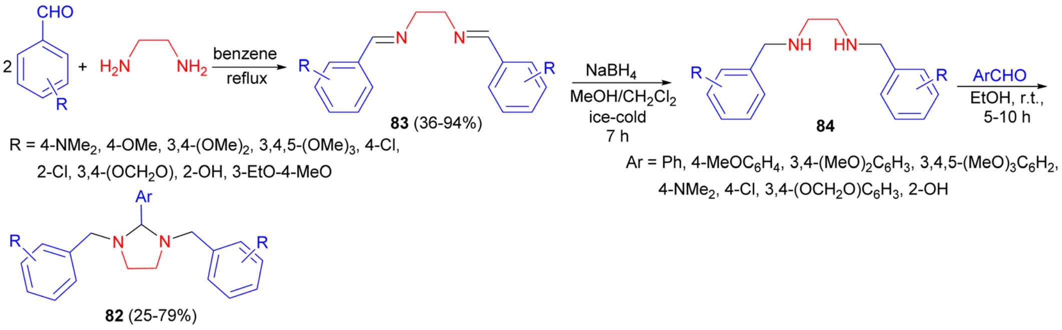
In addition, the Pearson group reported deprotonation of the imine **98** in THF or benzene, with LDA in cyclohexane which cannot lead to cycloaddition owing to the absence of an alkene, resulted in the formation of the imidazolidines **99** and **100** in 83% yield after 5 hours. Interestingly, the regioselectivity of the dimerization was found to depend on the solvent, providing complementary results. Also, the reaction of (D,L-)-stilbenediamine **101** with acetone in THF at room temperature for overnight afforded imidazolidine **102**. The crude compound **102** was dissolved in absolute ethanol and treated with NaBH$_4$ in EtOH for overnight resulted (1*R**, 2*S**)-*N*-(1-methylethyl)-1,2-diphenyl-1,2-ethanediamine **103** in 89% yield.

Then, compound **103** was treated with 5-hexenal or with 5-phenyl-5-hexenal in ether for overnight afforded imidazoldines **104** (88%) and **105** (86%), respectively (Scheme 31).[48]

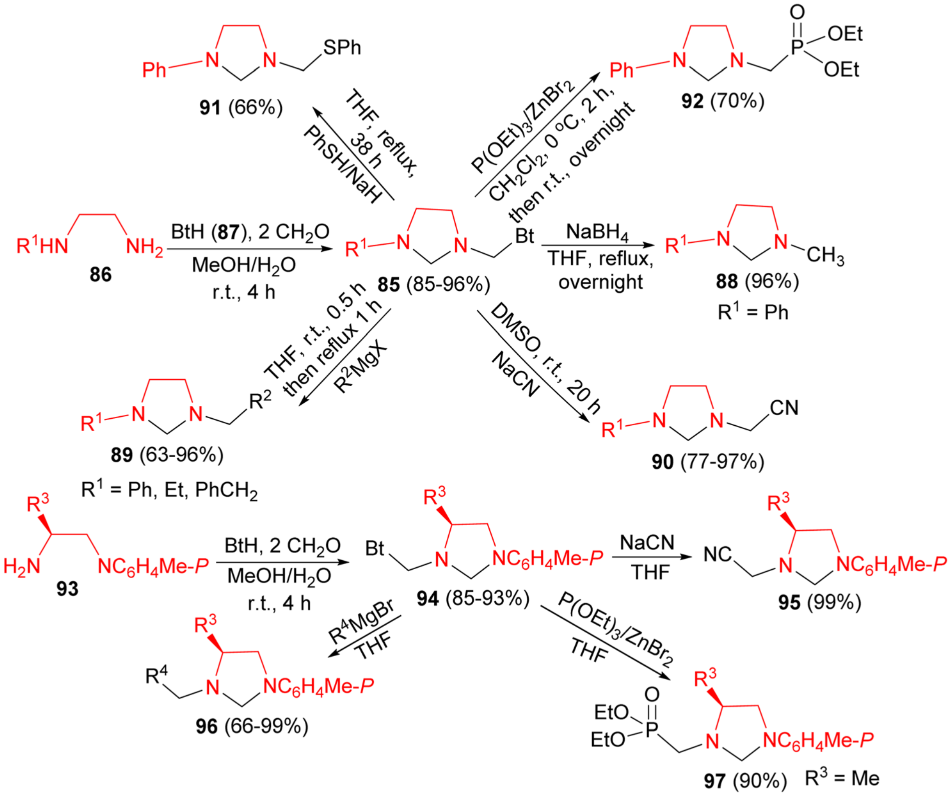
In 2003, Kelarev and co-workers revealed that by acylating bisazomethine **106** with aromatic and heteroaromatic acid chlorides in acetonitrile (boiling, 2–3 hours) in the presence of triethylamine, 1,3-diacyl-2-[3,5-di(*tert*-butyl)-4-hydroxyphenyl] imidazolidines **107** were formed in good yields (Scheme 32).[49]



Scheme 28 Synthesis of unsymmetrical imidazolidines **75**, **77**, **78–81** by Mannich reaction.



Scheme 29 Synthesis of 1,2,3-trisubstituted tetrahydroimidazoles **82**.

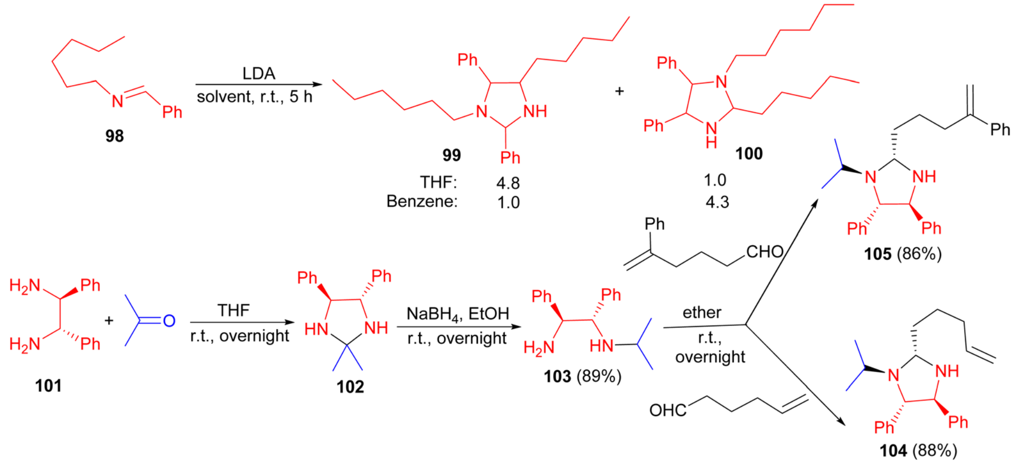


Scheme 30 Convenient syntheses of unsymmetrical imidazolidines **85**, **88–92** and **94–97**.

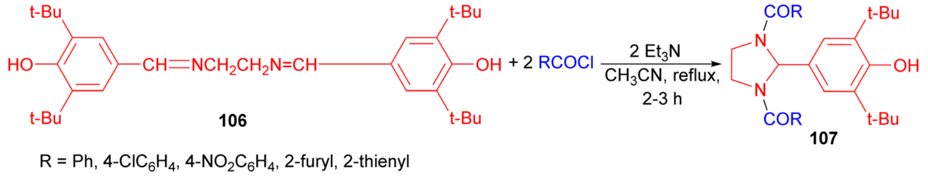
Next, Khan and Gupta reported synthesis and evaluation of anti-inflammatory and analgesic activity of some 1,3-diphenyl-2-aryltetrahydroimidazoles **108** in 54–60% yields *via* condensation of 1,2-dianilinoethane (**109**) with various aldehydes in EtOH at room temperature for 6–8 hours (Scheme 33). These compounds demonstrated significant anti-inflammatory effects compared to animals treated with normal saline. Furthermore, their analgesic activity was assessed. Compounds **108a–b** exhibited similar effectiveness to aspirin. The Maximum Tolerated Dose (MTD) for all compounds was determined to be greater than 1800 mg kg^{-1}.[50]

After that, the Hu group demonstrated unsymmetrical imidazolidines **110** were obtained in 75–91% yields by treating monoalkoxycarbonyl vicinal diamines **111** at room temperature with aqueous 37% formaldehyde in the presence of montmorillonite KSF as a solid catalyst in THF at room temperature for 1 hour (Scheme 34). The imidazolidines were shown to be useful intermediates in a novel protection strategy for the synthesis of peptide analogues containing a reduced glycine amide bioisostere. Moreover, the imidazolidine intermediate was cleaved conveniently and efficiently by 50% TFA in methylene chloride.[51]

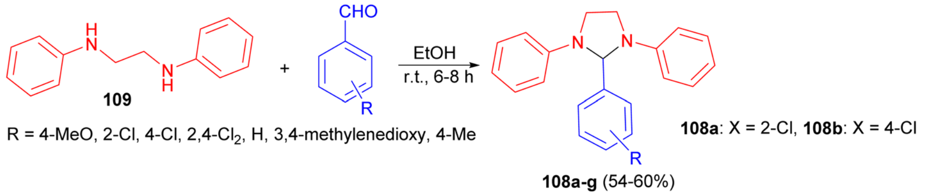
In addition, a procedure for the asymmetric synthesis of imidazolidines **112–113** in 37–80% yields have been reported. The 1,3-dipolar cycloaddition between nonracemic *p*-tolylsulfinimines **114** and azomethine ylides **115** generated *in situ* from iminoesters and LDA produces *N*-sulfinylimidazolidines **112–113** in THF at −78 to 4 °C for 20 hours with a high degree of



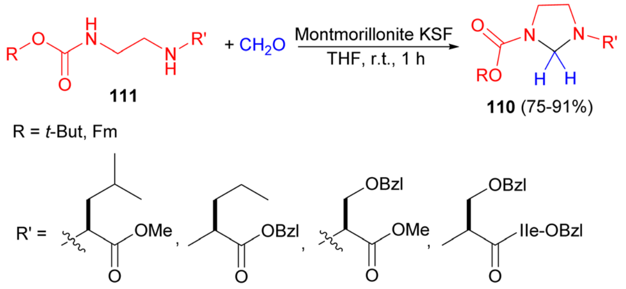
Scheme 31 Synthesis of imidazolidine derivatives **99**, **100**, **102**, **104** and **105**.



Scheme 32 Synthesis of 1,3-diacyl-2-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]imidazolidines **107**.



Scheme 33 Synthesis of 1,3-diphenyl-2-aryltetrahydroimidazoles **108**.

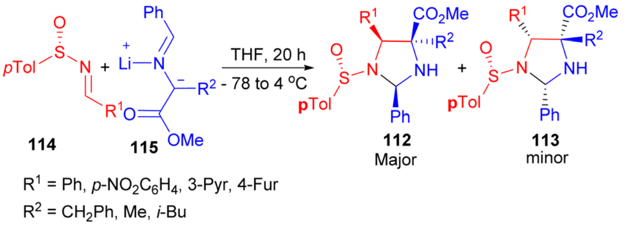


Scheme 34 Montmorillonite KSF catalyzed synthesis of unsymmetrical imidazolidines **110**.

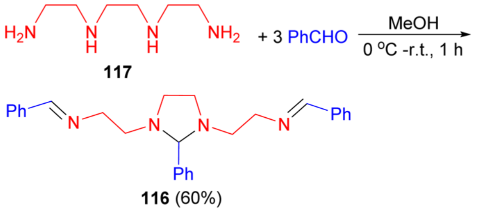
stereo control (Scheme 35). In contrast, the presence of Lewis acids promotes formation of the cycloadducts through a highly diastereoselective process with opposite stereochemistry.[52]

In 2004, Ray and co-workers described synthesis of tetraaza *m*-bis(bidentate) acyclic ligand **116** in 60% yield through the condensation reaction of one equivalent of trien **117** and 3 equivalents of benzaldehyde in MeOH at low temperature for 1 hour (Scheme 36). This ligand yielded new cationic dicopper(I/I) and dicopper(II/II) complexes in good yield.[53]

Next, the Hedrick group reported synthesis of imidazolidine derivatives **118** in 68–96% yields by the reaction of ethylene diamines **119** with benzaldehyde derivatives in glacial acetic acid/CH_2Cl_2/toluene/Et_2O in the presence of *p*-toluenesulfonic acid/anhydrous magnesium sulfate/Na_2SO_4 or absence of these catalyst at room temperature or warm conditions from 30 minutes to 24 hours (Scheme 37). Moreover, the



Scheme 35 Asymmetric synthesis of imidazolidines **112–113**.



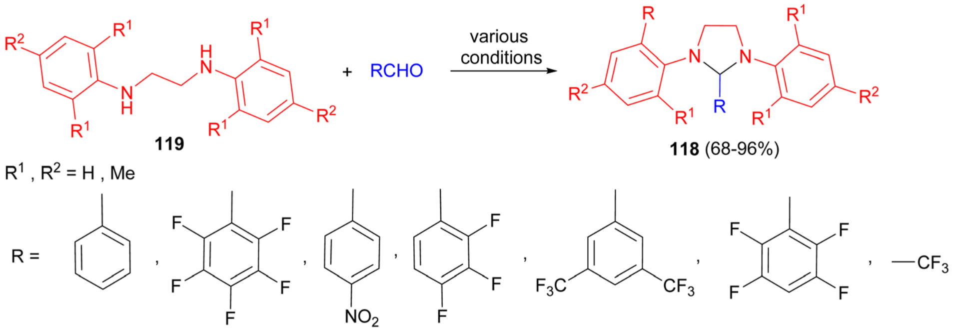
Scheme 36 Synthesis of tetraaza *m*-bis(bidentate) acyclic ligand **116**.

pentafluorobenzene-based adducts are stable at room temperature. Thermolysis of these adducts generates the carbenes in solution, which they have shown are effective organic catalysts for transesterification reactions and ring-opening polymerization reactions. These adducts also provide convenient synthons for the generation of transition-metal complexes.[54]

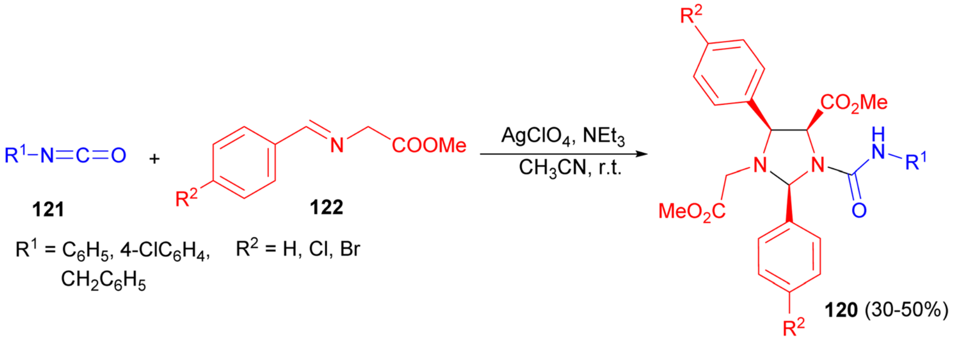
In 2005, the Erkizia group reported that substituted imidazolidines **120** are the unexpected cycloadducts obtained in 30–50% yields through the reaction between imines **121** and isocyanates **122** in the presence of $AgClO_4$ and NEt_3 in CH_3CN at room temperature (Scheme 38). The reaction is shown to take place *via* stepwise [3 + 2] cycloaddition between the *N*-metallated azomethine ylide formed *in situ* and the starting imine, followed by nucleophilic addition of the resulting imidazolidine on the sp hybridized carbon atom of the isocyanate.[55]

Further, Elmali *et al.* described synthesis of imidazolidine **123** in 56.8% yield *via* the reaction of triethylenetetramine **117** with 5-chlorosalicylaldehyde in methanol at room temperature (Scheme 39). Then, **123** reacts with $Fe(ClO_4)_2 \cdot 6H_2O$ in aqueous methanol to form the mononuclear $[Fe(L)](ClO_4)$ complex with the imidazolidine ring cleaved by hydrolysis.[56]

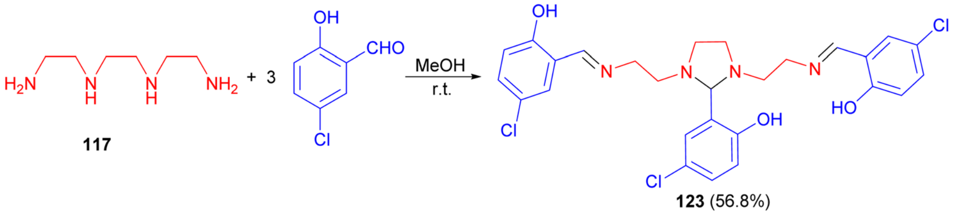
In 2006, Ghandi and co-workers demonstrated that cyclocondensation of *N*,*N*′-bis(2-pyrimidinyl)methanediamine **124** with glyoxal in alcohols (MeOH, EtOH, PrOH and i-PrOH) using formic acid as catalyst under reflux conditions for 20 hours led to the formation of the corresponding 4,5-dialkoxy-1,3-bis(2-



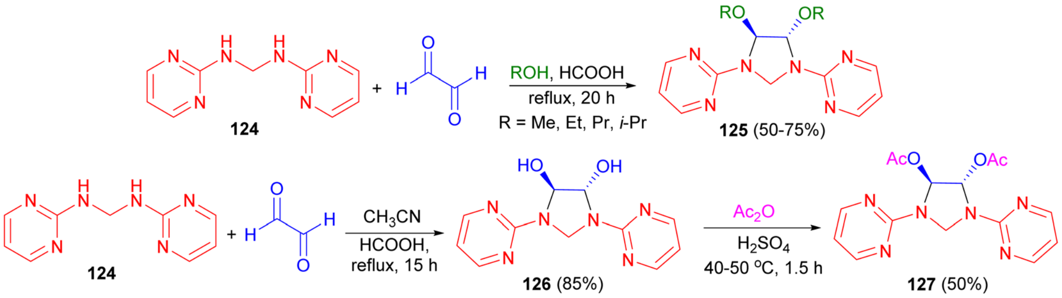
Scheme 37 Synthesis of imidazolidine derivatives **118** in various conditions.



Scheme 38 $AgClO_4$ catalyzed preparation of substituted imidazolidines **120**.



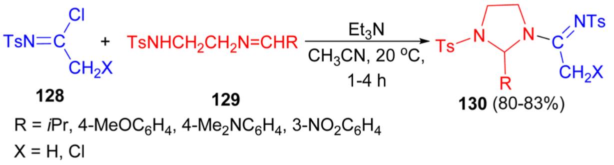
Scheme 39 Synthesis of imidazolidine **123**.



Scheme 40 Formic acid catalyzed synthesis of imidazolidine derivatives **125–127**.

pyrimidinyl)imidazolidines **125** in 50–75% yields. 4,5-Dihydroxy-1,3-bis(2-pyrimidinyl) imidazolidine **126** was obtained after 15 hours in 85% yield when the reaction was carried out in refluxing acetonitrile in the presence of formic acid. Moreover, the reaction of compound **126** with acetic anhydride in the presence of H_2SO_4 at 40–50 °C for 1.5 hours resulted in the formation of the corresponding *trans*-4,5-diacetoxy-1,3-bis(2-pyrimidinyl)imidazolidine **127** in 50% yield. Based on ^{1}H-NMR analysis, it was found that the *trans*-isomers were selectively obtained in these cyclocondensation reactions (Scheme 40).[57]

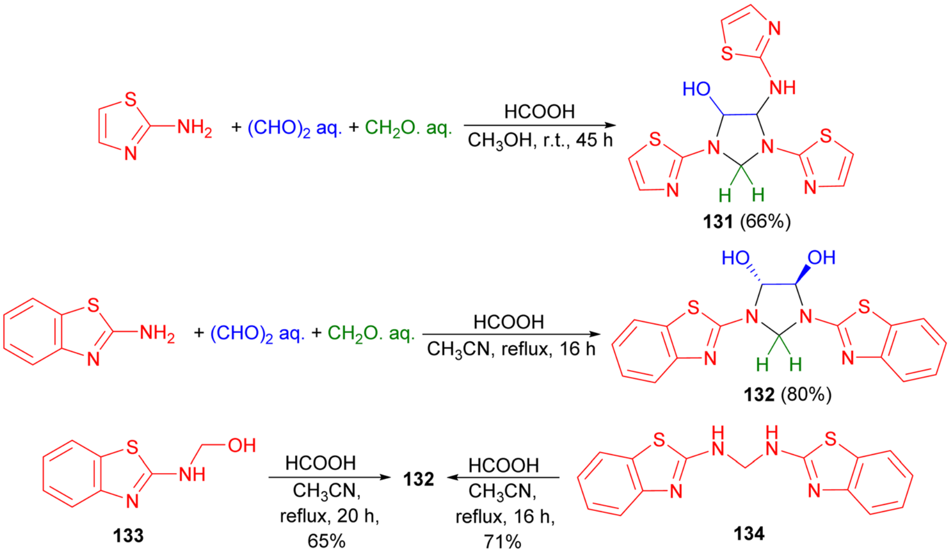
In addition, reactions of *N*-tosylimidoyl chlorides **128** with the Schiff bases of the general formula $TsNH(CH_2)_2N{=}CHR$ **129** using Et_3N in CH_3CN at 20 °C for 1–4 hours afforded 2-substituted 1-tosyl-3-(1-tosyliminoalkyl)imidazolidines **130** in 30–83% yields (Scheme 41).[58]



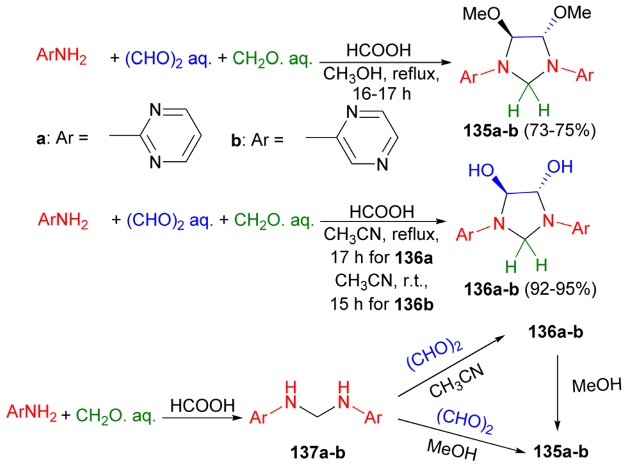
Scheme 41 Synthesis of 2-substituted 1-tosyl-3-(1-tosyliminoalkyl) imidazolidines **130**.

In 2007, Ghandi and Olyaei revealed that the reaction of 2-aminothiazole with aqueous glyoxal and aqueous formaldehyde in MeOH using HCOOH as catalyst at room temperature for 45 hours produced imidazolidine **131** in 66% yield. On the other hand, acid catalyzed one-pot three-component reaction of 2-aminobenzothiazole, aqueous glyoxal and aqueous formaldehyde in CH_3CN under reflux conditions for 16 hours afforded *trans*-4,5-dihydroxy-1,3-bis(2-benzothiazolyl)imidazolidine **132** in 80% yield. Finally, the reaction of compound **133** or **134** with aqueous glyoxal in refluxing CH_3CN using HCOOH as catalyst for 16–20 hours produced **132** (Scheme 42).[59]

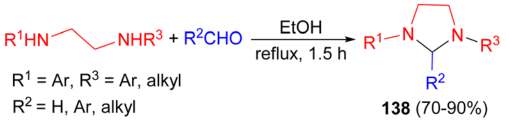
Next, four-component reaction of aminodiazines (2-aminopyrimidine and 2-aminopyrazine), glyoxal and formaldehyde in methanol under reflux conditions for 16–17 hours afforded *trans*-4,5-dimetoxy-1,3-bis(2-pyrimidinyl)imidazolidine (**135a**) in 75% yield and *trans*-4,5-dimetoxy-1,3-bis(2-pyrazinyl) imidazolidine (**135b**) in 73% yield, respectively. Changing methanol to acetonitrile resulted the corresponding 1,3-bis(2-pyrimidinyl) and-1,3-bis(2-pyrazinyl)-derivatives of *trans*-4,5-dihydroxyimidazolidine (**136a–b**) in 92–95% yields. The



Scheme 42 Preparation of imidazolidines **131** and **132** starting from heteroaryl amines.



Scheme 43 Formic acid catalyzed synthesis of imidazolidine derivatives **135** and **136** starting from aminodiazines.

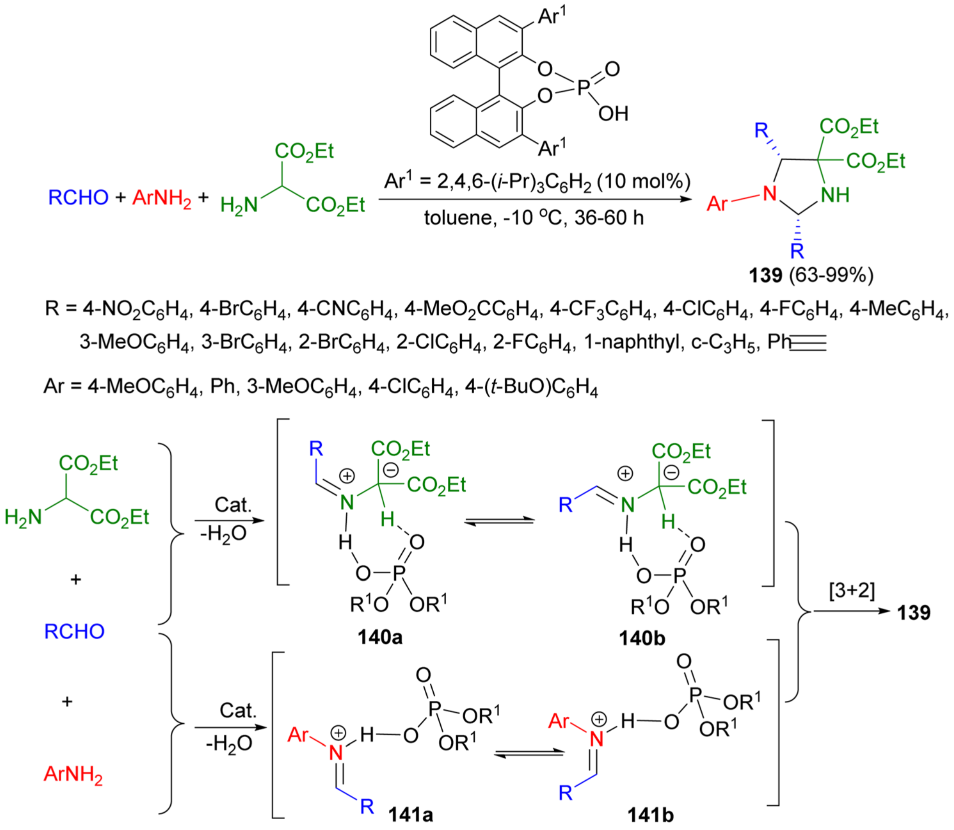


Scheme 44 Synthesis of imidazolidines **138** as anti-trypanosoma cruzi agents.

proposed mechanism is illustrated in Scheme 43. The condensation of aminodiazines with formaldehyde produces the intermediates **137a–b**, which then undergo reaction with glyoxal to form **136a–b.** Subsequent the reaction of **136a–b** with methanol leads to the formation of **135a–b**, respectively.[60]

In 2008, Perillo *et al.* described synthesis of a series of imidazolidines **138** in 70–90% yields by the reaction of the corresponding *N*,*N*′-disubstituted ethylenediamines and aldehydes or aqueous formaldehyde (37%, excess) in ethanol under reflux during 1.5 hours (Scheme 44). Some of the derivatives were found to have high and selective activity as anti-trypanosoma cruzi agents.[61]

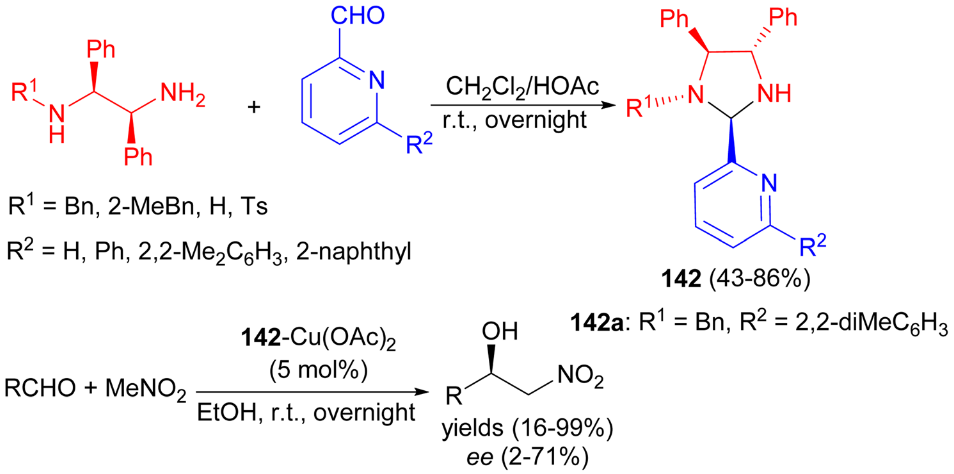
After that, a chiral Brønsted acid as catalyst applied for the synthesis of chiral imidazolidines **139** in 63–99% yields with high levels of stereoselectivity (up to 91/9 dr and 98% ee) *via* 1,3-dipolar cycloaddition reaction of aldehydes, amino esters, and anilines in toluene at −10 °C for 36–60 hours. The proposed mechanism is outlined in Scheme 45. Intermediates **140a** or **140b** as a chiral dipole obtained by the reaction of aldehyde with amino ester in the presence of catalyst. An imine generated *in situ* from an aldehyde and an amine could be activated by formation of an iminium species, either **141a** or **141b**, with a Brønsted acid and showed high reactivity toward nucleophiles. The iminium intermediates would be captured by the chiral Brønsted acid activated dipole **140a** or **140b** to thereby undergo an enantioselective [3 + 2] cycloaddition.[62]



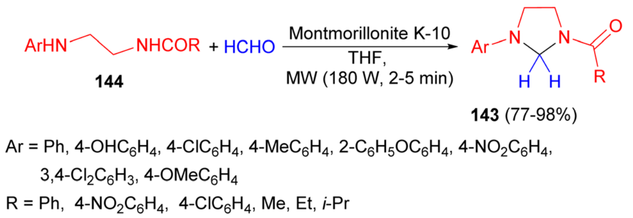
R = 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-CNC_6H_4, 4-$MeO_2CC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 3-BrC_6H_4, 2-BrC_6H_4, 2-ClC_6H_4, 2-FC_6H_4, 1-naphthyl, c-C_3H_5, Ph≡

Ar = 4-$MeOC_6H_4$, Ph, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-(*t*-BuO)C_6H_4

Scheme 45 Chiral Brønsted acid catalyzed synthesis of chiral imidazolidines **139**.



Scheme 46 Synthesis of chiral imidazolidine-pyridines **142**.



Scheme 47 Synthesis of 1-acyl-3-arylimidazolidines **143** using montmorillonite clay K-10.

In 2009, Arai *et al.* reported condensation of chiral diamines and aldehydes in CH_2Cl_2/HOAc at room temperature for overnight gave a series of chiral imidazolidine-pyridines **142** in 43–86% yields with high diastereoselectivities. The ability of these compounds to act as chiral ligands was examined in the catalytic Henry reaction. Compound **142a** showed better selectivity to provide the adduct with 71% ee (Scheme 46).[63]

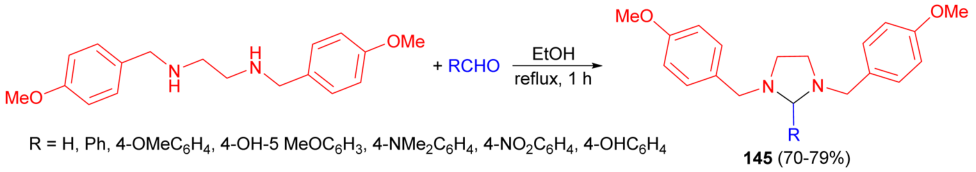
Next, the synthesis of 1-acyl-3-arylimidazolidines **143** in 77–98% yields were performed by the reaction of *N*-acyl-*N*′-arylethylenediamines **144** with formaldehyde in THF in the presence of montmorillonite clay K-10 as a catalyst under microwave irradiation (180 W) for 2–5 minutes (Scheme 47).[64]

In 2010, de Carvalho and his group disclosed synthesis of imidazolidine derivatives **145** in 70–79% yields by the classical method involving condensation between *N*,*N*′-disubstituted ethylenediamine with a variety of aromatic aldehydes in EtOH under reflux conditions for 1 hour (Scheme 48). The compounds showed a good activity against *Leishmania* without cytotoxicity on macrophages at the maximum concentration tested. 1,3-Bis(*p*-methoxybenzyl)imidazolidine showed the best activity on intracellular amastigotes, with IC_{50} value of 9.4 μg mL^{-1}. In addition, none of compounds were cytotoxic against mammalian cells.[65]

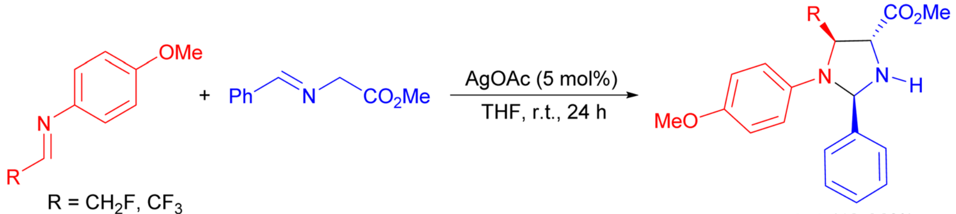
Next, the Chen group explored an instance of diastereoselective silver-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with imine compounds in THF at room temperature for 24 hours. This new method provided synthetically useful, highly substituted tetrahydroimidazole derivatives **146** with efficiency and high diastereoselectivity (Scheme 49).[66]

After that, Nenajdenko *et al.* reported synthesis of trifluoromethylated imidazolidines **147** in 35–97% yields by the reaction of β-halogeno-β-trifluoromethyl styrenes bearing an EWG at the aromatic ring with *N*,*N*′-binucleophile (ethylenediamine, *N*-methylethylenediamine, *N*,*N*′-dimethylethylenediamine) either in the refluxing THF for 7 hours or without solvent at room temperature from 1 hour to 7 days (Scheme 50).[67]

In 2011, the Helion group reported that the reductive coupling of imines in the presence of the lanthanide-originated zirconocene equivalent in THF for 1.5–12 hours afforded imidazolidines **148** in 70–85% yields under mild conditions in good yields with high diastereoselectivity. The proposed mechanism is shown in Scheme 51. Imines are partly converted (1.5 mmol of imine for 0.5 mmol of zirconocene) to diazirconacyclopentanes **149**. During hydrolysis, **149** gives

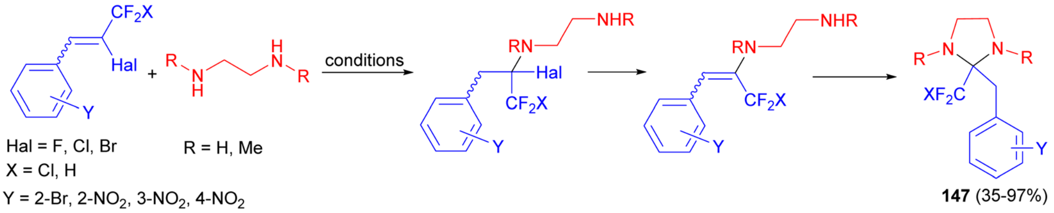


Scheme 48 Synthesis of imidazolidine derivatives **145**.



146 (42-96%)

Scheme 49 AgOAc catalyzed synthesis of highly substituted tetrahydroimidazole derivatives **146**.



147 (35-97%)

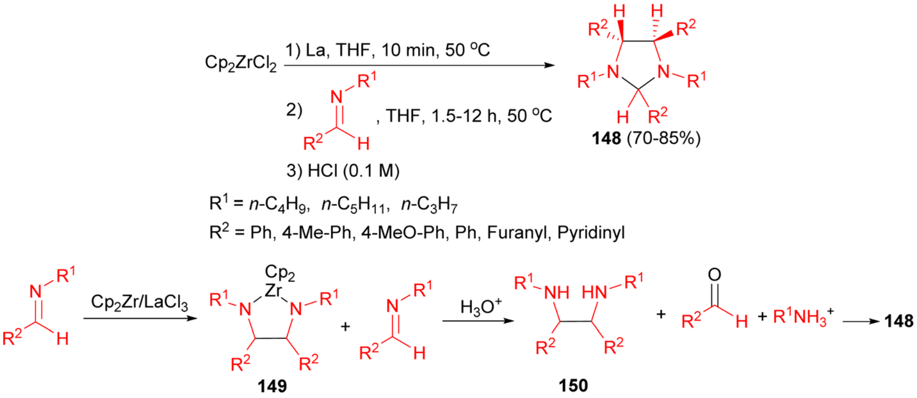
Scheme 50 Synthesis of trifluoromethylated imidazolidines **147**.

corresponding diamines **150** and residual *N*-alkyl aldimines are hydrolysed to aldehydes, thus diamines **150** react slowly with aldehydes to give corresponding imidazolidines **148**.[68]

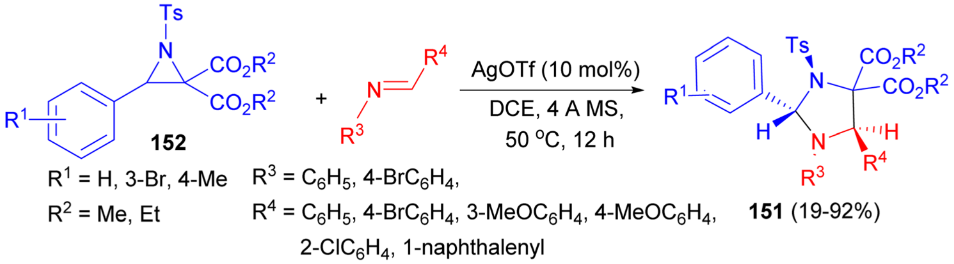
The Lu group developed a diastereoselective synthesis of *trans*-2,5-disubstituted imidazolines **151** in 19–92% yields *via* the reaction of *N*-tosylaziridine 2,2-dicaboxylates **152** with *trans*-imines. The reaction involves a regioselective cleavage of the C–C bond of the aziridine ring and a diastereoselective [3 + 2] cycloaddition. AgOTf as catalyst in DCE was proved to be an effective Lewis acid catalyst for the formation of *trans*-2,5-imidazolidines at 50 °C after 12 hours. In the proposed mechanism, catalyzed by Lewis acid, the aziridine ring is opened to form azomethine ylide *via* a regioselective cleavage of the C–C bond. Then [3 + 2] cycloaddition reaction of the intermediate with *trans*-imine *via* the stable transition state afforded *trans*-2,5-imidazolidines (Scheme 52).[69]

An efficient synthesis of highly substituted tetrahydroimidazole derivatives **153** 45–94% yields by means of visible light-induced intramolecular cyclization reactions of 1,2-diamine derivatives described. This photoredox catalytic reaction in the presence of 1.0 mol% $Ru(bpy)_3Cl_2$ with O_2 exhibited high diastereoselectivity and afforded the desired products at room temperature after 9–72 hours. A proposed mechanism and stereochemical course of this reaction depicted in Scheme 53. The addition of the nitrogen anion to the iminium ion from its *Re* is much more favorable than that to its *Si* face due to the steric repulsion. When the reaction time was prolonged, product *epi*-2 could be converted into the thermodynamically more stable *cis* form under the reaction conditions.[70]

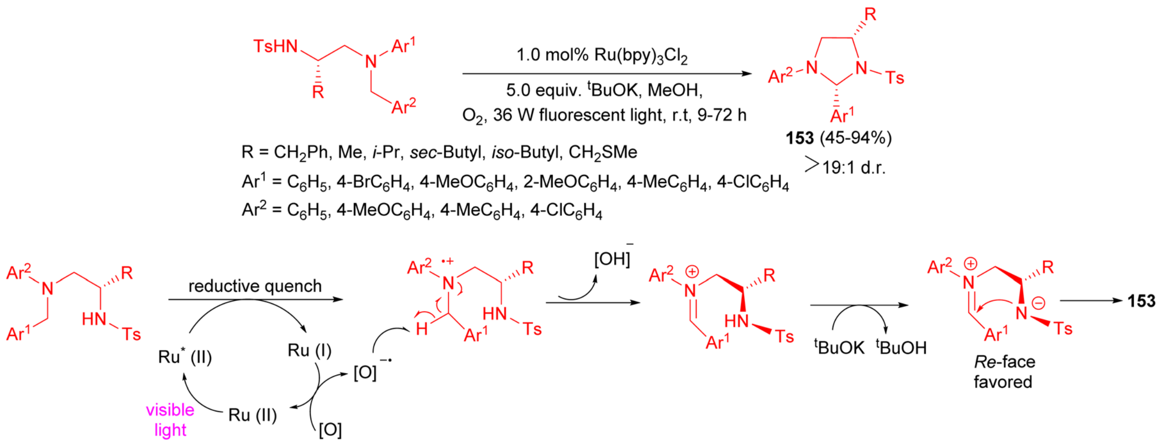
The Lloyd-Jones group reported synthesis of imidazolidines **154** by the reaction of *N*-Ts and *N*-Boc derivatives of 1,2-diamines **155** with large range of electron-deficient alkenes *via* aza-Wacker reaction using Pd(II) as catalyst under the oxidative conditions (benzoquinone, DME, 40 °C) for 21 hours. In the proposed mechanism, as illustrated in Scheme 54, activation of the electron-deficient alkene by coordination to Pd(II)



Scheme 51 Synthesis of imidazolidines **148** in the presence of the lanthanide-originated zirconocene.



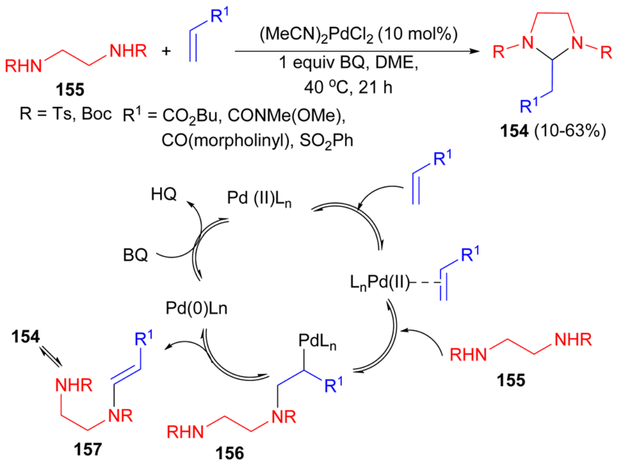
Scheme 52 Synthesis of *trans*-2,5-disubstituted imidazolines **151** using AgOTf as catalyst.



Scheme 53 Ru(bpy)$_3$Cl$_2$ catalyzed diastereoselective synthesis of tetrahydroimidazole derivatives **153**.

is followed by amino-palladation leading to the σ–Pd(II) species **156**. β-Hydride elimination leads to the enamide **157** and Pd(0) which is then reoxidized by BQ to the active Pd(II) catalyst.[71]

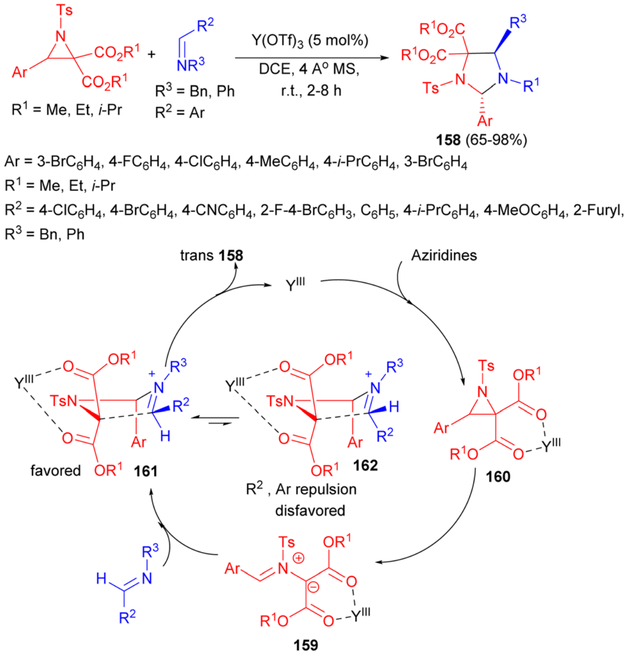
In 2012, Zhang *et al.* developed an efficient method for the diastereoselective synthesis of imidazolidines **158** through the reaction of aziridines with imines using Lewis acid catalyst (Y(OTf)$_3$) in DCE at room temperature for 2–8 hours. In this procedure, the diastereoisomeric ratios are ranged from 1 : 1 to more than 50 : 1. Furthermore, both electron-deficient and electron-rich imines and aziridines exhibited excellent reactivity, yielding good to high yields (65–98%). A model that accounts for the *trans* selectivity observed in this cycloaddition is proposed in Scheme 55. A possible path is that the azomethine ylide **159** is first produced by C–C bond cleavage of **160**, formed from aziridines through the selective coordination of Y(OTf)$_3$ to the dicarboxylate groups. Subsequent diastereoselective addition of the imine would afford two zwitterionic intermediates, **161** and **162**, which can be interconverted through iminium isomerization. Intermediate **162** is less stable than intermediate **161**, owing to the steric hindrance of R and Ar, which are both in pseudo axial orientations within the envelope transition state, thus the *trans* isomer is produced preferentially.[72]



Scheme 54 Synthesis of imidazolidines **154** in the presence of Pd(II) as catalyst.

After that, two series of 4-substituted-imidazolidines **163** and **164** in 53–72% yields were synthesized by reacting different tetrahydro-di-Schiff bases **165** and **166** with *p*-diethylaminobenzaldehyde/dimethylaminobenzaldehyde in EtOH at room temperature for 5 hours (Scheme 56). The title compounds were evaluated for their antibacterial and antifungal actions against some selected microbes. The results of microbiological evaluation revealed that two compounds (**164**) were good in their antibacterial as well as antifungal actions.[73]

In 2013, the Muthusubramanian group developed an atom-efficient, catalyst-free and environmentally friendly approach towards the synthesis of 1,3,4-trisubstituted imidazolidines **167**



Scheme 55 $Y(OTf)_3$ catalyzed synthesis of imidazolidines **158**.

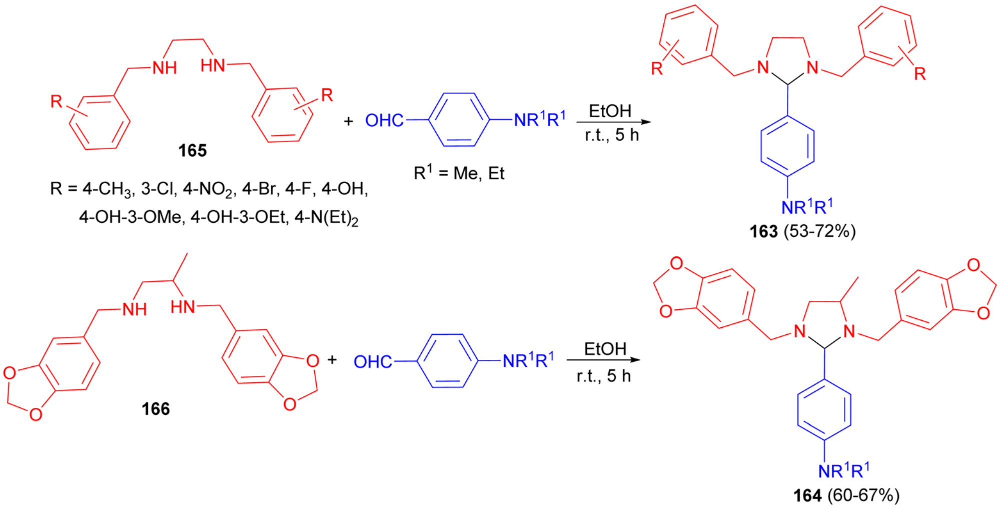
through a multicomponent reaction involving monophenacyl anilines **168**, aromatic amines and formaldehyde. The reaction proceeds in refluxing ethanol for 3 hours providing higher yields (77–94% yields) of the imidazolidines **167**. The mechanism for the formation of **167** is depicted in Scheme 57 in which two possible paths, route **A** and **B**, have been suggested. Imine **169** formed by the reaction of substituted aniline with formaldehyde could have undergone Mannich type reaction with the enolic form of monophenacyl aniline resulting in **170**. **170** could have reacted with formaldehyde ultimately yielding **167** after dehydration. The initial formation of *N*-hydroxylmethyl derivative **171** has been proposed in route **B**. Compound **171** undergoes reaction with imine **169** resulting in the imidazolidine derivative **167**.[74]

In addition, Olyaei and his group reported a facile, one-pot stereoselective synthesis of *trans*-4,5-dihydroxy-2-aryl-1,3-bis(heteroaryl)imidazolidines **172** in 75–88% yields by a cyclocondensation reactions of heteroarylamines, benzaldehydes and aqueous glyoxal in the presence of guanidinium chloride as a polyfunctional organocatalyst under solvent-free conditions for 23–76 minutes. The proposed mechanism is shown in Scheme 58. The catalyst initially acts as a hydrogen-bond donor to activate the aldehyde by formation of a six-membered ring. Subsequently, a Schiff base was formed by nucleophilic addition of the amine to the aldehyde and dehydration in the presence of the catalyst acting as an acid. Next, the Schiff base is further attacked by a second amine to give gem-diamine as intermediate **173**. Finally, nucleophilic addition of **173** to the carbonyls of glyoxal gave the final product **172**.[75]

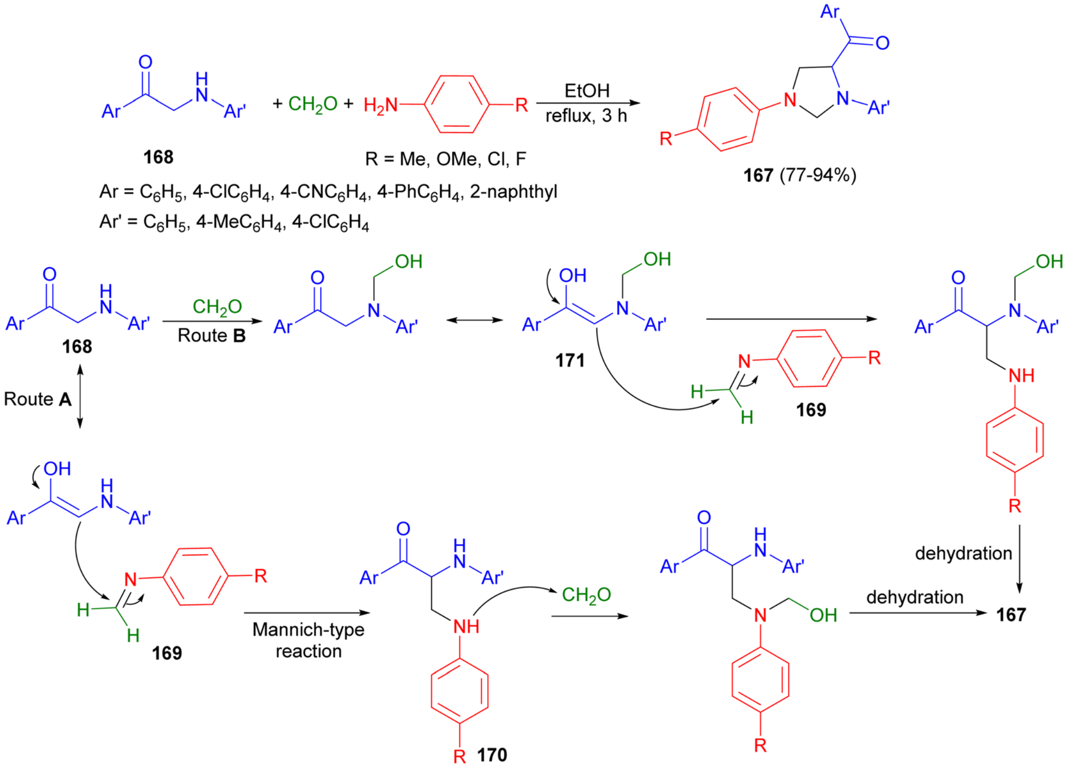
After that, a series of substituted-imidazolidine derivatives **174** synthesized in 53–71% yields by the reaction of *N*,*N*-bis(substituted-benzyl)ethane-1,2-diamines **175** with *p*-diethyl/dimethylaminobenzaldehyde in EtOH for 5 hours (Scheme 59). The results of biological evaluation of these compounds revealed that some of the compounds exhibited anti-inflammatory and analgesic activities. Additionally, these derivatives showed superior GI safety profile as compared to that of the standard drug in terms of low severity index.[76]

In 2013, the Wang group developed the first catalytic asymmetric synthesis of fluorinated 2,4-*trans*-imidazolidines **176** with excellent diastereoselectivity *via* Cu(I)/(S,Rp)-PPFOMe (3 mol%) catalyzed 1,3-dipolar cycloaddition of azomethine ylides **177** with various fluorinated imines **178** using Et_3N in Et_2O at −20 °C for 1–3 hours (Scheme 60).[77]

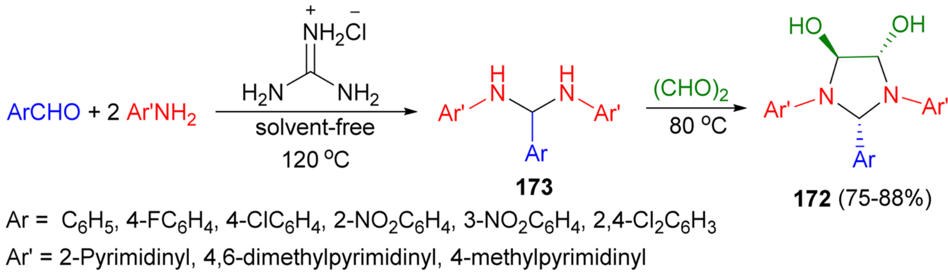
After that, the Wang group reported synthesis of imidazolidine **179** in 89% yield *via* cascade reaction between *N*-phenyl glycine (**180**) and *N*-tosylimine (**181**) in the presence of 2 mol% fluorescein using an 11 W fluorescent bulb in MeOH at room temperature for 24 hours. A cascade process which contained



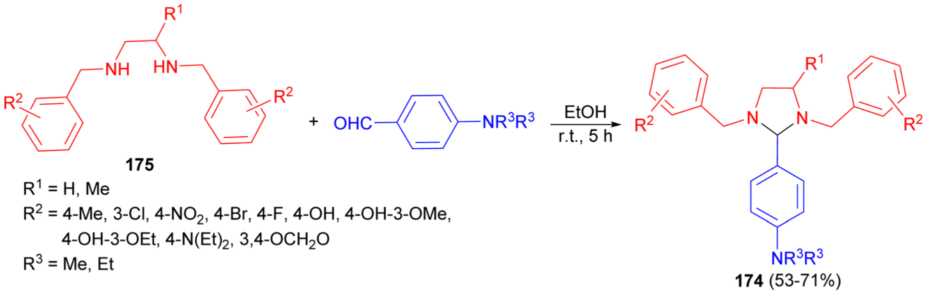
Scheme 56 Preparation of 4-substituted-imidazolidines **163** and **164**.



Scheme 57 Catalyst-free synthesis of 1,3,4-trisubstituted imidazolidines **167**.



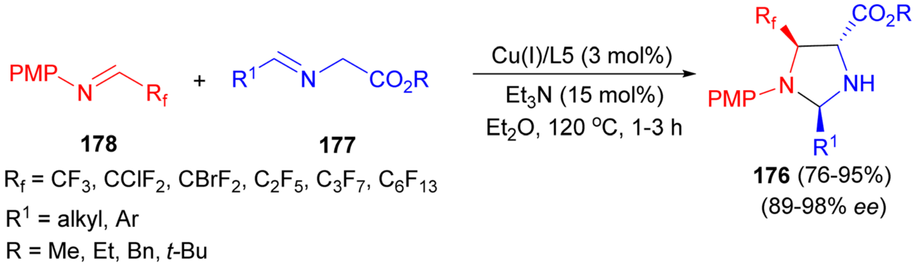
Scheme 58 Guanidinium chloride catalyzed synthesis of *trans*-4,5-dihydroxy-2-aryl-1,3-bis(heteroaryl)imidazolidines **172**.



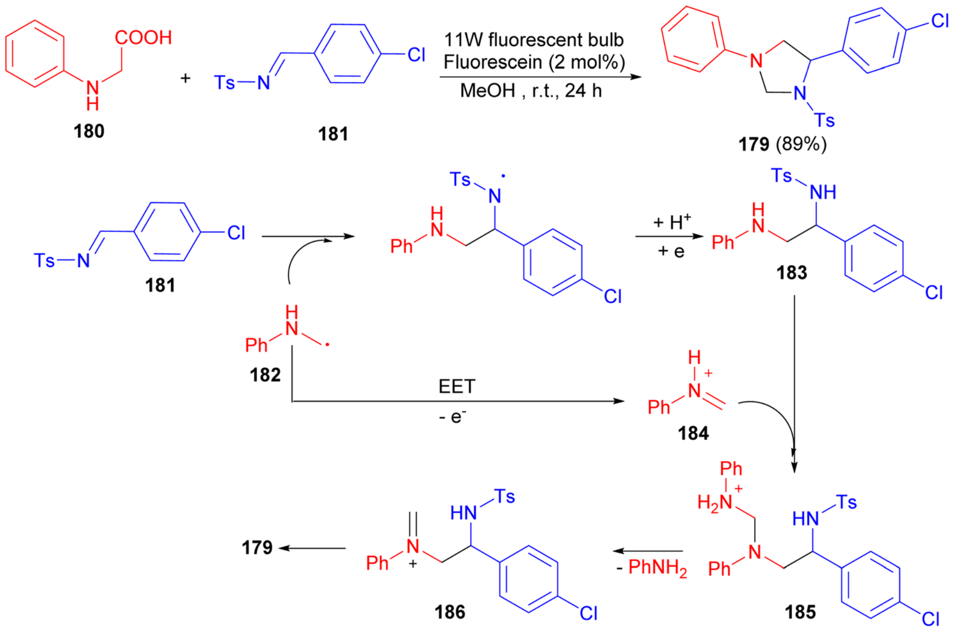
Scheme 59 Preparation of substituted-imidazolidine derivatives **174**.

both radical and ionic pathways was proposed for its formation (Scheme 61). The α-amino radical **182** was added to the **181** to afford a diamine intermediate **183.** This adduct was added to iminium ion **184** to form ammonium intermediate **185.** Losing an aniline led to iminium cation **186,** which cyclized to form product **179.**[78]

In 2014, a palladium complex bearing a chiral ammonium-phosphine hybrid ligand-catalyzed asymmetric [3 + 2]



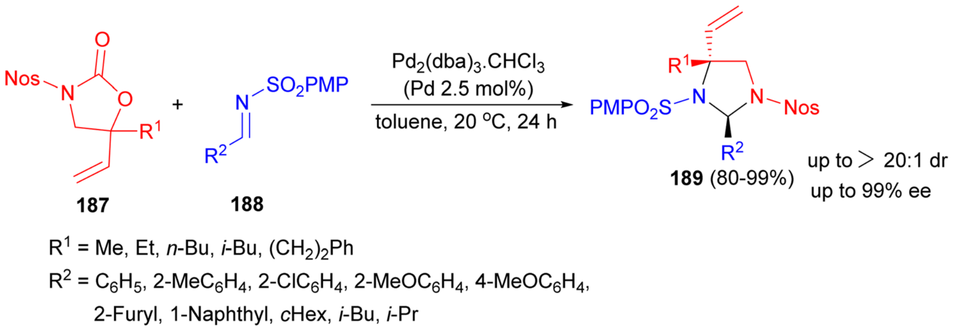
Scheme 60 Asymmetric synthesis of fluorinated 2,4-*trans*-imidazolidines **176**.



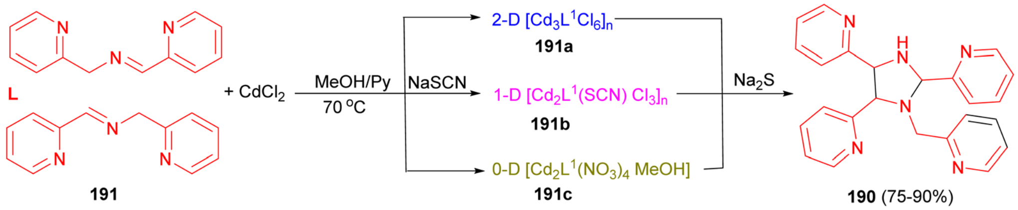
Scheme 61 Fluorescein catalyzed synthesis of imidazolidines **179** using an 11 W fluorescent bulb.

annulation reaction between racemic 5-vinyloxazolidinones **187** and *N*-sulfonyl imines **188** in toluene at 20 °C for 24 hours resulted imidazolidines **189** bearing α-amino quaternary stereocenters in 80–99% yields with excellent diastereo- and enantioselectivities (Scheme 62).[79]

Next, one convenient Cd^{II}-mediated C–C/C–N bond-forming strategy toward asymmetric tetra-(2-pyridine)-substituted imidazolidine **190** was reported by the Lin group. These compounds were formed from *in situ* solvothermal [3 + 2] asymmetric coupling dimerization of *N*-(2-pyridylmethyl)-pyridine-2-carbaldimine (**191**) with $CdCl_2$/$CdCl_2$ + NaSCN/$CdCl_2$ + $NaNO_3$ in the mixed solvents of methanol and pyridine at 70 °C or so for 3 days. Moreover, **190** could be obtained effectually from all three complexes, $[Cd_3L_1Cl_6]_n$ (**191a**),



Scheme 62 Palladium catalyzed synthesis of imidazolidines **189**.



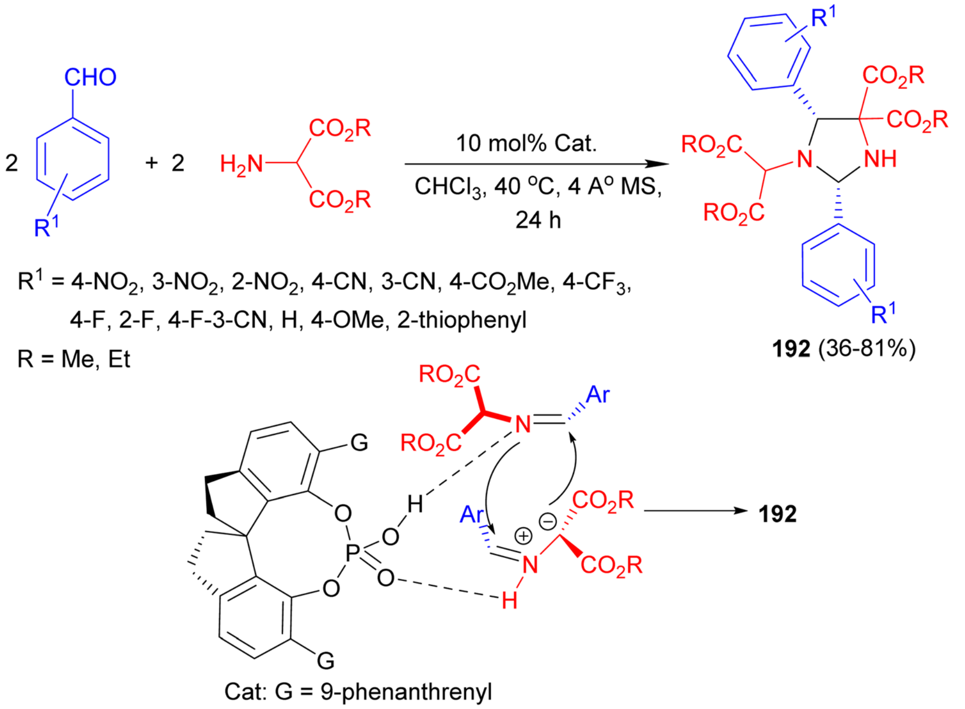
Scheme 63 Cd^{II} catalyzed synthesis of tetra-(2-pyridine)-substituted imidazolidine **190**.

$[Cd_2L_1(SCN)Cl_3]_n$ (**191b**) and $Cd_2L_1(NO_3)_4(MeOH)$ (**191c**), through the reactions of those compounds with Na_2S (Scheme 63).[80]

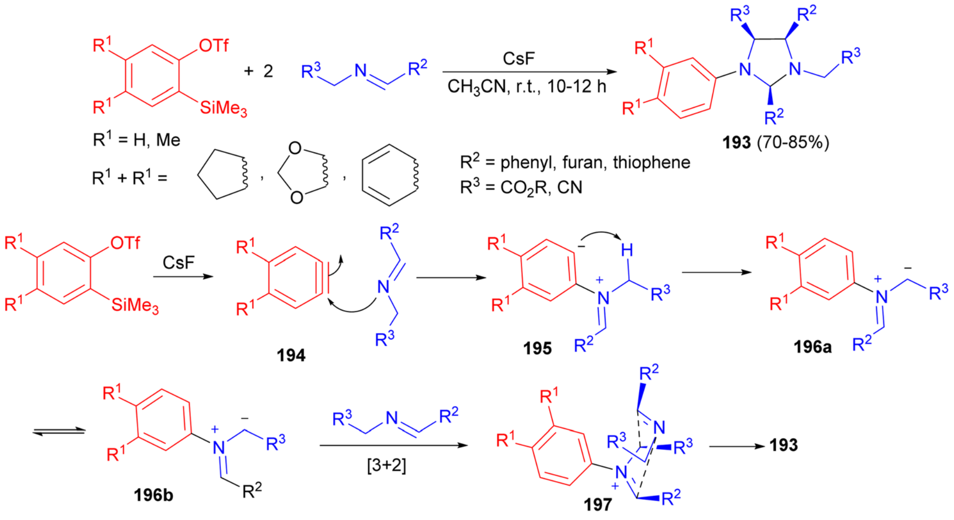
In addition, catalytic asymmetric homo-1,3-dipolar cycloadditions of azomethine ylides were established *via* SPINOL-derived chiral phosphoric acid-catalyzed pseudo four-component reactions of aldehydes and 2-aminomalonates in $CHCl_3$ at 40 °C for 24 hours, resulted in the stereoselective construction of chiral imidazolidine scaffolds 192 with two stereogenic centers in generally high yields and with good stereoselectivities (36–81% yields, >20 : 1 dr, up to 93% ee). In the proposed mechanism as depicted in Scheme 64, the catalyst acted as a Brønsted acid/Lewis base bifunctional catalyst to simultaneously activate both the azomethine ylide and the aldimine *via* hydrogen bonding interactions, which facilitated subsequent [3 + 2] cycloadditions.[81]

In 2015, the Hwu group an efficient method developed for the direct synthesis of various imidazolidines **193** in good to excellent yields (70–85%) and excellent diastereoselectivity from two equivalents of Schiff bases and one equivalent of 2-(trimethylsilyl)aryl triflates using CsF in CH_3CN at room temperature for 10–12 hours. Scheme 65 illustrated a plausible mechanism by which arynes **194** can function as "initiators" of heterocyclic ring formation. After they are generated by the 1,2-elimination of silylphenyl triflates with CsF, arynes **194** first act as electrophiles to react with the Schiff bases. Then the nucleophilic aryl carbanionic center in the resultant betaines **195** abstracts an acidic proton at the g position to form ylides **196.** Steric congestion between the two phenyl groups in ylides **196a** with the *cis* configuration caused their isomerization to the *trans* isomers **196b**. Then a regioselective [3 + 2] cycloaddition takes place between azomethine ylides **196b** and the second equivalent of Schiff bases *in situ*. The remarkably high degree of endo stereocontrol and excellent diastereofacial discrimination of the transition state **197** cause the imidazolidines **193.**[82]

In 2016, Husain group synthesized a number of substituted-imidazolidine derivatives **198** in 51–70% yields starting from *N*,*N*′-bis(substituted-benzyl)ethane-1,2-diamines **199** and aromatic aldehydes in absolute ethanol. This reaction mixture was properly shaken for 5 hours using mechanical shaker and



Scheme 64 SPINOL-derived chiral phosphoric acid-catalyzed synthesis of chiral imidazolidine scaffolds **192**.



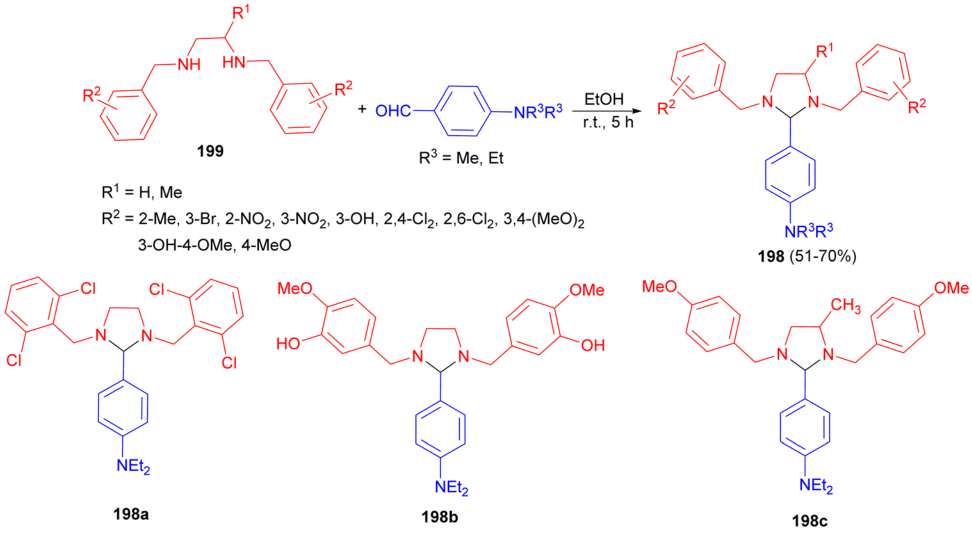
Scheme 65 CsF catalyzed diastereoselective synthesis of imidazolidines **193**.

then kept in a refrigerator for whole night. The results of biological testing indicated that among the synthesized compounds only three imidazolidine derivatives **198a–c** possess promising anti-inflammatory and analgesic actions. Additionally, these derivatives displayed superior GI safety profile (low severity index) with respect to the positive control, Indomethacin (Scheme 66).[83]

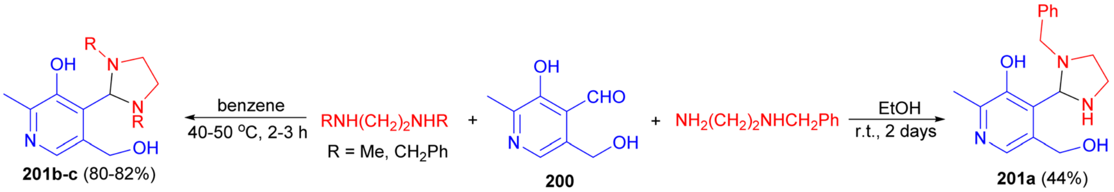
Interaction of pyridoxal (3-hydroxy-5-hydroxymethyl-2-methylisonicotinaldehyde) (**200**) with amines, mono- and disubstituted diamines in EtOH at room temperature for 2 days or in benzene at 40–50 °C for 2–3 hours led to the formation of imidazolidines **201a–c** in 44–82% yields (Scheme 67).[84]

Copper(I) thiophene-2-carboxylate catalyzed regio- and chemoselective synthesis of indoloimidazolidines **202** in 73–84% yields by the reaction of the four-component reaction of diazoamides **203**, electron-withdrawing imines **204**, electron-donating aldehydes and amines **205** in 1,2-DCE under reflux conditions. The initially generated azomethine ylide from diazoamide and imine, formed from electron-donating aldehyde and amine, underwent [3 + 2]-cycloaddition with electron-withdrawing imine furnished indoloimidazolidine **202** in a chemo- and diastereoselective manner (Scheme 68).[85]

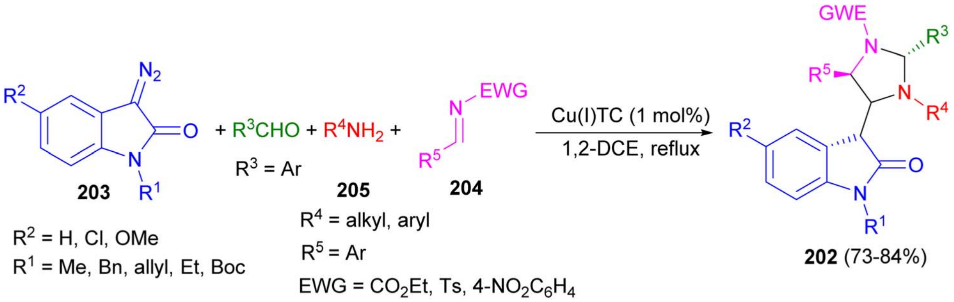
On water oxidative C(sp^3)–H functionalization C–N bond formation using tetrabutylammonium iodide (TBAI) as the catalyst and *tert*-butyl hydroperoxide in water (T-Hydro) as the oxidant at 60 °C for 4–5 hours afforded a potential route for the construction of functionalized imidazolidines **206** and **207** in 61–84% yields. The proposed mechanism is depicted in Scheme 69. Thus, the oxidation of TBAI by T-Hydro may give iodine, *tert*-butoxyl radical, and hydroxyl ion (step (i)). Single electron transfer (SET) reduction of iodine may regenerate the catalyst with the formation of the radical cation (step (ii)). Homolysis of the methyl C–H bond induced by *tert*-butoxyl radical may give the iminium **208**, which may convert into the



Scheme 66 Synthesis of substituted-imidazolidine derivatives **198**.



Scheme 67 Preparation of imidazolidines **201**.

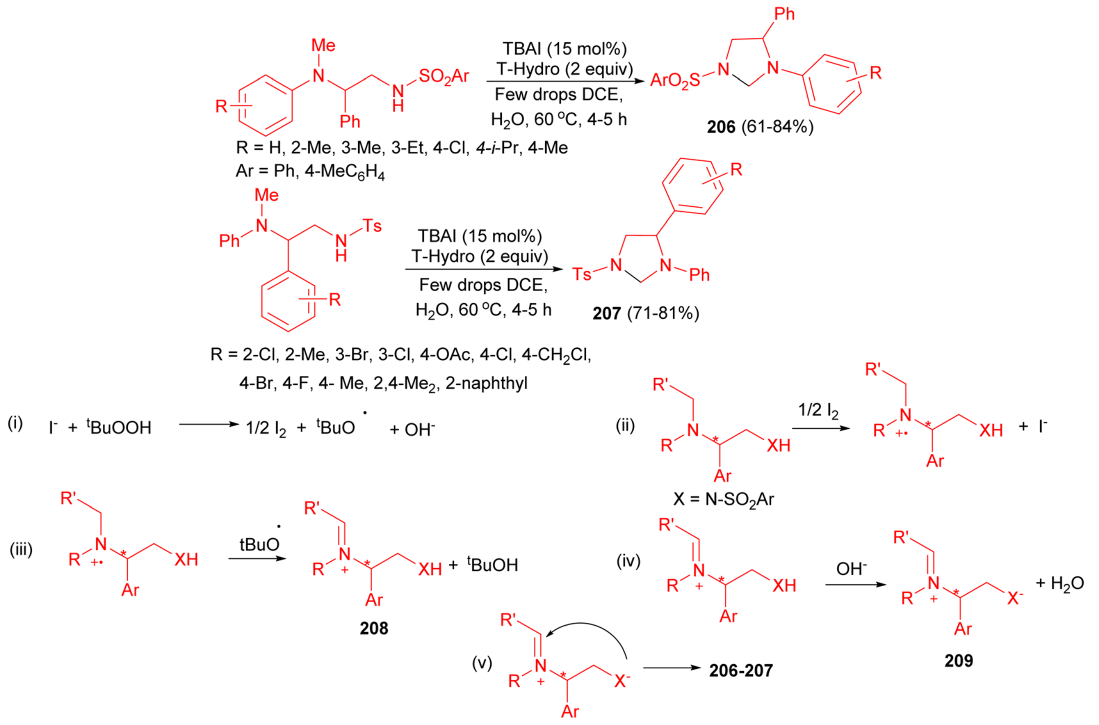


Scheme 68 Copper(I) thiophene-2-carboxylate catalyzed regio- and chemoselective synthesis of indoloimidazolidines **202**.

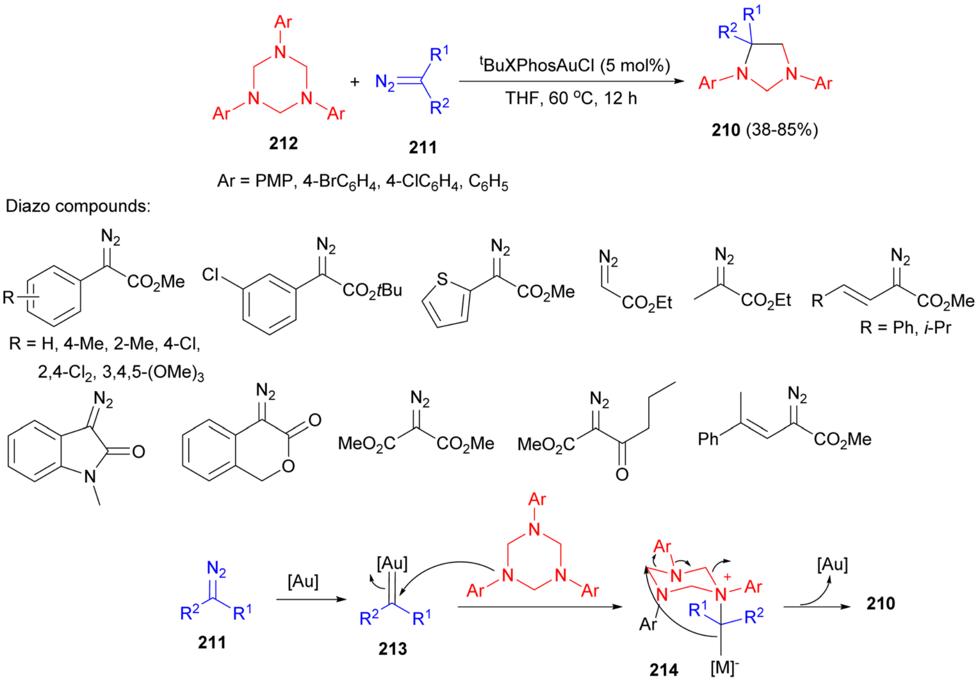
target heterocycles **206** and **207** *via* the intermediate **209** (steps (iv) and (v)).[86]

The Sun group described gold-catalyzed synthesis of imidazolidines **210** in 38–85% yields by the reaction of donor/acceptor diazo esters **211**, including aryl diazoacetates, alkyl diazoacetate, vinyl diazoacetates, cyclic diazo compounds and acceptor/acceptor diazoesters, with triazines **212** in the presence of ^{t}BuXPhosAuCl (5 mol%) in THF at 60 °C for 12 hours. The possible route by the formation of **210** illustrated in Scheme 70. First, the reaction of **212** with metal carbene **213** provides the intermediate **214** by ylide formation. The intramolecular electrophilic trapping associated with rearrangement, and subsequent reductive elimination affords the cycloaddition product **210**.[87]

In 2017, an efficient synthesis of polysubstituted imidazolidines **215** in 42–81% yields using Pd(0)-catalyzed double-



Scheme 69 Construction of imidazolidines **206** and **207** using TBAI as the catalyst and *tert*-butyl hydroperoxide as the oxidant.

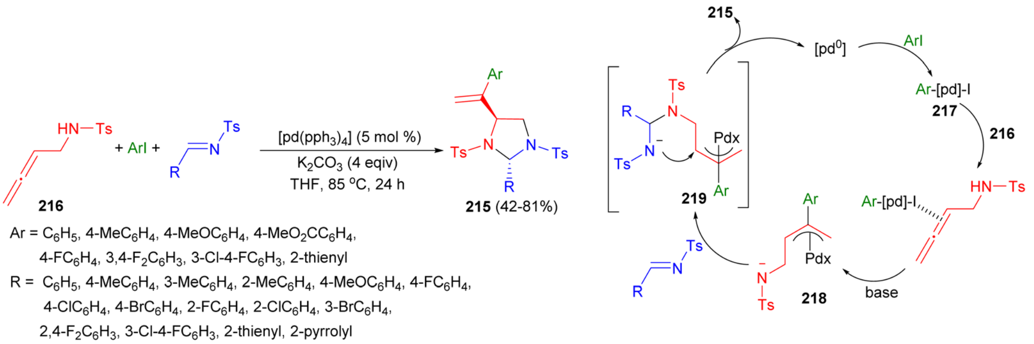


Scheme 70 ^{t}BuXPhosAuCl catalyzed synthesis of imidazolidines **210**.

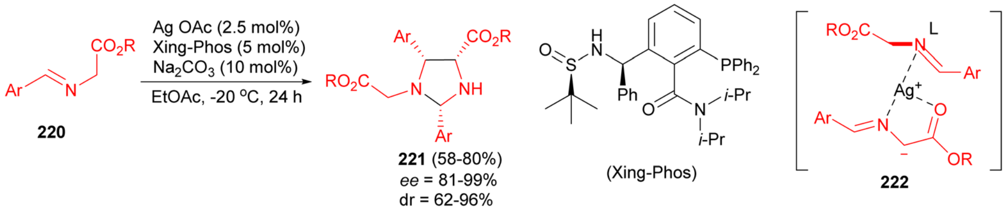
addition–cyclization of 2,3-allenyl amines **216** with aryl iodides and imines in the presence of K_2CO_3 in THF at 85 °C for 24 hours was reported by Gong and co-workers. A plausible mechanism for this cyclization reaction is proposed in Scheme 71. Oxidative addition of the aryl iodide to Pd^0 affords arylpalladium species **217**. Coordination of one of the allene double bonds to electrophilic complex **217**, and subsequent carbopalladation, affords π-allyl species **218**, which reacts with imine and base to afford π-allyl species **219**. Finally, intermediate **219** undergoes intramolecular nucleophilic attack on the inner π-allylic carbon atom, affording the imidazolidine structure, thereby releasing the active catalytic species.[88]

Next, stereocontrolled dimerization-type homo-1,3-dipolar [3 + 2] cycloaddition reaction of glycine aldimino esters **220** for creating new heterocycles bearing multiple stereogenic centers developed through the chiral phosphine ligand-involved silver catalysis. A variety of chiral imidazolidines **221** could be obtained with high yields and good diastereoselectivities as well as excellent enantioselectivities by employing Xing-Phos as chiral P-ligand in EtOAc at −20 °C for 24 hours. They believed that the homo-1,3-dipolar [3 + 2] cycloaddition of imino esters/azomethine ylides controlled by the silver/Xing-Phos catalyst aroused predominately from the steric repulsion and non-covalent interaction between the Xing-Phos ligand and glycine aldimino ester during the Mannich addition and subsequent intramolecular *N*-acetalization (cyclization) of the intermediate **222** (Scheme 72).[89]

An enantioselective synthesis of biologically important imidazolidines **223** has been achieved *via* a tandem [3 + 2] cycloaddition/1,4-addition reaction of azomethine ylides **224** and aza-*o*-quinone methides **225** using Ag(I) salts as the pre-catalyst and ferrocenylphosphine P–N ligand **226** as the chiral ligand in the presence of KOH and 18-crown-6 in DCM at −30 °C for 4 hours. With the use of this tool, various imidazolidine



Scheme 71 Pd(0)-catalyzed synthesis of polysubstituted imidazolidines **215**.



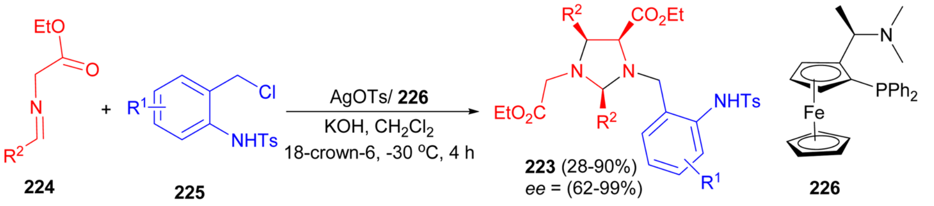
Ar = C_6H_5, 4-FC_6H_4, 4-MeC_6H_4, 4ClC_6H_4, 4-FC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-$SiMe_3C_6H_4$, 3-FC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 3-BrC_6H_4, 3-$MeOC_6H_4$
R = Me, Bn

Scheme 72 Silver/Xing-Phos-catalyzed synthesis of chiral imidazolidines **221**.

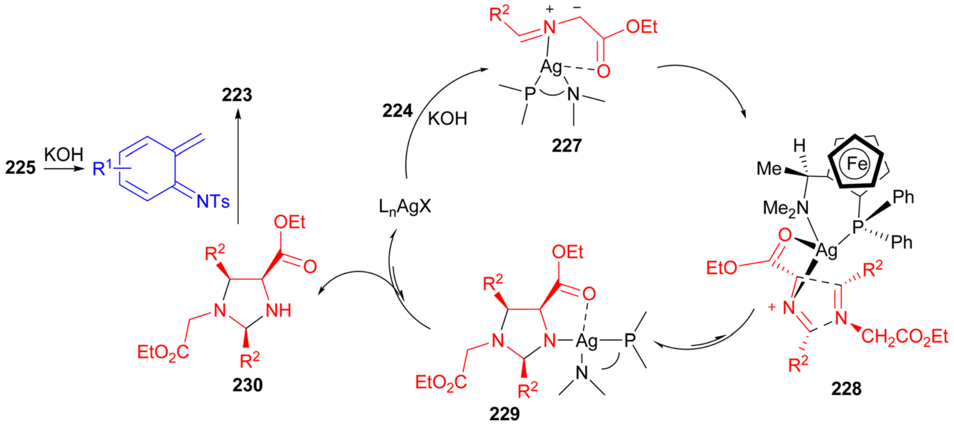
derivatives were obtained in 28–90% yields with excellent diastereoselectivities and enantioselectivities (62–99%). A plausible mechanism is proposed in Scheme 73. Treatment of **224** with a base in the presence of the *in situ* generated silver complex would lead to the formation of the metalloazomethine ylide **227** as an active species. A regioselective [3 + 2] cycloaddition of azomethine ylides **227** and the second equivalent of Schiff base **224** then occurs. The high degree of endo stereocontrol and excellent diastereofacial discrimination of the transition state **228** generates the imidazolidine complex **229** as the exclusive intermediate. The intermediate **229** was protonated to form the intermediate **230**, which was then captured by a *o*-QM generated *in situ* from **225** to accomplish the final product **223**.[90]

The Punniyamurthy group reported stereospecific copper catalyzed nucleophilic ring opening in the presence of *tert*-butyl hydroperoxide to afford functionalized imidazolidines **231** starting from *N*-sulfonylaziridines **232** and *N*-alkylanilines **233** in DCE at 60 °C. The products were obtained after 1.5–10 hours in 42–89% yields and high optical purities (95–99% ee) with excellent functional group tolerance. In the proposed mechanism as illustrated in Scheme 74, single-electron transfer (SET) reduction of $Cu(OTf)_2$ using the nitrogen lone pair of **234** may lead to the formation of an intermediate **235**. Homolysis of the *N*-methyl C–H bond using *tert*-butoxy radical can generate imine derivative **236**, which may lead to cyclization to furnish the target heterocycles. Oxidation of $Cu(OTf)_2^-$ using TBHP may regenerate $Cu(OTf)_2$ to complete the catalytic cycle.[91]

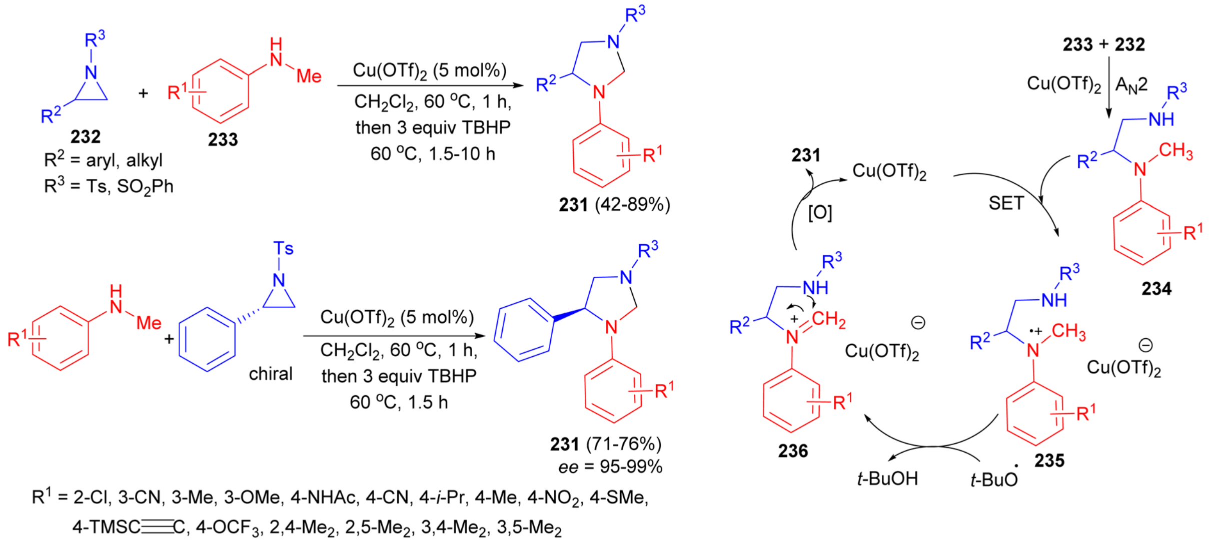
The Sun group further explored a protocol toward imidazolidines **237** through a stepwise [2 + 1 + 2] process using tosylhydrazones **238** and hexahydro-1,3,5-triazines **239** as the substrates under metal-free reaction conditions in the presence



R^1 = H, 3-Cl, 3-F, 4-F, 5-F, 3-CH_3, 4-CH_3, 5-CH_3, 6-CH_3, 4-OMe
R^2 = 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 2-thienyl, 2-naphthyl



Scheme 73 Enantioselective synthesis of imidazolidines **223** using AgOTs and ferrocenylphosphine P–N ligand.

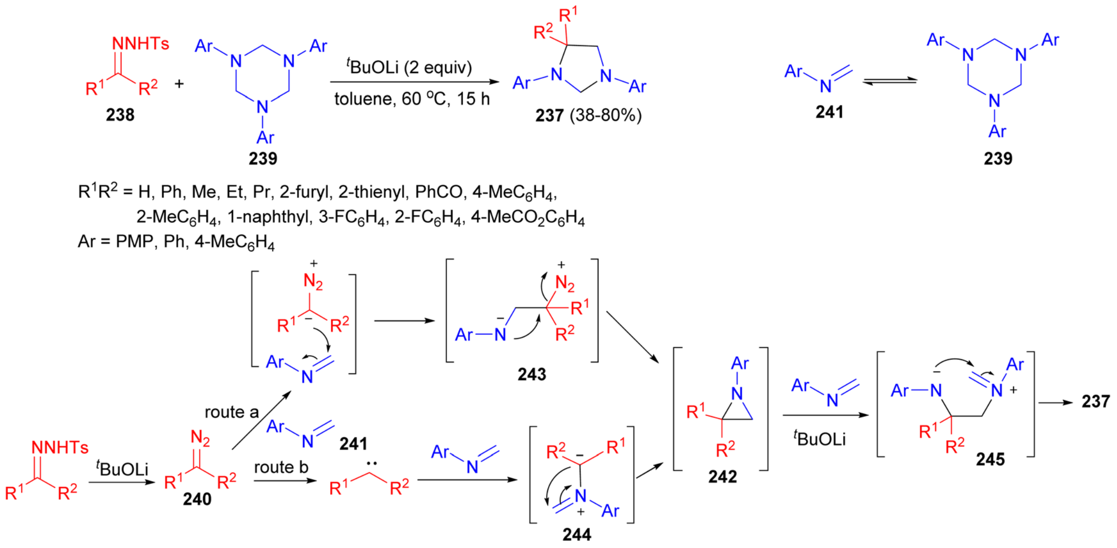


Scheme 74 $Cu(OTf)_2$ catalyzed synthesis of functionalized imidazolidines **231**.

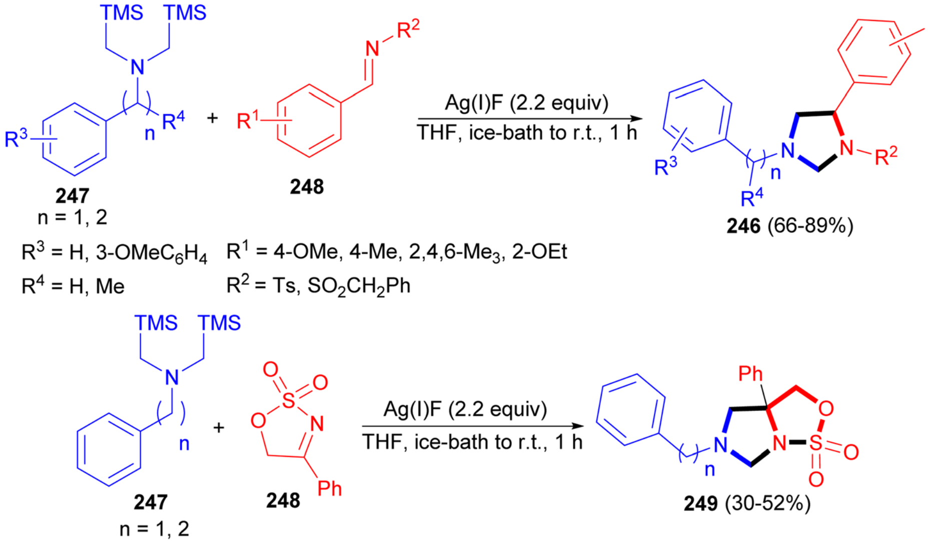
of ^{t}BuOLi in toluene at 60 °C for 15 hours. Importantly, the role of ^{t}BuOLi confirmed not only to release the diazo but also to promote the cycloaddition. Mechanistically, in this process, diazo **240** is slowly released from tosylhydrazone **238** by ^{t}BuOLi. The cycloaddition would be initiated by the first nucleophilic addition between diazo and formaldimine **241**, generating aziridine intermediate **242** through transition state **243** or **244**. Then, a base-promoted ring opening reaction of aziridine by another molecule of **241** occurs and delivers the final product **237** (38–80% yields) *via* intermediate **245** (Scheme 75).[92]

In addition, Laha and co-workers reported synthesis of *N*-sulfonyl imidazolidines **246** in 66–89% yields *via* 1,3-dipolar cycloaddition reaction of nonstabilized azomethine ylides **247** and *N*-sulfonyl aldimine or ketimines **248** using AgF in THF at ice-bath to room temperature for 1 hour. The strategy could complement the preparation of *N*-sulfonyl imidazolidines *via* selective *N*-sulfonylation. Furthermore, novel ring cleavage reactions of *N*-sulfonyl imidazolidines yielded synthetically useful 1,2-diamines that are otherwise difficult to prepare. Moreover, reaction of **247** with *N*-sulfonyl ketimine **248** gave sulfamidate fused imidazolidine **249** bearing a quaternary center (Scheme 76).[93]

Further, the Sun group demonstrated iron-catalyzed cycloaddition reaction of diazo surrogates **250** with hexahydro-1,3,5-triazines using a mixture of MnO_2 and $MgSO_4$ in CH_2Cl_2 at 0 °C to room temperature for 7 hours afforded imidazolidine derivatives **251** in 41–84% yields. Next, the reaction of substituted phenyl diazoacetates **252** with hexahydro-1,3,5-triazines **253** in the presence of 5 mol% of $Fe(acac)_3$, resulted the corresponding products **254** in 52–80% yields. In addition, cycloaddition of



Scheme 75 Metal-free synthesis of imidazolidines **237** in the presence of ^{t}BuOLi.

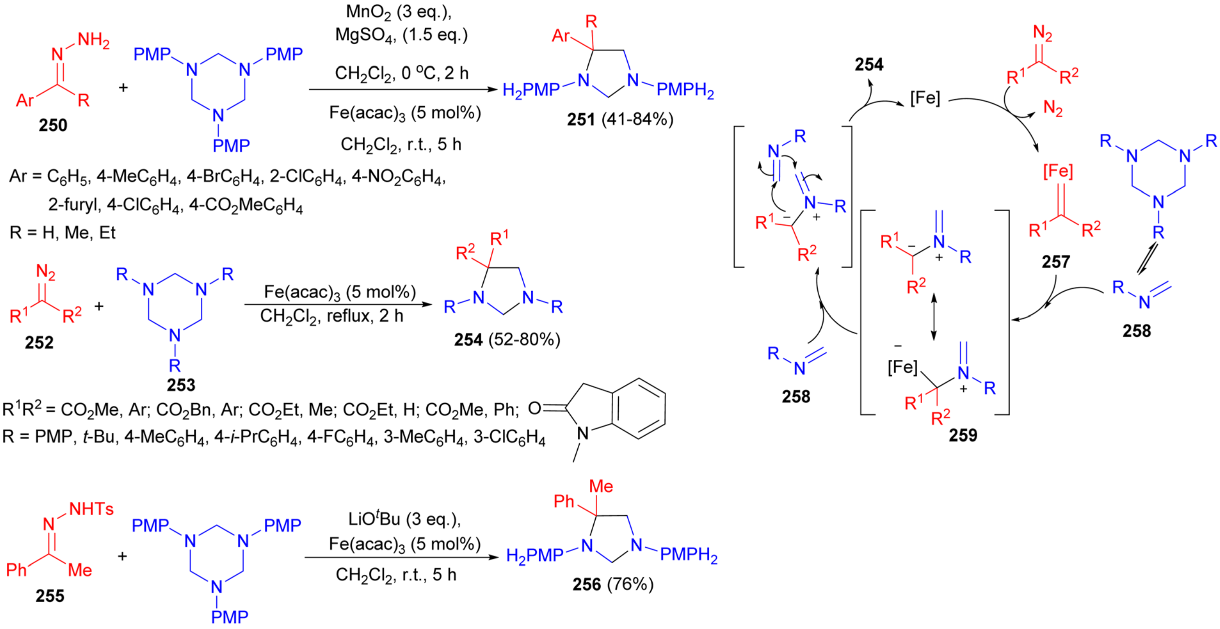


Scheme 76 Synthesis of *N*-sulfonyl imidazolidines **246** and sulfamidate fused imidazolidine **249**.

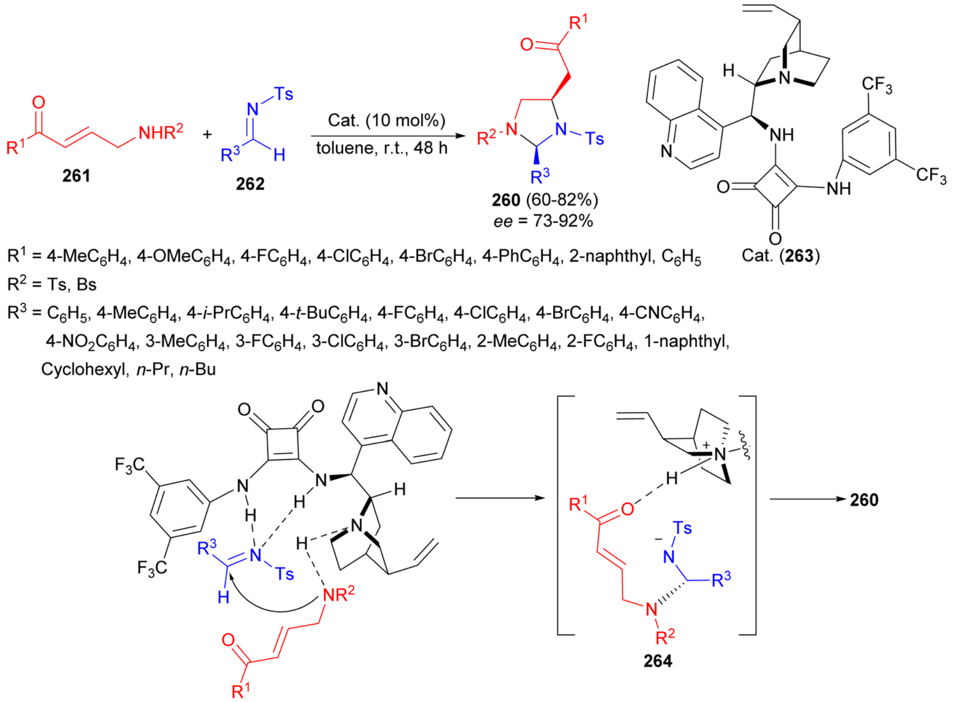
a tosyl hydrazine **255** with hexahydro-1,3,5-triazines led to the formation of imidazolidine **256** in 76% yield. The plausible reaction mechanism is proposed in Scheme 77. Firstly, the reaction of the diazo compound with the iron catalyst generates iron-carbene **257**. Then, *N*-methyleneamine **258** (formed *in situ* from hexahydro-1,3,5-triazines) reacts rapidly with **257** to afford **259**, which undergoes nucleophilic attack by another molecule of **258**, followed by ring closing to give the final cycloaddition product and the iron catalyst regenerates.[94]

In 2018, the highly diastereo- and enantioselective synthesis of 2,4-disubstituted imidazolidines **260** in 60–82% yields developed *via* a formal [3 + 2] cyclization reaction of bidentate aminomethyl enones **261** and *N*-tosyl imines **262** in the presence of bifunctional squaramide catalyst **263** in toluene at room temperature for 48 hours. A plausible TS depicted in Scheme 78 which dictates a bifunctional mode of activation by the catalyst. Since the C═N of **262** is activated by hydrogen bonding of the squaramide motif, *Re* face is blocked. Thus, the addition of deprotonated **261** will take place only from the *Si* face and thus intermediate **264** is formed. Intermediate **264** then undergoes Michael addition from the *Re* face of enone moiety to provide product **260**.[95]

Further, the Huo group revealed a straightforward and efficient aerobic oxidative dehydrogenative formal [2 + 3]-



Scheme 77 Iron-catalyzed synthesis of imidazolidine derivatives **251**, **254** and **256**.



R^1 = 4-MeC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-PhC$_6$H$_4$, 2-naphthyl, C$_6$H$_5$
R^2 = Ts, Bs
R^3 = C$_6$H$_5$, 4-MeC$_6$H$_4$, 4-*i*-PrC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CNC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-MeC$_6$H$_4$, 3-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 1-naphthyl, Cyclohexyl, *n*-Pr, *n*-Bu

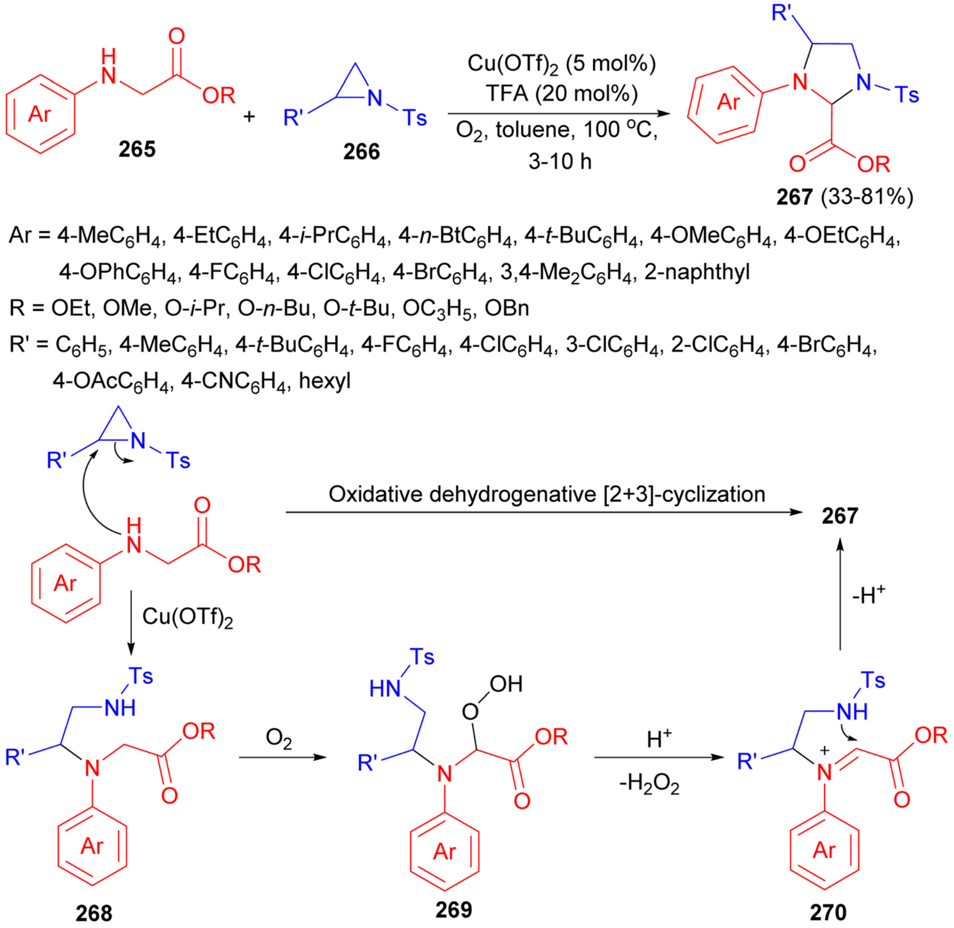
Scheme 78 Organocatalytic asymmetric synthesis of 2,4-disubstituted imidazolidines **260**.

cyclization of glycine derivatives **265** with aziridines **266**. The reaction provides facile access to a series of highly functionalized imidazolidine derivatives **267** in 33–81% yields and diastereomeric ratios up to 3.3 : 1 using Cu(OTf)$_2$ and TFA in toluene at 100 °C for 3–10 hours. In this process, aziridine **266** is initially attacked by glycine derivative **265** to form ring-opened intermediate **268** (S$_N$2). Intermediate **268** is then auto-oxidized to give hydroperoxide intermediate **269**. Subsequently, iminium ion intermediate **270** is then formed from **269** through an acid catalyzed S$_N$1-type procedure. Finally, intramolecular C–N bond formation results in the desired product **267** (Scheme 79).[96]

The tandem nucleophilic addition–cycloaddition reaction developed for the synthesis of functionalized imidazolidine derivatives **271** by the reaction of a variety of α-iminoesters **272** with silylaryl triflates **273** at −10 °C in the presence of Ag(Tf$_2$N), chiral ligand **274**, CsF and 18-crown-6 in acetonitrile for overnight. This asymmetric cycloaddition afforded imidazolidine derivatives with high yields (up to 99%), complete regioselectivities, and excellent diastereo (>20 : 1)- and enantioselectivities (up to 97% ee) (Scheme 80). In this process, aryne-induced ylides working as 1,3-dipoles for asymmetric cycloaddition is the notable feature of the present reaction. In the tandem reaction, the [3 + 2] cycloaddition of aryne induced ylides with metallized α-iminoesters and metal-catalyzed [3 + 2] cycloaddition of azomethine ylide with α-iminoesters are two concurrent pathways to imidazolidines.[97]

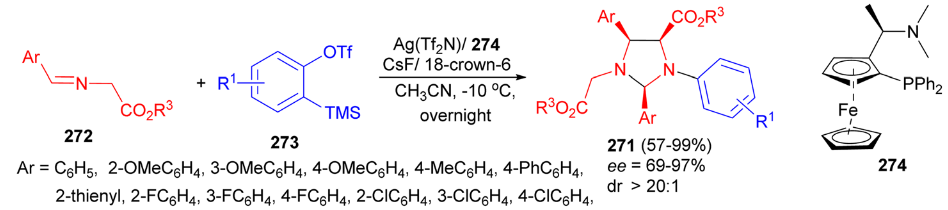
The Feng group reported a highly efficient and stereoselective synthesis of enantioenriched imidazolidines **275** by rhodium-catalyzed intermolecular [3 + 2] cycloaddition reaction of chiral vinyl aziridines **276** and oxime ethers **277** using AgSbF$_6$ in DCE at −5 °C for 12 hours. This method delivers enantioenriched imidazolidines in up to 99% yield and up to 99% ee by a chirality-transfer strategy. A plausible mechanism is proposed in Scheme 81. Both the olefin and the nitrogen atom in vinylaziridine **276** could coordinate to the rhodium catalyst to give complex **278**, which led to enyl (σ + π) rhodium species **279** with the retention of configuration formed by oxidative addition. Subsequently, nucleophilic attack of the oxime ether **277** onto the rhodium complex **279** from the back face would produce the intermediate **280** with a net inversion of absolute configuration and regenerate the rhodium catalyst. Finally, intermediate **280** underwent intramolecular cyclization to afford the less sterically hindered [3 + 2] cycloadducts **275**.[98]

A palladium-catalyzed controllable cyclization of vinyl ethylene carbonates **281** with 1,3,5-triaryl-1,3,5-triazinanes **282** has been reported by Yang group. The reaction proceeds through formal migration [2 + 3] cycloaddition in MeOH/H$_2$O at 80 °C for 2 hours. The transformation affords imidazolidine derivatives **283** in 26–96% yields. A plausible mechanism is proposed in Scheme 82. The reaction begins with the oxidative addition of Pd(0) to vinyl ethylene carbonate **281**, generating the zwitterionic *p*-allyl palladium intermediate **284** by releasing carbon dioxide. Meanwhile, three imines are generated *in situ* from triazinane **282** *via* C–N bond cleavage, which would attack **284** followed by reductive elimination to produce the formal [5 + 2] cycloaddition product **285** and regenerate Pd(0) species. Under controllable conditions, the 7-membered ring product **285** could further undergo oxidative addition with Pd(0) species to give intermediate **286**, which is then captured by imine and delivers the ten-membered palladacycle **287**. Subsequently, reductive elimination and intramolecular aza [3,3]-sigmatropic



Ar = 4-MeC$_6$H$_4$, 4-EtC$_6$H$_4$, 4-*i*-PrC$_6$H$_4$, 4-*n*-BtC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-OEtC$_6$H$_4$, 4-OPhC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3,4-Me$_2$C$_6$H$_4$, 2-naphthyl
R = OEt, OMe, O-*i*-Pr, O-*n*-Bu, O-*t*-Bu, OC$_3$H$_5$, OBn
R' = C$_6$H$_5$, 4-MeC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-OAcC$_6$H$_4$, 4-CNC$_6$H$_4$, hexyl

Scheme 79 Synthesis of functionalized imidazolidine derivatives **267** using Cu(OTf)$_2$ and TFA.



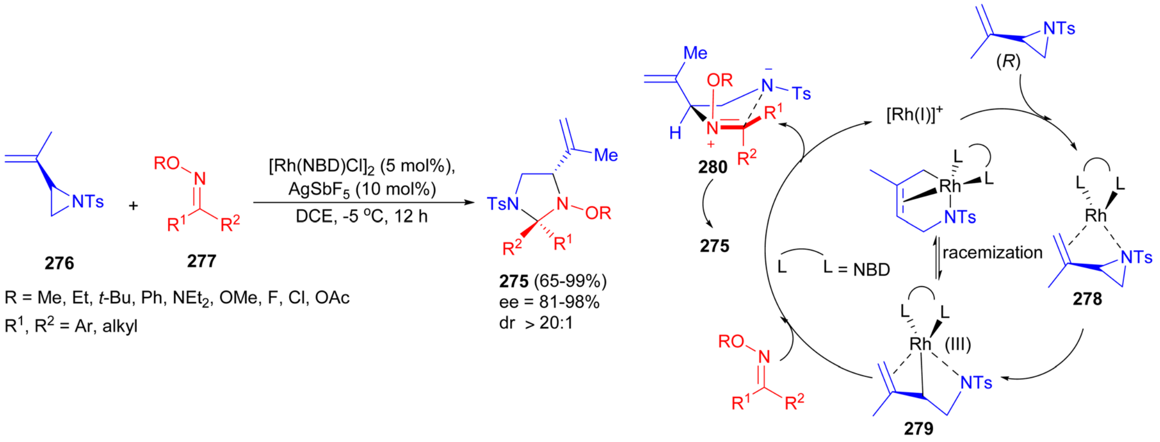
Ar = C$_6$H$_5$, 2-OMeC$_6$H$_4$, 3-OMeC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-PhC$_6$H$_4$, 2-thienyl, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CF3C$_6$H$_4$
R^3 = Et, Me
∗ R^1 = 3,4-Me$_2$, 3,4-F$_2$, 3,4-OCH$_2$O

Scheme 80 Synthesis of functionalized imidazolidine derivatives **271** in the presence of Ag(Tf$_2$N).

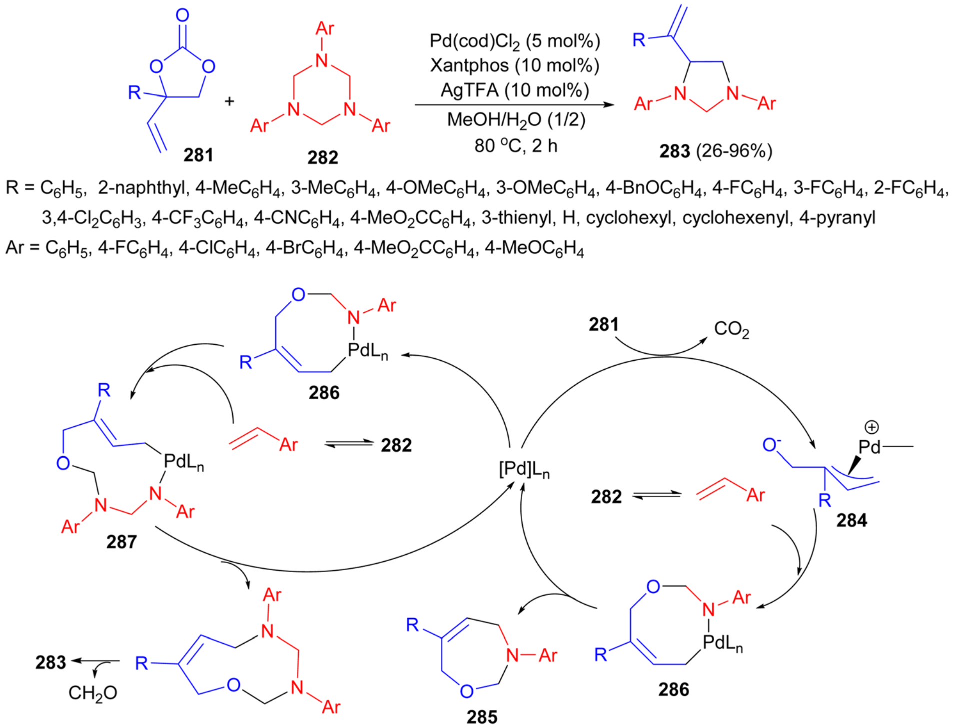
rearrangement events take place to furnish the formal migration [2 + 3] cycloaddition product **283** with extrusion of formaldehyde.[99]

In 2019, Mani *et al.* reported the Mannich reaction of pyrrole (**288**) with a mixture of ethylenediamine dihydrochloride (**289**) and formaldehyde using K$_2$CO$_3$ in aqueous methanol at 0 °C gave a mixture of products N^1,N^1,N^2,N^2-tetrakis(pyrrol-2-ylmethyl)ethane-1,2-diamine **290** and 1,3-bis(pyrrol-2-ylmethyl) imidazolidine **291** which were isolated in 14% and 1% yield, respectively, after basic alumina column chromatography (Scheme 83). The X-ray structure of **291** along with intermolecular hydrogen bonding in its crystal lattice.[100]

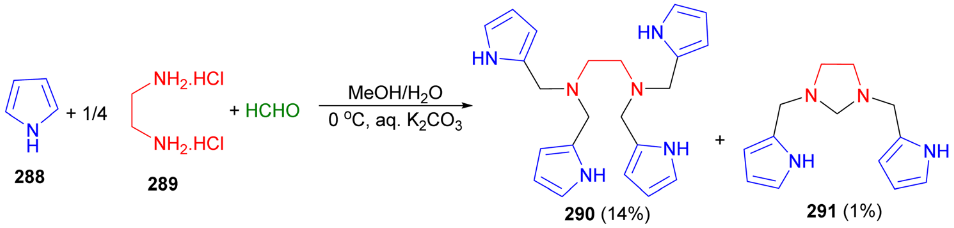
The Tu group described synthesis of functionalized imidazolidines **292** in 36–92% yields *via* unprecedented 1,3-dipolar cycloadditions of 1,3,5-triazinanes **293** with aziridines **294** in the presence of ZnBr$_2$ in toluene at 80 °C for 36 hours. A plausible mechanism is depicted in Scheme 84. The formaldimine was first generated in the presence of Lewis acid. Next, formaldimine attacked the activated aziridine through a second-order nucleophilic substitution (S$_N$2)-like pathway, leading to the inversion of configuration and the ring open of the



Scheme 81 Rhodium-catalyzed synthesis of enantioenriched imidazolidines **275**.

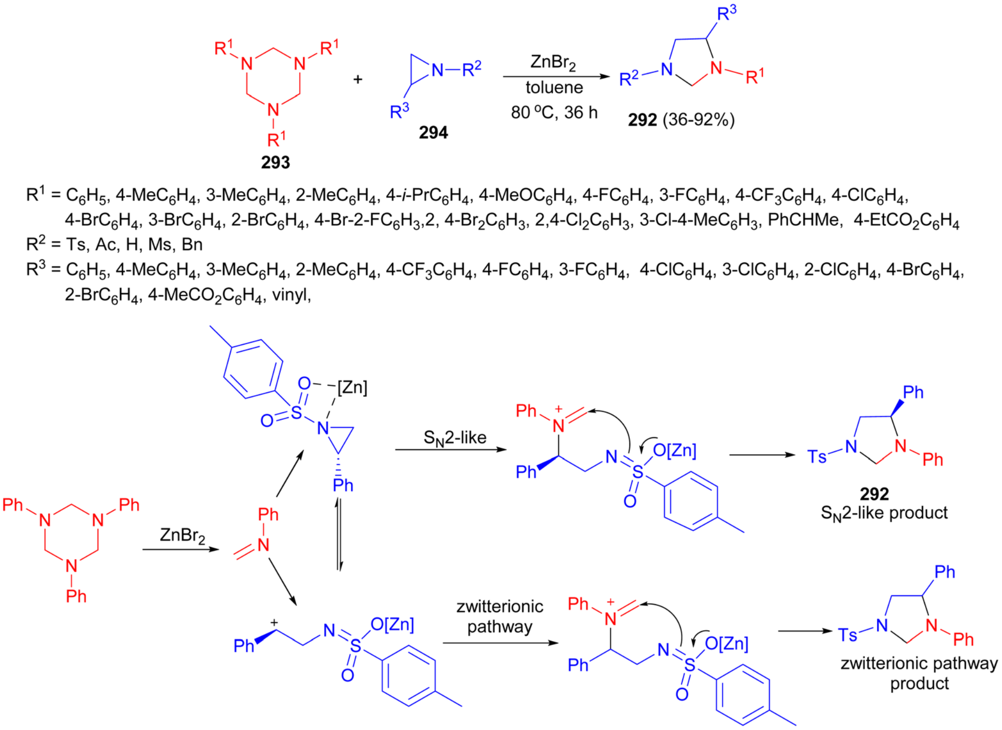


Scheme 82 Palladium-catalyzed synthesis of imidazolidine derivatives **283**.



Scheme 83 Synthesis of 1,3-bis(pyrrol-2-ylmethyl)imidazolidine **291**.

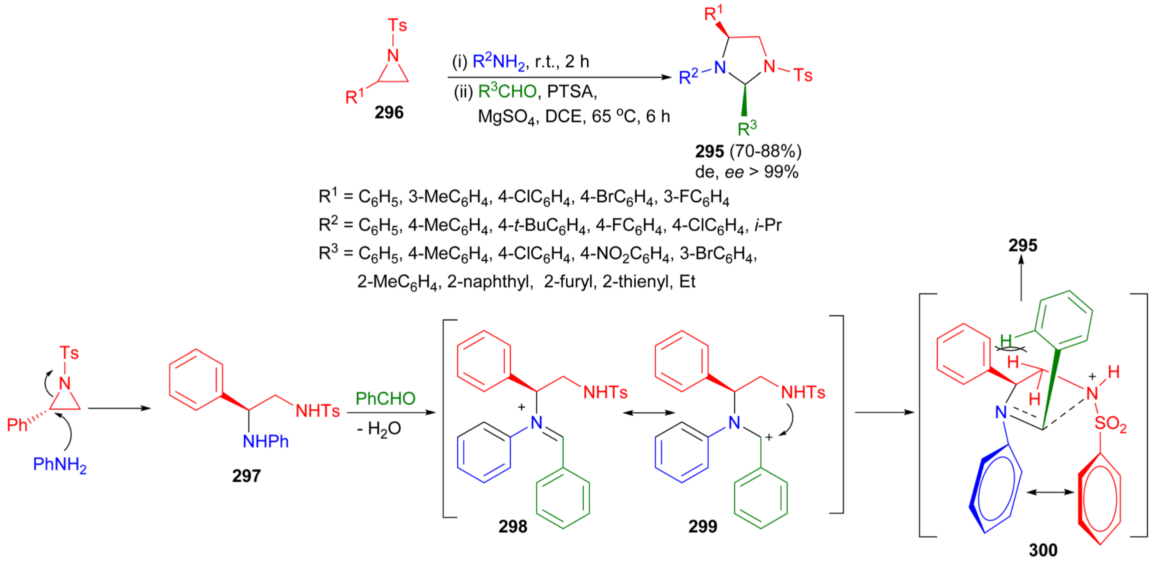
aziridine. Meanwhile, the racemic product was generated through the ring opened zwitterion, which served as both a nucleophile and an electrophile to react with *N*-phenyl formaldimine. The ee value of **292** suggested that the ring opened zwitterionic pathway product dominated over the S_N2-like product.[101]



R^1 = C_6H_5, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-*i*-PrC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-FC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 4-Br-2-FC_6H_3,2, 4-$Br_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 3-Cl-4-MeC_6H_3, PhCHMe, 4-$EtCO_2C_6H_4$
R^2 = Ts, Ac, H, Ms, Bn
R^3 = C_6H_5, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-$CF_3C_6H_4$, 4-FC_6H_4, 3-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, 4-$MeCO_2C_6H_4$, vinyl,

Scheme 84 $ZnBr_2$ catalyzed synthesis of functionalized imidazolidines **292**.

In 2020, Ghorai and co-workers developed a mild one-pot stereospecific synthetic route to highly functionalized imidazolidines **295** *via* S_N2-type ring-opening of the corresponding activated aziridines **296** with amines followed by *p*-toluenesulfonic acid catalyzed intramolecular cyclization with aldehydes using $MgSO_4$ in DCE at 65 °C for 6 hours. The methodology tolerates a variety of functional groups and furnishes the desired products in high yields (up to 92%) with excellent stereoselectivities (ee > 99%). Interestingly, imidazolidines were formed as the *cis*-isomers. A plausible mechanism is depicted in Scheme 85. The ring-opening reaction of activated aziridines proceed *via* a regioselective S_N2-type pathway. Amine nucleophile attacks the aziridine at the benzylic position to produce the corresponding ring-opening product **297**, which in the presence of acid catalyst and additive $MgSO_4$ forms the corresponding iminium ion **298** when reacted with aldehyde. Subsequently, the intramolecular nucleophilic attack by the tosyl amide on the iminium ion



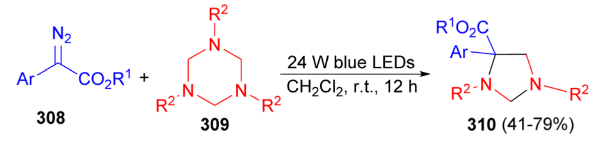
R^1 = C_6H_5, 3-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-FC_6H_4
R^2 = C_6H_5, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, *i*-Pr
R^3 = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-BrC_6H_4, 2-MeC_6H_4, 2-naphthyl, 2-furyl, 2-thienyl, Et

Scheme 85 Synthetic of highly functionalized imidazolidines **295** *via* S_N2-type ring-opening of aziridines.

probably through the cationic intermediate **299** occurs in such a way that it leads to the more favorable TS **300** where the electronic 1,4-π–π stacking interaction outweighs the steric repulsion arising from the interaction between the *ortho*-hydrogens of the aromatic ring at C-2 and methylene hydrogen at C-5 of the ring to produce the 2,4-*cis* diastereomer **295** of imidazolidine derivatives as the only product.[102]

The Hu group described the effectiveness of trifluoromethylated *N*-acylhydrazones **301** as dipolarophiles in conducting 1,3-dipolar cycloaddition with azomethine ylides **302**. This reaction occurs in the presence of $AgNO_3$ and Et_3N in toluene at room temperature, yielding trifluoromethylated imidazolidines **303** in 76–91% yields after 24 hours. A proposed mechanism is depicted in Scheme 86. The *in situ*-formed azomethine ylides **302** was coordinated to the Ag(I) to give complex **304**, which performed addition reaction to the C=N of **301** to generate the zwitterionic intermediate **305**. The silver atom switched from the nitrogen atom of imine ester to the *N'*-nitrogen atom of trifluoromethylated *N*-acylhydrazone to form the species **306**. Rotation of C–N σ-bond formed intermediate **307**, which performed cyclization to give the final product **303**.[103]

In 2021, the Wang and Xuan group demonstrated a visible light-promoted divergent cycloaddition of α-diazo esters **308** with hexahydro-1,3,5-triazines **309** in DCM at room temperature for 12 hours. This reaction yielded a series of imidazolidine frameworks **310** in 41–79% yields (Scheme 87). It is noteworthy that the reaction occurs under sole visible light irradiation without the need for exogenous photo redox catalysts. Mechanistic studies based on control experiment results and DFT calculations revealed that both 1,3,5-triazines and the *in situ* formation of formaldimines could serve as carbene trapping reagents to form key nitrogen ylide intermediates.[104]



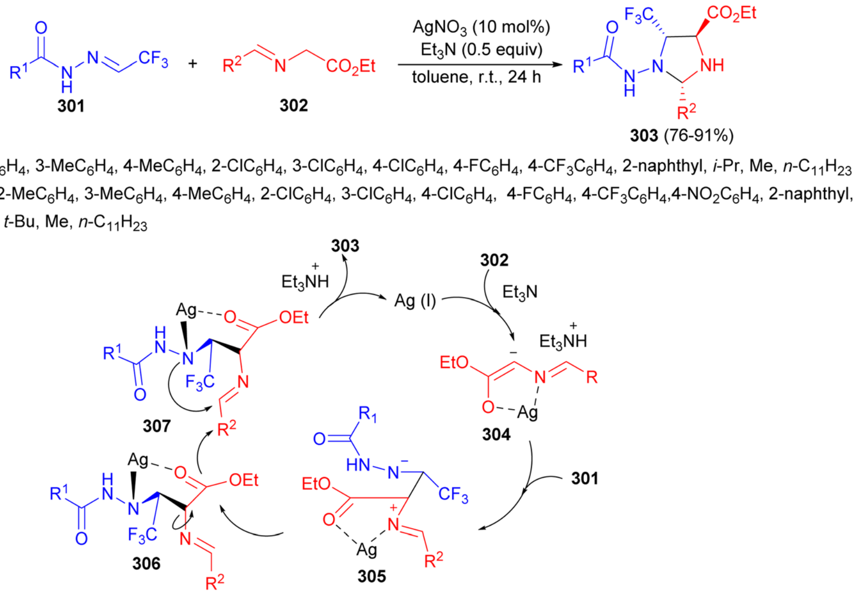
Ar = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, 3,4-$OCH_2OC_6H_3$, 2-naphthyl, 4-$AdCO_2C_6H_4$, 4-$OBsC_6H_4$
R^1 = Me, Et, *i*-Pr, cyclobuthyl, cyclopentyl, $CH_2CH_2C{\equiv}CH$, $CH_2C(Me)CH_2$
R^2 = PMP, C_6H_5, 4-MeC_6H_4, 4-FC_6H_4, 3-ClC_6H_4

Scheme 87 Synthesis of a series of imidazolidine frameworks **310** under sole visible light irradiation.

The synthesis of 1,3-disubstituted imidazolidines **311** in 34–80% yields was reported by the Ye and Fu group. To begin, diamine **312** reacted with formaldehyde in water at 100 °C for 0.5–2 hours, yielding intermediate imidazolidines **313**. Subsequently, aromatic acyl chloride in acetone was added to imidazolidines **313** under pH = 8–10, resulting in the formation of imidazolidines **311** after 2 hours. The bioassay results indicated that the majority of the target compounds exhibited softening activity against nicosulfuron in sensitive Kennian 1 maize (Scheme 88).[105]

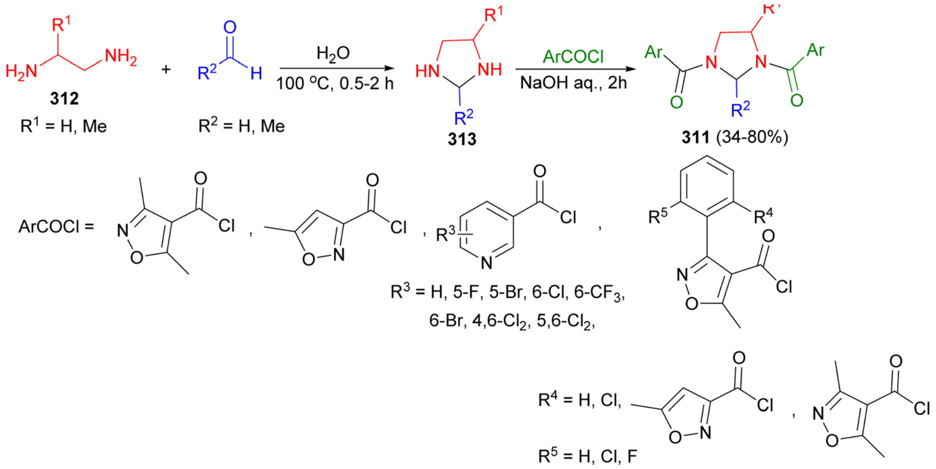
The reaction of equimolar amounts of pyridoxal **314** and 1,2-propylenediamine **315** in EtOH at 0 °C afforded the formation of monoamine **316** after 12 hours, which affords as a cyclic 5-(hydroxymethyl)-2-methyl-4-(4-methylimidazolidin-2-yl)pyridin-3-ol tautomer **317** in 100% yield (Scheme 89).[106]

Synthesis of methyl (2*E*)-3-[3-benzyl-2-(3-methoxy-3-oxoprop-1-yn-1-yl)-2-(1-naphthyl)imidazolidine-1-yl]acrylate **318**, has been reported *via* domino-reaction, employing easily available 1-benzyl-2-(1-naphthyl)-4,5-dihydro-1*H*-imidazole **319** and methyl propiolate (**320**) in dry ether at room temperature for 3 hours in 92% yield. The mechanism of imidazolidine **320** formation includes the conjugated addition of 2-imidazoline **318** at the triple bond of the first alkyne molecule, leading to the zwitterion **321**, which then deprotonates the second methylpropiolate

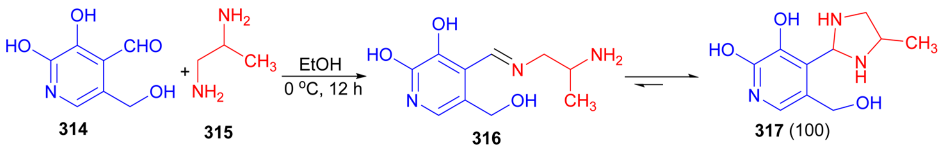


R^1 = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 2-naphthyl, *i*-Pr, Me, *n*-$C_{11}H_{23}$
R^2 = C_6H_5, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 2-naphthyl, 2-furyl, *t*-Bu, Me, *n*-$C_{11}H_{23}$

Scheme 86 $AgNO_3$ catalyzed synthesis of trifluoromethylated imidazolidines **303**.



Scheme 88 Synthesis of 1,3-disubstituted imidazolidines **311**.



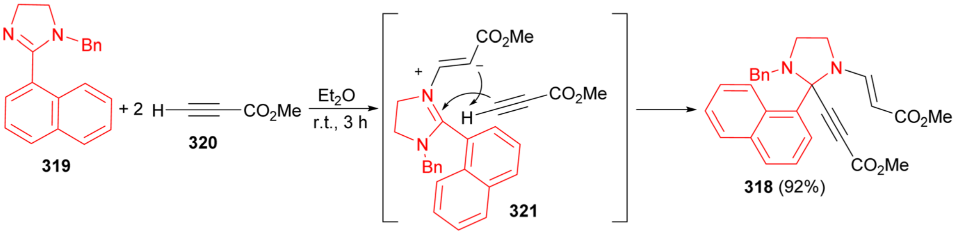
Scheme 89 Synthesis of cyclic 5-(hydroxymethyl)-2-methyl-4-(4-methylimidazolidin-2-yl)pyridin-3-ol tautomer **317**.

molecule to form an acetylenide ion. At the final stage, nucleophilic addition of the obtained acetylenide ion occurs at the position 2 of the 2-imidazolinium ion (Scheme 90).[107]

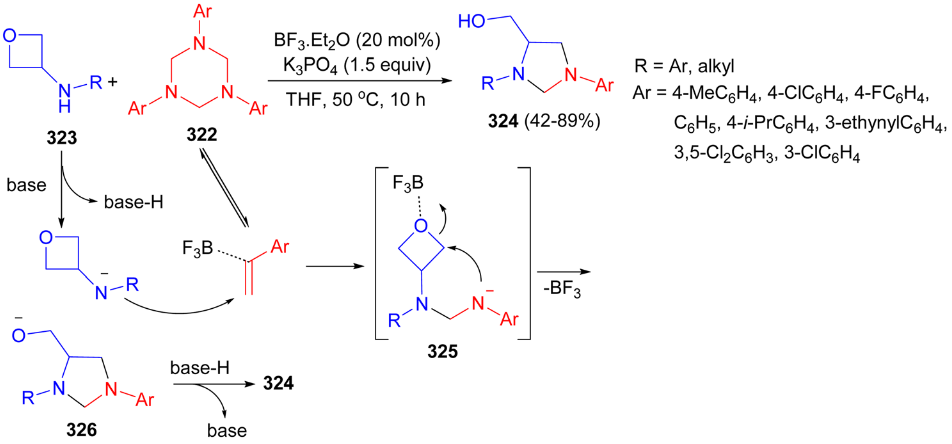
The Jia group disclosed a facile $BF_3\cdot Et_2O$-catalysed [3 + 2] annulation between readily available 1,3,5-triazinanes **322** and 3-aminooxetanes **323** in THF at 50 °C for 10 hours furnishing a wide range of 4-hydroxymethyl imidazolidines **324** in useful to good yields. A plausible [3 + 2] annulation reaction mechanism is proposed in Scheme 91. With the assistance of $BF_3\cdot Et_2O$, the nucleophilic addition of **323** to **322** affords a usually unstable intermediate **325** under basic conditions. The intermediate **325** further undergoes an intramolecular ring-opening produce intermediate **326.** The intermediate **326** generate the 4-hydroxymethyl imidazolidine product **324**. It should be noted that the ring-opening step should be fast enough to outcompete the decomposition of intermediate **325.**[108]

A strategy of asymmetric carbonyl catalysis *via* a chiral Lewis acid-bonded aldehyde has been developed for the direct Mannich/condensation cascade reaction of glycine ester **327** with aromatic aldimines **328.** The co-catalytic system of 2-picolinaldehyde and chiral YbIII-*N*,*N*′-dioxides as the Lewis acid catalyst was identified to be efficient in EtOH at 35 °C for 48 hours, providing a series of trisubstituted imidazolidines **329** in moderate to good yields (up to 66%), and excellent diastereo- and enantioselectivities with high diastereo- and enantioselectivities (up to 95 : 5 dr, 97% ee). Enantiodivergent synthesis was achieved *via* changing the sub-structures of the chiral ligands. The reaction could be carried out in a three-component version involving glycine ester, aldehydes, and anilines with equally good results. The chiral *N*,*N*′-dioxide/$Yb(OTf)_3$ complex bonded aldehyde enabled carbonyl activation of glycine ester for α-addition transformation (Scheme 92).[109]

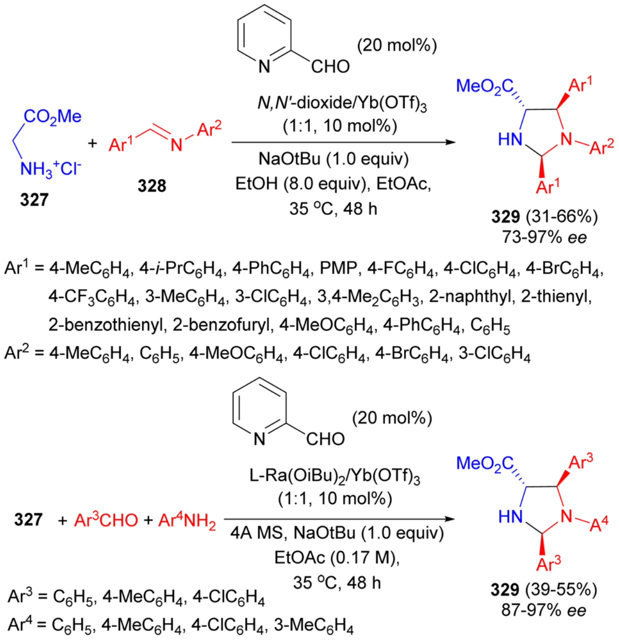
A $Y(OTf)_3$-catalyzed [3 + 2] cycloaddition of 1,3,5-triazinanes **330** with donor–acceptor aziridines **331** has been developed by Lin and co-workers. The reaction conducted in DCM at 30 °C for 12 hours yielded substituted imidazolidines **332** in 39–98% yields. A plausible mechanism is depicted in Scheme 93. In the presence of $Y(OTf)_3$, the formaldimine **333** was first generated and the 1,3-dipole **334** was produced *in situ* from the ring-opening reaction of the donor acceptor aziridine, followed by



Scheme 90 Synthesis of imidazolidine derivative **318** *via* domino-reaction.



Scheme 91 A facile $BF_3 \cdot Et_2O$-catalysed synthesis of 4-hydroxymethyl imidazolidines **324**.



Scheme 92 2-Picolinaldehyde and chiral YbIII-*N*,*N*′-dioxides catalyzed synthesis of a series of trisubstituted imidazolidines **329**.

a [3 + 2] cycloaddition between the formaldimine **333** and 1,3-dipole **334**, furnishing the desired product **332** through an S_N1-like pathway. Moreover, the compound **332A** exhibited promising anti-proliferative activity against a number of human cancer cell lines, which could serve as a hit compound for the anti-tumor research.[110]

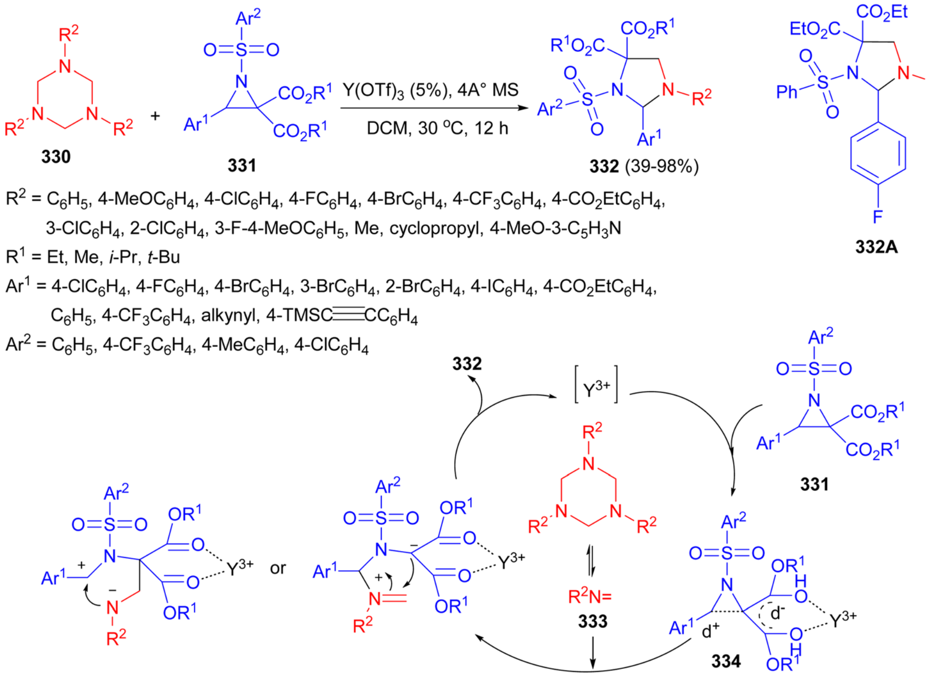
An unprecedented 1,3-dipole cycloaddition between acyclic CF_3-ketimines **335** and *N*-benzyl amine **336** has been allowed by tungsten (W) catalysis in *o*-xylene at 150 °C for 48 hours, resulting in a variety of imidazolidines **337** in 32–99% yields bearing a trifluoromethylated tetrasubstituted carbon center. A proposed mechanism is illustrated in Scheme 94. The coordination of reagent **336** with W catalyst occurred to form intermediate **338** through CO dissociation, which further generated azomethine **339** by releasing $W(CO)_5$ and TMSOMe. The active intermediate 339 could undertake a concerted 1,3-dipolar cycloaddition reaction with imine **340** to furnish **337** or might undergo a stepwise cyclization to give product **337** under the assistance of W catalyst.[111]

The Ma Group described the TiO_2 photocatalytic synthesis of five-membered N-heterocyclic imidazolidines **341** in 32–98% yields from a common imine (*N*-benzylidenebenzylamine) **342** and alcohols **343** *via* a 1,3-dipolar azomethine ylide intermediate, notably without pre-installed electron-withdrawing groups (EWG) on the substrates (Scheme 95).[112]

In 2022, Wang and co-workers reported a simple and practical method for the construction of 1,3,5-trisubstituted imidazolidine derivatives **344** *via* [3 + 2] cycloaddition reaction. This reaction could smoothly proceed between nonstabilized azomethine ylide **345**, generated *in situ* from *N*-(methoxymethyl)-*N*-(trimethylsilyl-ethyl)-benzyl amine (**346**), and 2-benzothiazolamines **347** in the presence of TFA in DCM at room temperature for 1 hour to deliver a wide scope of differently substituted imidazolidines in high yields (up to 98%). A possible mechanism for this transformation is proposed in Scheme 96. First, the nonstabilized azomethine ylide **345** from **346** is generated in the presence of TFA. Then, this nonstabilizedazomethine ylide could react with **347** to obtain the desired product **344** *via* [3 + 2] cycloaddition reaction with high regioselectivity.[113]

In addition, the Tamang group described the synthesis of highly stable $CsPbBr_3$ QD based photocatalysts using dibromoisocyanuric acid (DBI) as a benign non-toxic bromide precursor. The QDs were applied as a visible light photocatalyst for intramolecular cyclisation of diamines **348** and **349** to obtain a range of enantiopure bioactive heterocycles such as imidazolidines **350** and fused-imidazolidines **351** in high yields (isolated yield up to 82%, ee > 99%). The reaction carried out in open air at room temperature in DCM for 3–14 hours. The proposed mechanism is depicted in Scheme 97.[114]

In 2023, Moloney *et al.* described the reaction of diethyl aminomalonate hydrochloride **352**, along with 2 eq. of substituted benzaldehydes and benzylamine under basic conditions and heated to more than 100 °C in a Dean–Stark trap afforded



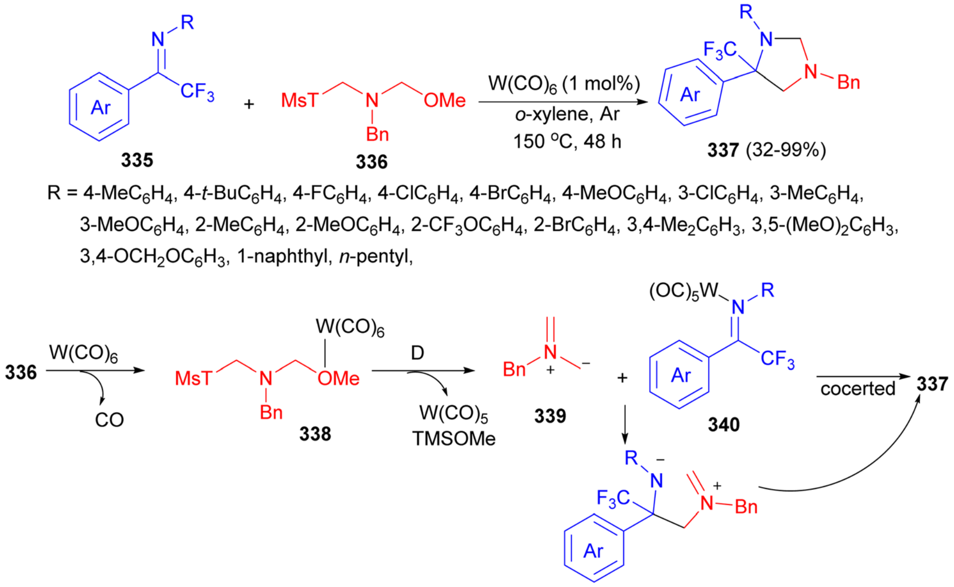
$R^2 = C_6H_5$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-$CO_2EtC_6H_4$, 3-ClC_6H_4, 2-ClC_6H_4, 3-F-4-$MeOC_6H_5$, Me, cyclopropyl, 4-MeO-3-C_5H_3N

R^1 = Et, Me, *i*-Pr, *t*-Bu

Ar^1 = 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 4-IC_6H_4, 4-$CO_2EtC_6H_4$, C_6H_5, 4-$CF_3C_6H_4$, alkynyl, 4-TMSC≡CC_6H_4

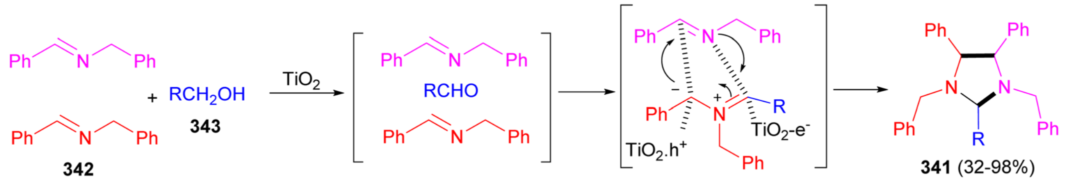
$Ar^2 = C_6H_5$, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 93 Y(OTf)$_3$-catalyzed synthesis of substituted imidazolidines **332**.



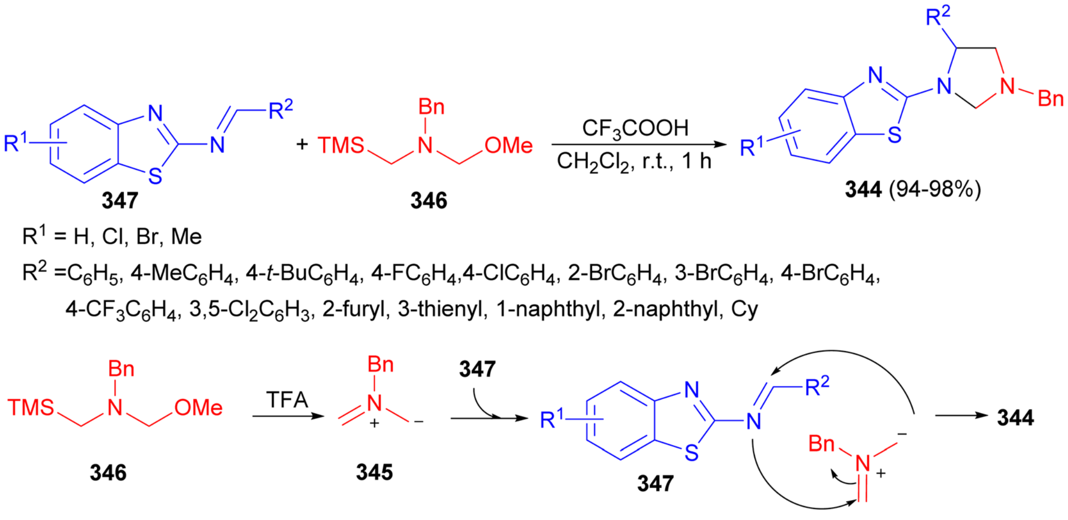
R = 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-$CF_3OC_6H_4$, 2-BrC_6H_4, 3,4-$Me_2C_6H_3$, 3,5-$(MeO)_2C_6H_3$, 3,4-$OCH_2OC_6H_3$, 1-naphthyl, *n*-pentyl,

Scheme 94 Tungsten catalyzed synthesis of imidazolidines **337**.

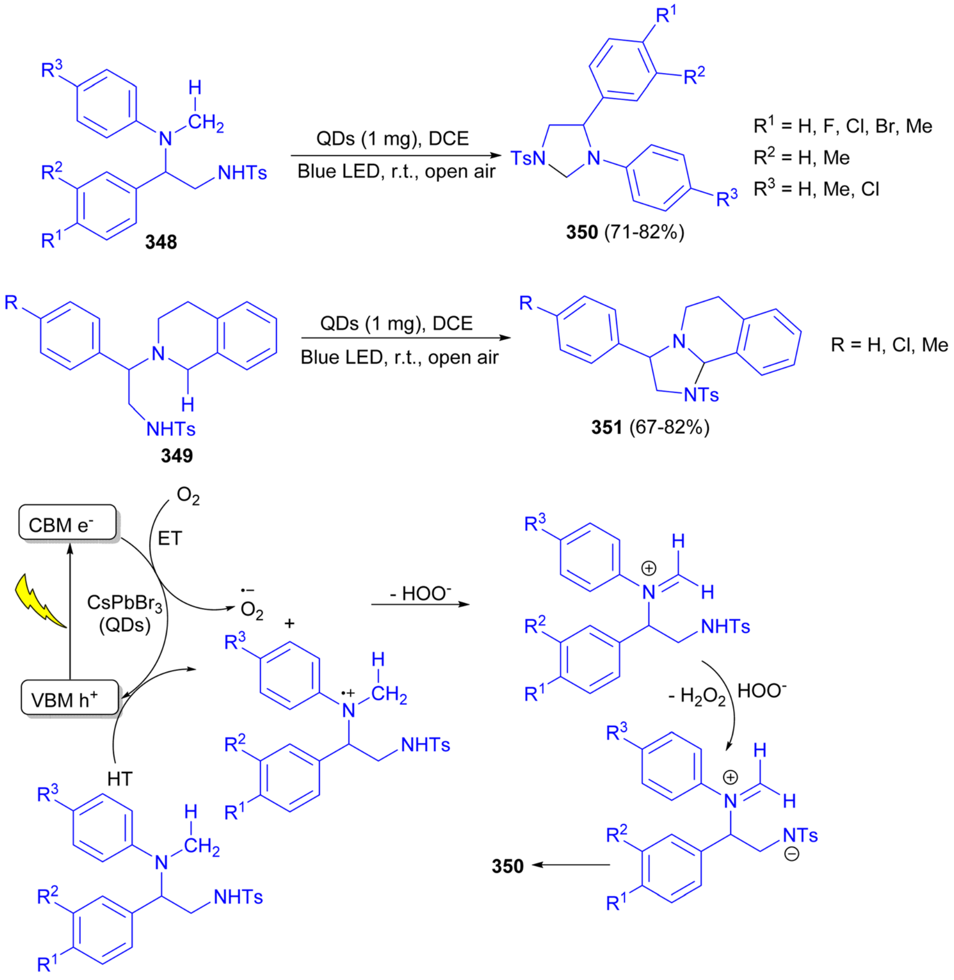


R = aliphatic, aromatic, EWG, EDG and electron-neutral group

Scheme 95 TiO$_2$ photocatalytic synthesis of imidazolidines **341**.

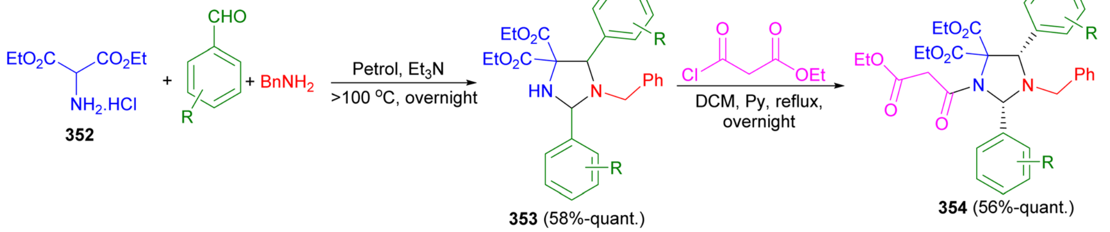


Scheme 96 TFA catalyzed synthesis of 1,3,5-trisubstituted imidazolidine derivatives **344**.



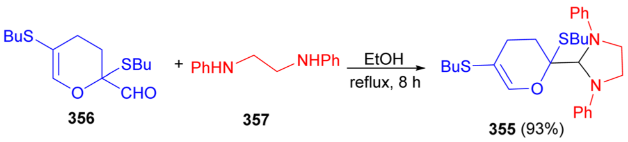
Scheme 97 Synthesis of imidazolidines **350** and **351** using QDs as a visible light photocatalyst.

imidazolidines **353** in 58%-quant. Yields, as either a single diastereomer or as a mixture of diastereomers, by a one-pot, three component 1,3-dipolar cycloaddition. Also, imidazolidines **353** were then *N*-acylated with ethyl malonyl chloride in DCM under reflux conditions for overnight to form imidazolidines **354** as single diastereomers in 56%-quant. Yields (Scheme 98).[115]



R = H, 4-Me, 4-MeO, 4-F, 4-Cl, 4-Br, 2,3-C_4H_4, 4-NO_2, 4-CF_3, 4-CN, 3-Br, 2-F

Scheme 98 Preparation of imidazolidines **353** and **354** under basic conditions.

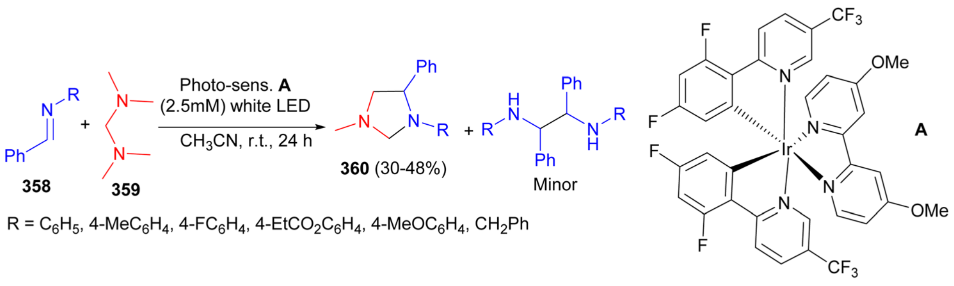


Scheme 99 Synthesis of 1,3-imidazolidine **355**.

The Vchislo group developed synthesis of 1,3-imidazolidine **355** in 93% yield from 2,5-bis-(butylsulfanyl)-2,3-dihydro-4*H*-pyran-2-carbaldehyde **356** and *N*,*N*′-diphenylethylenediamine **357** in EtOH at reflux for 8 hours. At room temperature, this reaction takes 12 days, while, upon heating, the duration to reaction completion is reduced to 8 hours (Scheme 99).[116]

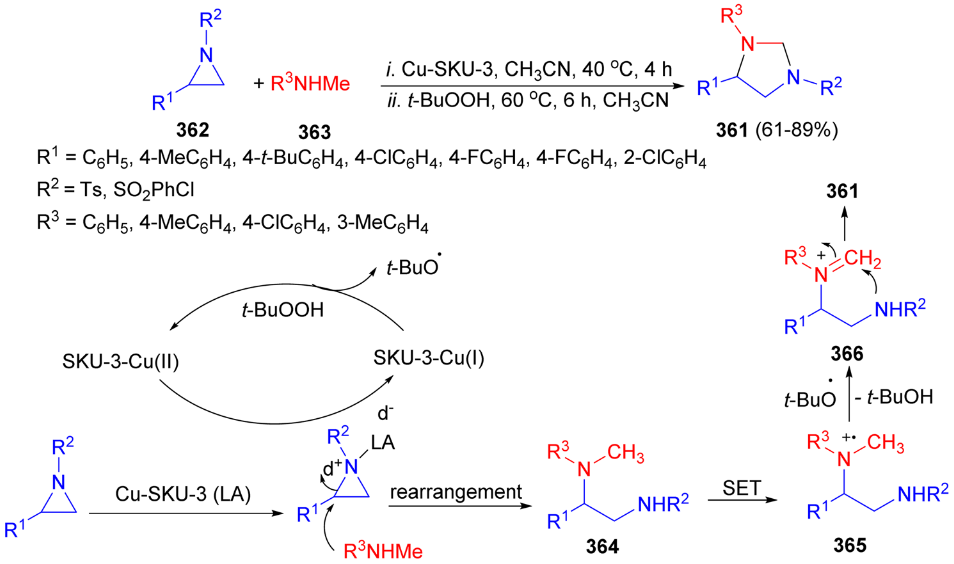
The Itoh group developed an unprecedented formal [3 + 2] photocycloaddition reaction of aromatic imines **358** with *N*,*N*,*N*′,*N*′-tetramethyldiaminomethane **359** to synthesize imidazolidines **360** in 30–48% yields using visible-light photo redox catalysis in CH_3CN at room temperature for 24 hours (Scheme 100).[117]

The Pariyar group utilized metal–organic framework (MOF), $[Cu(BTC)(Mim)]_n$ Cu-SKU-3, for the synthesis of biologically



R = C_6H_5, 4-MeC_6H_4, 4-FC_6H_4, 4-$EtCO_2C_6H_4$, 4-$MeOC_6H_4$, CH_2Ph

Scheme 100 Visible-light photoredox catalyzed synthesis of imidazolidines **360**.



R^1 = C_6H_5, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4
R^2 = Ts, SO_2PhCl
R^3 = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4

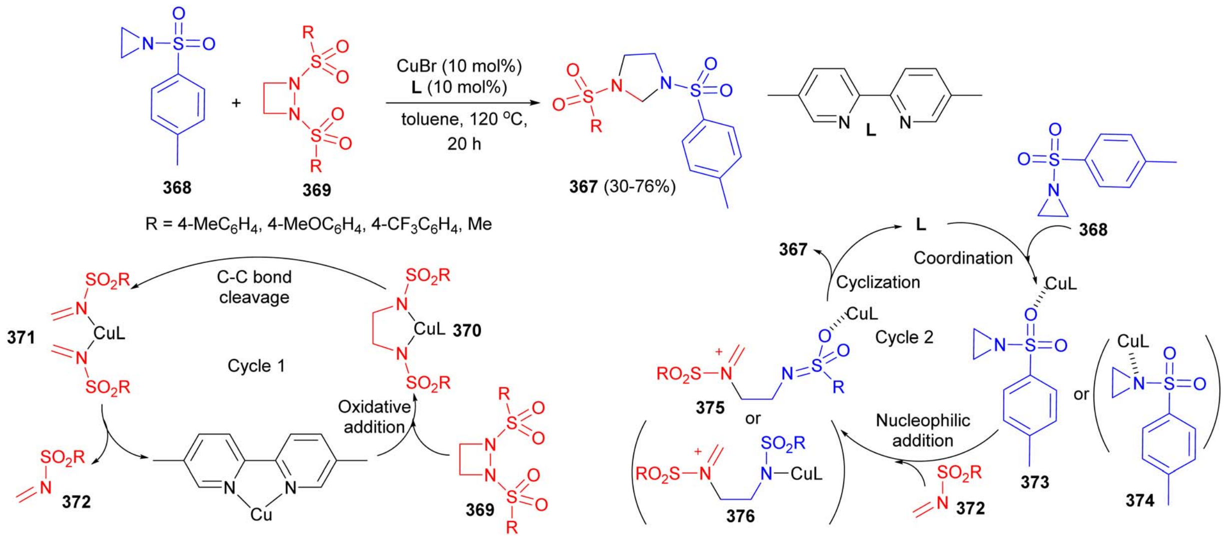
Scheme 101 Cu-SKU-3-catalyzed synthesis of substituted imidazolidines **361**.

valued chiral imidazolidine motifs **361** in a one-pot fashion starting from aziridines **362** and secondary amines **363**. The chiral imidazolidines are synthesized in good yield (up to 89%) and with high optical purity (ee > 98–99%). The proposed mechanism is depicted in Scheme 101. Initially, the ring-opening product **364** gets oxidized by Cu(II) metal center *via* single electron transfer (SET), forming a radical cation intermediate **365** stabilized by the framework's microenvironment. In the second step, the oxidation of the catalyst [Cu(I) to Cu(II)] using *t*BuOOH generates a tertiary butoxide radical (*t*BuȮ) that abstracts a hydrogen atom homolytically *via* sp^3 C–H bond cleavage forming an iminium ion intermediate **366**. Lastly, the consecutive intramolecular cyclization of intermediate **366** results in the formation of the desired product **361**.[118]

Cu-catalyzed synthesis of imidazolidines **367** in 30–76% yields through heterocyclic recombination between aziridines **368** and diazetidine **369** in toluene at 120 °C for 20 hours was reported by Murakami and co-workers. The proposed mechanism is illustrated in Scheme 102. The reaction involves two catalytic cycles: (1) the formation of imines from diazetidines **369**. The reaction of aziridine with the resulting imine. In cycle 1, Cu catalyst L reacts with diazetidine **369** to provide intermediate **370**. Reductive C–C bond cleavage provides the Cu intermediate **371**, which releases imine **372**. In cycle 2, copper-catalyst L activates aziridine **368** through coordination to give **373** (or **374**). Imine **372** then attacks **373** to furnish intermediate **375** (or **376**). Finally, ring-closing cyclization gives product **367**.[119]

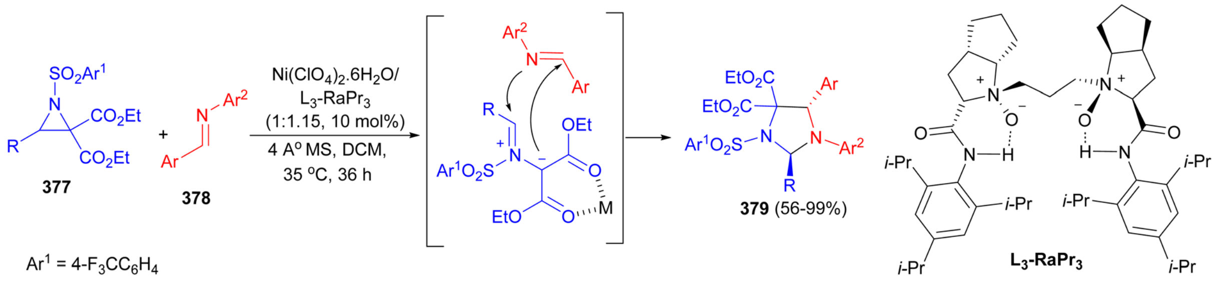
Liu and co-workers developed an enantioselective [3 + 2] cycloaddition of donor acceptor aziridines **377** with *N*-aryl protected imines **378** with a $Ni(ClO_4)_2 \cdot 6H_2O$/*N*,*N*′-dioxide catalyst system under nitrogen atmosphere in DCM at 35 °C for 36 hours, providing a broad range of chiral *trans*-substituted imidazolidine compounds **379** with good yields and excellent enantioselectivities (up to 99% yield, up to 98% ee) (Scheme 103).[120]

Murakami and co-workers described a copper-catalyzed reaction between aziridine **380** and imine **381**, utilizing ligand L in toluene at 120 °C for 20 hours, resulting in imidazolidine derivatives **382** in 25–99% yields. These developed reactions exhibited broad functional group compatibility to access a diverse array of potential bioactive 5-membered



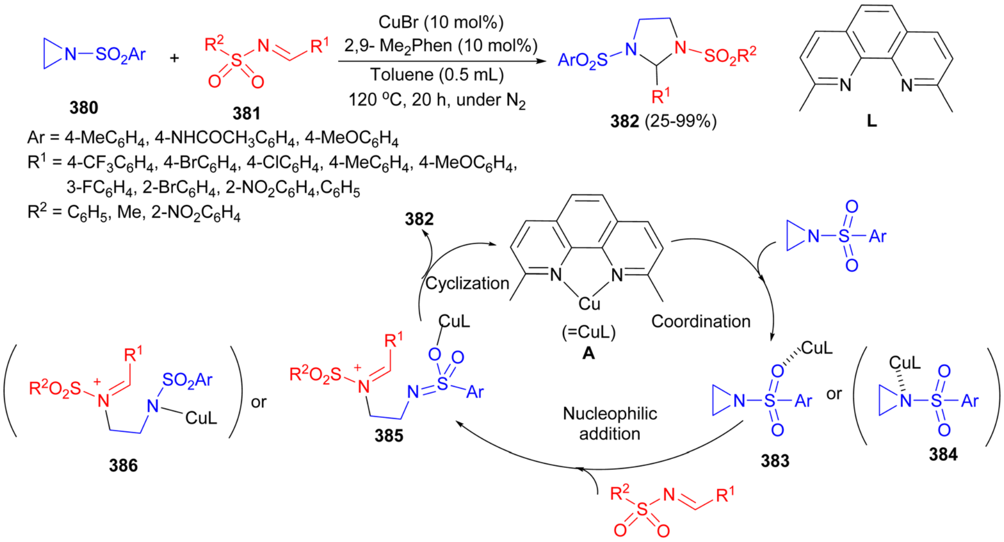
R = 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, Me

Scheme 102 Cu-catalyzed synthesis of imidazolidines 367.



Ar^1 = 4-F$_3$CC$_6$H$_4$
R = 3-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-IC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-OCF$_3$C$_6$H$_4$, trimethylsilylacetylene, 3-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 3,5-(MeO)$_2$C$_6$H$_3$, 2-naphthyl, C$_6$H$_5$,
Ar^2 = 4-BrC$_6$H$_4$

Scheme 103 Ni-catalyzed chiral *trans*-substituted imidazolidines 379.



Scheme 104 Copper-catalyzed synthesis of imidazolidine derivatives **382**.

azaheterocycles. A proposed mechanism is shown in Scheme 104. The reaction initiates with the coordination of aziridine **380** to copper catalyst A to give the corresponding intermediate **383** (or **384**). Subsequently, imine **381** attacks to open the aziridine ring to give intermediate **385** (or **386**). Finally, a cyclization reaction takes place from **385** to give product **382**.[121]

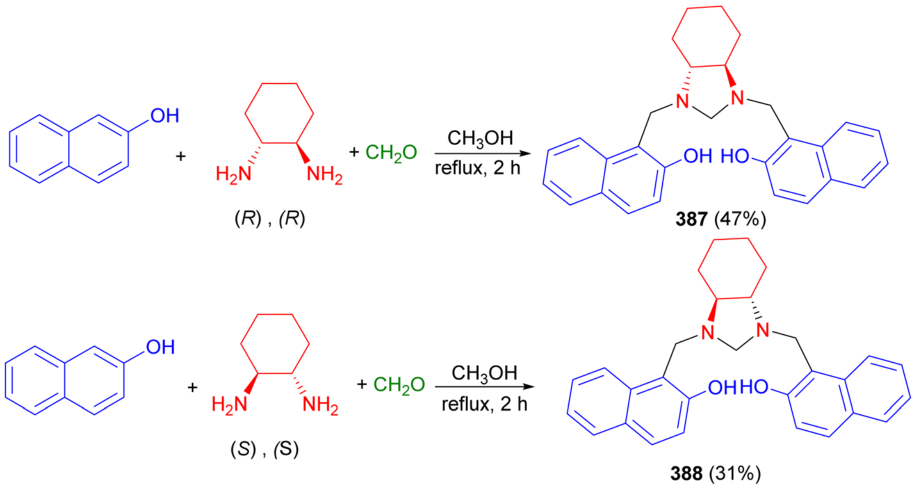
The Shivachev group reported the synthesis of imidazolidine **387** in 47% yield by three-component Mannich-type condensation reaction of naphthalene-2-ol, paraformaldehyde, and *R*,*R*-cyclohexane-1,2-diamine in methanol under reflux for 2 hours. Additionally, they synthesized imidazolidine **388** in 31% yield by using *S*,*S*-cyclohexane-1,2-diamine in an ethanol/water mixture in the presence of K$_2$CO$_3$ at 50 °C for 24 hours (Scheme 105).[122]

2.2. Synthesis of spiro-imidazolidines

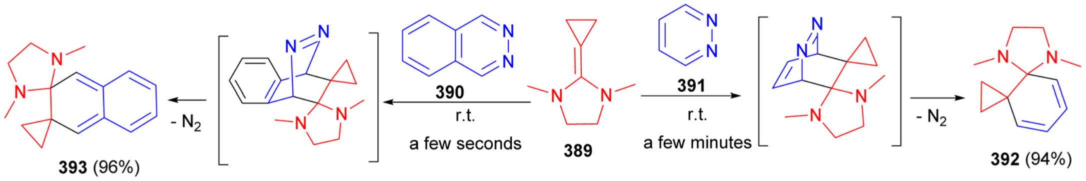
In 1987, Gruseck and Heuschmann reported the reaction of 2-cyclopropylidene imidazolidine **389** with 2,3-naphthacene **390** or pyridazine **391** as dienophiles afforded spiro-imidazolidines **392** and **393** in 94 and 96% yields, respectively. At 0 °C nitrogen evolution was complete within minutes with **391** and within seconds using **390**. The mechanism is outlined in Scheme 106.[123]

In 2006, Ishikawa *et al.* successfully isolated a spiro imidazolidine-oxazolidine intermediate **394** in the reaction of diphenylguanidinium salt **395** with (*Z*)-*R*-bromocinnamaldehyde **396** in the presence of tetramethylguanidine (TMG) in THF at −40 to −10 °C for 6 hours. In this reaction, compound **394** was obtained in a yield of 73%, along with *trans*-aziridine **397**, which was obtained in a yield of 9%. X-ray crystallographic analysis unambiguously revealed that the stereogenic centers of the spiro intermediate were in a *trans* configuration. The proposed mechanism is illustrated in Scheme 107.[124]

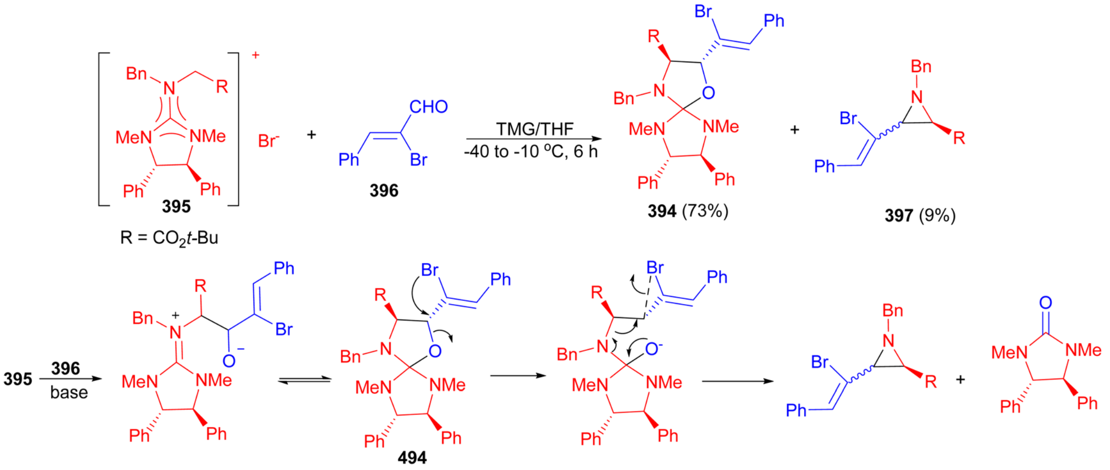
In 2011, an array of spiro imidazolidine derivatives **398** was synthesized in 88–98% yields by the reaction of 6-carbethoxy-3,5-diarylcyclohex-2-enones **399** with ethylene diamine using catalytic amount of activated fly ash under microwave



Scheme 105 Synthesis of imidazolidines **387** and **388**.



Scheme 106 Synthesis of spiro-imidazolidines **392** and **393**.



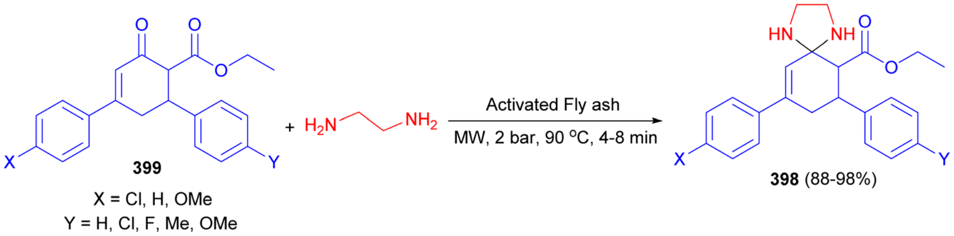
Scheme 107 Tetramethylguanidine (TMG) catalyzed synthesis of spiro imidazolidine-oxazolidine **394**.

irradiation at 90 °C for 4–8 min at 2 bar pressure and was screened for their antibacterial and antifungal activities (Scheme 108). The results revealed that some of these compounds against *P. aeruginosa*, *S. aureus*, *K. pneumonia*, *β-H. streptococcus*, *M. luteus*, *P. vulgaris*, *M. gypseum* and *C. albicans* exhibited excellent antibacterial activity at a minimum inhibitory concentration (MIC) value of 6.25 μg mL^{-1}.[125]

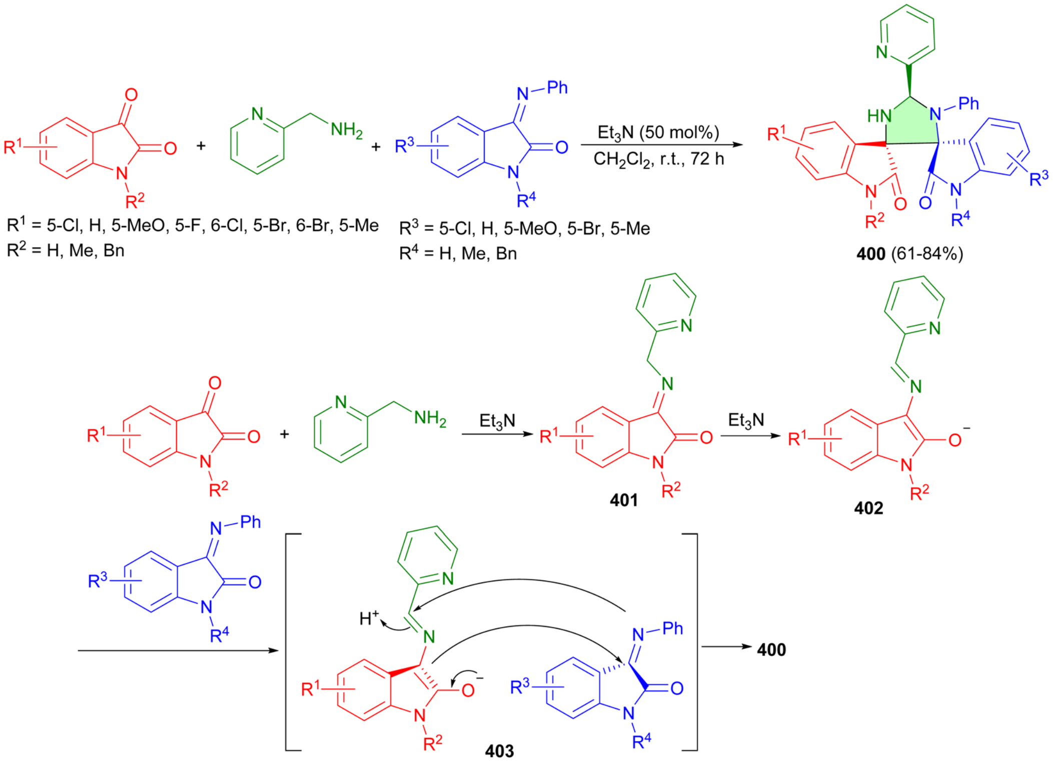
In 2015, Zhao and co-workers reported preparation of imidazolidine-dispirooxindoles **400** in 61–84% yields with up to >99 : 1 diastereoselectivity through the [3 + 2] cycloaddition of isatins, 2-(aminomethyl)pyridine and isatin-based imines in the presence of Et_3N in anhydrous CH_2Cl_2 at room temperature for 72 hours. The proposed mechanism is depicted in Scheme 109. Initially, under catalysis of Et_3N, isatin condenses easily with 2-(aminomethyl)pyridine to afford imine **401**. Subsequently, the deprotonation of imine **401** with Et_3N give rise to enolate **402**. Finally, the cyclization of the resulted enolate **402** with imine formed diastereoisomer **400** *via* the transition state **403**.[126]

In addition, an acid-promoted (3,5-dinitrobenzoic acid (3,5-DNBA)) self-1,3-dipolar cycloaddition of ketimines derived from isatins and benzylamines in THF at room temperature for 12 hours developed to assemble unprecedented dispirooxindole-imidazolidine derivatives **404**. Generally, excellent diastereoselectivities (only single stereoisomer formed) and good yields (up to 94%) were obtained. A plausible reaction pathway illustrated in Scheme 110. Imine **405** was firstly generated from the condensation between isatin and amine in the presence of acid. A subsequent 1,2-prototropy of **405** led to the formation of azomethine ylide **406**. When these two reaction partners approaching each other, transitions state **407** could be generated. Presumably, it would be favored. The subsequent cycloaddition resulted in the formation of dispirooxindole-imidazolidine **404**.[127]

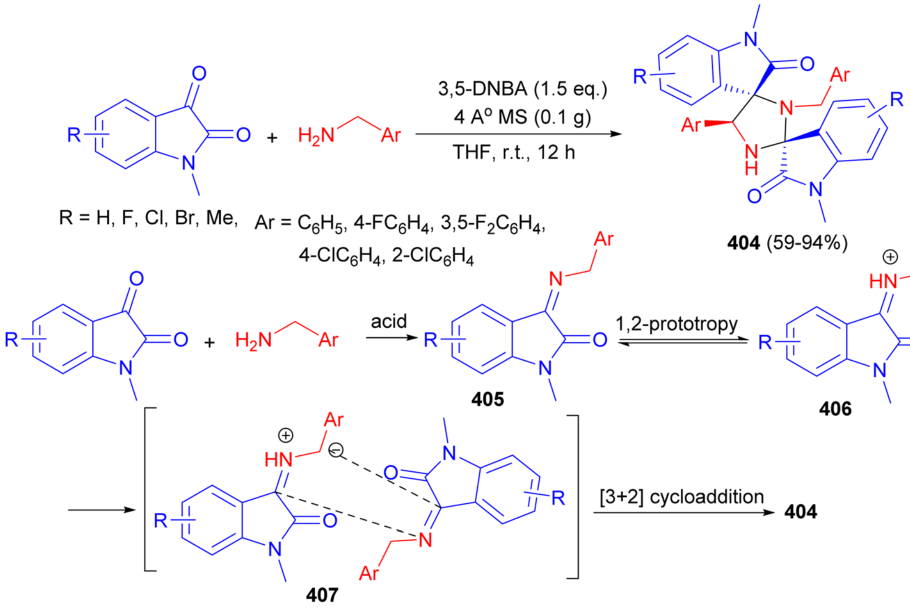
In 2016, a catalytic asymmetric chemoselective 1,3-dipolar cycloaddition of azomethine ylide with imines established *via* a three-component reaction of isatin derived imines, aldehydes



Scheme 108 Synthesis of spiro-imidazolidine derivatives **398** using catalytic amount of fly ash under microwave irradiation.

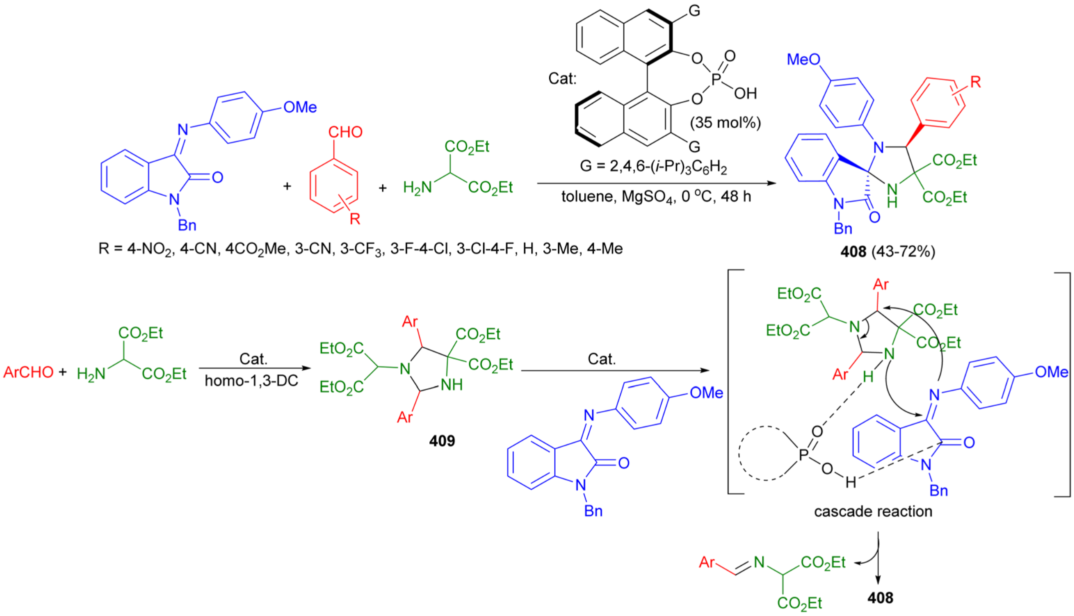


Scheme 109 Preparation of imidazolidine-dispirooxindoles **400** in the presence of Et_3N.



Scheme 110 3,5-Dinitrobenzoic acid promoted synthesis of dispirooxindole-imidazolidine derivatives **404**.

and amino-ester in the presence of chiral phosphoric acid in toluene at 0 °C for 48 hours, which efficiently constructed biologically important spiro[imidazolidine-2,3′-oxindole] **408** frameworks in good yields, high diastereo- and enantioselectivities (43–72% yields, 97 : 5 ee, all >95 : 5 dr). In the proposed mechanism, as illustrated in Scheme 111, initially, in the presence of catalyst, a homo-1,3-DC occurred, which generated the key intermediate **409**. Then, again promoted by catalyst *via* dual hydrogen bonding activation, this key intermediate **409** performed an enantioselective cascade reaction with isatin-derived imine, which ultimately gave the experimentally observed product **408** with concomitant regeneration of the azomethine ylide.[128]

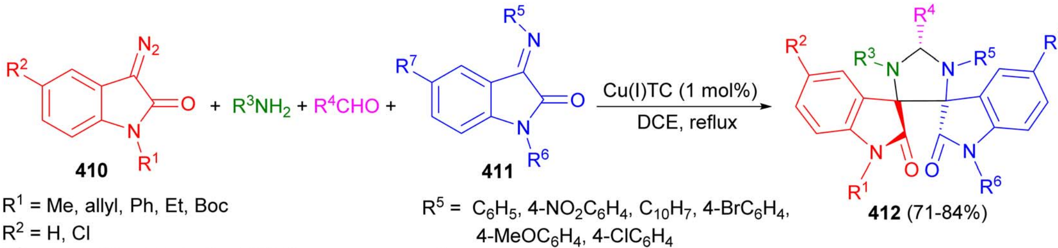


Scheme 111 Preparation of spiro[imidazolidine-2,3′-oxindole] **408** in the presence of chiral phosphoric acid.

Next, regioselective 1,3-dipolar cycloaddition reaction of appropriate diazoamide **410**, anilines, aldehydes and ketimine derived from boc-protected isatin **411** in the presence of copper(I) thiophene-2-carboxylate as catalyst in DCE refluxing under nitrogen atmosphere at room temperature afforded dispiroimidazolidine **412** in 71–84% yields in a chemo- and diastereoselective manner (Scheme 112). Mechanistically, the electron-donating imines, generated from amines and aromatic aldehydes, chemoselectively react with electron deficient copper carbenoid, generated from cyclic diazoamide, affording the respective intermolecular azomethine ylides. The S-shaped conformation of azomethine ylide intermediate in providing the stereoselective products.[129]

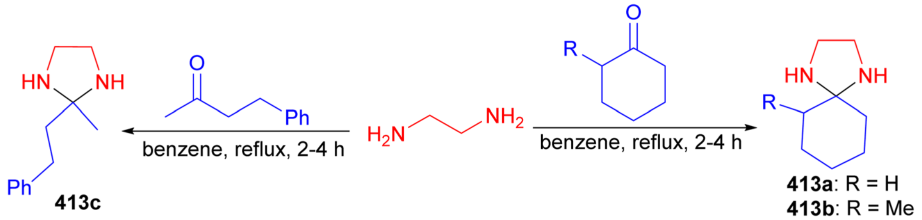
In 2018, the Wazzan group reported synthesis of imidazolidine derivatives **413a–c** by the reaction of 1,2-ethylenediamine with the appropriate cyclic ketones in dry benzene under reflux condition using dean-stark trap until no more water was collected (about 2–4 hours). The three imidazolidine derivatives tested were good corrosion inhibitor for X60 steel in 1 M HCl solution and they functioned as mixed-type inhibitors during the electrochemical acid corrosion of the steel in 1 M HCl. Moreover, experimentally determined inhibition efficiency increases in the order: **413c** > **413b** > **413a** (Scheme 113).[130]

A facile and efficient synthesis of spiro[imidazolidine-4,3′-indolin]-2′-imines **414** in 36–89% yields *via* a copper(I)-catalyzed cascade reaction of 3-diazoindolin-2-imines **415** with 1,3,5-triazines **416** in DCE at room temperature for 12 hours. The cascade process involves the formation of a copper–carbene intermediate and a formal [2 + 2 + 1] cycloaddition. They proposed two plausible reaction mechanisms, as shown in Scheme 114. First, the copper-carbene intermediate **417** is generated from **415.** In the next step, there are two possible pathways to obtain product **414.** In pathway a, the nucleophilic addition of 1,3,5-triazine derived formaldimine **418** to copper-carbene **417** generates ylide **419,** which releases Cu(I) to form ylide **420.** Subsequent addition with another formaldimine gives intermediate **421.** Finally, **421** undergoes an intramolecular nucleophilic addition to furnish the final product **414.**[131]



R^1 = Me, allyl, Ph, Et, Boc
R^2 = H, Cl
R^3 = C_6H_5, Me, 4-BrC_6H_4, 4-FC_6H_4,
R^4 = C_6H_5, 4-$NO_2C_6H_4$, 2,3-(MeO)2C_6H_3, 4-BrC_6H_4, 4-$MeOC_6H_4$
R^5 = C_6H_5, 4-$NO_2C_6H_4$, $C_{10}H_7$, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4
R^6 = Me, Et, Bn, Boc
R^7 = H, Br

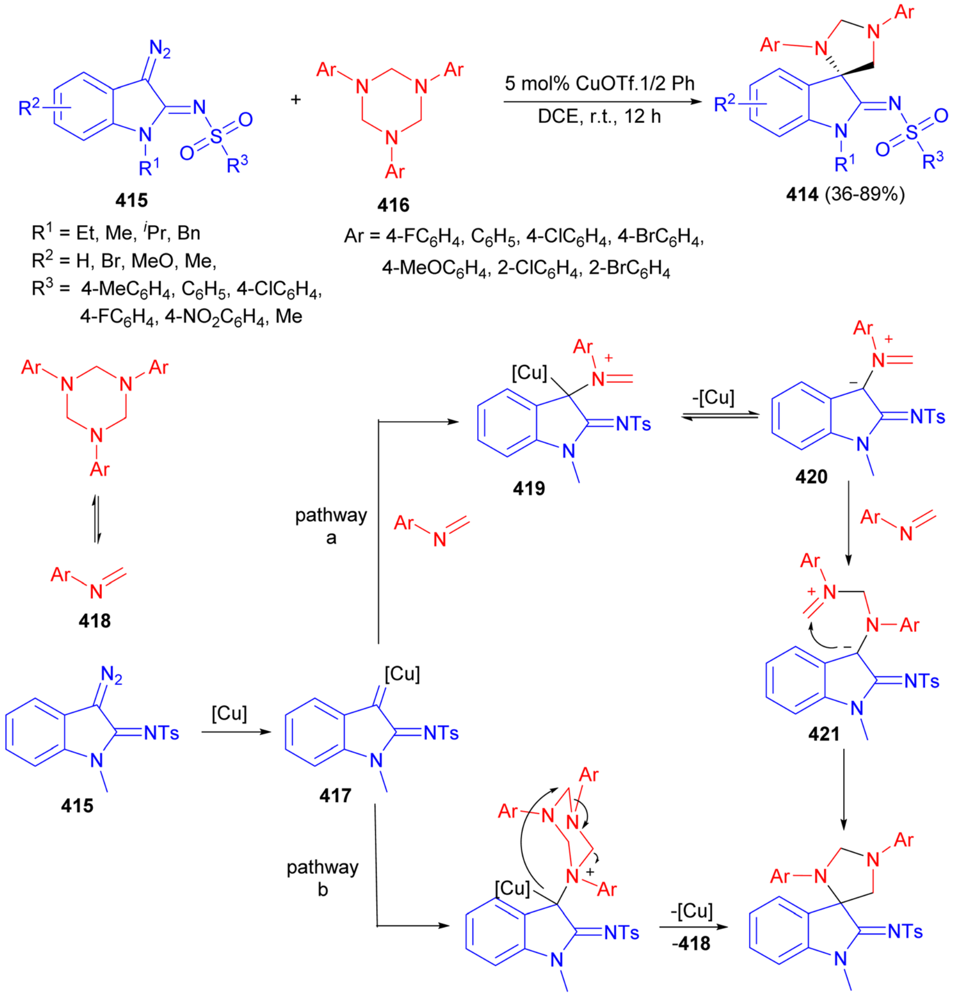
Scheme 112 Copper(I) thiophene-2-carboxylate catalyzed synthesis of dispiroimidazolidine **412**.



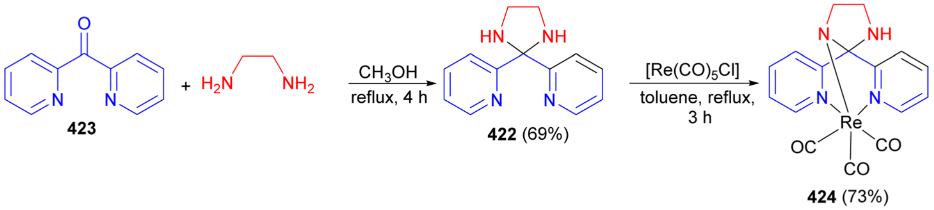
Scheme 113 Synthesis of imidazolidine derivatives **413a–c**.

In 2020, Habarurema and co-workers reported synthesis of imidazolidine **422** in 69% yield from the reaction of the bridging pyridyl; 2,2′-dipyridylketone (**423**) with 1,2-diaminoethane in methanol at reflux temperature under nitrogen for 4 hours. Then, rhenium(I) complex **424** of this compound synthesized in 73% yield in toluene at reflux for 3 hours under nitrogen (Scheme 115).[132]

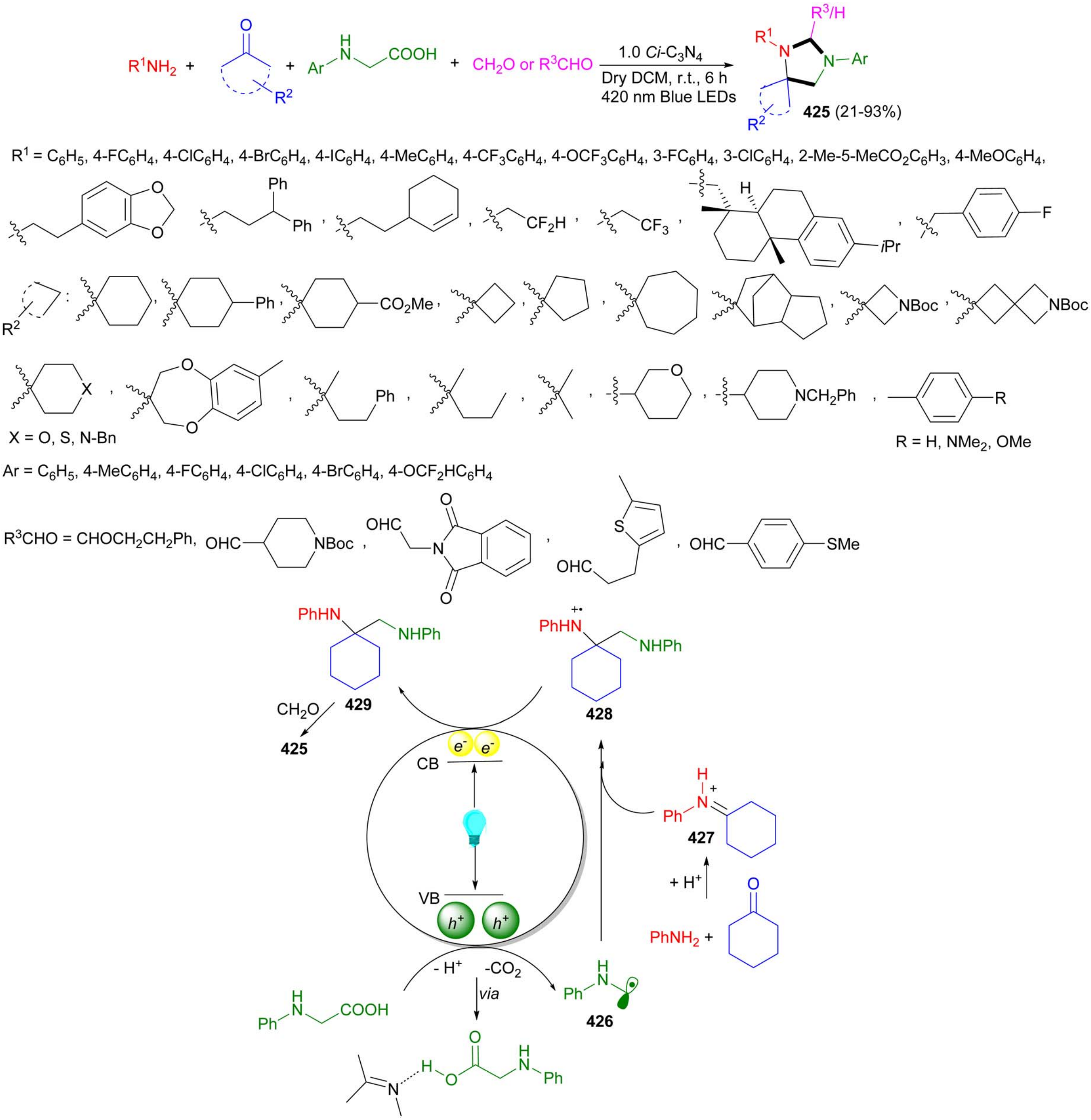
Recently, the Guo group developed heterogeneous carbon nitride photocatalyst for the four-component synthesis of spiroimidazolidines **425** in 21–93% yields under visible light irradiation, starting from simple amines, cyclic ketones, amino acids, and aldehydes in DCM at room temperature for 6 hours. The heterogeneous nature of the catalytic system enables the recovery and reuse of the photocatalyst without loss of reactivity, and the multicomponent reaction can be carried out in a continuous flow fashion. A plausible mechanism is proposed in Scheme 116. Initially, the oxidation of α-amino acid by the photogenerated holes at the VB of 1.0 *Ci*-C_3N_4 leads to rapid decarboxylation, producing α-amino radical intermediate **426** with the release of CO_2 and proton. In the meantime, primary amine and ketone undergo a condensation process to *in situ* generate iminium ion species **427** in the presence of protons. Then the α-amino radical 426 undergoes a free radical addition to the iminium ion species **427** to give radical adducts **428**,



Scheme 114 Copper(I)-catalyzed synthesis of spiro[imidazolidine-4,3′-indolin]-2′-imines **414**.



Scheme 115 Synthesis of imidazolidine **422** and spiroimidazolidine **424**.

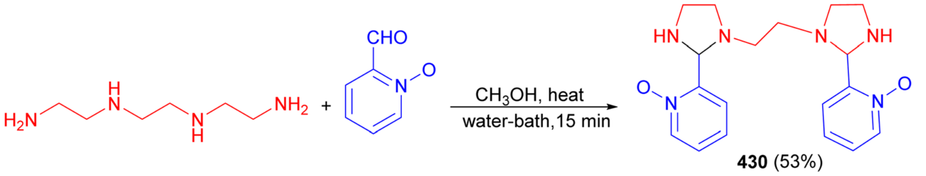


Scheme 116 Carbon nitride photocatalyzed synthesis of spiro-imidazolidines **425**.

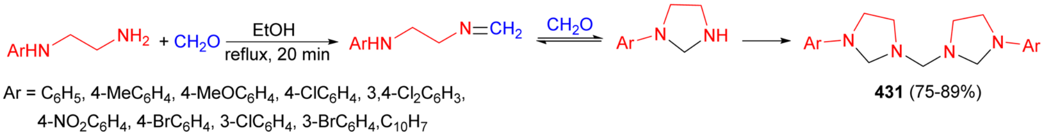
which is subsequently reduced by visible-light-induced electrons *via* a single electron transfer process. The generated diamine species **429** reacts with paraformaldehyde to form the final spiro-imidazolidine product **425**.[133]

2.3. Synthesis of bis-imidazolidines

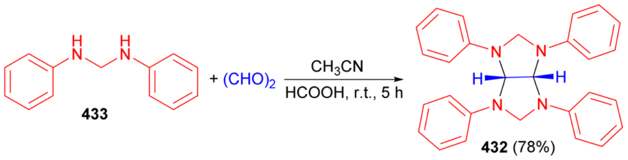
In 1999, the Boca group reported synthesis of bis-imidazolidine **430** in 53% yield by the condensation of triethylenetetramine



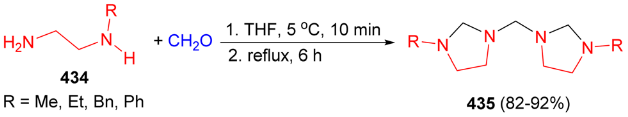
Scheme 117 Synthesis of bis-imidazolidine **430**.



Scheme 118 Preparation of bis(3-arylimidazolidinyl-1)methanes **431**.



Scheme 119 Synthesis of 2,4,6,8-tetraphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane **432**.



Scheme 120 Synthesis of bis(3-alkyl-imidazolidin-1-yl)methanes **435**.

with 2-pyridinecarboxaldehyde *N*-oxide in CH_3OH under heating on the water bath for 15 min (Scheme 117).[134]

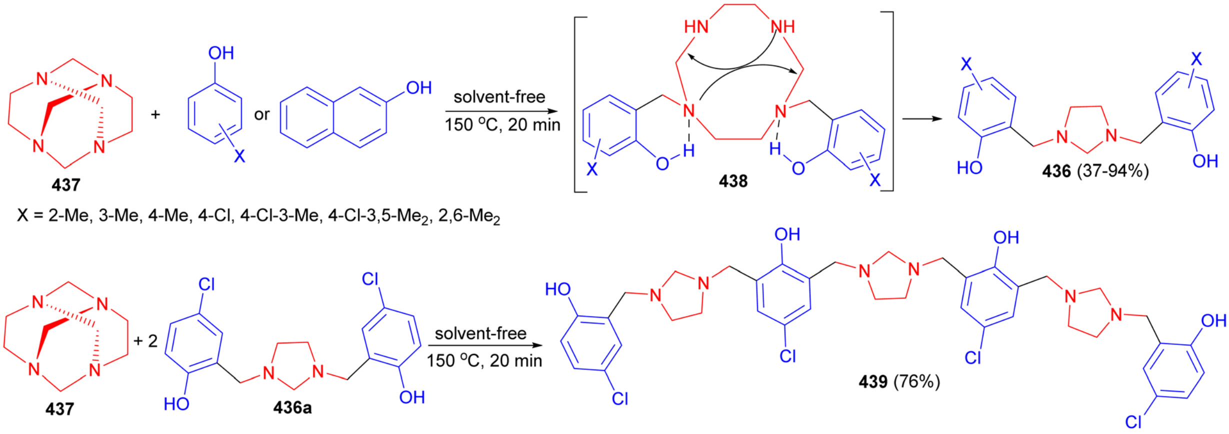
After that, bis(3-arylimidazolidinyl-1)methanes **431** synthesized in 75–89% yields by condensation reaction between *N*-arylethylenediamines and an excess aqueous formaldehyde (37%) in ethanol under reflux conditions (Scheme 118). All synthesized compounds showed antibacterial activity against *Escherichia coli*, *Micrococcus luteus*, *Bacillus subtilis*, *Listeria monocytogenes*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[135]

Next, Ghandi and his group demonstrated synthesis of 2,4,6,8-tetraphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane **432** in 78% yield by the reaction of *N*,*N*′-bisphenylmethanediamine **433** (2.0 mmol) with glyoxal (1.0 mmol, 40% aq.) in the presence of formic acid as catalyst in acetonitrile at room temperature for 5 hours (Scheme 119).[136,137]

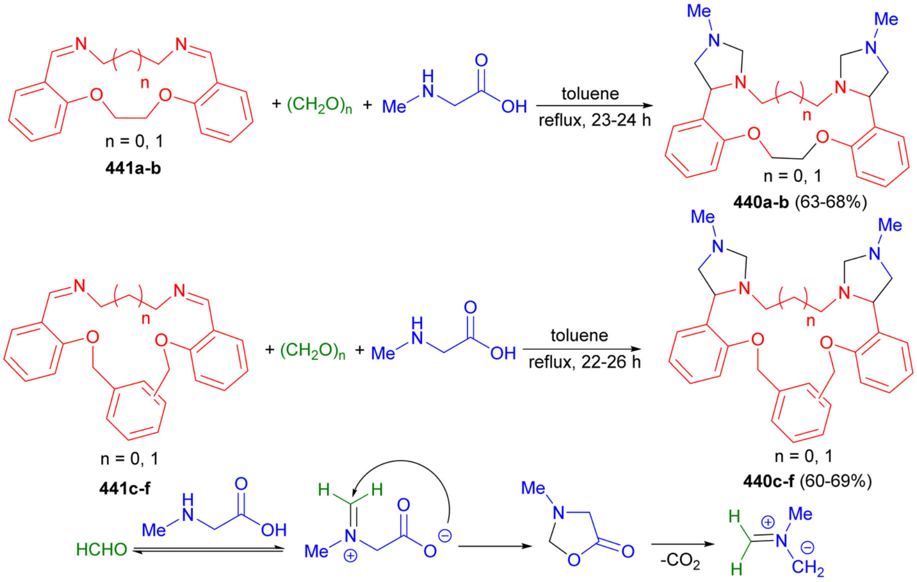
Recently, the condensation reactions between *N*-alkylethylenediamines **434** and aqueous formaldehyde in THF at 5 °C for 10 minutes and maintained at reflux for 6 hours afforded bis(3-alkylimidazolidin-1-yl)methanes **435** in 82–92% yields (Scheme 120).[138]

2.4. Synthesis of tris-imidazolidines

In 2013, synthesis of imidazolidines **436** in 37–94% yields reported by the reaction of a series of phenol derivatives with macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) (**437**) under solvent-free conditions at 150 °C for 20 minutes. The reaction proceeds through intramolecular cyclization *via* intermediate **438**. Moreover, the formation of **439** depend on the stoichiometric ratio. When employing a 1 : 2



Scheme 121 Preparation of imidazolidines **436** and trimer of benzylimidazolidine **439**.



Scheme 122 Synthesis of macrocyclic imidazolidines **440a–f**.

(TATD 1 : imidazolidine **436a**) ratio, the major product is a trimer of benzylimidazolidine **439** (Scheme 121).[139]

2.5. Synthesis of macrocyclic imidazolidines

In 2009, Raghunathan and co-workers described one-pot three-component synthesis of macrocyclic imidazolidines **440a–f** in 60–69% yields *via* a facile [3 + 2] cycloaddition reaction of azomethine ylide, derived from paraformaldehyde and sarcosine, with various macrocyclic imines **441a–f** as dipolarophiles in toluene under reflux conditions for 22–26 hours as illustrated in Scheme 122.[140]

3 Conclusions

This review highlights various synthetic strategies to the imidazolidines, chiral imidazolidines with high diastereoselectivities and enantioselectivities, bis-imidazolidines, and spiro-imidazolidines by approaching different methodologies. The general synthetic strategy for preparing imidazolidine derivatives involves the condensation of aldehydes or ketones with 1,2-diamines under various conditions. Additionally, other synthetic methodologies for these scaffolds include intermolecular amination reactions, Mannich cyclization, reactions of aziridines with imines, amines, or diazetidines, condensation reactions of methane diamines with glyoxal or imines, and reactions of 1,3,5-triazines with diazoesters, tosylhydrazones, vinyl ethylene carbonates, aziridines, or 3-aminooxetanes *via* [3 + 2] formal cycloadditions and 1,3-dipolar cycloadditions. Moreover, imidazolidine derivatives have reported to possess a wide range of biological and pharmaceutical applications such as anti-inflammatory, anti-bacterial, anti-trypanosoma cruzi agents, anti-fungal, anti-proliferative and analgesic activity.

Data availability

No new data were generated for this article.

Author contributions

All authors discussed the concept of this article, and contributed to the scientific writing of the original manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

We have no conflicts of interest to disclose.

Acknowledgements

The authors thank the Research Council of Imam Khomeini International University and Qazvin Islamic Azad University for their support.

References

1 R. H. Jiao, S. Xu, J. Y. Liu, H. M. Ge, H. Ding, C. Xu, H. L. Zhu and R. X. Tan, *Org. Lett.*, 2006, **8**, 5709–5712.
2 K. Macharoen, Q. Li, A. M. Veronica, J. M. Corbin, C. B. Lebrilla, S. Nandi and K. A. Mcdonald, *Int. J. Mol. Sci.*, 2020, **21**, 6896.
3 B. Malgesini, B. Forte, D. Borghi, F. Quartieri, C. Gennari and G. Papeo, *Chem.–Eur. J.*, 2009, **15**, 7922–7929.
4 Y. Nakao, J. Kuo, W. Y. Yoshida, M. Kelly and P. Scheuer, *J. Org. Lett.*, 2003, **5**, 1387–1390.
5 Z. Y. Mao, H. Geng, T. T. Zhang, Y. P. Ruan, J. L. Ye and P. Q. Huang, *Org. Chem. Front.*, 2016, **3**, 24–37.
6 G. Yu, G. Zhou, M. Zhu, W. Wang, T. Zhu, Q. Gu and D. Li, *Org. Lett.*, 2016, **18**, 244–247.

7 J. Clardy, J. P. Springer, G. Béchi, K. Matsuo and R. Wightman, *J. Am. Chem. Soc.*, 1975, **97**, 663–665.

8 A. Erkkila, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470.

9 T. Arai, A. Mishiro, N. Yokoyama, K. Suzuki and H. Sato, *J. Am. Chem. Soc.*, 2010, **132**, 5338–5339.

10 M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485–496.

11 A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2011, **133**, 4260–4263.

12 I. R. Sadarangani, S. Bhatia, D. Amarante, I. Lengyel and R. A. Stephani, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2507–2509.

13 X. X. Jiang, Y. Q. Wang, G. Zhang, D. Fu, F. T. Zhang, M. Kai and R. Wang, *Adv. Synth. Catal.*, 2011, **353**, 1787–1796.

14 M. van der Stelt, J. Cals, S. Broeders-Josten, J. Cottney, A. A. van der Doelen, M. Hermkens, V. de Kimpe, A. King, J. Klomp, J. Oosterom, I. P. Rooij, J. de Roos, M. van Tilborg, S. Boyce and B. James, *J. Med. Chem.*, 2011, **54**, 7350–7362.

15 M. C. Caterina, I. A. Perillo, L. Boiani, H. Pezaroglo, H. Cerecetto, M. González and A. Salerno, *Bioorg. Med. Chem.*, 2008, **16**, 2226–2234.

16 V. Sharma and M. S. Khan, *Eur. J. Med. Chem.*, 2001, **36**, 651–658.

17 R. J. Ferw and J. L. Riebsomer, *Chem. Rev.*, 1954, **54**, 593–613.

18 R. A. Donia, J. A. Shotton, L. O. Bentz and G. E. P. Smith, *J. Org. Chem.*, 1949, **14**, 952–961.

19 J. H. Billman, J.-Y. Chen Ho and L. R. Caswell, *J. Org. Chem.*, 1957, **22**, 538–539.

20 L. V. Jaenlcke and E. Erode, *Justus Liebigs Ann. Chem*, 1959, **624**, 120–136.

21 M. M. Joullie, G. M. J. Slusarczuk, A. Dey, P. B. Venuto and R. H. Yocum, *J. Org. Chem.*, 1967, **32**, 4103–4105.

22 J. W. Lown, J. P. Moser and R. Westwo, *Can. J. Chem.*, 1969, **47**, 4335–4345.

23 A. J. Birch and K. P. Dastu, *Aust. J. Chem.*, 1973, **26**, 1363–1364.

24 J. Hine and K. W. Narducy, *J. Am. Chem. Soc.*, 1973, **95**, 3362–3368.

25 H. Suzuki, M. Ohashi, K. Itoh, I. Matsuda and Y. Ishii, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1922–1924.

26 G. P. Tuszynski and R. G. Kallen, *J. Am. Chem. Soc.*, 1975, **97**, 2860–2875.

27 J. F. W. Keana, R. S. Norton, M. Morello, D. V. Engen and J. Clardy, *J. Am. Chem. Soc.*, 1978, **100**, 934–937.

28 K. Amornraksa and R. Grigg, *Tetrahedron Lett.*, 1980, **21**, 2197–2200.

29 A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, 1985, **41**, 3803–3812.

30 A. Rivera, G. I. Gallo and M. E. Gaybn, *Synth. Commun.*, 1993, **23**, 2921–2929.

31 M. Perisamy, M. R. Reddy and J. V. Bhaskar Kanth, *Tetrahedron Lett.*, 1996, **37**, 4767–4770.

32 I. Coldham, P. M. A. Houdayer, R. A. Judkins and D. R. Witty, *Synlett*, 1996, 1109–1111.

33 J. Li, S. Wang, J. Hu and W. Chen, *Tetrahedron Lett.*, 1999, **40**, 1961–1962.

34 P. K. S. Chowdhury, U. Mokhopadhyay and D. Ray, *Indian J. Chem.*, 1999, **38**, 1159–1163.

35 H. A. Craig, J. R. Goerlich, W. J. Marshall and M. Unverzagt, *Tetrahedron*, 1999, **55**, 14523–14534.

36 V. Y. Sosnovskikh and P. A. Kutsenko, *Russ. Chem. Bull.*, 1999, **48**, 540–551.

37 K. Tanaka and R. Shiraishi, *Green Chem.*, 2000, **2**, 272–273.

38 I. K. Kavrakova and M. J. Lyapova, *Collect. Czech. Chem. Commun.*, 2000, **65**, 1580–1586.

39 A. Rivera, J. F. León, J. Rivera, E. C. Parra, J. Purmova, E. Burgueno-Tapia and P. Joseph-Nathan, *Synth. Commun.*, 2000, **30**, 2029–2040.

40 G. V. Pokhvisneva and O. A. Lukyanov, *Russ. Chem. Bull.*, 2000, **49**, 894–898.

41 V. Sharma and M. S. Y. Khan, *Eur. J. Med. Chem.*, 2001, **36**, 651–658.

42 I. Coldham, R. C. B. Copley, T. F. N. Haxell and S. Howard, *Org. Lett.*, 2001, **3**, 3799–3801.

43 Z. Liz and Y. Zhang, *Org. Prep. Proced. Int.*, 2001, **33**, 185–187.

44 V. Dryanska, I. Pashkuleva, S. Simova and S. Angelova, *J. Chem. Res.*, 2001, 457–459.

45 A. R. Katritzky, K. Suzuki and H.-Y. He, *J. Org. Chem.*, 2002, **67**, 3109–3114.

46 M. S. Y. Khan and G. Chawla, *Indian J. Chem.*, 2002, **41**, 653–663.

47 A. R. Katritzky, K. Suzuki and H.-Y. He, *J. Org. Chem.*, 2002, **67**, 3109–3114.

48 W. H. Pearson, M. A. Walters, M. K. Rosen and W. G. Harter, *Arkivoc*, 2002, 91–111.

49 V. I. Kelarev, M. A. Silin and O. A. Borisova, *Chem. Heterocycl. Compd.*, 2003, **39**, 729–735.

50 M. S. Y. Khan and M. Gupta, *Indian J. Chem.*, 2003, **42**, 2086–2090.

51 J. Zhao, V. Pattaropong, Y. Jiang and L. Hu, *Tetrahedron Lett.*, 2003, **44**, 229–232.

52 A. Viso, R. Fernandez de la Pradilla, A. Garcia, C. Guerrero-Strachan, M. Alonso, M. Tortosa, A. Flores, M. Martinez-Ripoll, I. Fonseca, I. Andre and A. Rodriguez, *Chem.–Eur. J.*, 2003, **9**, 2867–2876.

53 M. Bera, P. K. Nanda, U. Mukhopadhyay and D. Ray, *J. Chem. Sci.*, 2004, **116**, 151–158.

54 G. W. Nyce, S. Csihony, R. M. Waymouth and J. L. Hedrick, *Chem.–Eur. J.*, 2004, **10**, 4073–4079.

55 E. d. Erkizia, E. Aldaba, Y. Vara, A. Arrieta, H. Gornitzka and F. P. Cossio, *Arkivoc*, 2005, 189–199.

56 C. T. Zeyrek, A. Elmali and Y. Elerman, *Z. Naturforsch.*, 2005, **60**, 520–526.

57 M. Ghandi, F. Salimi and A. Olyaei, *J. Heterocycl. Chem.*, 2006, **43**, 791–794.

58 G. V. Pokhvisneva and O. A. Lukyanov, *Russ. Chem. Bull.*, 2006, **55**, 903–906.

59 M. Ghandi and A. Olyaei, *J. Heterocycl. Chem.*, 2007, **44**, 323–327.

60 M. Ghandi, A. Olyaei and F. Salimi, *Synth. Commun.*, 2007, **37**, 247–256.

61 M. C. Caterina, I. A. Perillo, L. Boiani, H. Pezaroglo, H. Cerecetto, M. Gonzalez and A. Salerno, *Bioorg. Med. Chem.*, 2008, **16**, 2226–2234.

62 W.-J. Liu, X.-H. Chen and L.-Z. Gong, *Org. Lett.*, 2008, **10**, 5357–5360.

63 T. Arai and K. Suzuki, *Synlett*, 2009, 3167–3170.

64 M. C. Caterina, M. V. Corona, I. Perillo and A. Salerno, *Heterocycles*, 2009, **78**, 771–781.

65 G. S. G. de Carvalho, P. A. Machado, D. T. S. de Paula, E. S. Coimbra and A. D. da Silva, *Sci. World J.*, 2010, **10**, 1723–1730.

66 H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *J. Org. Chem.*, 2010, **75**, 7468–7471.

67 V. G. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, E. S. Balenkova, E. V. Kondrashov, I. A. Ushakov and A. Yu. Rulev, *J. Org. Chem.*, 2010, **75**, 5679–5688.

68 M. Soueidan, F. Helion, J.-L. Namy and J. Szymoniak, *Tetrahedron Lett.*, 2011, **52**, 1348–1350.

69 Z. Jiang, J. Wang, P. Lu and Y. Wang, *Tetrahedron*, 2011, **67**, 9609–9617.

70 J. Xuan, Y. Cheng, J. An, L.-Q. Lu, X.-X. Zhang and W.-J. Xiao, *Chem. Commun.*, 2011, **47**, 8337–8339.

71 L. D. Elliott, J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Org. Lett.*, 2011, **13**, 728–731.

72 X. Wu and J. Zhang, *Synthesis*, 2012, **44**, 2147–2154.

73 M. S. Y. Khan, A. Husain, S. Sharma and M. Rashid, *Indian J. Pharm. Sci.*, 2012, **74**, 80–83.

74 S. Kaladevi, N. Paul, S. Muthusubramanian and S. Sivakolunthu, *Tetrahedron Lett.*, 2013, **54**, 3702–3705.

75 A. Olyaei, M. Karbalaei Karimi and R. Razeghi, *Tetrahedron Lett.*, 2013, **54**, 5730–5733.

76 A. Husain, R. Bhutani, D. Kumar and D.-S. Shin, *J. Korean Chem. Soc.*, 2013, **57**, 227–233.

77 Q.-H. Li, L. Wei, X. Chen and C.-J. Wang, *Chem. Commun.*, 2013, **49**, 6277–6279.

78 L. Chen, C. S. Chao, Y. Pan, S. Dong, Y. C. Teo, J. Wang and C.-H. Tan, *Org. Biomol. Chem.*, 2013, **11**, 5922–5925.

79 K. Ohmatsu, S. Kawai, N. Imagawa and T. Ooi, *ACS Catal.*, 2014, **4**, 4304–4306.

80 Y.-J. Ou, Z.-P. Zheng, X.-J. Hong, L.-T. Wan, L.-M. Wei, X.-M. Lin and Y.-P. Cai, *Cryst. Growth Des.*, 2014, **14**, 5339–5343.

81 R.-Y. Zhu, C.-S. Wang, F. Jiang, F. Shi and S.-J. Tu, *Tetrahedron: Asymmetry*, 2014, **25**, 617–624.

82 S. P. Swain, Y.-C. Shih, S.-C. Tsay, J. Jacob, C.-C. Lin, K. C. Hwang, J.-C. Horng and J. R. Hwu, *Angew. Chem.*, 2015, **127**, 10064–10068.

83 A. Husain, A. Ahmad, S. A. Khan, M. Asif, R. Bhutani and F. A. Al-Abbasi, *Saudi Pharm. J.*, 2016, **24**, 104–114.

84 L. K. Kibardina, A. V. Trifonov, R. H. Bagautdinova, A. B. Dobrynin, E. M. Pudovik, A. R. Burilov and M. A. Pudovik, *Russ. J. Gen. Chem.*, 2016, **86**, 607–612.

85 S. Muthusamy and S. G. Kumar, *Org. Biomol. Chem.*, 2016, **14**, 2228–2240.

86 V. Satheesh, M. Sengoden and T. Punniyamurthy, *J. Org. Chem.*, 2016, **81**, 9792–9801.

87 C. Zhu, G. Xu and J. Sun, *Angew. Chem.*, 2016, **55**, 11867–11871.

88 J. Hu, B. Kong, Y. Liu, B. Xu, Y. Zhao and P. Gong, *ChemCatChem*, 2017, **9**, 403–406.

89 B. Yu, X.-F. Bai, J.-Y. Lv, Y. Yuan, J. Cao, Z.-J. Zheng, Z. Xu, Y.-M. Cui, K.-F. Yang and L.-W. Xu, *Adv. Synth. Catal.*, 2017, **359**, 3577–3584.

90 H. Jia, H. Liu, Z. Guo, J. Huang and H. Guo, *Org. Lett.*, 2017, **19**, 5236–5239.

91 M. Sengoden, A. Bhowmick and T. Punniyamurthy, *Org. Lett.*, 2017, **19**, 158–161.

92 P. Liu, G. Xu and J. Sun, *Org. Lett.*, 2017, **19**, 1858–1861.

93 J. K. Laha, K. P. Jethava, K. S. Satyanarayana Tummalapalli and S. Sharma, *Eur. J. Org Chem.*, 2017, 4617–4624.

94 P. Liu, C. Zhu, G. Xu and J. Sun, *Org. Biomol. Chem.*, 2017, **15**, 7743–7746.

95 S. Mukhopadhyay and S. C. Pan, *Chem. Commun.*, 2018, **54**, 964–967.

96 H. Li, S. Huang, Y. Wang and C. Huo, *Org. Lett.*, 2018, **20**, 92–95.

97 H. Jia, Z. Guo, H. Liu, B. Mao, X. Shi and H. Guo, *Chem. Commun.*, 2018, **54**, 7050–7053.

98 T.-Y. Lin, H.-H. Wu, J.-J. Feng and J. Zhang, *Org. Lett.*, 2018, **20**, 3587–3590.

99 Y. Yang and W. Yang, *Chem. Commun.*, 2018, **54**, 12182–12185.

100 D. Jana, T. Guchhait, V. Subramaniyan, A. Kumar and G. Mani, *Tetrahedron Lett.*, 2019, **60**, 151247.

101 L. Tu, Z. Li, T. Feng, S. Yu, R. Huang, J. Li, W. Wang, Y. Zheng and J. Liu, *J. Org. Chem.*, 2019, **84**, 11161–11169.

102 S. Tarannum, S. Sk, S. Das, I. A. Wani and M. K. Ghorai, *J. Org. Chem.*, 2020, **85**, 367–379.

103 F. Zhao, K.-H. Wang, L. Wen, Z. Zhao, Y. Hu, W. Xu, D. Huang, Y. Su, J. Wang and Y. Hu, *Asian J. Org. Chem.*, 2020, **9**, 1036–1039.

104 X. Cheng, B.-G. Cai, H. Mao, J. Lu, L. Li, K. Wang and J. Xuan, *Org. Lett.*, 2021, **23**, 4109–4114.

105 T. Kang, S. Gao, L.-X. Zhao, Y. Zhai, F. Ye and Y. Fu, *J. Agric. Food Chem.*, 2021, **69**, 45–54.

106 R. H. Bagautdinova, L. K. Kibardina, A. R. Burilov and M. A. Pudovik, *Russ. J. Gen. Chem.*, 2021, **91**, 1265–1270.

107 A. S. Golubenkova, N. E. Golantsov and L. G. Voskressensky, *Molbank*, 2021, **2021**, M1176.

108 J. Zhang, Y.-F. Li, F.-C. Jia, Y. Gao and X.-Q. Hu, *Org. Chem. Front.*, 2021, **8**, 6616–6621.

109 X. Zhong, Z. Zhong, Z. Wu, Z. Ye, Y. Feng, S. Dong, X. Liu, Q. Peng and X. Feng, *Chem. Sci.*, 2021, **12**, 4353–4360.

110 Z. Shi, T. Fan, X. Zhang, F. Zhan, Z. Wang, L. Zhao, J.-S. Lin and Y. Jiang, *Adv. Synth. Catal.*, 2021, **363**, 2619–2624.

111 Z. Chen, Y. Zhou, T. Hu, H.-Y. Xiong and G. Zhang, *J. Org. Chem.*, 2021, **86**, 7714–7724.

112 A. Liu, D. Ma, Y. Qian, J. Li, S. Zhai, Y. Wang and C. Chen, *Org. Biomol. Chem.*, 2021, **19**, 2192–2197.

113 K.-K. Wang, Y.-L. Li, M.-Y. Wang, J. Jing, Z.-Y. Wang and R. Chen, *RSC Adv.*, 2022, **12**, 28295–28298.

114 B. Gurung, S. Pradhan, D. Sharma, D. Bhujel, S. Basel, S. Chettri, S. Rasaily, A. Pariyar and S. Tamang, *Catal. Sci. Technol.*, 2022, **12**, 5891–5898.

115 L. Saney, T. Panduwawala, X. Li, K. E. Christensen, M. Genov, A. Pretsch, D. Pretsch and M. G. Moloney, *Org. Biomol. Chem.*, 2023, **21**, 4801–4809.

116 E. A. Verochkina, V. G. Fedoseeva, L. I. Larina and N. V. Vchislo, *Arkivoc*, 2023, 202311977.

117 K. Itoh, N. Ishii, A. Takashino, A. Hara, S. Kon, T. Mizuguchi, F. Karaki, S. Hirayama, Y. Shibagaki, K. Nagai, N. Sato, K. Tokunaga, M. Suzuki, M. Hashimoto and H. Fujii, *J. Photochem. Photobiol., A*, 2023, **434**, 114239.

118 D. Sharma, S. Rasaily, S. Chettri, D. Sureka, S. Tamang and A. Pariyar, *Inorg. Chem.*, 2023, **62**, 4540–4549.

119 D. Higuchi, S. Matsubara, H. Kadowaki, D. Tanaka and K. Murakami, *Chem.–Eur. J.*, 2023, e202301071.

120 J. Qiao, S. Wang, X. Liu and X. Feng, Enantioselective [3+2] Cycloaddition of Donor-Acceptor Aziridines and Imines to Construct 2,5-*trans*-Imidazolidines, *Chem.–Eur. J.*, 2023, **29**, e202203757.

121 K. Hashimoto, D. Higuchi, S. Matsubara and K. Murakami, *Front. Chem.*, 2023, **11**, 1272034.

122 M. Tavlinova-Kirilova, K. Dikova, M. K. Marinova, M. Kamenova-Nacheva, R. Rusew, H. Sbirkova-Dimitrova, B. Shivachev, K. Kostova and V. Dimitrov, *Crystals*, 2023, **13**, 1495.

123 U. Gruseck and M. Heuschmann, *Tetrahedron Lett.*, 1987, **28**, 6027–6030.

124 W. Disadee, T. Ishikawa, M. Kawahata and K. Yamaguchi, *J. Org. Chem.*, 2006, **71**, 6600–6603.

125 V. Kanagarajan, J. Thanusu and M. Gopalakrishnan, *J. Enzyme Inhib. Med. Chem.*, 2011, **26**, 280–287.

126 H.-W. Zhao, X.-Q. Chen, Z. Yang, T. Tian, B. Li, W. Meng, X.-Q. Song and H.-L. Pang, *RSC Adv.*, 2015, **5**, 103116–103122.

127 Y.-H. Sun, Y. Xiong, C.-Q. Peng, W. Li, J.-A. Xiao and H. Yang, *Org. Biomol. Chem.*, 2015, **13**, 7907–7910.

128 Y.-M. Wang, H.-H. Zhang, C. Li, T. Fan and F. Shi, *Chem. Commun.*, 2016, **52**, 1804–1807.

129 S. Muthusamy and S. G. Kuma, *Tetrahedron*, 2016, **72**, 2392–2401.

130 N. Wazzan, I. B. Obot, H. Faidallah and J. Adhes, *Sci. Technol.*, 2018, **32**, 2569–2589.

131 Y. Zhou, F. Ma, P. Lu and Y. Wang, *Org. Biomol. Chem.*, 2019, **17**, 8849–8852.

132 G. Habarurema, J. Mukiza, T. I. A. Gerber, T. Mukabagorora, E. C. Hosten and R. Betz, *J. Organomet. Chem.*, 2020, **906**, 121033.

133 J. Tian, L. Zhao, C. Yang, C. Yang, L. Guo and W. Xia, *ACS Catal.*, 2023, **13**, 866–876.

134 M. Boca, P. Baran, R. Boca, G. Kickelbick, F. Renz and W. Linert, *Inorg. Chem. Commun.*, 1999, **2**, 188–190.

135 I. Perillo, E. Repetto, M. C. Caterina, R. Massa, G. Gutkind and A. Salerno, *Eur. J. Med. Chem.*, 2005, **40**, 811–815.

136 M. Ghandi, F. Salimi and A. Olyaei, *Molecules*, 2006, **11**, 556–563.

137 A. Kakanejadifard and S. M. F. Farnia, *Tetrahedron*, 1997, **53**, 2551–2556.

138 R. Colorado-Peralta, S. A. Sánchez-Ruiz and A. Flores-Parra, *Organics*, 2023, **4**, 297–312.

139 A. Rivera and R. Quevedo, *Tetrahedron Lett.*, 2013, **54**, 1416–1420.

140 S. Kathiravan and R. Raghunathan, *Synlett*, 2009, 1126–1130.