Chapter 1

A Brief Overview on the Applications of Pyridinium Salts for the Synthesis of Aza-fused Heterocycles and as a Reagent

1.1 INTRODUCTION

Onium salts are salt like compounds comprising a complex cation and an anion, in which the central atom is of an element with nonmetallic character (nitrogen, phosphorus, oxygen, sulfur, chlorine, bromine, iodine, etc.) and named as "ammonium", "phosphonium", "oxonium", "sulfonium", "chloronium", "bromonium" and "iodonium" respectively. According to the nomenclature rules of IUPAC, "polyatomic cations formed by adding more protons to monatomic anions than are required to give a neutral unit have the ending -onium" (**Figure 1.1**).[1] Among variously available onium salts, nitrogen containing salts are one of the most primitive as well as highly pursued onium compound in organic chemistry.

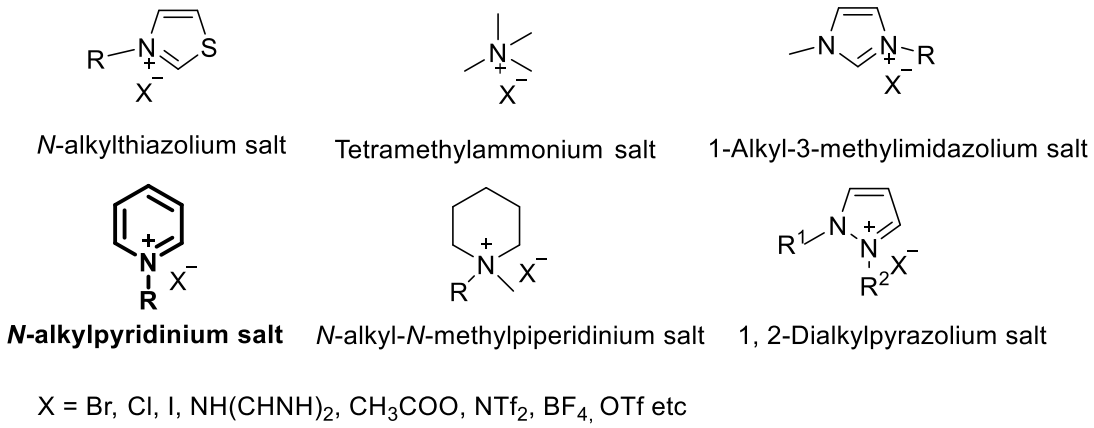


Figure 1.1 Representative examples of some of the nitrogen containing onium salts

Pyridinium salt is a nitrogen containing six membered cyclic onium salt derived from pyridine. These salts are considered highly privileged molecules as indicated by their presence in numerous natural and biologically important compounds. Several marine based natural products like Njaoaminiums, Pachychalines, and Simplakidine A contain pyridinium based scaffolds as an active molecule (**Figure 1.2**).[2-4] Their ability to bind with the DNA, induce easy permeability in biological membranes and stable transfection of several mammalian cells make these salts interesting targets for the design of pharmacological agents, which are used to treat and prevent a variety of disorders.[5-6] Pyridinium salts are known to inhibit the growth of microorganisms such as bacteria and fungi.[7] These salts have extensively utilized as an active ingredient in cosmetics like lotion, skin cream and hair conditioner, disinfectants, dyes, agrochemicals, and various anti-bacterial and antifungal medicines.[8-10]

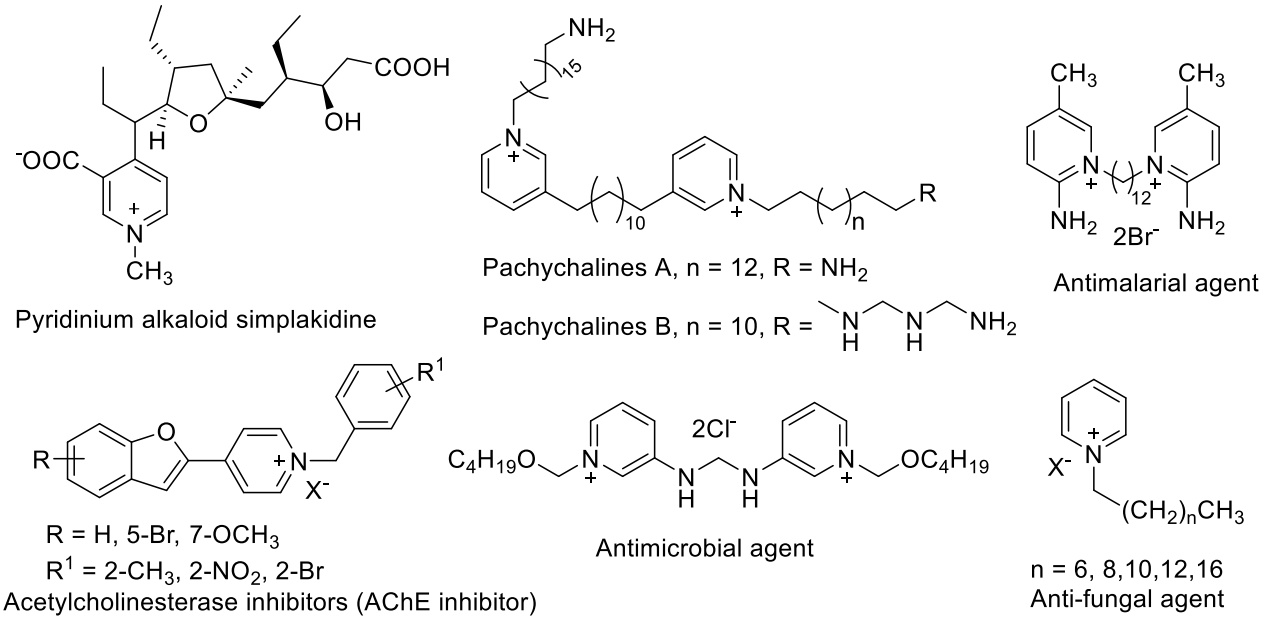


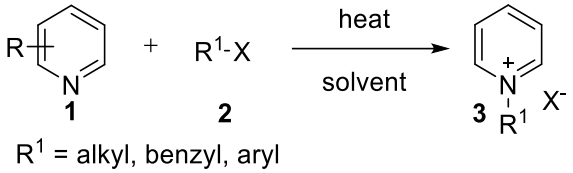
Figure 1.2 Examples of naturally occurring and biologically important pyridinium salts

During the last few decades, the use of pyridinium salts in organic transformations has received meticulous attention around the world due to their profuse chemical as well as physical properties such as high thermal stability, non-coordinating nature, very low to negligible vapor pressure, good solvating ability, tunable solubility and ease of recyclability. These salts are also known as ionic liquids when their melting point is below the boiling point of water (100 °C), and are solely composed of ions in their molten states. The wide-ranging applications and versatility of these salts stem from the ease of their structural variation, in which properties such as amphiphilicity, lipophilicity and solubility can be tuned.[11]

Not surprisingly, because of their diverse properties, several synthetic routes have been developed for synthesis as well as the application of pyridinium salts and consequently, led to numerous research articles and reviews.[12-13] Recently, Afonso *et al.* published an excellent review covering an overview of pyridinium salts from their synthesis, reactivity and catalysis as pyridinium ionic liquids (PyILs), along with their material applications and biological activities.[14]

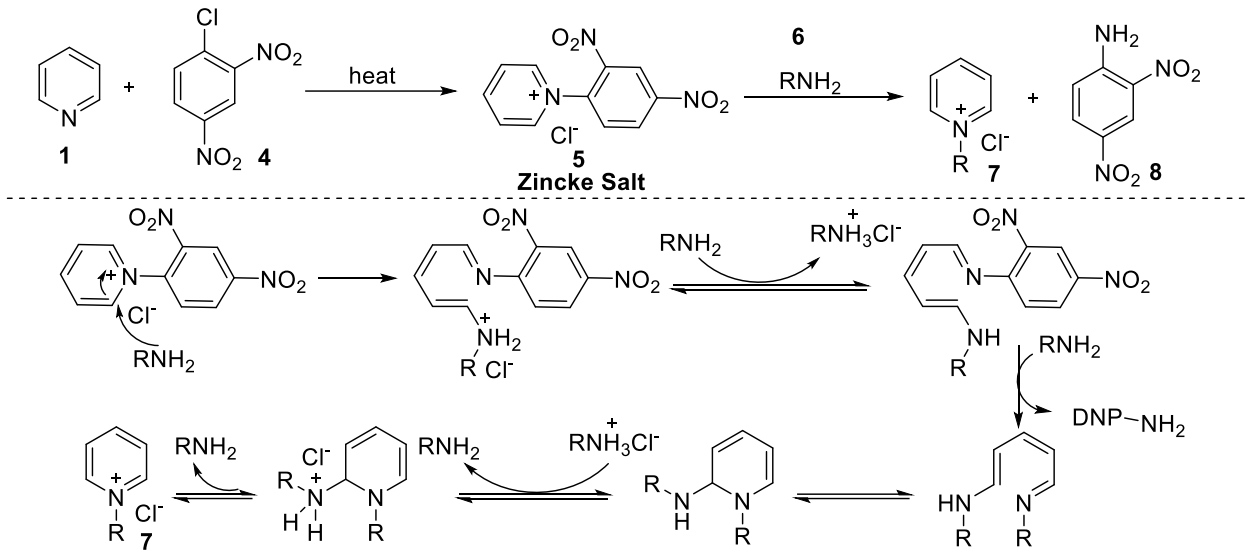
1.2 SYNTHESIS OF PYRIDINIUM SALTS

A wide variety of pyridinium salts can be made by combining variously substituted pyridines with a wide range of anions. The traditional method for the synthesis of pyridinium salts (**3**) is quaternization reaction of pyridine/ derivatives of pyridine (**1**) with alkyl/aryl halides (**2**) *via* S_N2 type reaction known as a Menshutkin reaction (**Scheme 1.1**).[15] Over time, numerous innovative methods have been developed to access pyridinium salts.



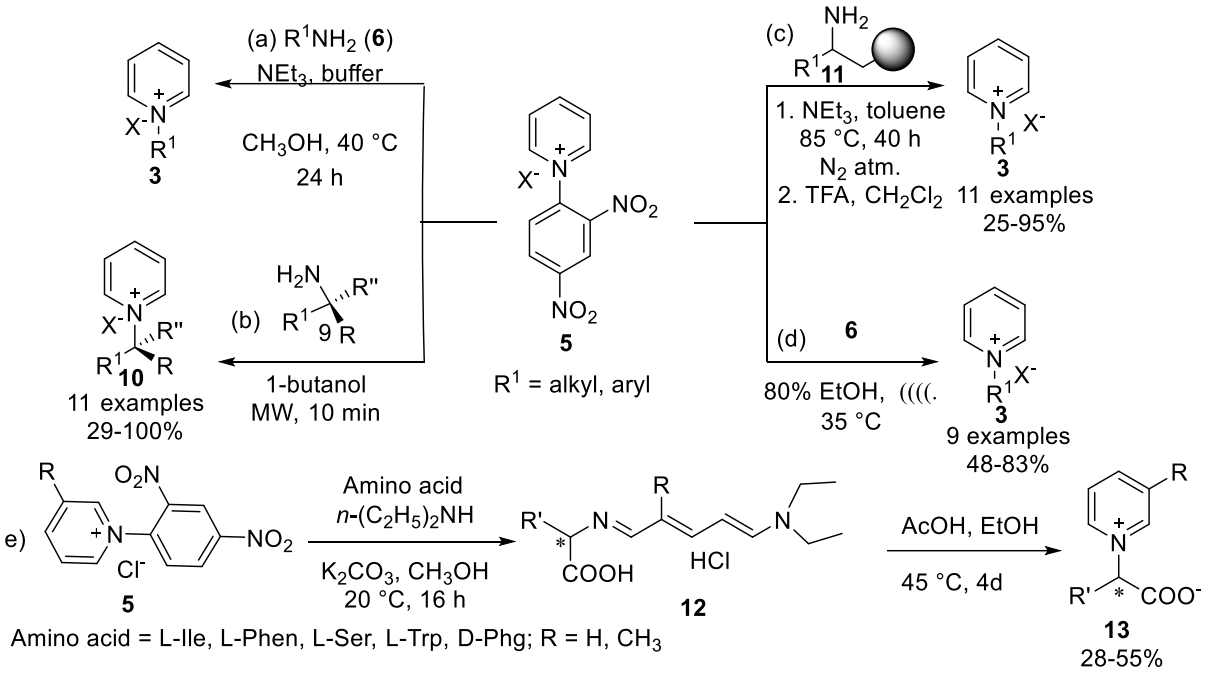
Scheme 1.1 Traditional method for synthesis of pyridinium salts

The pyridinium salts can be synthesized from a Zincke salt i.e. 1-(2,4-dinitrophenyl)pyridinium salt (**5**), which can be synthesized by the reaction between pyridine derivative (**1**) and 1-chloro-2,4-dinitrobenzene (**4**). These highly electrophilic salts were reported by Zincke in 1904 which readily undergo reaction with primary amines (**6**) to produce pyridinium chloride (**7**) in the acidic or basic medium. The reaction in which a pyridine derivative is converted into a pyridinium salt by reaction with 1-chloro-2,4-dinitrobenzene and **6** is known as Zincke reaction (**Scheme 1.2**).[16-17]



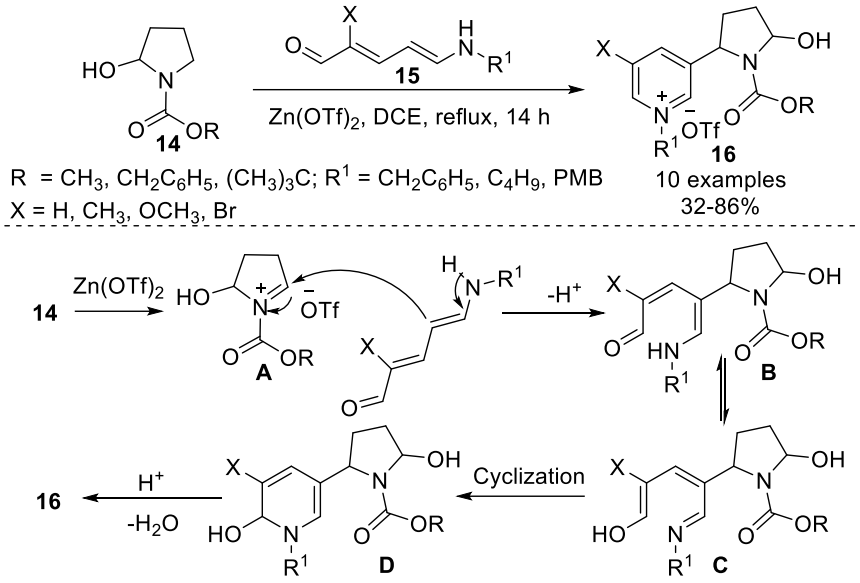
Scheme 1.2 General reaction and mechanism for Zincke reaction

These Zincke salts (**5**) have been extensively utilized by researches to synthesize varieties of pyridinium salts. For example, Marvell *et al*. used Zincke salts (**5**) to synthesize *N*-arylpyridinium salts while Viana *et al*. synthesized chiral pyridinium salts (**10**) (**Scheme 1.3 a & b**).[18-19] M. J. Kurth *et al*. synthesized pyridinium salts by employing solid phase synthetic procedure. The reaction of different polymer bound primary amines (**11**) with 1-(2,4-dinitrophenyl)pyridinium salts (**5**), followed by cleavage from the polymer delivered the desired salts in good yields (**Scheme 1.3 c**).[20] Zhao *et al*. reported the ultrasound irradiation procedure to synthesize **3** based on Zincke reaction. The increased yields of salts and shorter reaction time were the advantages of the method (**Scheme 1.3 d**).[21] The synthesis of pyridinium salts from the reaction of Zincke salt with primary amine required elevated temperature, however, Marazano *et al.* developed a modified method to synthesize N-alkylpyridinium salts from Zincke salt of 3-alkylpyrine at ambient temperature. The addition of 1 equiv of a secondary amine to reaction allowed the formation of isolable intermediate aminopentadiene imine salts (**12**) which underwent cyclization in acidic medium to give pyridinium salts (**13**) (**Scheme 1.3 e**). Additionally, the reaction was also extended to primary amines containing polar functionality, as exemplified by a synthesis of a pyridinium salt in 55% yield from L-carnosine. The reaction was successful in the preparation of chiral pyridinium salts (**13**), while the lower yields of the salts being a major disadvantage of the methodology.[22]



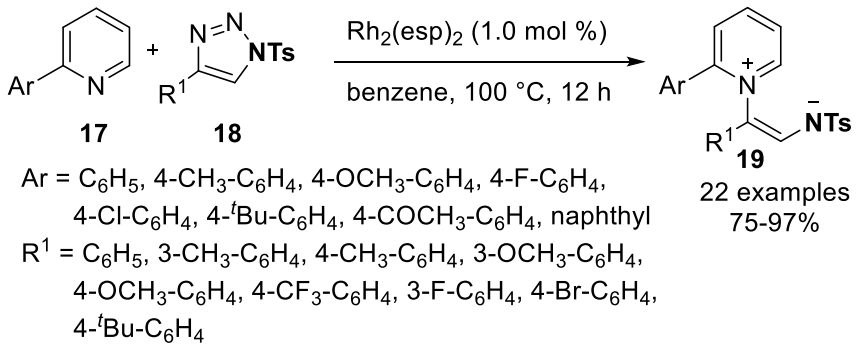
Scheme 1.3 Synthesis of pyridinium salt from Zincke salt

The new method for the synthesis of pyrrolidine substituted pyridinium salts (**16**) was reported by Delpech and co-workers. The addition of 5-alkylaminopenta-2,4-dienals (**15**) onto *N*-acyliminium ions (**A**), generated *in situ* from alkyl 2-hydroxypyrrolidine-1-carboxylate (**14**) in the presence of zinc triflate, followed by dehydrative cyclization led to the formation of pyrrolidine substituted pyridinium salts (**16**) (**Scheme 1.4**). Subsequently, the protocol was extended to synthesize of (±)-nicotine or (±)-anabasine natural products by *N*-dealkoxycarbonylation and –dealkylation reaction of some derivatives of pyridinium salts.[23]



Scheme 1.4 The synthesis of pyrrolidine substituted pyridinium salts

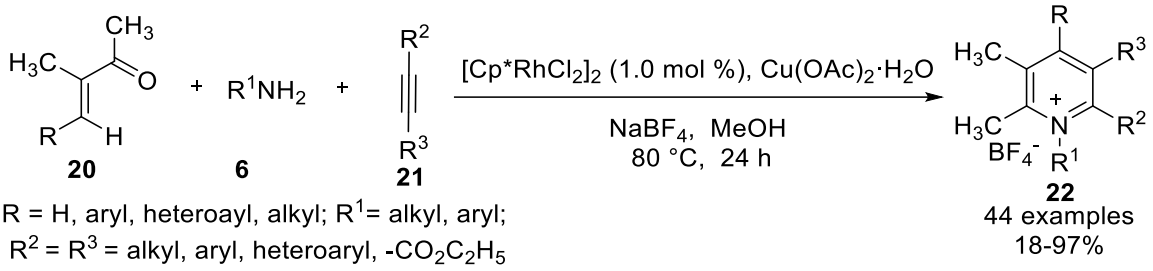
E. J. Yoo *et al.* reported construction of innovative pyridinium analogue (**19**) as isolable 1,5-dipoles by reaction between the 2-substituted pyridine (**17**) and 1-sulfonyl-1,2,3-triazole (**18**) in presence of $Rh_2(esp)_2$ as a catalyst (**Scheme 1.5**). The 1-sulfonyl-1,2,3-triazole (**18**) in presence of Rh(III) catalyst converted to azavinyl carbene which on the nucleophilic attack by pyridine resulted to 1,5-dipole pyridinium salt (**19**) with loss of nitrogen. The resultant methodology was further employed for the synthesis of 1,4-diazepines *via* unprecedented catalytic multicomponent [5 + 2] cycloaddition reactions of pyridines, 1-sulfonyl-1,2,3-triazoles, and activated alkynes.[24]



Scheme 1.5 Rhodium-catalyzed synthesis of innovative pyridinium salts

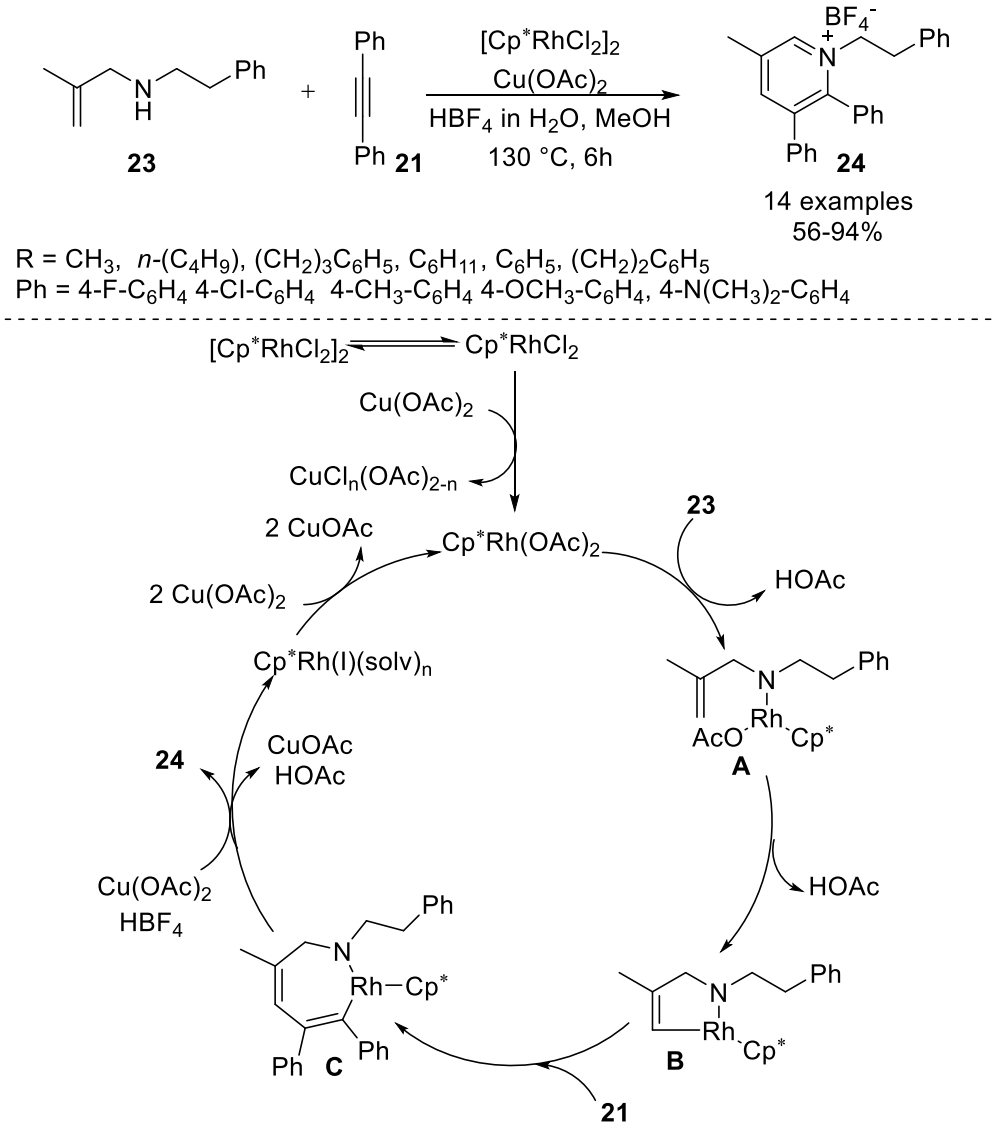
Cheng *et al.* described the synthesis of highly substituted pyridinium salts (**24**) from the multicomponent reaction of vinyl ketones/aldehydes (**20**), amines (**6**), and internal alkynes (**21**)

using a rhodium catalyst $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2 \cdot H_2O$ as the oxidant (**Scheme 1.6**). The catalytic reaction proceeded through Rh(III)-catalyzed alkenyl C−H bond activation and annulations involving the formation of five-membered and seven-membered rhodacycle. The utility of pyridinium salts towards the construction of highly substituted pyridines was demonstrated.[25]



Scheme 1.6 Multicomponent synthesis of highly substituted pyridinium salts *via* C-H activation

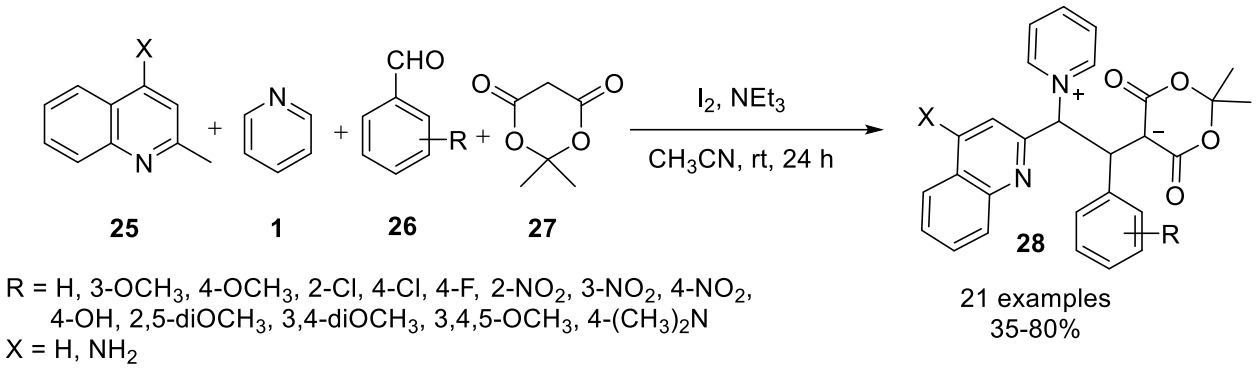
Jun *et al.* developed Rh(III)-catalyzed C−H activation reaction of secondary allylamines (**23**) and internal alkynes (**21**) for the preparation of pyridinium salts (**24**) (**Scheme 1.7**). Based on experimental observations, the rhodacycle involved mechanism was proposed. The reaction involved the formation of the five-membered rhodacyclic complex (**B**) from the chelation reaction of Rh(III) and allylic C-H of **23**. The five-membered rhodacyclic complex (**B**), next underwent insertion reaction with **21** to produce the seven-membered rhodacyclic comple (**C**). In the presence of HBF_4, the **C** underwent reductive elimination to finally produce pyridinium salt (**24**).[26]



Scheme 1.7 Rh(III)-catalyzed C−H activation reaction for the synthesis of pyridinium salts

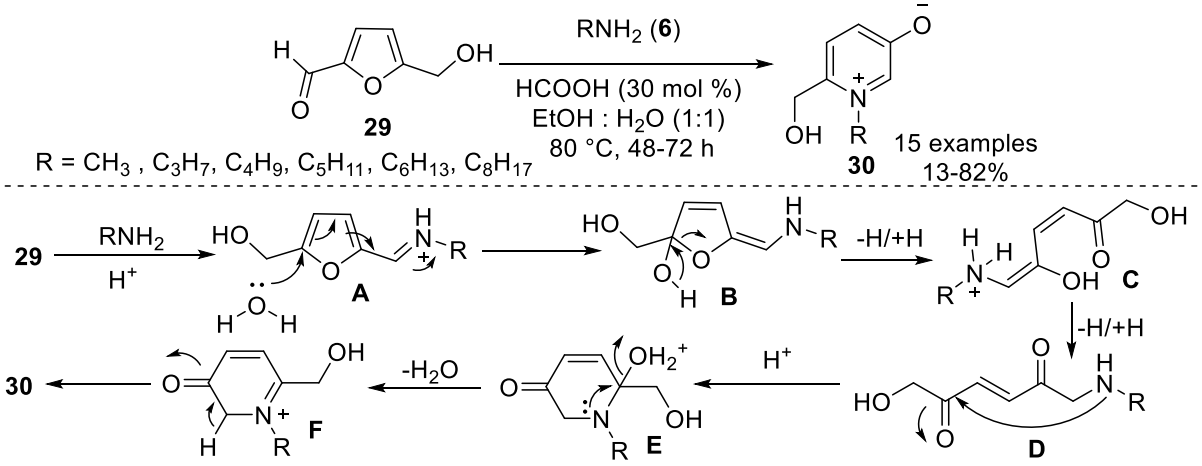
The iodine-mediated multicomponent reaction involving C-H bond functionalization approach for the synthesis of alkyl azaarene pyridinium salts was developed by Kumar and co-workers. The iodine-mediated multicomponent reaction between 2-methylquinoline (**25**), pyridine (**1**), benzaldehydes (**26**), and meldrum acid (**27**) in triethylamine in acetonitrile was performed to obtain series of pyridinium salts (**28**) in good to excellent yields (**Scheme 1.8**). The reaction proceeded through the C-H bond activation in which iodine activated the benzylic proton of 2-methylquinoline to form a 1-iodo-2-methylene-1,2-dihydroquinoline species. The nucleophilic attack of pyridine on 1-iodo-2-methylene-1,2-dihydroquinoline generated an intermediate 1-

(quinolin-2-ylmethyl)pyridinium iodide which on subsequent reaction with arylidene dione (an aromatic aldehyde meldrum acid adduct obtained *via* Knoevenagel condensation) formed alkyl azaarene pyridinium salts.[27]



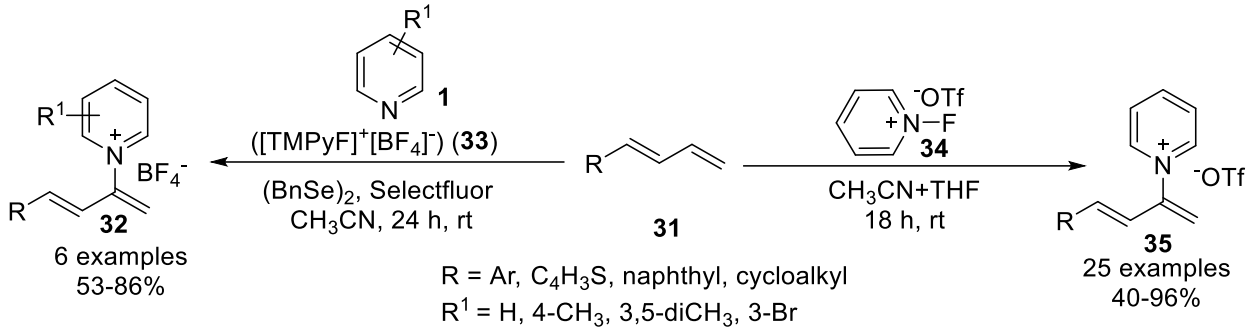
Scheme 1.8 Iodine-mediated multicomponent synthesis of the pyridinium salt

Alfonso and coworkers disclosed the organocatalyzed synthesis of *N*-alkylpyridinium salts (**30**) from 5-hydroxymethylfurfural (**29**) (derived from bio-mass). The formic acid-catalyzed reaction of 5-hydroxymethylfurfural (HMF) with a range of amines (**6**) led to the formation of *N*-alkyl-5-hydroxy-2-(hydroxymethyl)pyridinium (HPyr) (**30**) salts in moderate to good yields (**Scheme 1.9**). The process underwent through ring opening and closing metathesis. Initially, the imine (**A**) formed from the reaction of **29** and **6** underwent ring opening reaction by the attack of water leading to intermediate **D**. The intramolecular nucleophilic attack of nitrogen onto the C2-carbonyl group in **D** formed **E**, which on dehydration reaction yielded **30**.[28]



Scheme 1.9 Synthesis and mechanism of pyridinium salt from HMF

Zhao *et al.* developed an efficient approach for organoselenium-catalyzed regioselective C-H pyridination of 1,3-dienes (**31**) to form pyridinium salts (**32** & **35**). The organoselenium-catalyzed reaction was performed between 1,3-dienes (**31**) and *N*-fluoropyridinium triflate (**34**) as pyridine source while pyridine derivatives (**1**) were also employed for reaction in presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ($[TMPyF]^+[BF_4]^-$) (**33**) using selectfluor as the co-oxidant (**Scheme 1.10**).[29]



Scheme 1.10 Synthesis of pyridinium salts by organoselenium-catalyzed C-H pyridination of 1,3-dienes

1.1 APPLICATION OF PYRIDINIUM SALTS IN ORGANIC SYNTHESIS

Pyridinium salts have powerfully entered the world of synthetic and applied chemistry. The initial focus in the field has been to make use of these as an alternative to volatile organic compounds (VOCs) in various organic transformations due to their unique chemical and physical properties. Now, these salts have advanced far from their reaction media status. Over the last couple of years, different types of salts have been synthesized with desired properties for specific chemical tasks by incorporating a defined functional group to the anion, cation or both.[30] These innovative task specific salts have been utilized as solvents,[31] catalysts,[32-33] and reagents.[34] Subsequently, these salts further evolved to be applied as non-linear optical materials (NLO),[35] electrolyte,[36-37] cationic surfactants[38] and dyes.[39]

The everlasting fascination for pyridinium salts in organic synthesis is due to it being a versatile precursor for the construction of organic frameworks. The pyridinium salts are regarded as significant entities having boundless synthetic value as key intermediates for the assembly of

pharmacologically active indole,[40] piperidine,[41] dihydro,[42] and tetrahydropyridine containing natural products.[41] The functionalization of pyridine using electrophilic aromatic substitution as well as nucleophilic aromatic substitution reactions is a challenging task due to its poor reactivity. However, this anomaly of pyridine was resolved by transforming it to pyridinium salts. The pyridinium species are more electrophilic and nucleophilic than the unactivated parent heterocycle. Additionally, the acidity of the α-C−H bond is increased in the pyridinium reagents, supporting in easy deprotonation and associated chemistries, compared to the reaction of pyridine derivatives with strong bases. Charette and group assembled the reports regarding the functionalization of these activated species by the addition of nucleophiles and electrophiles, as well as by transition metal-mediated functionalization in the form of a very informative review article.[43]

However, recent developments in the applicability of this ubiquitous species as a reagent and in the synthesis of aza-fused heterocyclic entities is also an interesting aspect to study and discussed in this chapter.

1.3.1 As a Synthon for Synthesis of Bicyclic Aza-fused Heterocycles

The existence of nitrogen-containing heterocyclic compounds as a privileged structure in several natural products and pharmacologically importance molecules make them interesting entity. In this respect, *N*-fused/aza-fused heterocyclic compounds are important building blocks for new materials with interesting electronic, mechanical, or biological properties. The heterocyclic precursors such as indolizine, imidazopyridine, pyrazolopyridines, pyrrolopyrimidine, pyrrolopyrazine etc. represent the examples of 10π e^- *N*-fused heterocycles in which one nitrogen is present at the junction of two aromatic rings (**Figure 1.3**).

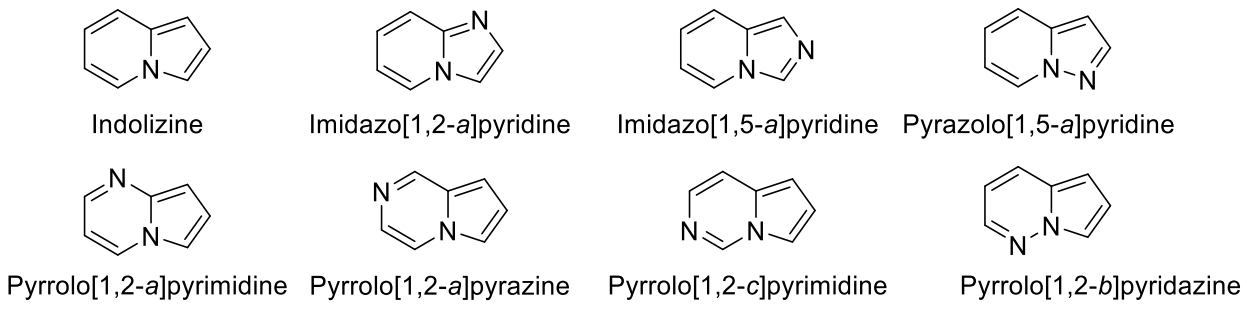
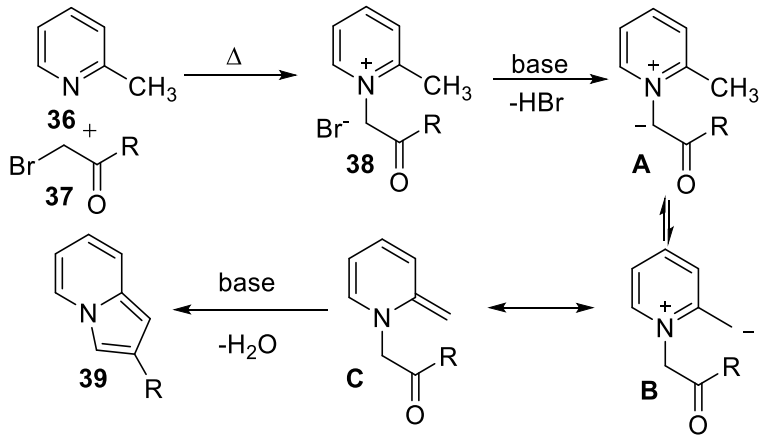


Figure 1.3 Representative examples of bicyclic aza-fused heterocyclic molecules

Owing to the wide variety of applications in pharmaceutical, veterinary and agrochemicals, direct and valuable strategies for the synthesis of *N*-fused heterocycles derivatives are highly desirable. A plethora of reports is available for the construction of these frameworks by employing several interesting approaches, such as multicomponent reactions, tandem sequences, and transition metal-catalyzed C–H functionalization etc. by utilizing varieties of reactive precursors.[44-45] In this respect, pyridinium salts have also been exploited as key starting material for synthesis of aza-fused heterocycles such as indolizines, pyrazolopyridines, and imidazo[1,2-*a*]pyridines.

1.3.1.1 Synthesis of Indolizine

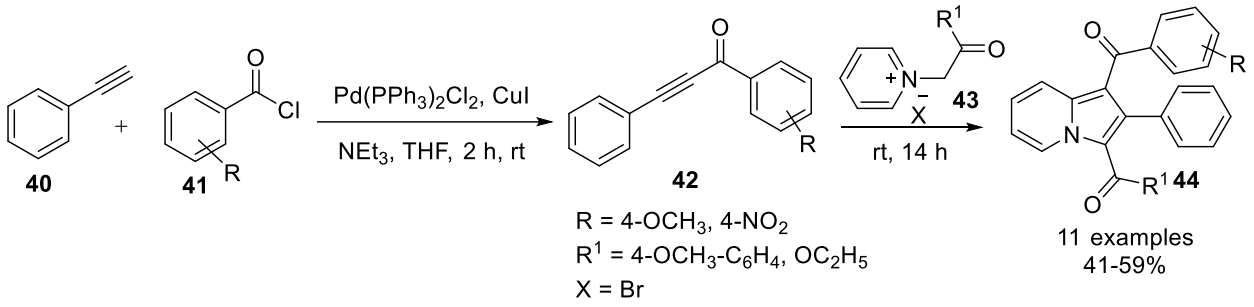
The utility of pyridinium salts in the area of *N*-fused heterocyclic series formation was well established in form of a very first example for the synthesis of 2-substituted indolizine series by Prof. Tschitschibabin in 1927. The report emerged as a basic and traditional approach towards the synthesis of indolizines (**39**) and known as Tschitschibabin indolizine synthesis, in which the base-mediated intramolecular cyclization of 1-(2-oxoalkyl)-2-methylpyridinium salt (**38**) formed by the *N*-alkylation of 2-methylpyridine (**36**) with α-halo ketones (**37**) was carried out (**Scheme 1.11**).[46]



Scheme 1.11 Tschitschibabin indolizine synthesis

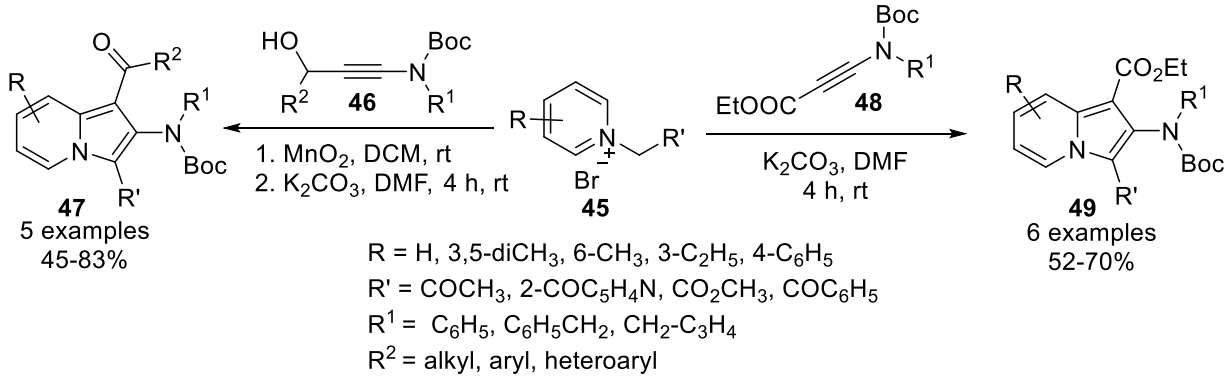
Mueller and co-workers described the palladium-catalyzed one-pot multicomponent sequential reaction of arene carbonyl chloride (**41**), terminal alkynes (**40**) and 1-(2-oxoethyl) pyridinium bromide (**43**) for the synthesis of indolizines (**Scheme 1.12**). The reaction followed two consecutive steps, Sonogashira coupling reaction between arenecarbonyl chloride (**42**) and terminal alkynes (**40**) leading to the formation of activated intermediate ynone (**42**), then [3+2]

cycloaddition reaction of ynone with pyridinium salt. The resultant cycloadduct dihydroindolizine immediately oxidized to indolizines. The synthesized molecules found to be highly fluorescent with high quantum yield. [47] Recently, Yavari *et al.* also reported multicomponent reaction approach for the construction of 1,2,3-trisubstitiuted indolizines starting from **40**, **41**, and pyridinium salt (prepared *insitu* from iodine catalyzed reaction of acetophenone and pyridine).[48]



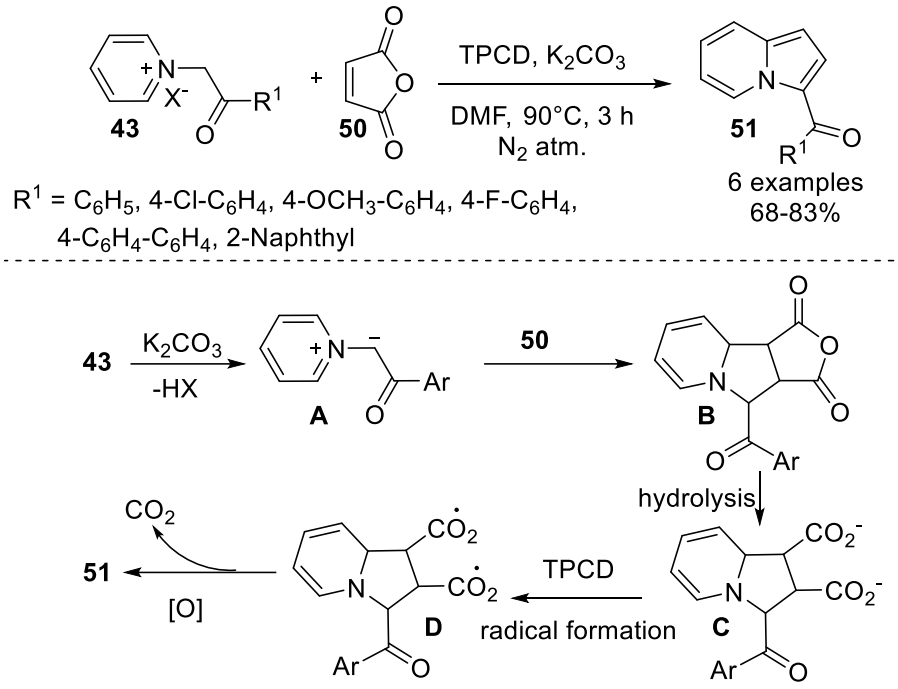
Scheme 1.12 One pot multicomponent sequential synthesis of indolizines

The 1,3-dipolar nature of the pyridinium salts makes them interesting precursor for the synthesis of indolizines *via* [3+2] cycloaddition reaction with alkynes or alkenes.[49-51] Cossy and co-workers reported synthesis of 2-aminoindolizines (**47** and **49**) by base-promoted 1,3-dipolar cycloaddition of pyridinium ylides (**45**) with electron-deficient ynamides (**46** or **48**) (**Scheme 1.13**). The cycloaddition reaction afforded an efficient access to a variety of substituted 2-aminoindolizines, a valuable precursor for the synthesis of more complex nitrogen heterocycles. The approach was extended to synthesize indolizinoquinolinone using copper-catalyzed intramolecular amination reaction of the appropriate 2-aminoindolizine derivative.[52]



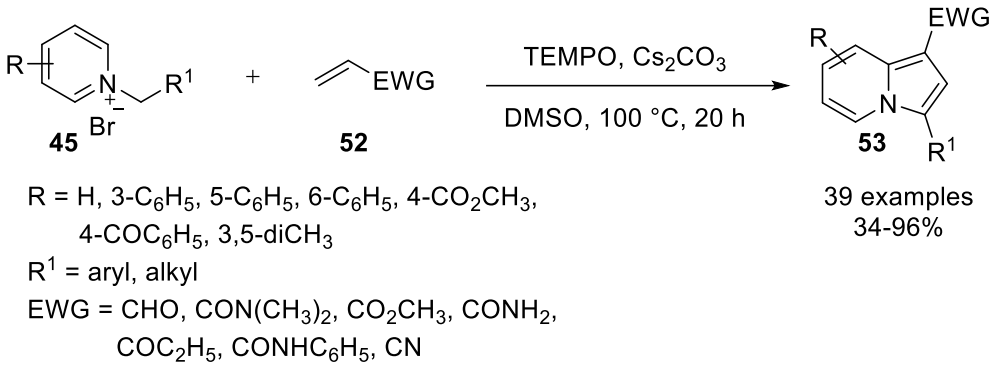
Scheme 1.13 Synthesis of 2-aminoindolizines using pyridinium ylide

Xu and group reported the tetrakispyridinecobalt(II) dichromate (TPCD)-mediated one-pot tandem reaction involving intermolecular 1,3-dipolar cycloaddition reaction of pyridinium salt (**43**) with dipolarophile maleic anhydride (**50**) to synthesize 3-aroyl indolizine (**51**) *via* oxidative bisdecarboxylation (**Scheme 1.14**). The mechanism of reaction involved base-mediated [3+2] cycloaddition followed by TPCD-mediated oxidative bisdecarboxylation and aromatization. The methodology was also applied for the synthesis of varieties of 1-acylpyrrolo[1,2-*a*]quinolones and 1-acylpyrrolo[2,1-*a*]isoquinolines derivatives in good to excellent yields.[53]



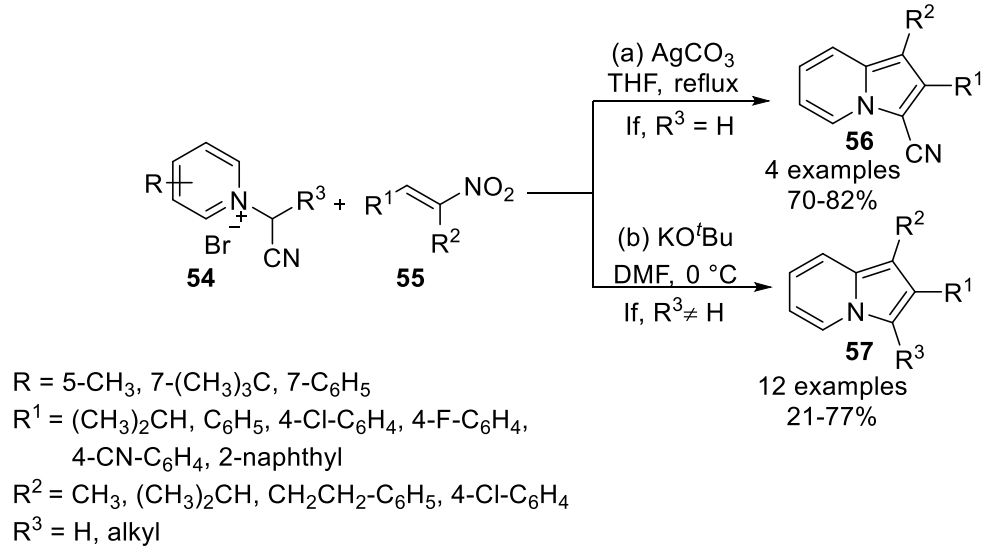
Scheme 1.14 Synthesis of 3-acylindolizine from pyridinium salt and maleic anhydride

Wang *et al.* reported the synthesis of 1,3-disubstituted indolizines (**53**) using 1,3-cycloadition reaction of 1-benzyl/alkylpyridinium bromide (**45**) with alkenes (**52**) using Cs_2CO_3 as base and TEMPO as an oxidant (**Scheme 1.15**). The 1,3-dipolar cycloaddition reaction of previously unexplored 1-alkylpyridinum salts was also studied in order to synthesis novel 3-alkyl indolizines in good to excellent yields. The broad substrate scope, environmentally benign method and simpler procedure were salient features of the protocol.[54]



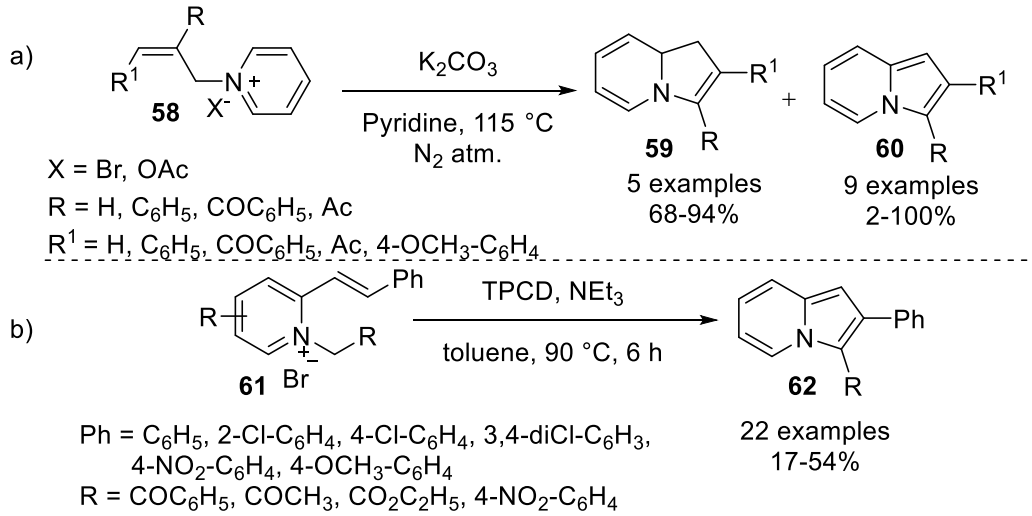
Scheme 1.15 Synthesis of 3-alkyl/arylindolizine *via* 1,3-cycloadition reaction of 1-benzyl/alkylpyridinium bromide with alkenes

Kucukdisli and Opatz developed [3+2] cycloaddition reaction of 1-(1-cyanoalkyl)pyridinium triflate (**54**) and nitroolefins (**55**) to construct polysubstituted indolizines. The nature of alkyl group on 1-(1-cyanoalkyl)pyridinium triflate (**54**) affected the reaction outcome. When 1-(1-cyanomethyl)pyridinium triflate (**54**) was used as a reactive partner then silver carbonate was required as base leading to the formation of 3-cyanoindolizine derivatives (**56**) (**Scheme 1.16** (**a**)), however when 1-(1-cyanoalkyl)pyridinium triflate was used then polysubstituted indolizines (**57**) formed on the action of KO^{t}Bu as a base (**Scheme 1.16** (**b**)). The reaction proceeded through the formation of common intermediate 2,3-dihydroindolizine-3-carbonitrile of which the acidity of α-hydrogen controlled the outcome of the reaction. [55]



Scheme 1.16 Synthesis of polysubstituted indolizines from 1-(1-cyanoalkyl)pyridinium triflate

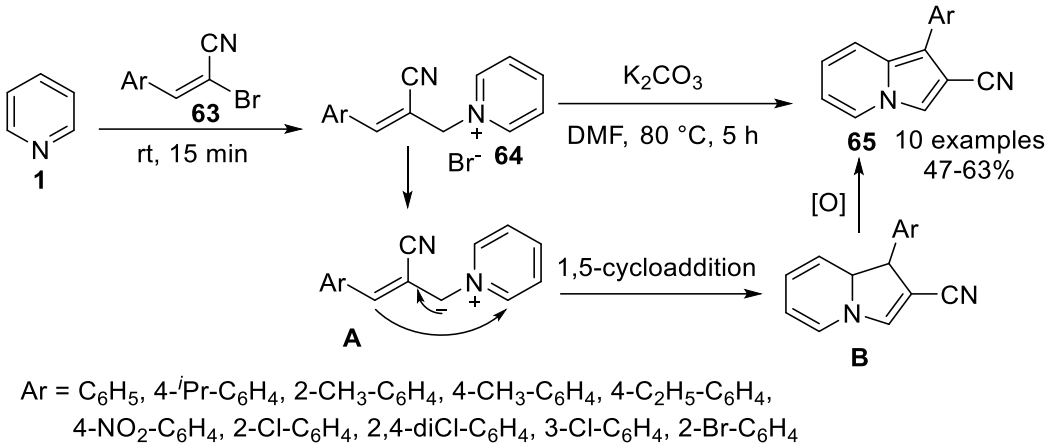
Even though 1,3-dipolar cycloaddition reactions of pyridinium salts are most sought after reactions for designing indolizine scaffolds, the 1,5-dipolar cyclisation reactions of this fascinating synthon were also studied by researchers. In 1972, Pohjala and co-workers disclosed a new method for base-catalyzed conversion of pyridinum salt of 4-bromo-1,3-diphenylbut-2-en-1-one (**58**) into the corresponding 2,3-disubstitute dihydroindolizines (**59**) and indolizine derivatives (**60**) in high yields. Though, in some cases, mixtures of dihydroindolizine and indolizine derivatives were also obtained (**Scheme 1.17**(**a**)).[56] Hu *et al*. reported the synthesis of 1-unsubstituted-2-aryl indolizine derivatives (**62**) by 1,5-dipolar cyclization of 2-(2-phenylethynyl) pyridinium salt (**61**) in presence of triethyl amine as a base and tetrakis(pyridine)cobalt (II) dichromate (TPCD) as an oxidant. It was believed that the 2-(2-phenylethynyl) pyridinium salt (**61**) in presence of triethyl amine formed an active ylide, one of the resonance structures of the which underwent 1,5-dipolar cyclization to afford dihydroindolizines which could have aromatized *in situ* by TPCD to yield indolizines. It was found that the outcome of the reaction was highly influenced by the presence of TPCD and the aryl group on the double bond in 2-vinylpyridinium salt (**61**) (**Scheme 1.17**(**b**)).[57]



Scheme 1.17 Synthesis of indolizine by 1,5-dipolar cyclization of the pyridinium salt

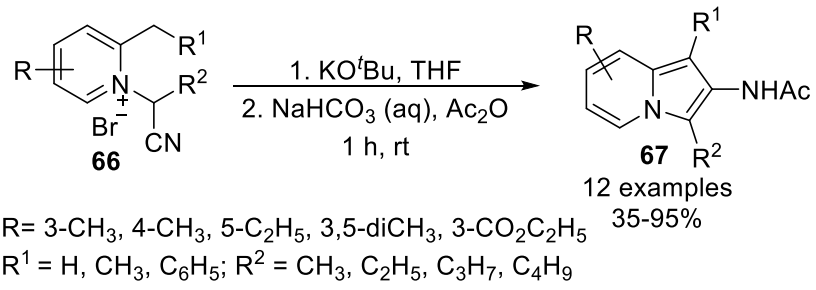
Basavaiah and co-workers utilized pyridinium salts derived from pyridine and Baylis-Hillman bromides (**63**) as a versatile synthon for construction of 2-cyanoindolizines (**65**). Initially, the appropriate pyridinium salts (**64**) were prepared from quaternization reaction of **1** and Baylis-Hillman bromides (**63**). In presence of a base, the salt formed an active ylide (**A**) which rearranged to promote 1,5-intramolecular cyclization reaction between the C-2 position of pyridine ring and

C`-3 position of allyl chain to synthesize **65** (**Scheme 1.18**). The approach was also utilized for the facile synthesis of benzo-fused indolizine, pyrrolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]isoquinoline derivatives.[58]



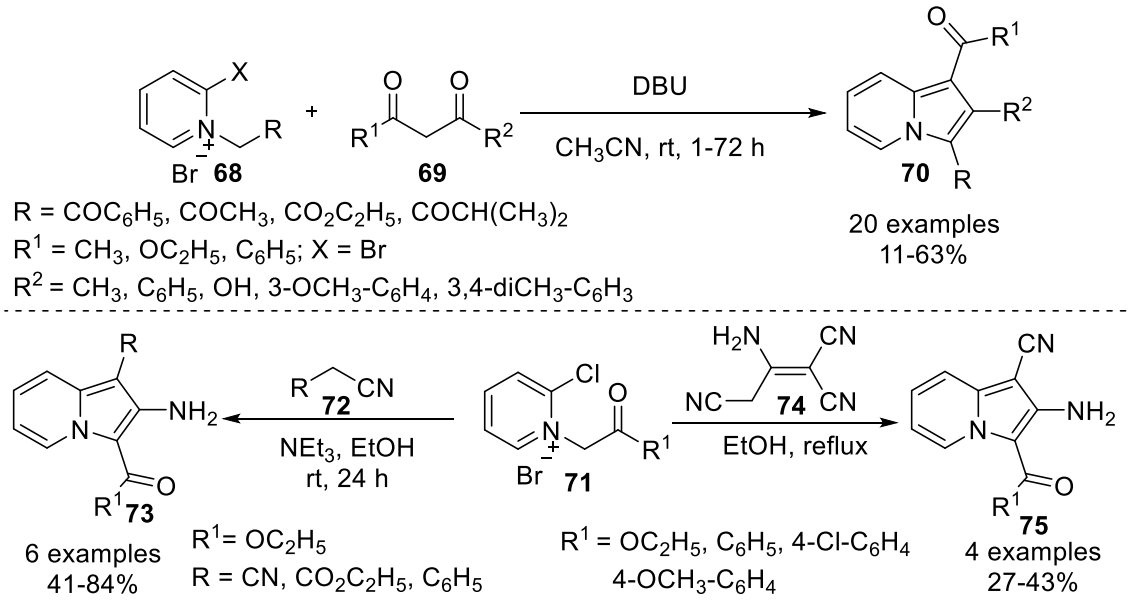
Scheme 1.18 The synthesis of indolizine from pyridinium salt

Kucukdisli and Opatz developed base-mediated 5-*exo-dig* cyclization of 2-alkyl-1-(1-cyanoalkyl)pyridinium salts (**66**) as a new and simple two-step method for the synthesis of 2-aminoindolizines (**67**) (**Scheme 1.19**). It was found that the 2-aminoindolizine formed was readily converted into the ring-opened amino ketone by autoxidation. To prevent this phenomenon, the *in situ N*-acetylation of the products was carried out by treating with acetic anhydride. The applicability of the method was extended to synthesize the biologically active β-carboline alkaloid harmine.[59]



Scheme 1.19 Synthesis of 2-aminoindolizines *via* 5-*exo-dig* cyclization of 2-alkyl-1-(1-cyanoalkyl)pyridinium salts

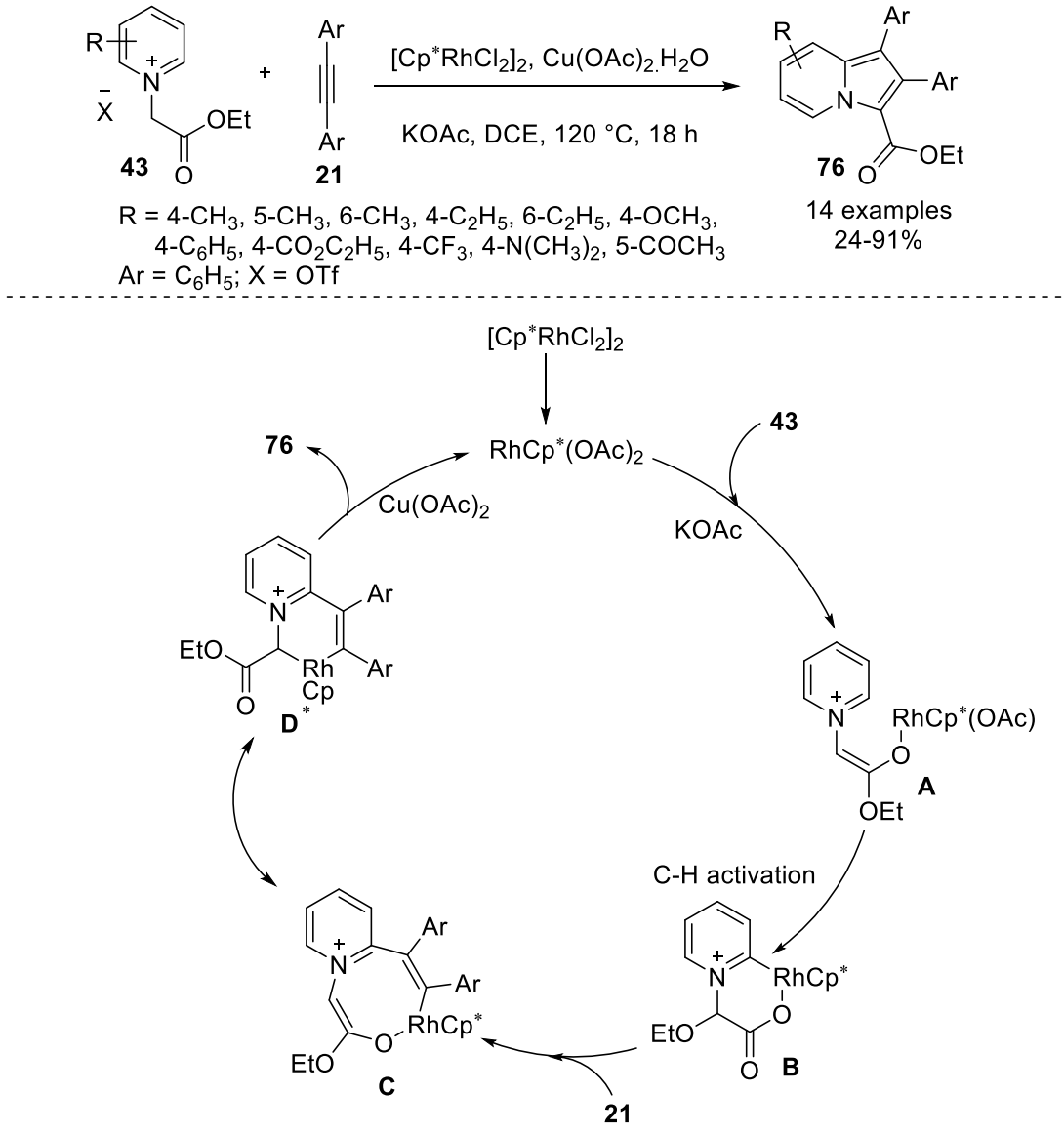
The use of 2-halopyridinium salts as active starting material for synthesis of indolizine was first demonstrated by Krohnke. The synthesis of 2-aminoindolizines was carried out from the reaction between 2-chloropyridinium ylides and either malononitrile or ethyl cyanoacetate in the presence of Hunig'**s** base (diisopropylethylamine).[60-61] Nugent and Murphy reported the reaction of α-keto esters and α-diketones (**69**) with 2-bromo pyridinium salts (**68**) in the presence of DBU for a rapid and convenient synthesis of substituted indolizines (**70**). The duo also achieved success in the synthesis of 2-hydroxyindolizines by the use of diethyl malonate as the dicarbonyl component. The nucleophilic substitution by the dicarbonyl anion at the C-2 position of pyridinium salt followed by intramolecular cyclization afforded the indolizine ring system (**Scheme 1.20**(**a**)).[62] Khoroshilov and co-workers also established the synthesis of poly-functionalized indolizine ring system (**73** or **75**) using 2-halopyridinium salts (**71**) and active methylene compounds such as acetonitrile derivatives (**72**) and malononitrile dimers (**74**) under basic reaction medium (**Scheme 1.20**(**b**)).[63-64]



Scheme 1.20 Synthesis of indolizine ring system from 2-halopyridinum salts

Wang and co-workers described rhodium-catalyzed oxidative annulation reaction of pyridinium trifluoromethanesulfonate salts (**43**) with internal alkynes (**21**) for construction of 3-carboxylated indolizines (**76**) *via* cleavage of C(sp^2)−H/C(sp^3)−H bonds (**Scheme 1.21**). The **43** in presence of base converted into active pyridinium ylide which reacted with active catalyst Cp*Rh$(OAc)_2$ to

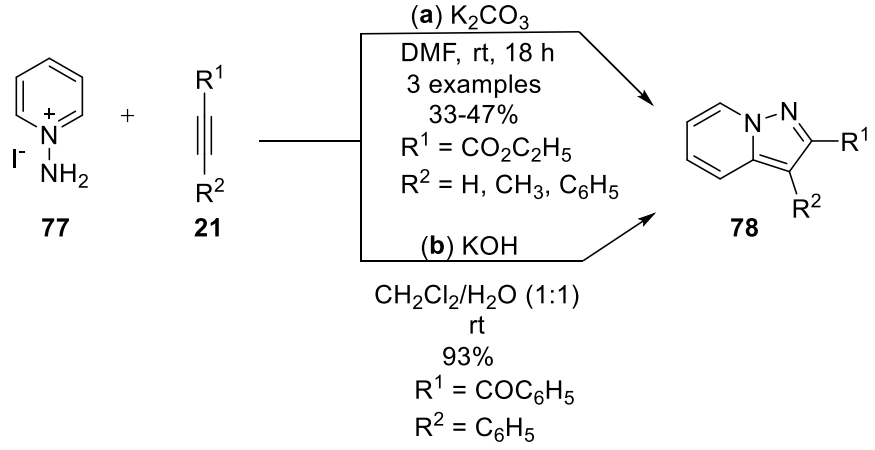
form a six-membered rhodacyclic intermediate (**B)** *via* C-H activation. An alkyne coordination and migratory insertion into the six-membered rhodacyclic intermediate (**B)** afforded a strained eight-membered rhodacycle (**C)** which existed in equilibrium with the six-membered rhodacycle (**D**). Next, **D** underwent reductive elimination and aromatization to give the **76** leaving the Rh(I) species to reoxidize by oxidant $Cu(OAc)_2$ into the active Rh(III) catalyst for the next catalytic cycle.[65]



Scheme 1.21 Rhodium-catalyzed C-H activation of pyridinium salt for the synthesis of indolizines

1.3.1.2 Synthesis of Pyrazolo[1,5-*a*]pyridines

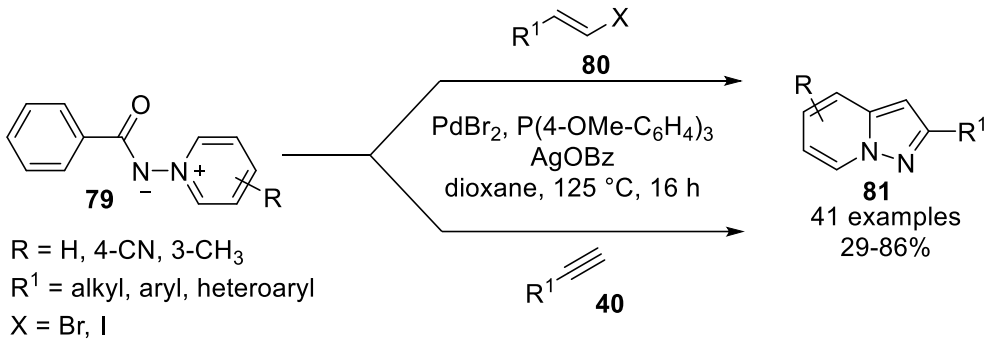
The presence of pyrazolo[1,5-*a*]pyridine motif in drugs showing potent diuretic and anti-hypertensive effects demands the exploration of new methods for assembly of this fascinating molecule. Numerous methods have been described by researches using different synthetic procedures and reagents.[66-69] In this regard, the probability of exploitation of pyridinium salts in the synthesis of pyrazolo[1,5-*a*]pyridines was initiated by Anderson and research group. The K_2CO_3-catalyzed 1,3-dipolar cycloaddition reaction of *N*-amino pyridinium iodide (**77**) with dipolarophiles *i.e.* electron deficient alkynes (**21**) was explored for construction of 2,3-disubstituted pyrazolo[1,5-*a*]pyridines (**78**) (**Scheme 1.22(a)**).[70] The same synthetic strategy was utilized by Akahane and co-workers to attempt the synthesis of a series of adenosine A_1 receptor antagonist having pyrazolo[1,5-*a*]pyridine as core scaffold.[71] The disadvantage of the method was lower yield of **78**. To address the issue, Zanka and coworkers reported the two-phase synthetic approach in which dichloromethane and water system was used as a solvent and acetynyl ketone (**21)** was employed as an efficient dipolarophile in 1,3-dipolar cycloaddition reaction with pyridine *N*-imine (**82**). The two-phase system facilitated smooth isolation of the pyrazolopyridine in remarkably high yield and quality compared to earlier reports (**Scheme 1.22(b)**).[72]



Scheme 1.22 The synthesis of pyrazolo[1,5-*a*]pyridine

Charette and co-workers reported synthesis of 2-substituted pyrazolo[1,5-*a*]pyridine (**81**) using direct reaction of *N*-iminopyridinium ylides (**79**) with alkenyl halide (**80**) or alkynes (**40**) in the presence of palladium as catalyst and silver benzoate as a base (**Scheme 1.23**). It was believed that alkenyl halides were converted to alkyne under the action of silver and palladium catalyst which

in turn converted to silver acetylide. Next, the palladium-mediated C(sp^2-H) activation of pyridinium salt and addition with silver acetylide followed by reductive elimination produced final product. Additionally, an alternate mechanism was also proposed involving the oxidative addition of palladium catalyst to alkenyl iodide followed by insertion to pyridinium salt to yield C-2 alkenylated pyridinium salt. The alkenylated pyridinium salt underwent intramolecular cyclization to give the desired molecule with the expulsion of benzoyl moiety. [73-74]

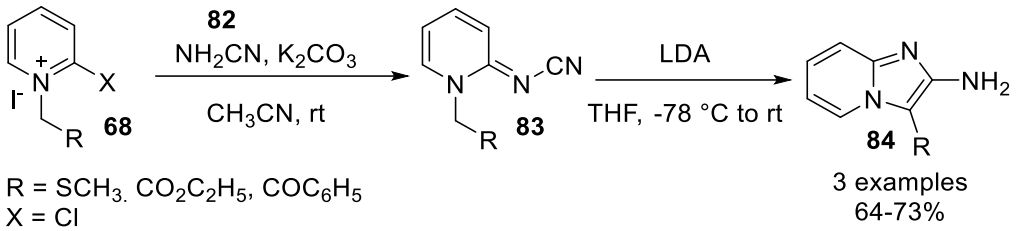


Scheme 1.23 The synthesis of 2-substituted pyrazolo[1,5-*a*]pyridine from pyridinium salt

1.3.1.3 Synthesis of Imidazo[1,2-*a*]pyridines

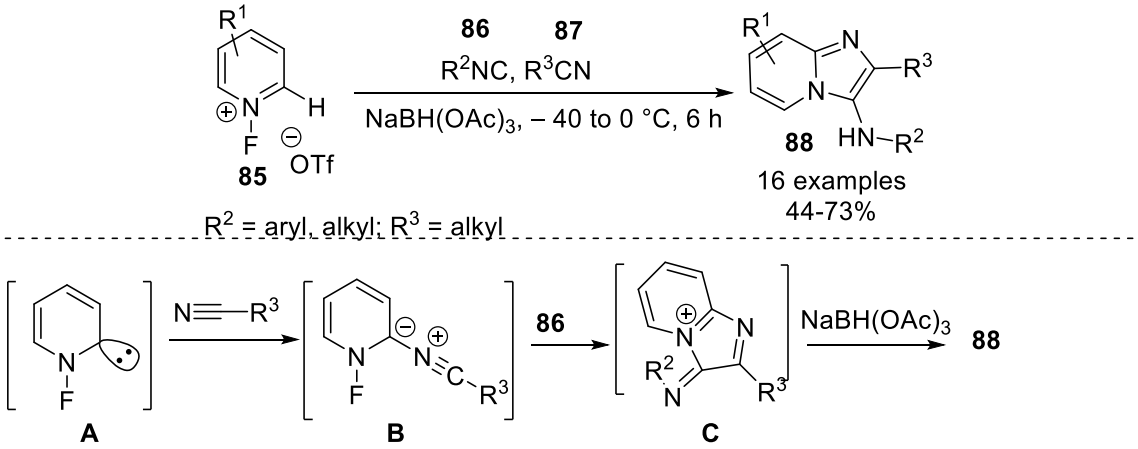
Imidazo[1,2-*a*]pyridines are a privileged structural motif possessing a broad range of biological activities.[75-77] The profuse applications of imidazo[1,2-*a*]pyridines have gathered considerable attention among various research groups in its synthesis and functionalization. Consequently, several interesting synthetic routes such as multicomponent approach, tandem reaction, and transition metal-catalyzed C–H functionalization by employing a variety of starting materials have been developed.[78] In this regards, pyridinium salts as one of the interesting starting material for the synthesis of the aza-fused heterocyclic framework, have also been utilized for construction of imidazo[1,2-*a*]pyridine scaffolds.

Hamdauchi and co-workers synthesised 2-aminoimidazo[1,2-*a*]pyridines (**84**) from the base-mediated reaction of 2-halopyridinium salt (**68**) and cyanamide (**82**). The **68** underwent nucleophilic substitution reaction with cyanamide (**82**) under the mild basic condition to furnish *N*-(alkylpyridin-2(1*H*)-ylidene)cyanamide (**83**). The intramolecular cyclisation reaction of (**83**) with LDA led to the formation of 2-aminoimidazo[1,2-*a*]pyridines (**84**). It was noted that the salts bearing benzoyl group at the C-6 position did not tolerate in reaction (**Scheme 1.24**).[79]



Scheme 1.24 Synthesis of 2-aminoimidazo[1,2-*a*]pyridine from pyridinium salts

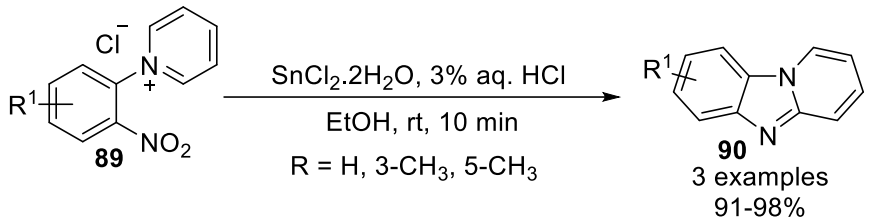
On the other hand, Kiselyov reported the new route for the synthesis of 3-aminoimidazo[1,2-*a*] pyridines (**88**) using the three-component reaction of *N*-fluoropyridinium salts (**85**), isonitriles (**86**) and nitriles (**87**) in the presence of $NaBH(OAc)_3$. 2-Acetamidopyridines were formed as major by-products in this reaction. The substituents on **86** and **87** did not affect the outcome of the three-component process while nature of substituents on *N*-fluoropyridinium salt (**85**) highly influenced the yield of desired products with the formation of a by-product, 2-acetamidopyridines. The reaction was believed to proceeds *via* formation of carbene intermediate **A** through the proton abstraction from C-2 position of pyridinium salt **85**. Subsequently, carbene **A** reacted with nitrile **93** to afford nitrilium ylide **B**. Elimination of fluoride followed by addition of isonitrile (**86**) offered the bicyclic pyridinium species **C**. Finally, reduction of **C** with $NaBH(OAc)_3$ followed by aromatization gave the desired fused imidazoles **88** (**Scheme 1.25**).[80]



Scheme 1.25 Synthesis of 3-aminoimidazo[1,2-*a*]pyridines from *N*-fluoropyridinum salt

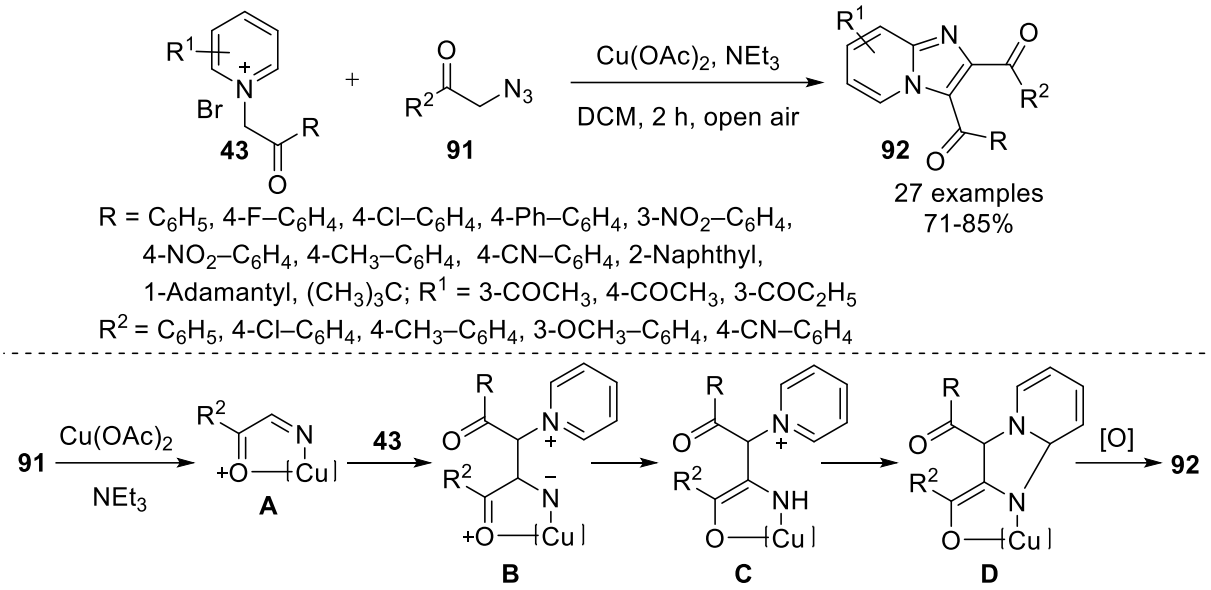
Begunov *et al.* described $SnCl_2$-catalyzed reductive cyclization strategy for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyridines (**90**) from the 2-nitroaryl substituted pyridinium salts (**89**)

(**Scheme 1.26**).[81] The reaction proceeded within less than 1 minute, while the long term isolation of the target compounds, as well as the recycling of the reducing agent, were noted disadvantages. To circumvent these issues, they also carried out the electrochemical reduction of 2-nitroaryl substituted pyridinium salts to synthesis the desired product.[82] Subsequently, other metal chlorides like $TiCl_3$, VCl_3, $SnCl_2$, and $FeCl_2$ were also studied for the electrochemical reduction of pyridinium salts.[83]



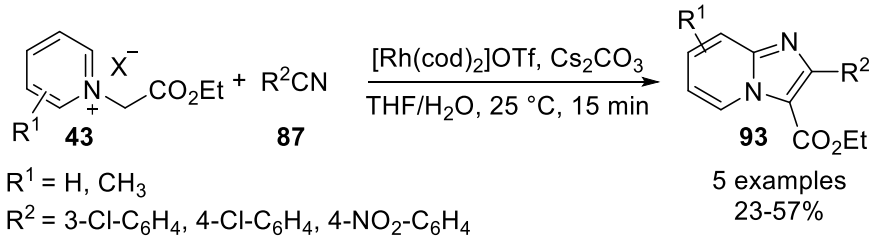
Scheme 1.26 Synthesis of benzo[4,5]imidazo[1,2-*a*]pyridines from 2-nitroaryl substituted pyridinium salts

Kamal and Maurya group utilized copper-catalyzed 1,3-dipolar cycloaddition reaction of pyridinium ylides (**43**) with phenacyl azides (**91**) for the regioselective synthesis of imidazo[1,2-*a*]pyridines (**92**) (**Scheme 1.27**). The preliminary idea behind the strategy was the fact that the phenacyl azide in presence of a base might convert into reactive imine species, which could undergo [3+2] cycloaddition reaction with pyridinium ylide. However, it was believed that the phenacyl azide could also form a chelated imine (**A**) in presence of base and $Cu(OAc)_2$, which in turn on the nucleophilic attack by reactive pyridinium ylide furnished intermediate **B** which easily isomerizes to another reactive intermediate **C**. The amine group of intermediate **C** behaved like a soft base due to chelation with copper, and swiftly attack the C-2 position of pyridinium salt (soft acid) to give intermediate **D**, which on aerial oxidation produced the desired product. The substitution on pyridinium ylide highly influenced the reaction outcome. The reaction of 3-acetyl, 3-ethoxycarbonyl, and 4-acetyl pyridinium salts resulted in good yields of the product however the reaction was not successful with simple pyridinium salt, halogen and electron donating group bearing pyridinium salts.[84]



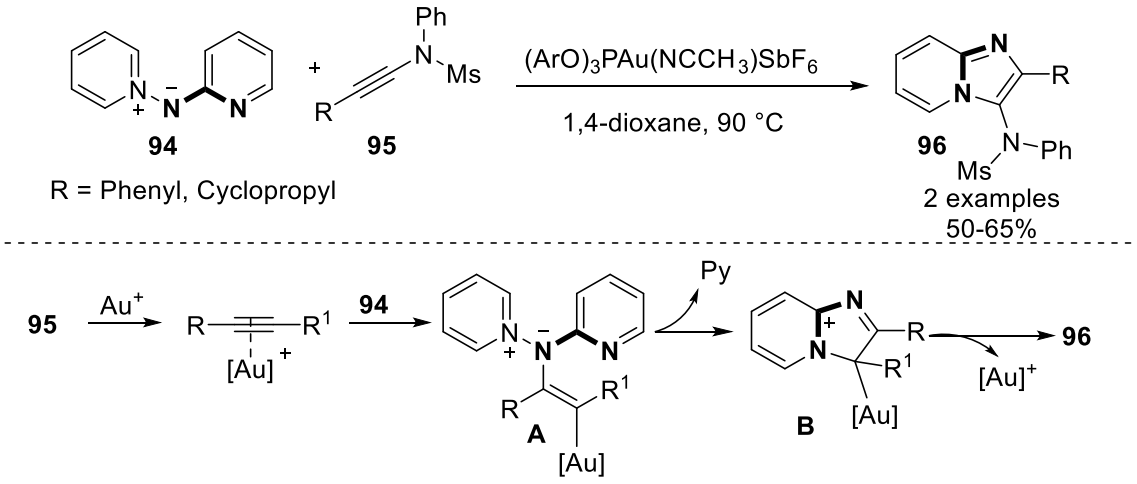
Scheme 1.27 Formation of imidazo[1,2-*a*]pyridines from the pyridinium bromide

Taran and co-workers efficiently employed immunoassay technique for the chemoselective synthesis of 3-carboxylated imidazo[1,2-*a*]pyridines (**93**) starting from 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium salt (**43**) and nitriles (**87**) using rhodium catalyst in which the 1,3-dipolar cycloaddition of **43** with **87** led to the formation of desired imidazo[1,2-*a*]pyridines (**93**) in good yields and lesser time (**Scheme 1.28**).[85]



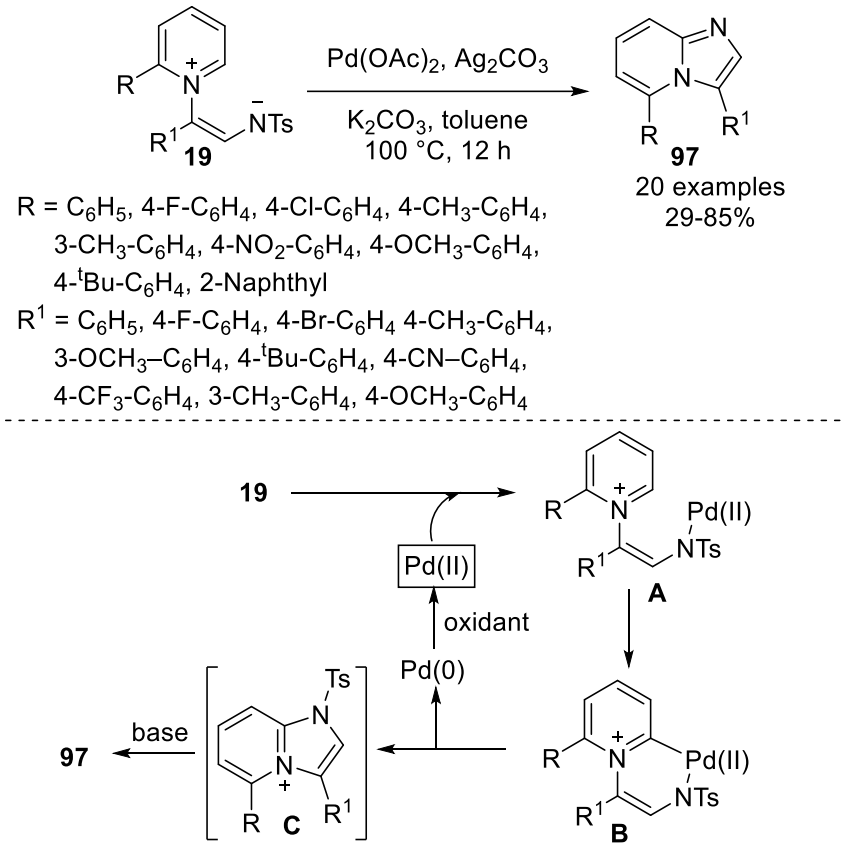
Scheme 1.28 Synthesis of 3-carboxylated imidazo[1,2-*a*]pyridines

Davies and co-worker reported the regioselective efficient synthesis of imidazo[1,2-*a*]pyridine scaffolds (**96**) using pyridinium *N*-(pyridinyl)aminides (**94**) as 1,3-*N*,*N* dipoles under Au-catalyzed [3+2] cycloaddition reaction with electron-rich alkynes (**95**) (**Scheme 1.29**). It was believed that the Au(I) activated the **95** which on the nucleophilic attack by **94** could form intermediate **A**. Next, **A** underwent cyclisation followed by elimination of pyridine molecule and then deaurative aromatization led to the formation of **96**.[86]



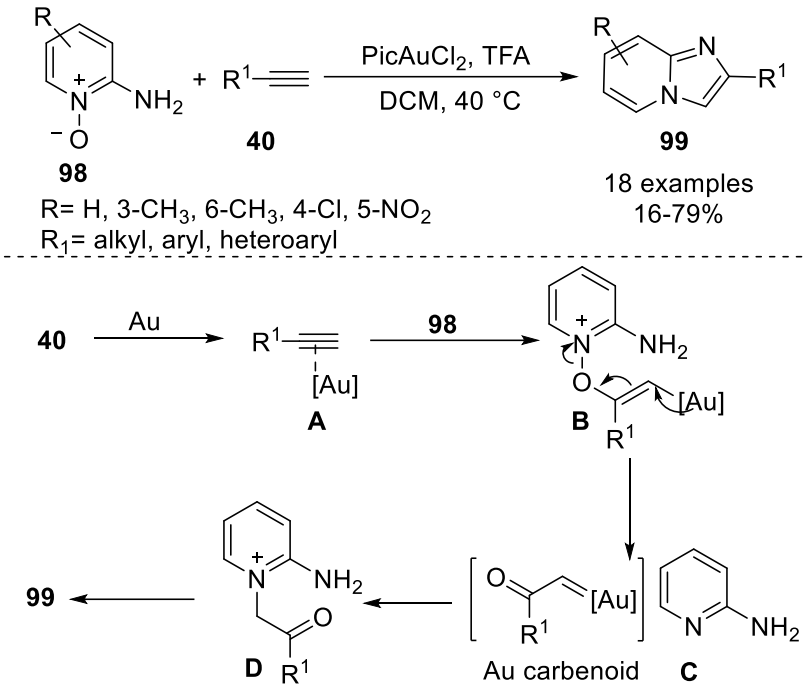
Scheme 1.29 Au-catalyzed synthesis of imidazo[1,2-*a*]pyridines

Baik and Joo group disclosed the palladium-catalyzed C-H amination reaction of pyridinium zwitterion (**19**) in an effort to synthesis 3,5-disubstituted imidazo[1,2-*a*]pyridine (**97**). The Pd(II) activated the **19** by forming reactive adduct **A** which in turn converted into intermediate **B** *via* C-H activation. The reductive elimination followed by desulfonylation of **B** afforded the formation of desired product. Finally, Pd(0) was oxidized to Pd(II) in presence of an oxidant (**Scheme 1.30**). The highly fluorescent 3,5-disubstituted imidazo[1,2-*a*]pyridines derivatives (**97**) were studied for their photophysical activities.[87]



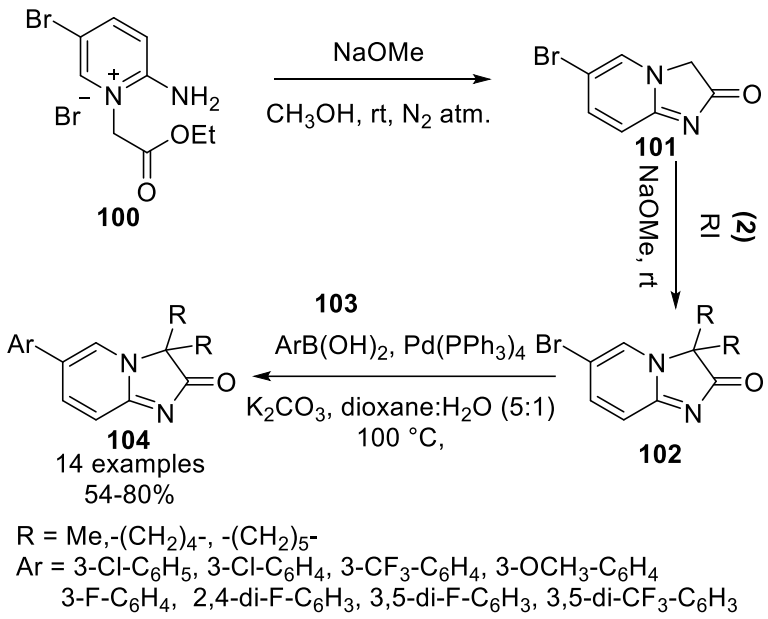
Scheme 1.30 The palladium-catalyzed C-H amination reaction of pyridinium zwitterion

The pyridine *N*-oxides are versatile and reactive species useful in introducing various functionalities on pyridines because of the inadequate possibilities of direct functionalization of pyridines and their derivatives because of their low reactivity and poor regioselectivity. Nowadays, the transition metal-catalyzed C-H activation of pyridine *N*-oxides emerged as a useful approach for the synthesis of small as well as complex heterocyclic motifs. In this respect, Toste group disclosed a novel route to access imidazo[1,2-*a*]pyridines (**99**) through PicAuCl-catalyzed redox reaction of 2-aminopyridine *N*-oxides (**98**) and terminal alkynes (**40**) in presence of TFA. Various aliphatic, aromatic, heterocyclic alkynes were conveniently participated under the optimized reaction conditions to give imidazo[1,2-*a*]pyridines (**99**) in good yields. It was proposed that addition of pyridine *N*-oxide to the pre-activated alkyne (**A**) produced vinyl gold intermediate (**B**) which rearranged to form gold-carbenoid. Finally, the reaction of aminopyridine (**C**) with gold-carbenoid to form pyridinium salt (**D**) and subsequent condensation furnished the desired products (**Scheme 1.31**).[88]



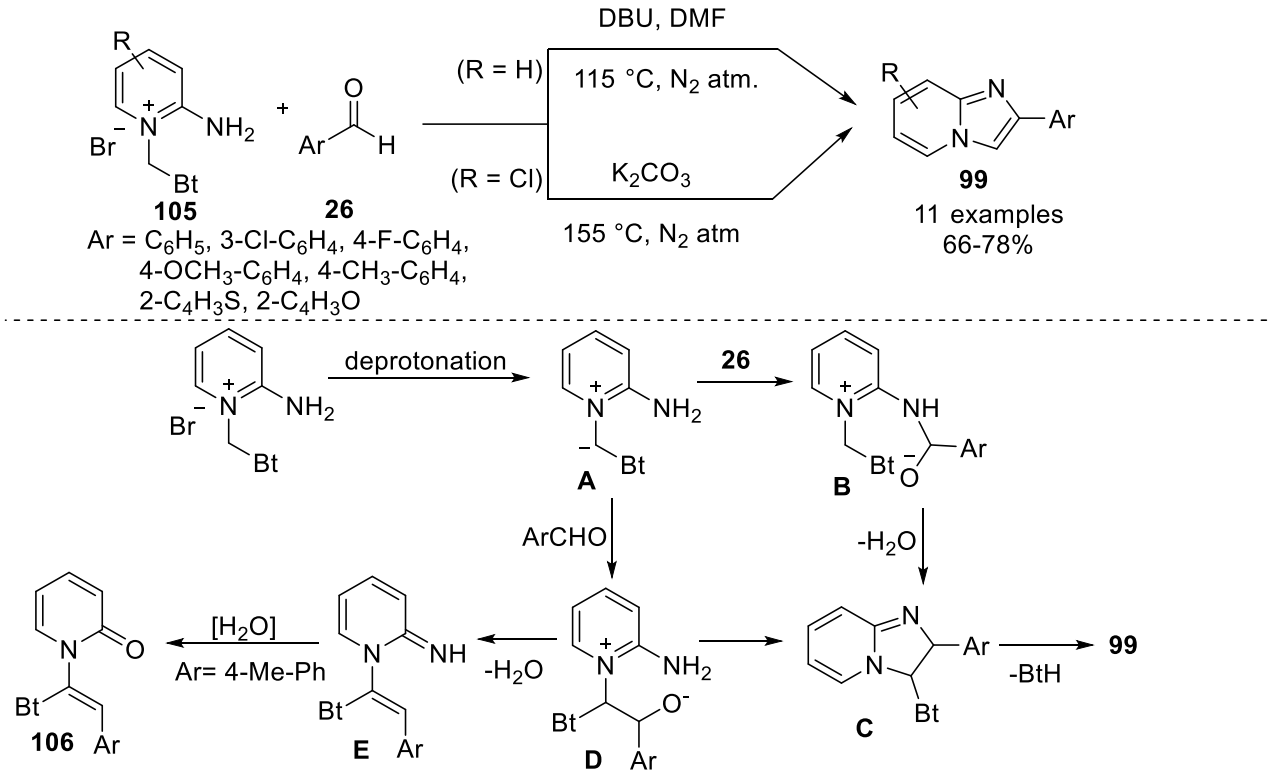
Scheme 1.31 Au-catalyzed synthesis imidazo[1,2-*a*]pyridines from 2-aminopyridine *N*-oxide

The construction of imidazo[1,2-*a*]pyridine scaffolds using the 2-amino functionalized pyridinium salts as starting material has evolved as a fascinating tool over the time. Jiang and co-workers reported the synthesis of 3,3-diphenyl-6-alkylimidazo[1,2-*a*]pyridin-2-ones (**104**) using the sequential reaction of 2-amino-5-bromopyridinium salt (**100**) with aryl halide (**2**) and benzene boronic acids (**103**). The reaction was believed to proceed *via* base-catalyzed formation of an intramolecular amide (**101**) from pyridinium salt with the elimination of HBr and ethanol, followed by base-catalyzed alkylation to form intermediate **102**. Next, the palladium-catalyzed Suzuki coupling reaction on **102** afforded the desired imidazo[1,2-*a*]pyridine-2-ones (**104**) (**Scheme 1.32**).[89]



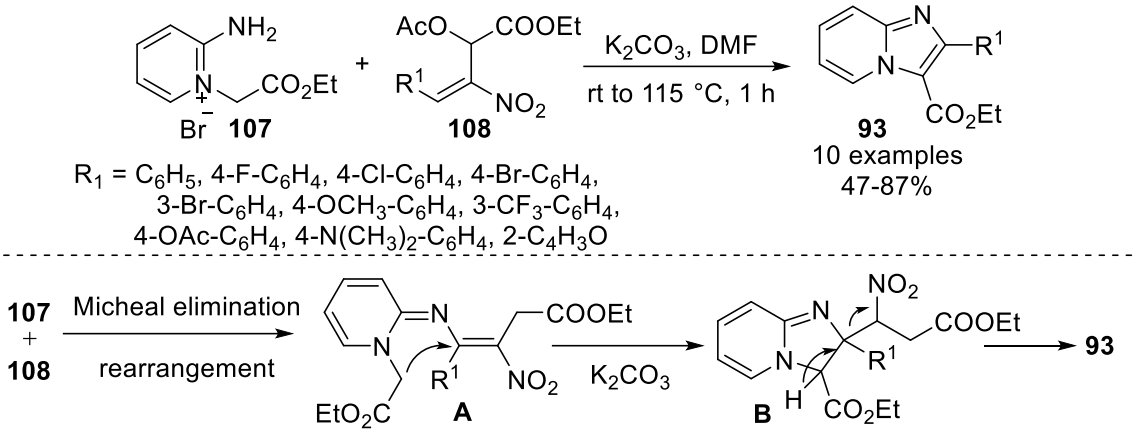
Scheme 1.32 Synthesis of 3,3-diphenyl-6-alkylimidazo[1,2-*a*]pyridin-2-ones

Katritzky *et al.* utilized the benzotriazole method for the synthesis of substituted arylimidazo[1,2-*a*]pyridine (**99**) using base-catalyzed condensation reaction of 2-amino-1-[α-benzotriazol-1-ylmethyl] pyridinium Chlorides (**105**) and aryl aldehydes (**26**). It was found that the outcome of the reaction was influenced by the substituent on pyridinium salt. For example, otherwise, the reaction was performed using DBU in DMF as solvent at 115 °C while the chloro-substituted pyridinium salt required stronger reaction condition like higher temperature *i.e.* 155 °C in the presence of stronger base K_2CO_3 without solvent. The reaction proceeded in two possible pathways. The first pathway involved the deprotonation of pyridinium salt to form azomethine ylide (**A)** which could react with **26** to produce intermediate **D**. The **D** could lead to the formation of desired product alkylimidazo[1,2-*a*]pyridine *via* ring closer followed by loss of benzotriazole. When the 4-methylbenzaldehyde was employed, **D** underwent hydrolysis to give the byproduct 1-[*a*-(Benzotriazol-1-yl)-2-(4-methylphenyl)ethenyl]-2(1*H*)-pyridinone (**106**). In the second pathway, pyridinium salt could react with an aldehyde to form imine (**B**). The ring closer of **B** followed by elimination of the benzotriazole molecule afforded the desired product (**Scheme 1.33**).[90]



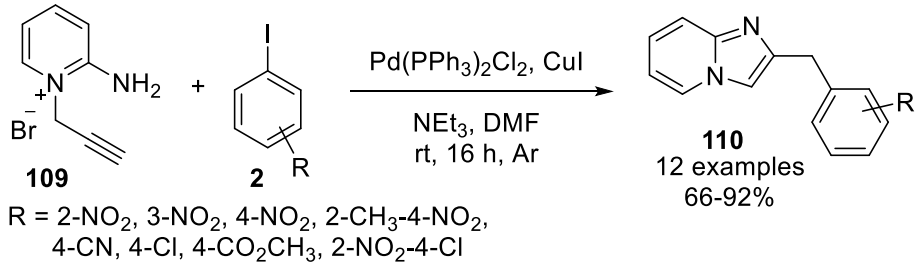
Scheme 1.33 The synthesis of imidazo[1,2-*a*]pyridines from 2-amino-1-[*a*-benzotriazol-1-ylmethyl]pyridinium chlorides

Zou and co-workers established the utility of MBHAs (**108**) and 2-amino functionalised pyridinium salts (**107**) for the construction of structurally diversified heterocyclic scaffolds by varying the nucleophilic partners. The developed method was highly efficient and verified the reactivity of all the electrophilic sites (*α, β, γ* and *δ*) of MBHAs to deliver **93**, indolizines, pyrroles, pyrazoles and benzo[*b*][1,6]oxazocin-2-ones with the respective coupling partners. It was found that MBHAs having electron-withdrawing substituents offered good yields of substituted imidazo[1,2-*a*]pyridines when compared to MBHAs of electron-rich groups. Michael-elimination and rearrangement provided the intermediate **A**. Intramolecular Michael addition at α-position of **A** produced **B** which afforded the desired imidazo[1,2-*a*]pyridines (**93**) through the elimination of ester counterpart (**Scheme 1.34**).[91]



Scheme 1.34 Synthesis of imidazo[1,2-*a*]pyridines from the reaction of a pyridinium salt and HBMAs

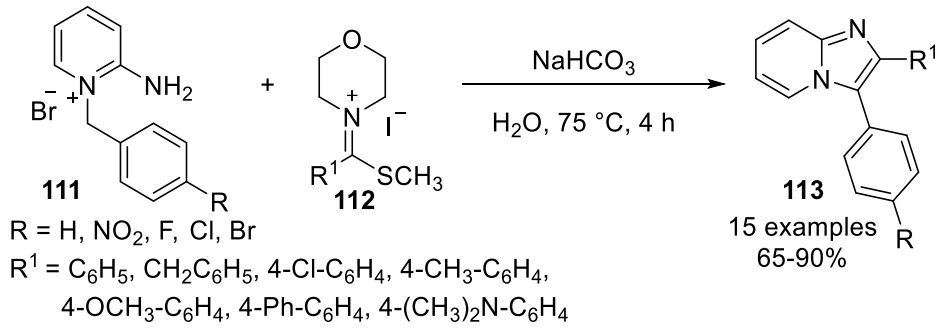
Bakherad and group reported palladium-catalyzed tandem Sonogashira coupling and heterocyclisation of 2-amino-1-(2-propynyl)pyridinium bromides (**109**) with aryl iodide (**2**) as an effort to construct 2-benzylimidazo[1,2-*a*]pyridines (**110**) (**Scheme 1.35**). The indispensable role of electron-withdrawing groups on aryl iodide for the success of this reaction was rationalized as in case of iodobenzene, 2-methylimidazo[1,2-*a*]pyridine was the major product which was a heterocyclization product without Sonogashira coupling.[92] The same group further extended their studies and apprehended that the transformation could be performed in aqueous media in the presence of sodium lauryl sulfate as a surfactant.[93]



Scheme 1.35 Synthesis of imidazo[1,2-*a*]pyridine from 2-amino-pyridinium bromides

Boeini and co-workers disclosed base-mediated condensation and cyclisation reaction of 2-amino-*N*-alkyl pyridinium (**111**) and *S*-alkyl thiouronium salts (**112** in an aqueous medium to synthesize 2,3-disubstituted imidazo[1,2-*a*]pyridine derivatives (**113**) (**Scheme 1.36**). Various pyridinium salts and thiouronium salts actively participated under the optimized reaction condition to afford imidazo[1,2-*a*]pyridines in good yields. The self-condensation of 2-amino-1-(4-

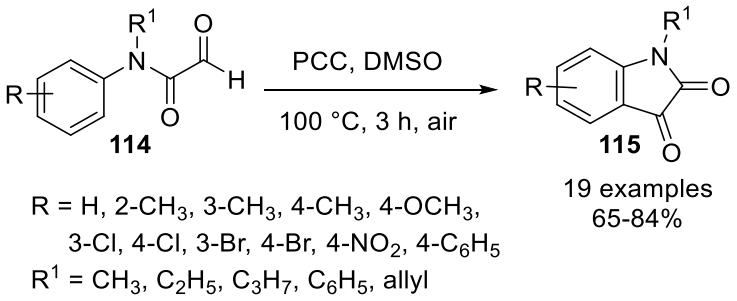
nitrobenzyl)pyridinium bromide in DBU to afford 2,3-disubstituted imidazo[1,2-*a*]pyridine was also observed. The reaction followed a nucleophilic attack of amino functional group of pyridinium salt (**121**) on thioformamidinium salt followed by cyclization and aromatization reaction.[94]



Scheme 1.36 Formation of imidazo[1,2-*a*]pyridine from 2-amino-*N*-alkyl pyridinium iodide

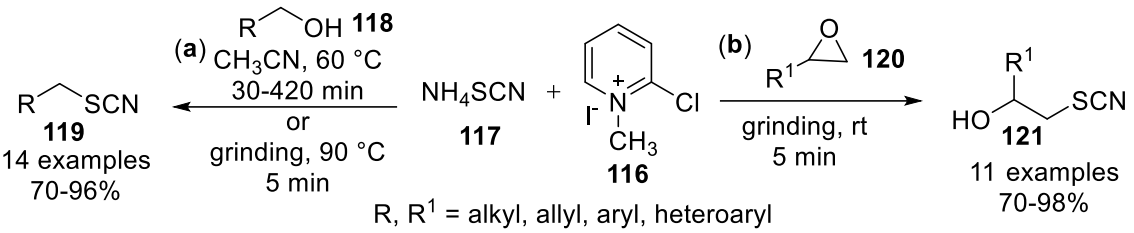
1.3.2 Pyridinium Salts as Reagent in Organic Transformation

Pyridinium chlorochromate (PCC) prepared from the reaction of chlorochromic acid and pyridine, is a well-known strong oxidising agent.[95] Similarly, Pyridinium dichromate (PDC) is obtained by addition of pyridine to a solution of chromium trioxide in water. Both are a very useful reagent for oxidation of primary and secondary alcohols to carbonyl compounds.[96-97] Pyridinium chlorochromate (PCC) has been used to synthesize isatins (**115**) from α-formyl amides (**114**) *via* one-pot intramolecular cyclization–oxidation reaction. The Friedel–Crafts route followed by α-formyl amides led to 3-hydroxy indolin-2-one which on subsequent oxidation in presence of PCC yielded isatin (**115**) (**Scheme 1.37**).[98]



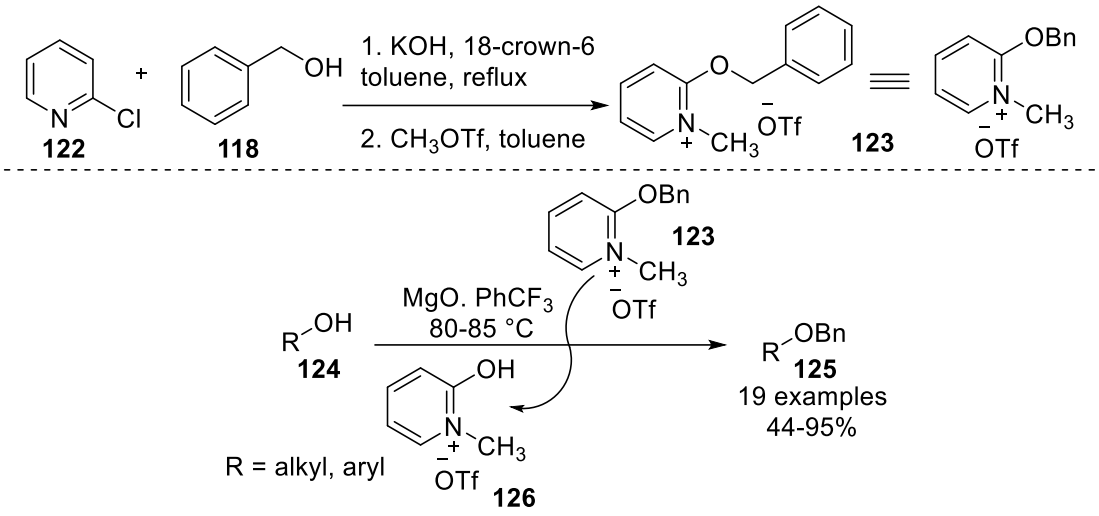
Scheme 1.37 Pyridinium chlorochromate-catalyzed conversion of α-formyl amides to isatins

Mokhtari and coworkers utilized 2-chloro-1-methylpyridinium iodide (**116**) as an efficient reagent for thiocyanation of primary alcohols (**118**) both under solvent and solvent-free conditions. The reaction was performed with **118** and ammonium thiocyanate (**117**) in presence of **116** both in reflux in acetonitrile and grinding method (**Scheme 1.38(a)**). The reaction was found to be more efficient in grinding method with less than 5 min reaction time.[99] The same reagent was applied by Azadi and group to synthesize thiocyanohydrins (**121**) from epoxides (**120**) using grinding method (**Scheme 1.38(b)**).[100]



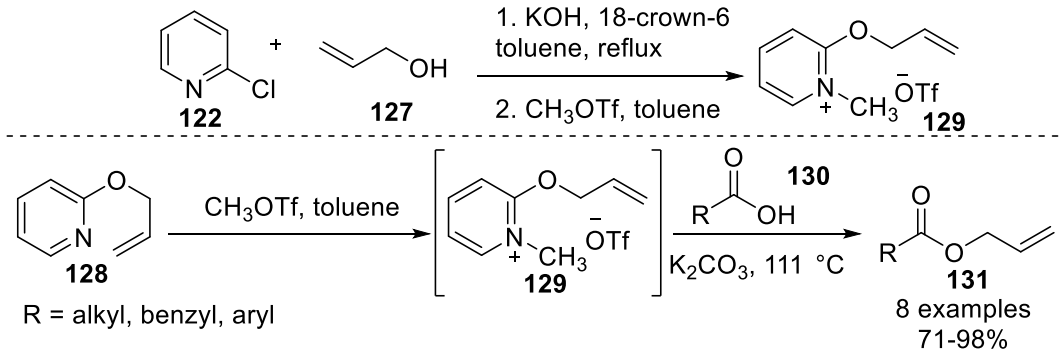
Scheme 1.38 Application of 2-chloro-1-methylpyridinium iodide as a thiocyanating reagent

2-Benzyloxy-1-methylpyridinium triflate (**123**) popularly known as Dudley's reagent is a bench stable, neutral organic salt that converts alcohols into benzyl ethers upon warming. The reagent was first reported by Dudley and co-workers as an efficient preactivated benzylation reagent for alcohols avoiding acidic or basic promoters. The 2-chloropyridine (**122**) was reacted with benzyl alcohol (**118**) in presence of KOH as base and 18-crown-6 as phase transfer catalyst to obtain 2-benzyloxypyridine which on reaction with methyl triflate converted to 2-Benzyloxy-1-methylpyridinium triflate (**123**). The reagent was efficiently applied for the benzylation of a variety of alcohols (**Scheme 1.39**).[101-102]



Scheme 1.39 Synthesis and application of Dudley's reagent

Albiniak and co-workers designed an allylating agent 2-allyloxy-1-methylpyridinium triflate (**129**) based upon Dudley's reagent (**123**) by replacing benzyl alcohol with allyl alcohol (**127**). The base-catalyzed the reaction of 2-chloropyridine (**122**) with allyl alcohol (**127**) followed by *N*-alkylation with methyltriflate afforded the 2-allyloxy-1-methylpyridinium triflate (**129**) as an amorphous solid which was difficult to isolate, and store. Thus the reagent was prepared *in situ* from the reaction of 2-(allyloxy)pyridine with methyltriflate and applied for the synthesis of allyl esters (**131**) from carboxylic acids (**130**) under basic medium (**Scheme 1.40**).[103]



Scheme 1.41 Synthesis of allyl esters by *in situ* generated 2-allyloxy-1-methylpyridinium triflate

1.4 CONCLUSION

The rich chemical reactivity of pyridinium salts has guided its application in the successful synthesis of several heterocyclic compounds. This chapter highlights the efforts directed toward the synthesis of the aza-fused heterocyclic compounds like indolizines, pyrozolo[1,5-*a*]pyridines and imidazo[1,2-*a*]pyridines from pyridinium salts. This chapter also depicts their value as an efficient reagent in benzoylation, thiocyanation reaction well as an oxidant for organic transformations. The reports depicted throughout this chapter have recognized as valuable and interesting due to the wealth of structures that can be synthesized from the pyridinium salts with interest in medicinal, material, and agrochemical sciences. The inspirations and ideas obtained from the present chapter are followed in remaining next chapters in which an effort to use pyridinium salt as efficient amide coupling reagent and in the synthesis of functionalized imidazo[1,2-*a*]pyridines have been described.

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