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Review

Nucleophilic Dearomatization of Activated Pyridines

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Abstract: Amongst nitrogen heterocycles of different ring sizes and oxidation statuses, dihydropyridines (DHP) occupy a prominent role due to their synthetic versatility and occurrence in medicinally relevant compounds. One of the most straightforward synthetic approaches to polysubstituted DHP derivatives is provided by nucleophilic dearomatization of readily assembled pyridines. In this article, we collect and summarize nucleophilic dearomatization reactions of -pyridines reported in the literature between 2010 and mid-2018, complementing and updating previous reviews published in the early 2010s dedicated to various aspects of pyridine chemistry. Since functionalization of the pyridine nitrogen, rendering a (transient) pyridinium ion, is usually required to render the pyridine nucleus sufficiently electrophilic to suffer the attack of a nucleophile, the material is organized according to the type of *N*-functionalization. A variety of nucleophilic species (organometallic reagents, enolates, heteroaromatics, umpoled aldehydes) can be productively engaged in pyridine dearomatization reactions, including catalytic asymmetric implementations, providing useful and efficient synthetic platforms to (enantioenriched) DHPs. Conversely, pyridine nitrogen functionalization can also lead to pyridinium ylides. These dipolar species can undergo a variety of dipolar cycloaddition reactions with electron-poor dipolarophiles, affording polycyclic frameworks and embedding a DHP moiety in their structures.

Keywords: pyridine; dearomatization; pyridinium salt; pyridinium ylide; cycloaddition; asymmetric catalysis

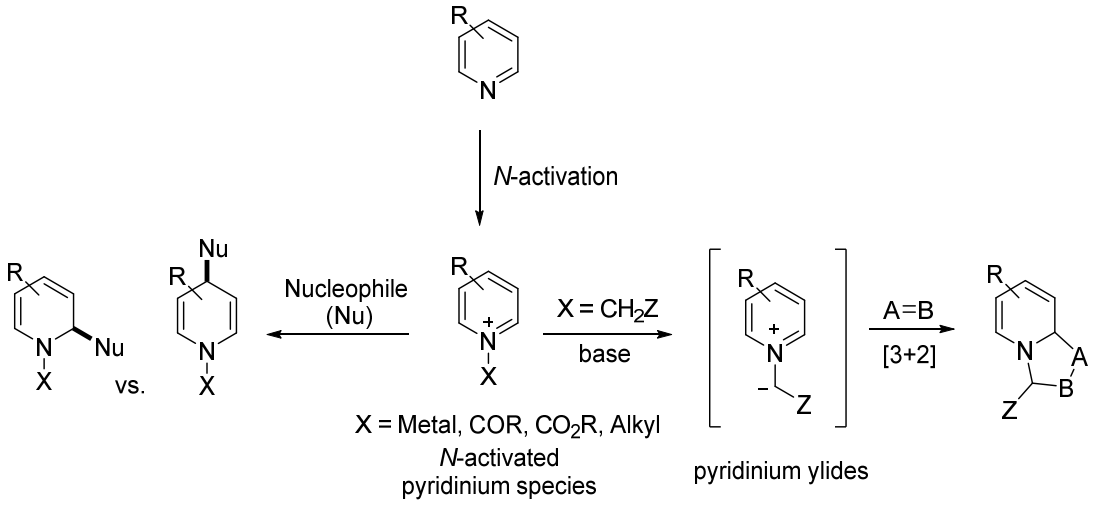
1. Introduction

Dihydropyridines (DHP) are important ring systems and can be found in numerous natural and synthetic compounds, many of which have interesting pharmacological properties. DHPs are among the most beneficial scaffolds that have revolutionized pharmaceutical research with unprecedented biological properties [1,2], besides serving as direct precursors of ubiquitous piperidine units.

Aside from the Hantzsch ring closure reactions and other procedures relying on similar principles [3–6], the regio- and stereoselective nucleophilic dearomatization of pyridines represents one of the most powerful tools for the construction of complex and biologically relevant hydropyridine or piperidine scaffolds [7–11]. This process can be accomplished in two conceptually different manners, namely, reductions and nucleophilic additions, both of which require pyridine as the electrophilic reaction partner. Reductions [12,13], i.e., addition of hydride nucleophiles, rely on the preparation of a pre-functionalized aromatic scaffold to be dearomatized in a late-stage process, whereas nucleophilic additions tackle the opportunity to build complexity during the same dearomatization reaction. In both cases, however, the pyridine nucleus usually requires activation to undergo successful dearomatization since pyridine itself is usually not electrophilic enough (Scheme 1).

Indeed, direct functionalization of pyridine remains a significant challenge due to the lower energy of the π-system relative to benzene. Consequently, electrophilic aromatic substitution is effective only in the presence of substituents that activate the pyridine ring. On the other hand, nucleophilic aromatic substitution can be achieved only with pyridine derivatives that contain good leaving groups or through the intermediacy of *N*-oxides (for recent examples see References [14,15]). Moreover, organometallic species derived from pyridine, particularly at the 2-position, have traditionally been unstable and difficult to access. The nucleophilicity of the nitrogen atom is usually employed to prepare cationic species that display enhanced electrophilic character. As a result, the use of pyridines, functionalized at nitrogen, to generate cationic pyridinium salts or neutral pyridinium ylides have become the preferred synthetic pathway for obtaining DHP derivatives.

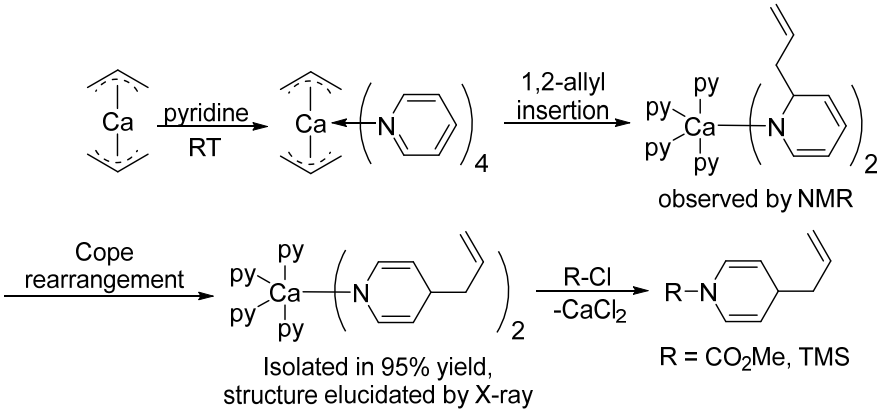
This review presents the functionalization of *N*-activated pyridinium species by the addition of nucleophiles to obtain the corresponding dihydropyridines. We focused our attention on papers published after 2010 since a complete review of nucleophilic dearomatization of pyridines appeared in early 2012 [10], along with a review on the chemistry of pyridinium ylides [16]. However, an extensive description of previously published manuscripts will be included when this allows for better comprehension of the specifics of the subject. Moreover, this review will not cover reductions (vide supra), procedures leading to pseudoaromatic anhydrobases (for recent examples see References [17–19]) and processes involving dearomatization and subsequent rearomatization with the aim of obtaining functionalized aromatic azines. The material is classified according to the pyridine activation strategy employed, which often dictates the reactivity pathways.



Scheme 1. Overview of the reported functionalization strategies.

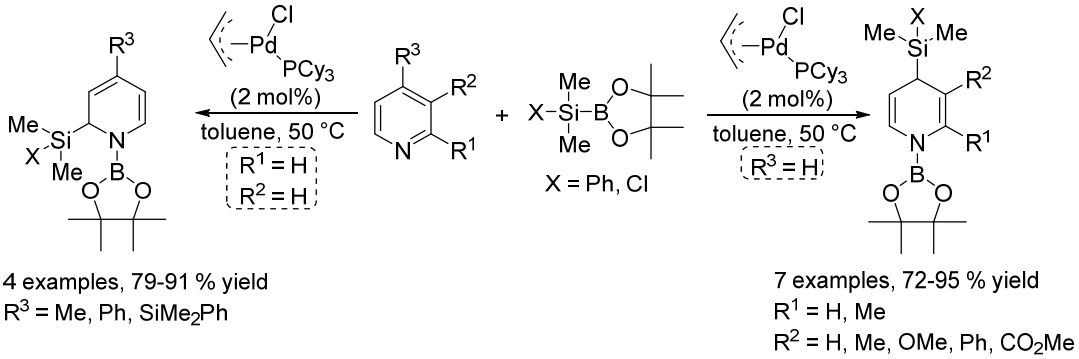
2. Transient *N*-Metal Activation

, Although the preparation of pyridinium salts (vide infra), with irreversible formation of N–C bonds, is the most commonly employed procedure, in some cases, transient activation through the formation of weaker *N*-metal bonds is possible. For example, in 2010, Maron and Okuda [20] demonstrated that unactivated pyridine can be inserted into the Ca-allyl bond of bis(allyl)calcium (Scheme 2). By reaction of excess pyridine with the organometallic regent, a stable calcium amide complex was isolated. It consisted of a central Ca-atom coordinated by four pyridines and two dearomatized 4-allyl-1,4-dihydropyridines. Isolation of this latter species was then possible via the decomposition of the complex with methyl chloroformate or trimethylsilyl chloride to achieve the *N*-substituted heterocycle and $CaCl_2$. According to the proposed mechanism, deduced by NMR spectroscopy and supported by Density Functional Theory (DFT) calculations, coordination of pyridine to Ca provides an activated species that rapidly undergoes 1,2-insertion, followed by a 1,3-shift (Cope rearrangement).



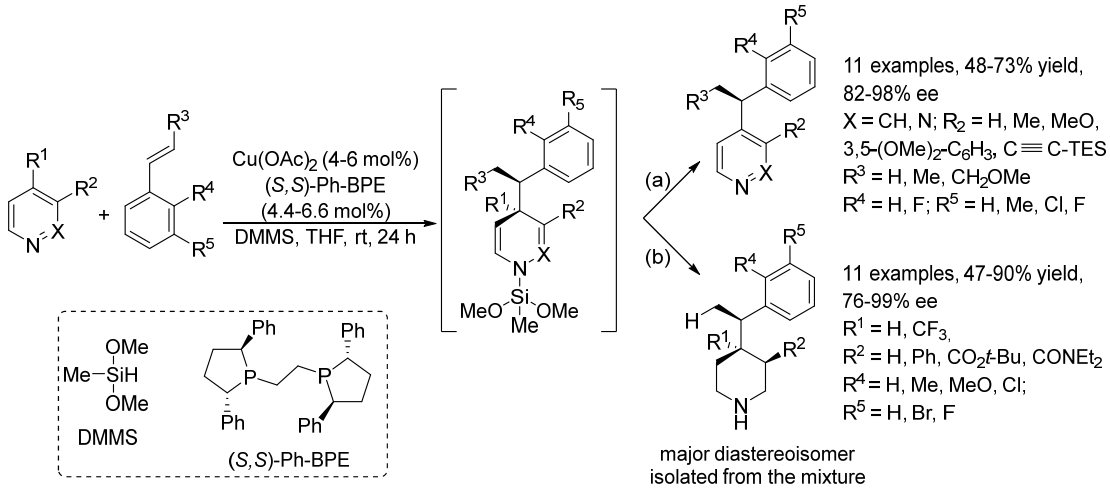
Scheme 2. Dearomatization of pyridine with an organocalcium reagent.

Besides many hydroborations and hydrosilylations of pyridines [21,22], which rely on a similar principle, Suginome developed a palladium-catalyzed silylboration reaction of simple pyridines in 2011 [23]. After insertion of the catalyst into the B–Si bond of the silylborating agent (Me_2PhSi-B(pin)), activation was achieved by transient coordination of the *N*-atom with the newly formed Pd-species. Regioselective insertion of pyridine into the Pd–B bond with introduction of the boryl group onto the nitrogen atom formed a π-allylpalladium complex that, upon reductive elimination, resulted in the formation of the dihydropyridine product (Scheme 3). Insertion of the silyl group proceeded with complete C-4 regioselectivity in the case of 4-unsubstituted pyridines, while C-2 selectivity was observed when substituents were installed onto the 4-position. In some cases, the dearomatized products were unstable and were conveniently oxidized to the corresponding silylated pyridines; however, isolation of the dihydropyridine was generally possible in very high yields.



Scheme 3. Dearomatization of pyridines using a silylboration strategy.

The first enantioselective example involving the nucleophilic dearomatization of pyridines without preactivation was developed very recently by Buchwald [24]. A chiral copper complex was shown to be able to efficiently catalyze the C-4 regioselective addition of styrenes to pyridines (and pyridazines) in the presence of excess dimethoxymethyl silane (Scheme 4). Unstable *N*-silyl-1,4-dihydropyridines were detected as the reaction products, by NMR analysis, and conveniently isolated, either by complete reduction to piperidines or by oxidation to the aromatic compound. A variety of ortho- and meta-substituted styrenes were tolerated, as well as 4- and 3-substituted pyridines that were transformed into the desired fully saturated piperidines in high yields and enantioselectivities, achieving, in the case of substituted heteroarenes, satisfactory diastereomeric ratios as well.



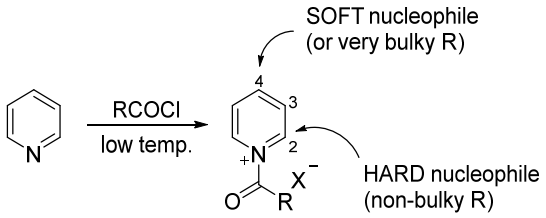
Scheme 4. Buchwald procedure for dearomatization of pyridine. Conditions: (**a**) O_2 or air, toluene, rt and (**b**) $NaBH_4$, AcOH, rt.

3. *N*-Acylpyridinium Salts and *N*-Sulfonylpyridinium Salts

3.1. N-Acylpyridinium Salts

Among the most useful activation methods, the preparation of pyridinium salts by reaction of *N*-atoms with various electrophiles has attracted much attention. Three categories of pyridinium cations can be prepared and successfully employed in dearomatization processes, namely, *N*-acyl, *N*-sulfonyl and *N*-alkylpyridinium salts.

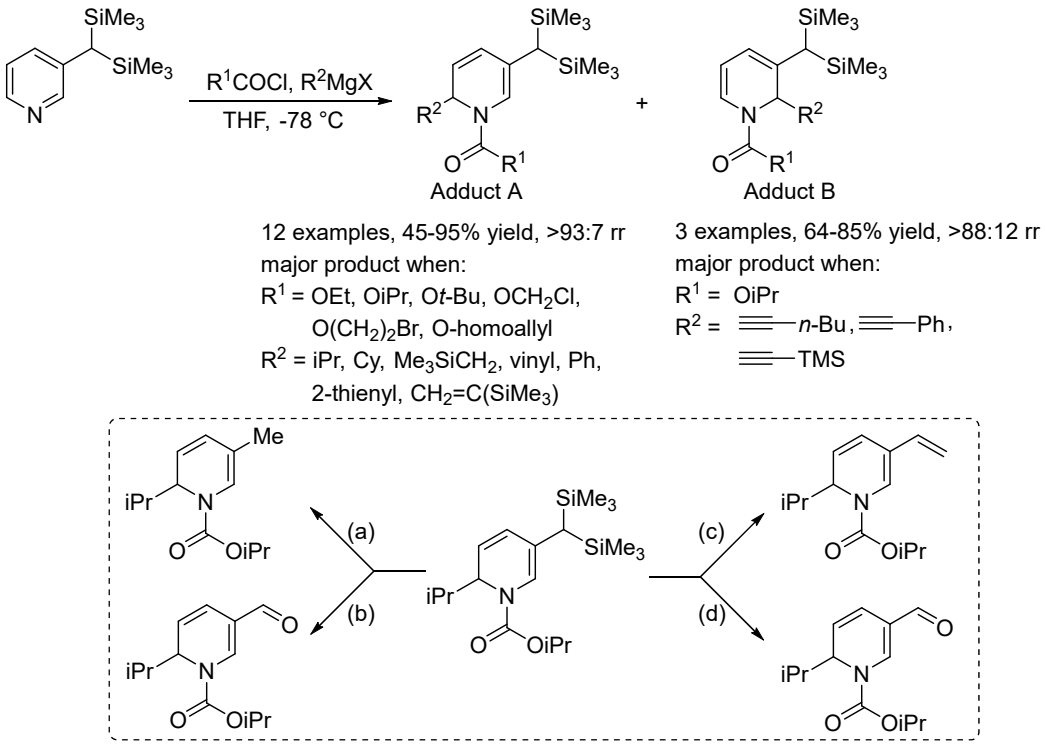
N-Acylpyridinium salts, unstable species generated at low temperatures and reacted in situ, have been extensively employed in dearomatization reactions with a variety of nucleophiles. However, a regioselectivity issue arises from the two different positions (C-2 or C-6 and C-4) prone to nucleophilic attack present on the pyridine nucleus. Both steric bulkiness and hard or soft nature of the nucleophile were found to be factors determining the regiochemical outcomes of such additions (Scheme 5). Although there are exceptions, hard nucleophiles are usually found to be selective towards the C-2 position, while softer nucleophiles react selectively towards the C-4 position. However, when a bulky *N*-acyl activating group is present, the amount of C-4 functionalized product may increase [10,25].



Scheme 5. Regioselectivity issues in *N*-acylpyridinium salts dearomatization.

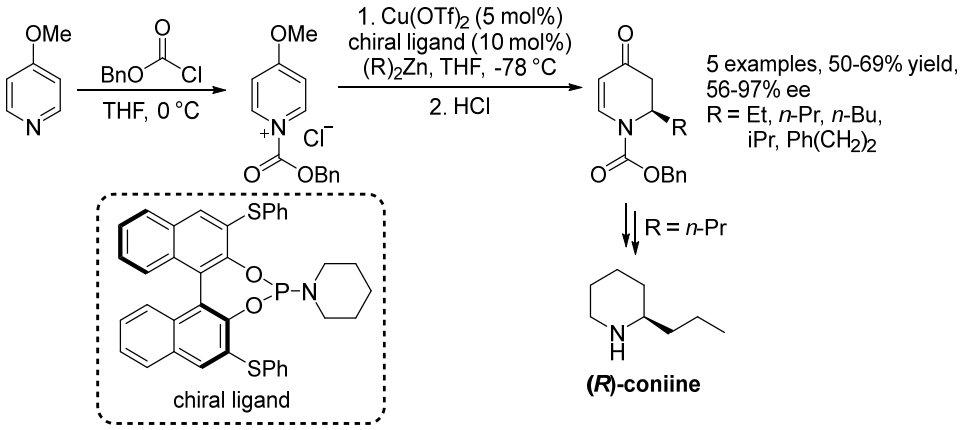
Regarding regioselectivity issues, substituted pyridines are even more challenging, now presenting three different electrophilic sites. On the other hand, substitution of the pyridine ring could also be employed to affect the regioselectivity of the nucleophilic addition. Thus, a bulky group at C-3 position, for example, discourages functionalization at C-4 and C-2, rendering the C-6 the only carbon available for a nucleophilic attack [26]. Following this concept, Song demonstrated that bulky 3-geminal bis(silyl) pyridines, upon activation with acyl chlorides and formation of *N*-acylpyridinium salts, react with Grignard reagents with very high C-6 selectivity [27]. However, when alkynyl magnesium halides were employed, an interesting regioselectivity switch in favor of the C-2 addition product was observed (Scheme 6). This was explained by taking into account the

relative stabilities of the two regioisomers, which reflect the stability of the respective "product-like" transition states. Indeed, adduct B (Scheme 6, Adduct B) was found to be more stable than adduct A (Scheme 6, Adduct A) due to stereoelectronic effects. Finally, the germinal bis(silyl) group could be productively turned into different functionalities, demonstrating the double utility of this moiety.



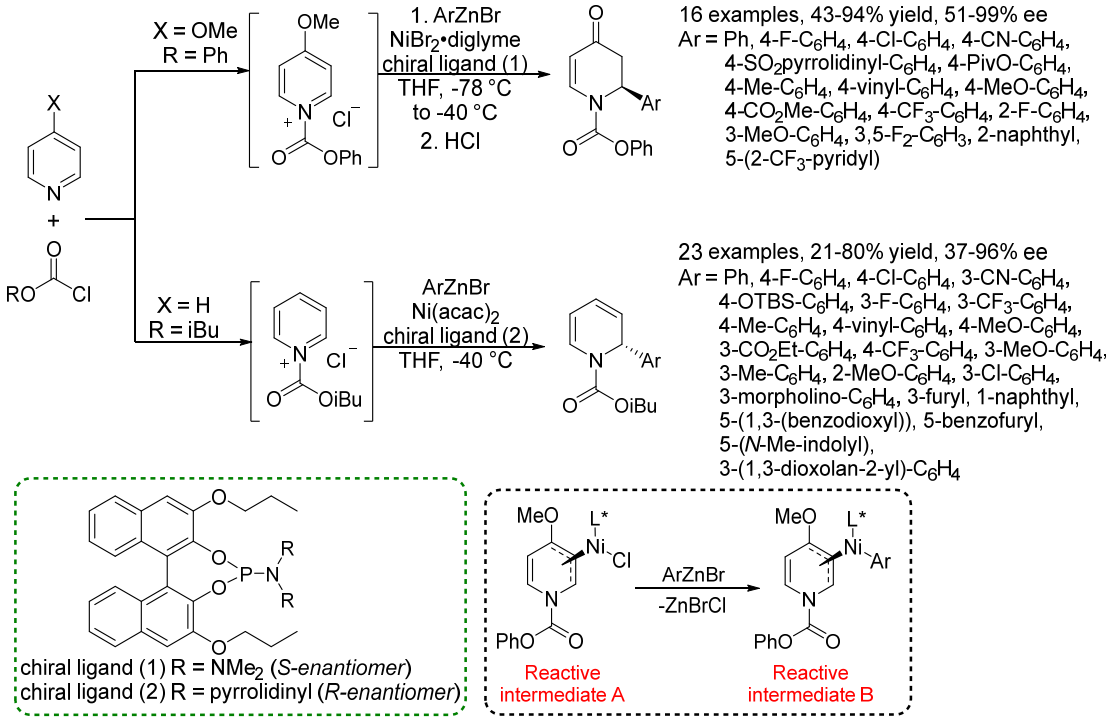
Scheme 6. Dearomatization of pyridines bearing bulky silyl groups at 3-position (rr = regioisomeric ratio). Conditions: (**a**) TBAF, $(HCHO)_n$, DMF, 80 °C; (**b**) 1. H_2, Pd/C, MeOH, 3 °C and 2. CAN, CH_3CN/H_2O, 0 °C; (**c**) TBAF, THF, rt; and (**d**) CAN, CH_3CN/H_2O, 0 °C.

The addition of organometallic reagents to *N*-acylpyridinium salts is an efficient strategy to construct chiral hydropyridine moieties when carried out under asymmetric catalysis. Organozinc reagents were thus found to be productive nucleophiles for regio- and enantioselective dearomatizations of *N*-acylpyridiniums. In 2009, Feringa's group developed a chiral copper/phosphoramidite catalyst for the asymmetric addition of various dialkylzinc nucleophiles to 4-methoxy-*N*-benzyloxycarbonyl pyridiniums, rendering, after acidic work-up, dihydropyrido-4-ones with exclusive C-2 functionalization [28]. One of the examples also served as a demonstration of a formal total synthesis of the alkaloid (*R*)-coniine (Scheme 7).



Scheme 7. Feringa's strategy for the dearomatization of 4-methoxypyridine.

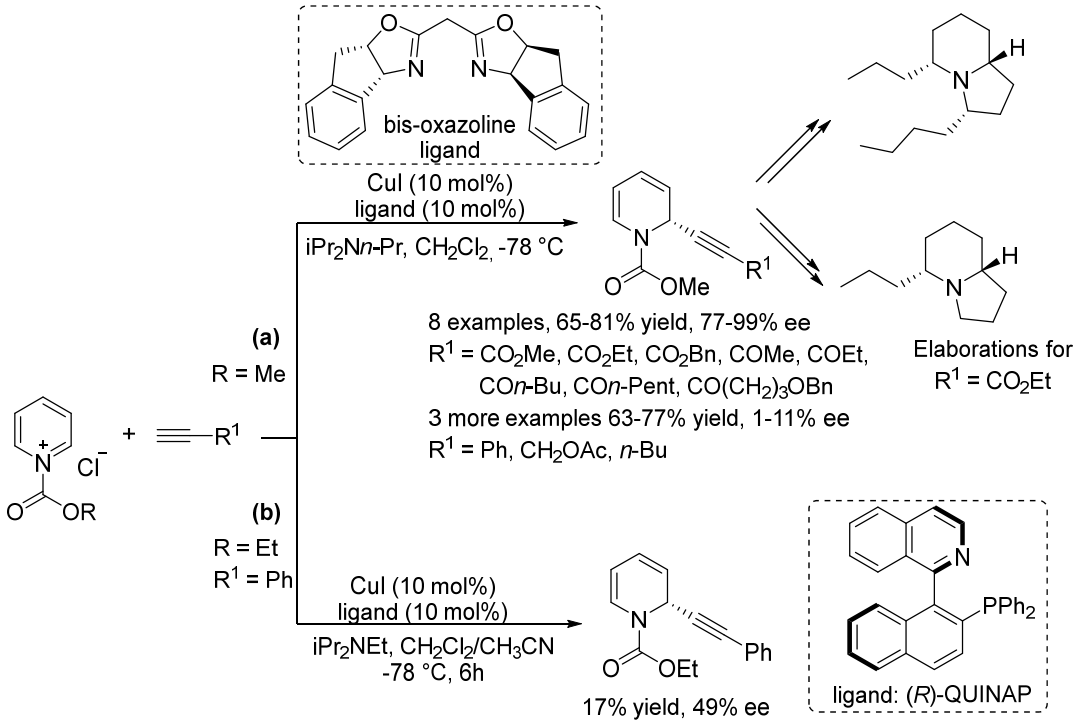
Doyle's group, on the other hand, relied on nickel catalysis when dealing with arylzinc as nucleophiles [29,30]. 4-Methoxypyridine and C-4 unsubstituted pyridines were productively dearomatized, after activation with chloroformates, under differently optimized reaction conditions (Scheme 8). In the case of 4-methoxypyridinium ions, isolation and characterization of an allyl-Ni(II) intermediate (Scheme 8, reactive intermediate A) shed light on the mechanism. It was thus postulated that a nucleophilic attack of the Ni(0) onto the pyridinium ion would render the observed intermediate species. This reactive intermediate A transmetalates with the arylzinc nucleophile to provide an allyl-aryl-Ni(II) complex (Scheme 8, reactive intermediate B) that, upon reductive elimination, delivers the final product and the regenerated catalyst. In both processes a great number of different arylzinc nucleophiles was tolerated, affording the respective 1,2-dihydropyridines in high yields and satisfactory selectivities. However, substitution on the pyridine ring was not explored.



Scheme 8. Doyle's strategy for the dearomatization of 4-methoxypyridine and simple pyridines.

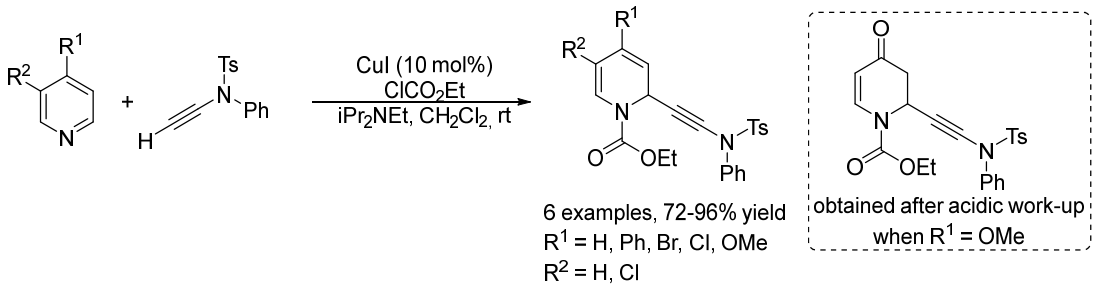
Reaction of *N*-acylpyridinium salts with copper acetylides, generated in situ from terminal alkynes and Cu catalysts, was explored by Ma in 2007 in an asymmetric fashion [31]. In the presence of chiral bis-oxazolines and with 10 mol% CuI, the reaction proceeded with high enantiomeric excesses and good yields for a variety of activated acetylenes (alkynoates and alkynones), affording asymmetric 1,2-dihydropiridines as the sole regioisomers (Scheme 9a). Unactivated alkynes reacted smoothly but with very low enantioselectivities.

The reactivity of different copper acetylides was further explored by Arndtsen one year later [32]. In the presence of a catalytic amount of CuCl and a different type of ligands, based on the QUINAP (1-(2-diphenylphosphino-1-naphthyl)isoquinoline) scaffold, phenylacetylene was reacted with *N*-ethoxycarbonyl pyridinium chloride with low yields and up to 49% ee (Scheme 9b). The methodology was then extended to quinolinium ions as well, reaching higher values of enantioselectivities and better yields.



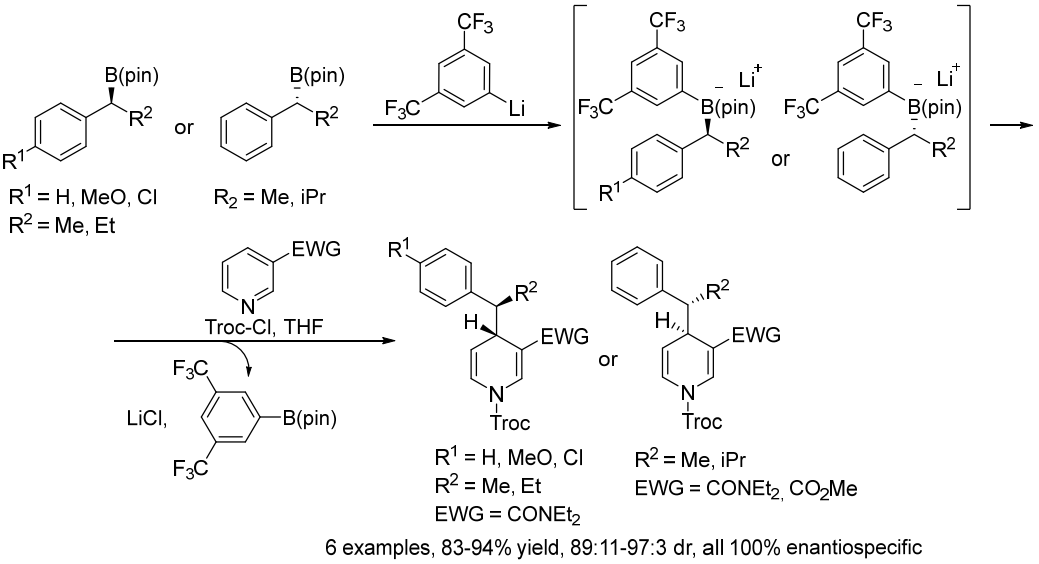
Scheme 9. Asymmetric dearomatization of pyridines with copper acetylides in the presence of (a) a chiral bis-oxazoline or (b) (*R*)-QUINAP

Albeit in a racemic process, different classes of acetylenes, namely ynamides, were also found to be competent substrates for the formation of copper acetylides in situ and the subsequent addition-dearomatization to N-acylpyridinium salts [33]. Both unsubstituted pyridine and C-3 and C-4 substituted pyridines afforded the respective 1,2-dihydropyridines as single regioisomers in high yields. As expected, when 4-methoxypyridine was engaged in the dearomatization process, a 4-dihydropyridone was obtained after acidic work-up (Scheme 10).



Scheme 10. Generation of copper acetylides from ynamides.

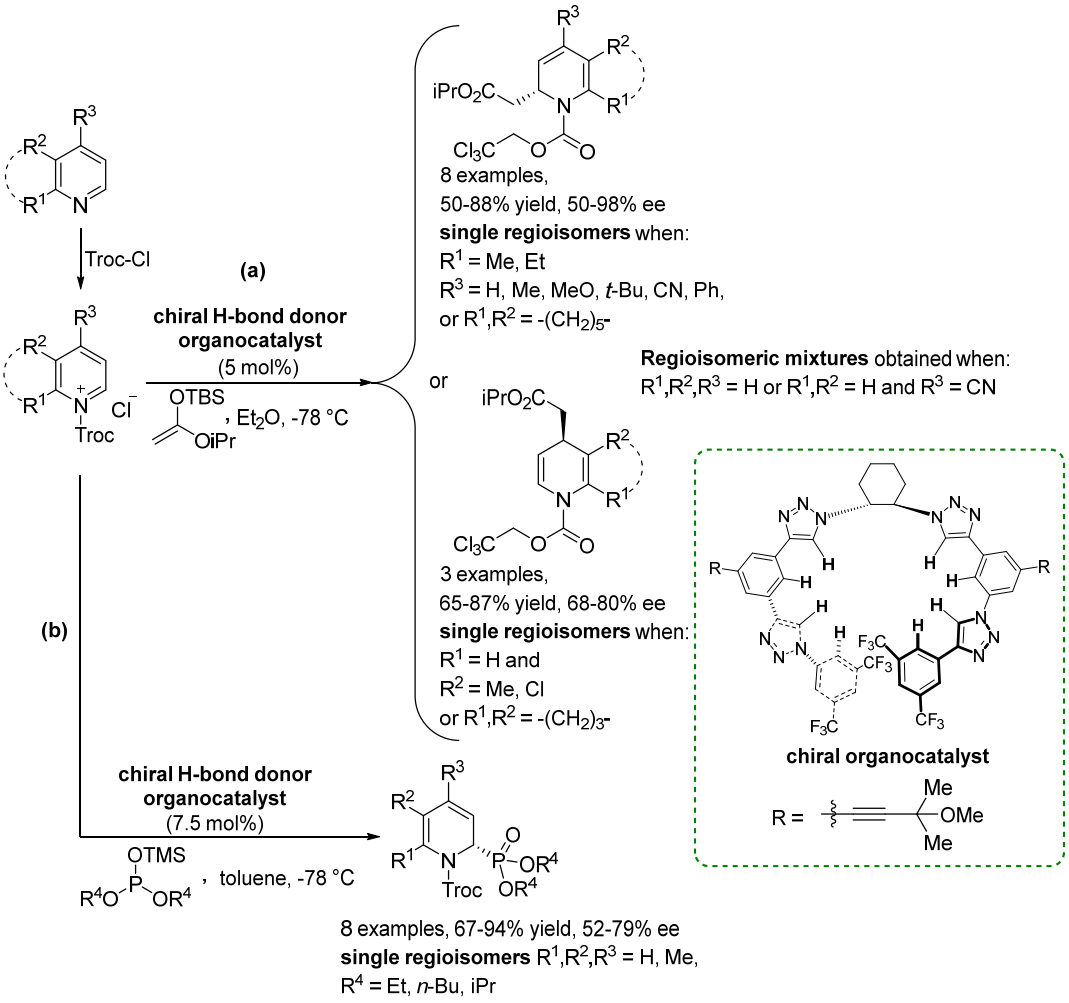
Aggarwal explored the addition of configurationally stable chiral lithiated boronic esters, a class of nucleophiles developed by his group, to *N*-acylpyridinium salts, activated by an EWG (electron-withdrawing group) group at the 3-position [34]. The reaction proceeded with high diastereoselectivities and complete retention of the enantioselectivity values of the starting boron-ates (Scheme 11). The unusually high diastereoselectivity observed was explained by considering a strong cation–π interaction between the cationic heterocycle and the electron-rich benzylic boron-ate complex, with concomitant minimization of steric interactions between the substituents on the complex and the non-planar substituents on the heterocycle.



Scheme 11. Dearomatization of *N*-acylpyridinium salts with chiral born-ate complexes.

A recent report by Mancheño introduced organocatalysis as a platform to induce stereoselectivity in the dearomatization of pyridinium salts [35], disclosing anion binding by multiple hydrogen bond donors as a suitable approach to this type of reactions. A silylketene acetal was used as nucleophilic partner. Variable C-2 or C-4 selectivities, depending on the substitution pattern at the pyridine ring, were observed. For example, a 3-EWG substituted pyridine substrate gave C-2/C-4 regioisomers in 61:39 ratio (Scheme 12a). Previous asymmetric organocatalytic examples were all limited to less demanding dearomatization of N-acylquinolinium and isoquinolinium substrates [36–45]. More recently, the dearomatization of N-acylpyridiniums was extended by employing dialkyl trimethylsilyl phosphites as nucleophiles, in the presence of the same hydrogen bonding organocatalyst [46]. The reaction afforded, in good yields and moderate enantioselectivities, a variety of 1,2-dihydropyridines, obtained as single regioisomers, disregarding the substitution pattern on the pyridinium electrophile and the steric nature of the alkyl chains on

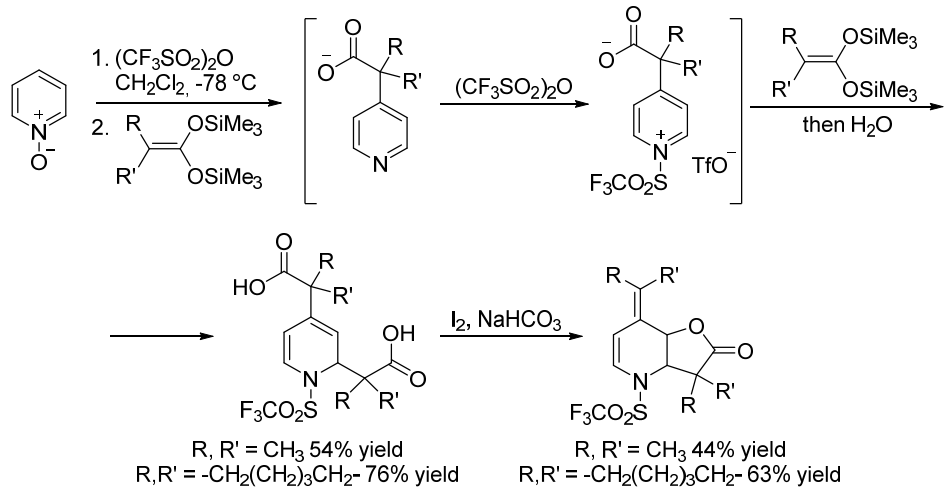
the phosphite nucleophile (Scheme 12b). The process was applicable to quinolinium ions with slightly improved stereoselectivity as well.



Scheme 12. Organocatalytic enantioselective dearomatizations of *N*-acylpyridinium salts with (**a**) a silylketene acetal or (**b**) dialkyl trimethylsilyl phosphites as nucleophiles.

3.2. N-Sulfonylpyridinium Salts

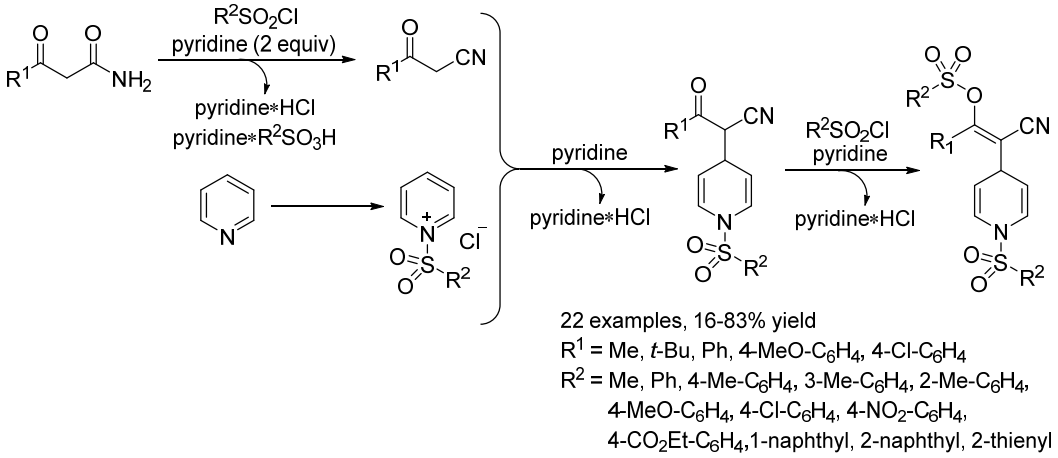
N-sulfonyl pyridinium cations behave similarly to *N*-acylpyridinium ions, i.e., they are usually unstable and produce stable dearomatized compounds. In the last eight years these electrophiles were sometimes employed to prepare substituted dihydropyridines. For example, in 2010, Álvarez-Toledano found that triflic anhydride could serve to activate pyridine *N*-oxides towards the nucleophilic addition of silyl ketene acetals, followed by elimination and rearomatization [47]. However, the product of this sequence, a 4-substituted pyridine, reacted with an excess of triflic anhydride to produce a highly electrophilic *N*-sulfonylpyridinium cation that underwent a dearomatization process with the same nucleophile, rendering a 2,4-disubstituted-1,2-dihydropyridine (Scheme 13). The product could also be engaged in a iodolactonization-decarboxylation-elimination process, to render tetrahydrofuro[3,2-*b*]pyridine-2(3*H*)-ones containing an exo-insaturation.



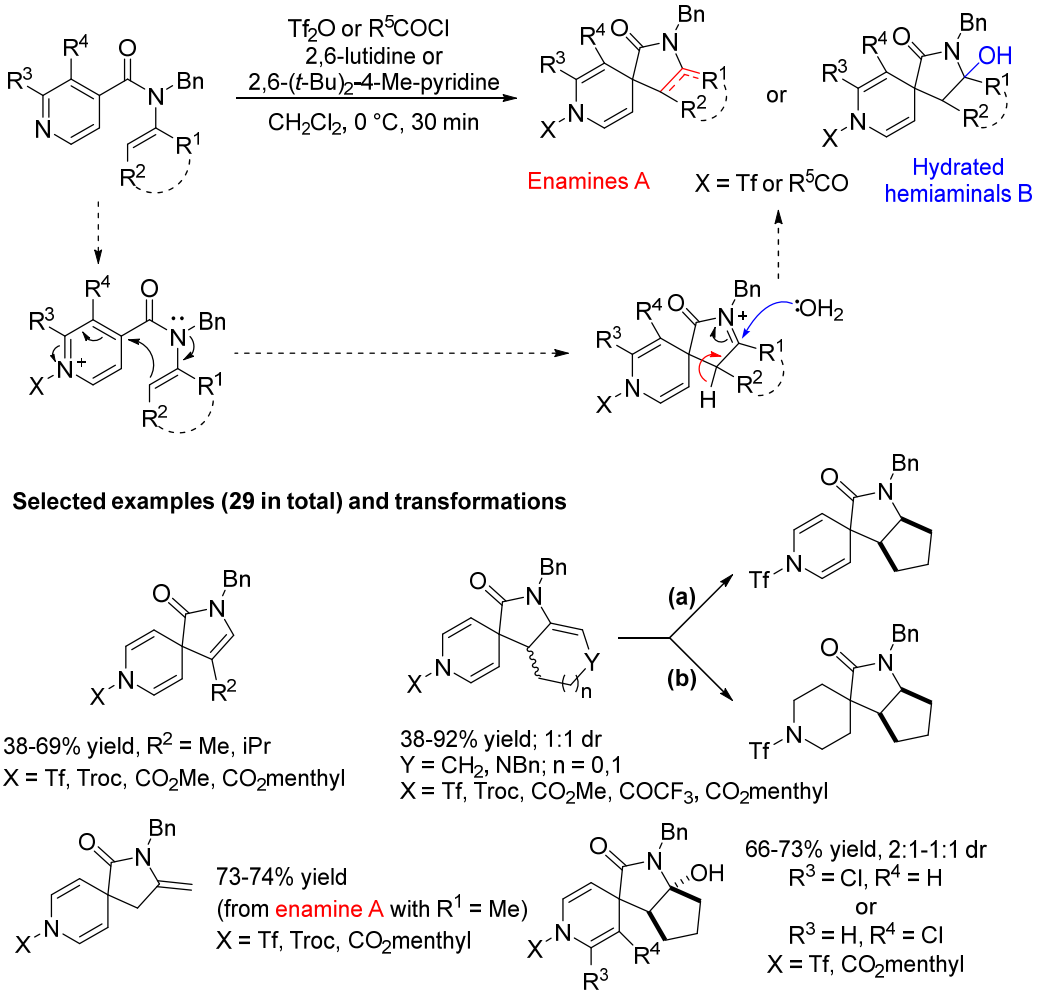
Scheme 13. Cascade *N*-oxide functionalization-pyridine dearomatization promoted by triflic anhydride.

In 2016, sulfonyl chlorides were employed by Zhang as activators, to achieve 4-olefinated-1,4-dihydropyridines from pyridine and 1,3-dicarbonyl compounds [48]. Acetoacetamide and benzoylacetamides were first dehydrated to the corresponding cyano compounds, reacting through their enol form with *N*-sulfonylpyridinium salts,generated in situ, in a highly C-4 regioselective manner (Scheme 14). The enol forms of the products were finally trapped by another equivalent of sulfonyl chloride to render stable *O*-sulfonyl enolates. Simple pyridine was always employed as heterocyclic moiety, acting also as a base in the many acid developing steps (dehydration, dearomatization, enolization), and was therefore introduced in excess. A variety of arenesulfonyl chlorides and differently substituted benzoylacetamides were tolerated, affording the corresponding dearomatized products moderate to good yields.

Triflic anhydride was employed by Clayden in 2013 to promote an intramolecular spirocyclization of *N*-alkenyl isonicotinamides [49]. If the unactivated substrate was completely inert, upon salification of the pyridinic nitrogen into a triflate salt, the enamide moiety became nucleophilic enough to promote dearomatization, generating a 1,4-dihydropyridine displaying a spirobicyclic structure (Scheme 15). Substitution of the pyridinium ring at C-2 and C-6 was explored, achieving the corresponding dearomatized products in good yields but low diastereoselectivities. Hydrated hemiaminals B (Scheme 15, compounds B) were sometimes observed instead of the usually obtained enamines A (Scheme 15, compounds A), probably because the *N*-acyliminium ion persisted until the hydrolysis step. On the other hand, a wide variety of substituents could be productively positioned on the nucleophilic double bond, including cyclic motifs, generating a certain degree of diversity on the obtained compounds. It is worth stressing that, when a carbon possessing eliminable hydrogens was placed at the α-position of the reactive double bond, elimination occurred preferentially exo to the newly formed cycle. Moreover, chloroformates, as well, instead of sulfonyl chlorides, could be engaged to activate the pyridine ring towards dearomatization. Chemoselective reductions and functionalizations of the three enaminic double bonds of the products were also possible.



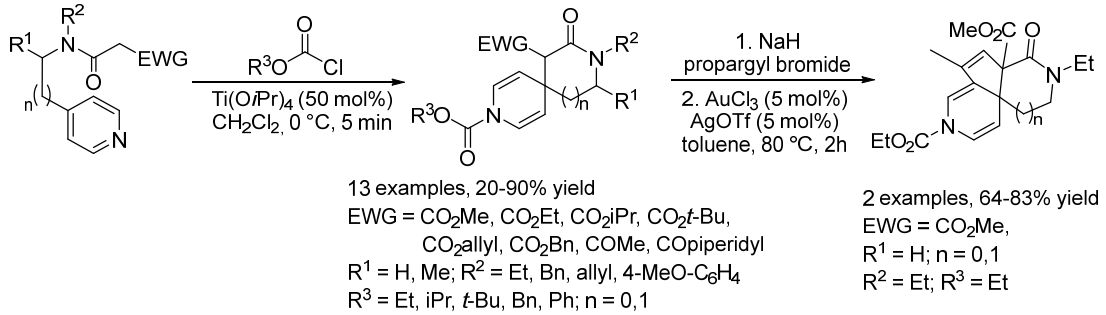
Scheme 14. Dearomatization of *N*-sulfonylpyridinium salts with 1,3-dicarbonyl compounds.



Scheme 15. Clayden's strategy for spirocyclization-dearomatization of isonicotinamides. (**a**) H_2 (50 bar), Pd/C, EtOH, EtOAc, H-cube; (**b**) H_2 (65 bar), Pd/C, EtOH, EtOAc, H-cube.

Such dearomatizing spirocyclizations were first explored by the Clayden group in 2008, when *N*-aryl isonicotinamides, activated by triflic anhydride, underwent dearomatization, with the aryl

group reacting in a Friedel-Crafts fashion to the C-4 position of the activated pyridinium [50,51]. More recently, Parameswarappa and Pigge developed a variation of this methodology, based on 4-aminomethyl- or 4-aminoethylpyridines, in which the nucleophile, tethered to the C-4 position of the pyridine ring, is generated by a Lewis-acid promoted enolization of a 1,3-dicarbonyl moiety [52–54]. Activation of the pyridine ring was always achieved by reaction with chloroformates and the enolization induced with Titanium(IV) isopropoxide. β-Ketoamides, β-carboxyalkylamides and β-amidoamides could be employed as pronucleophiles to construct five- or six-membered spirodihydropyridines (Scheme 16). The dearomatized products could be reduced to spiropiperidine derivatives or elaborated to form more complex heterocyclic frameworks via Au-catalyzed cycloisomerizations.



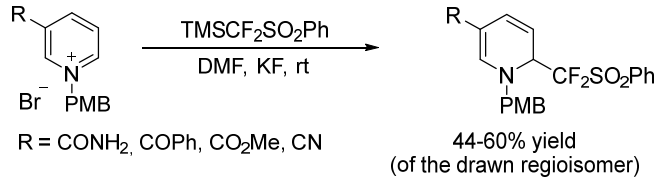
Scheme 16. Spirocyclization-dearomatization of 4-aminomethyl pyridines.

4. *N*-Alkylpyridinium Salts

In contrast to the unstable and transient nature of *N*-acyl species, the *N*-alkyl analogues are bench-stable crystalline solids that can be easily synthesized and isolated. On the other hand, *N*-acylpyridiniums rely on enhanced electrophilicity and hydropyridinic product stability, while *N*-alkyl cations are more inert and deliver less stable dearomatized products. For this reason, additional activation is often required to productively engage *N*-alkylpyridiniums in dearomatization reactions. This is commonly achieved by installing an electron-withdrawing group at the 3-position, resulting also in greater stability of the dearomatized products. The addition of organometallic reagents, stabilized anions and indole derivatives, to such electrophiles gave rise, in many cases, to mixtures of regioisomers, depending on the nature of the nucleophiles or the reaction conditions [10]. The utility of *N*-alkylpyridiniums dearomatization in organic synthesis is well demonstrated by its involvement in the total synthesis of several alkaloids. One of the most well-known and exploited methodologies is undoubtedly the so-called "Wenkert procedure", involving the (reversible) addition of a first nucleophile/reducing agent under basic conditions, followed by the trapping/stabilizing of the resulting dihydropyridine through a second nucleophilic attack, usually occurring under acidic conditions [10,55]. Although the methodology granted accessibility to a great number of structurally diverse natural compounds, these were obtained exclusively in racemic form; the first enantioselective variant was indeed reported very recently by the group of Shu-Li You. The authors reported a "simplified" procedure, involving a C-4 regioselective reduction of *N*-tryptylpyridinium salts (thus not generating any chiral center at the 4-position) followed by chiral phosphoric acid catalyzed Pictet Spengler cyclization. This was also applied to the total synthesis of (+)-deplancheine [56].

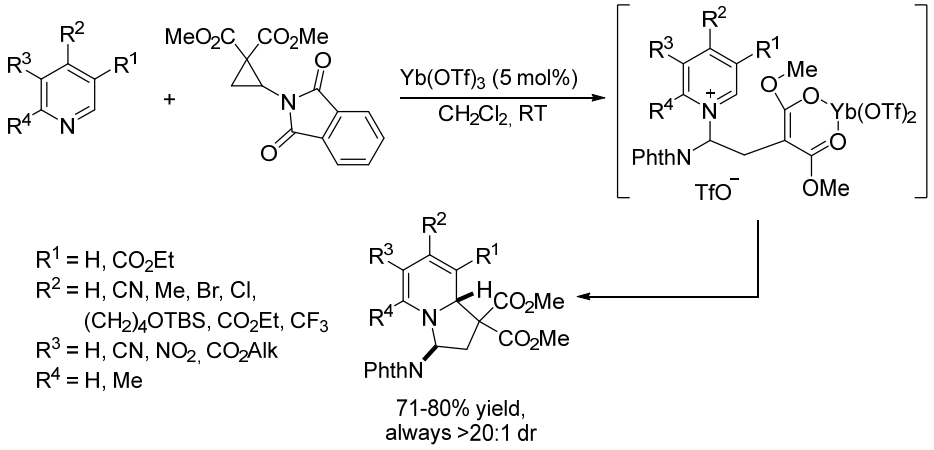
In the last ten years, *N*-alkyklpyridinium salts were almost exclusively employed as electrophiles in asymmetric dearomatizations. However, some recent non-asymmetric reports are present in the literature. For example, in 2012, Hu developed a nucleophilic difluoromethylation-dearomatization of *N*-benzylpyridinium bromides with difluoromethylsilanes [57]. The procedure, optimized for dihydroisoquinolinium ions, was then extended to aromatic electrophiles. However, balanced regioisomeric mixtures where usually obtained for

N-benzyl-3-acylpyridinium ions, rendering quite poor isolated yields of the single regioisomers (Scheme 17).



Scheme 17. Difluoromethylation-dearomatization of *N*-alkylpyridinium salts.

Waser's group reported a Lewis acid catalyzed dearomatization of azinium electrophiles, including activated pyridiniums, exploiting donor–acceptor aminocyclopropanes [58]. Both the electrophilic *N*-alkyl azinium cation and the nucleophile responsible for the dearomatization were generated simultaneously by the addition of the nucleophilic *N*-atom to the electrophilic cyclopropane. An intramolecular dearomatization followed, resulting in a formal [3 + 2] annulation (Scheme 18). The process served for the synthesis of diverse tetrahydroindolizine derivatives with high anti diastereoselectivities. For pyridine derivatives, the presence of at least one strong (or two weak) electron-withdrawing groups was necessary to observe productive dearomatization (otherwise the zwitterionic intermediate was isolated). However, pyridines bearing exceedingly electron-poor moieties (e.g., two strong EWG groups) were not nucleophilic enough even to commence the reaction sequence.

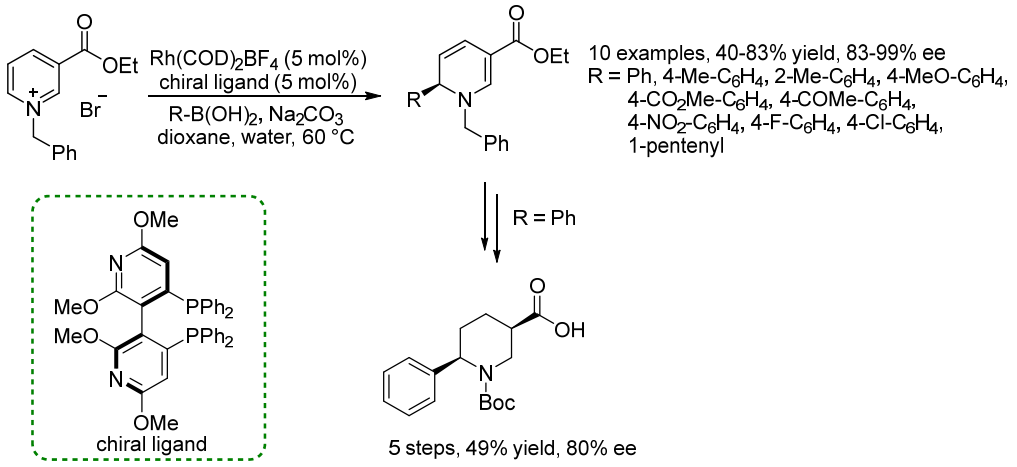


Scheme 18. Dearomatization of pyridines with donor-acceptor cyclopropanes.

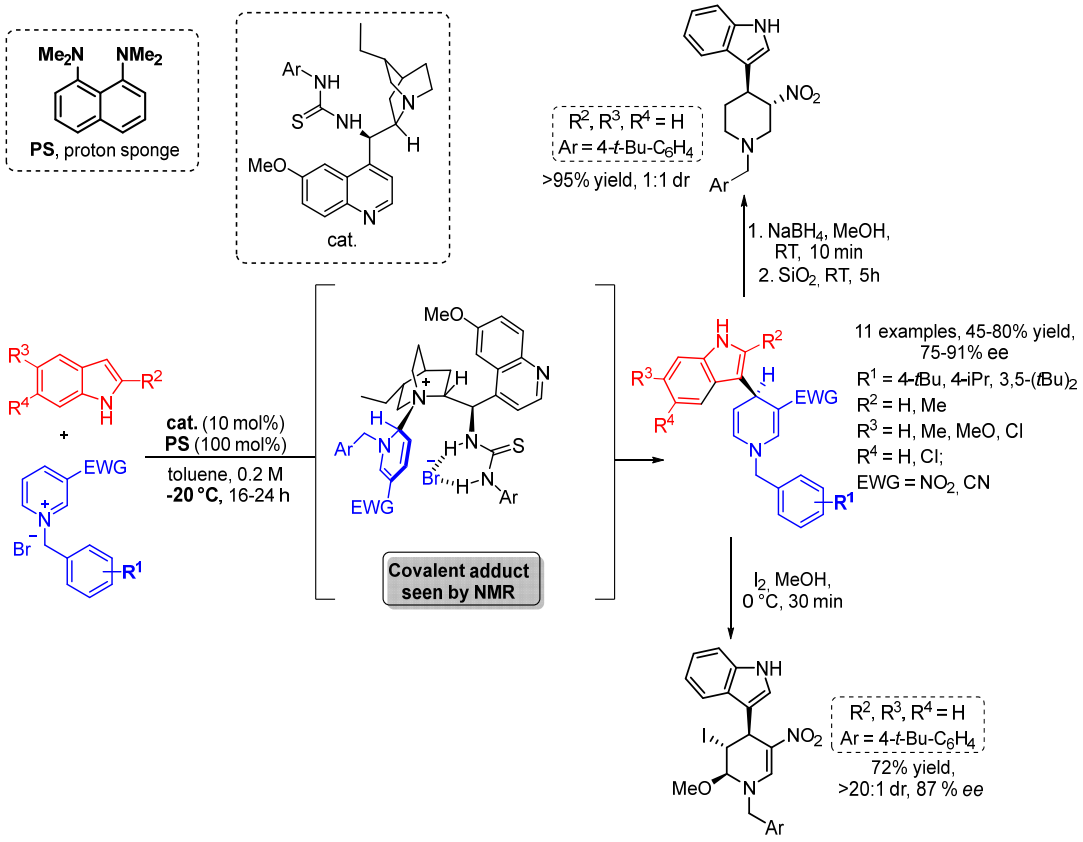
In sharp contrast with the high number of asymmetric dearomatizations of *N*-acylpyridinium salts, no example of asymmetric dearomatization of *N*-alkylpyridinium salts had been reported until 2011, when the highly enantioselective addition of aryl and alkenyl boronic acids to *N*-benzyl nicotinates, catalyzed by a chiral Rh-complex, was disclosed [59]. A variety of 6-substituted dihydropyridines were isolated in (generally) high yields and excellent enantioselectivities. Synthetically useful piperidines could also be obtained from the reaction product following simple reduction-deprotection sequences (Scheme 19).

In 2016, our group disclosed the first example of organocatalytic enantioselective dearomatization of *N*-alkylpyridinium salts [60]. Overcoming the poor reactivity (and dearomatized product instability) by placing an EWG group (such as nitro or cyano) at the 3-position, thus enhancing the electrophilicity of the cation, we were able to productively engage *N*-alkylpyridinium salts in nucleophilic dearomatizations, using indoles as reaction partners (Scheme 20). The reaction displayed complete C-4 regioselectivity, an unusual feature that rendered our procedure complementary to previously disclosed methods. Chiral bifunctional thiourea derivatives were found to be the optimal

catalysts for this reaction. Addressing the addition of the C-3, rather than the N-1, of the indole and finding a base that could scavenge the HBr formed, without promoting a racemic background reaction, were the main challenges during the optimization process. A careful tuning of the stereoelectronic characteristics of the pyridinium salts was a prominent feature to improve the enantioselectivity. We were thus able to synthesize chiral dihydropyridine scaffolds in good yields and good stereoselectivities. Importantly, the obtained heterocyclic compounds possess two reactive double bonds, which served as a synthetic handle for further elaborations. Finally, some experimental investigations led us to propose a reaction pathway showing the catalyst involved in the double (covalent and H-bond) activation of both of the reaction partners.



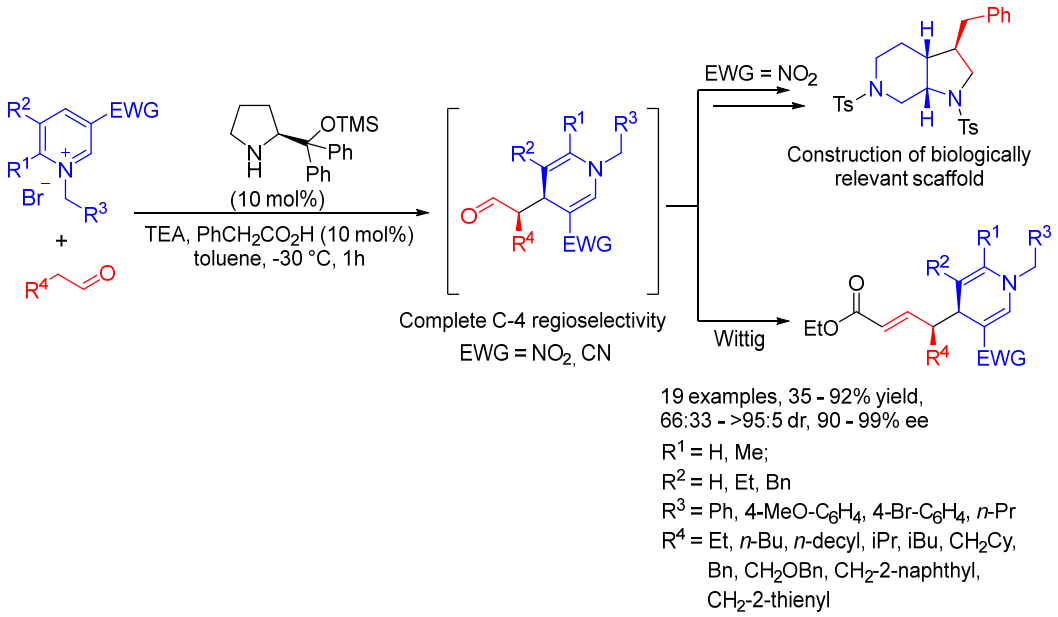
Scheme 19. Rh-catalyzed dearomatizations of *N*-benzyl nicotinates with boronic acids.



Scheme 20. Organocatalytic enantioselective dearomatization of *N*-alkylpyridinium salts with indoles.

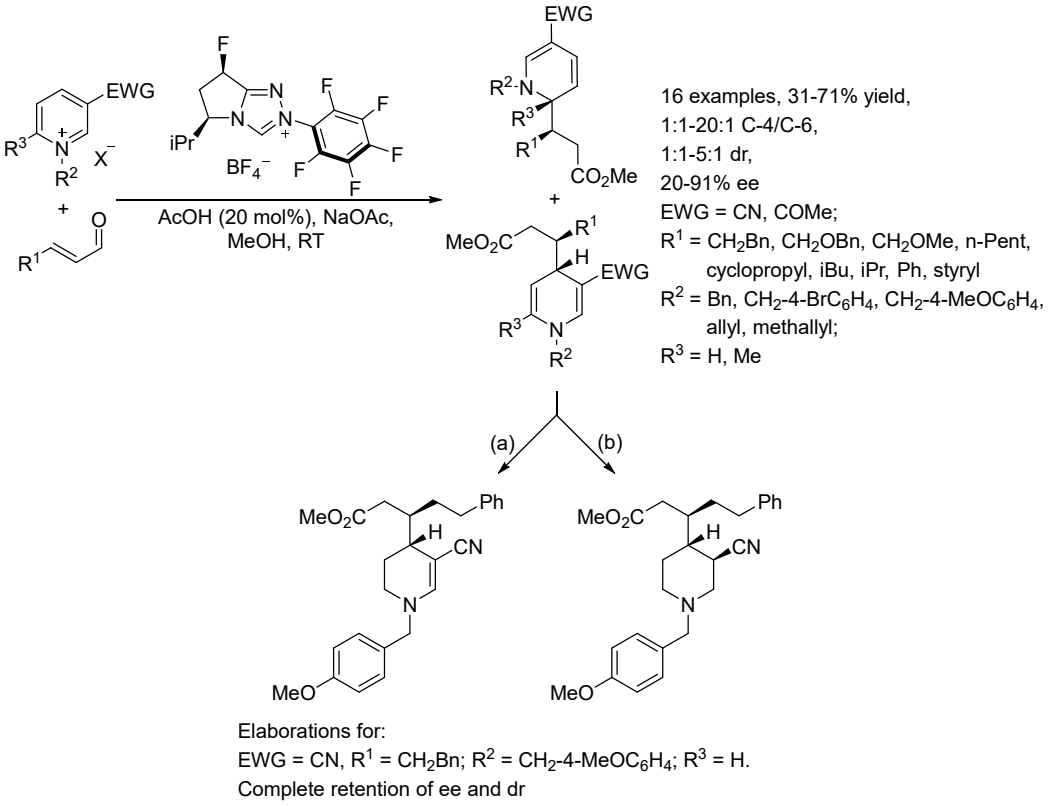
Shortly after, the reactivity of *N*-alkyl-3-nitro- or 3-cyano-pyridinium halides towards asymmetric nucleophilic dearomatization was extended by employing chiral enamines as nucleophiles [61]. These were generated by the reaction of chiral secondary amine organocatalysts [62,63] with enolizable aldehydes. Dearomatizations of acridinium [64,65], quinolinium and isoquinolinium salts with chiral enamine nucleophiles have been developed by different groups [40–44]. However, the dearomatization of benzo-fused azines is easier than that of pyridine itself, as the largest part of the aromaticity (phenyl ring) does not get lost during the process. Careful optimization of the reaction conditions enabled the achievement of a highly diastereo- and enantioselective process, displaying good yields and complete C-4 regioselectivity. The unstable functionalized aldehydes, obtained directly after the dearomatization reaction, were conveniently isolated after Wittig olefination (Scheme 21).

Importantly, the concomitant presence of the nitro and aldehyde groups could be employed for cyclization processes that, after a series of chemoselective reductions, led to the formation of precious octahydropyrrolo-[2,3-*c*]pyridines, core structures of anticancer peptidomimetics.



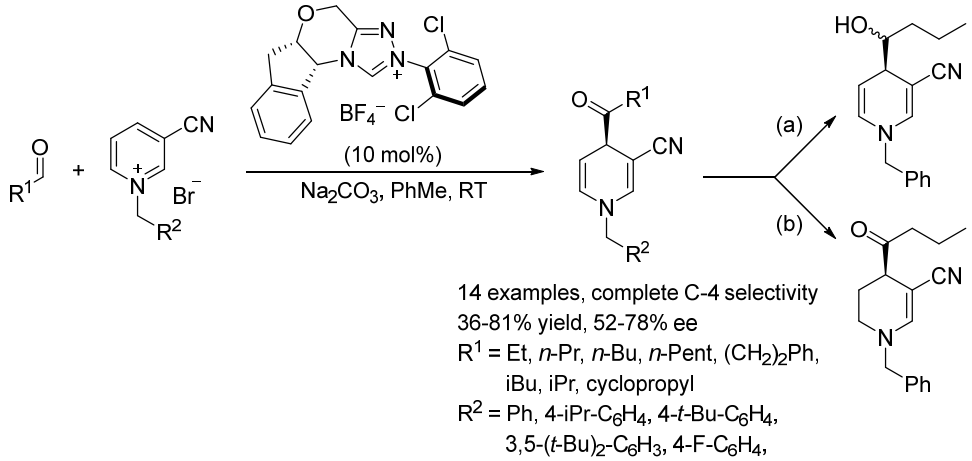
Scheme 21. Organocatalytic enantioselective dearomatization of *N*-alkylpyridinium salts with chiral enamines.

Two examples of *N*-alkyl pyridinium salt dearomatizations, employing chiral *N*-heterocyclic carbenes (NHCs) as catalysts and aldehydes as pro-nucleophiles, were developed. In 2017, Rovis' group reported the enantioselective β-functionalization of enals employing 3-cyanopyridinium cations as electrophiles [66]. The reaction produced 1,4-dihydropyridines as the major (but not sole) regioisomer with modest diastereoselectivities and generally good enantioselectivity values (Scheme 22). Key to the success of this reaction was the addition of catalytic amounts of acetic acid to improve the yield, preventing an off-cycle catalyst-pyridinium adduct trap. The dihydropyridine products could be selectively reduced to either tetrahydropyridines or piperidines, demonstrating the efficiency of the disclosed methodology, affording, directly from pyridines, all the different reduced forms of the heterocycle.



Scheme 22. Dearomatization of *N*-alkylpyridinium salts with enals, catalyzed by chiral *N*-heterocyclic carbenes (NHCs). Conditions: (**a**) $Pd(OH)_2$, H_2, MeOH, rt and (**b**) Et_3SiH, TFA, CH_2Cl_2, rt.

Shortly after, Massi and coworkers developed a similar process employing simple aldehydes as pro-nucleophiles [67]. 4-Acyl-1,4-dihydropyridines were obtained as the sole regioisomers in useful synthetic yields and up to 78% ee (Scheme 23). In this case, 3-cyanopyridinium halides were employed as activated *N*-alkyl pyridinium salts. Some reductions were performed on the obtained products. Interestingly, $NaBH_4$ could be selectively employed for the production of an alcohol functionality from the ketone moiety, while Pd-catalyzed hydrogenation afforded a tetrahydropyridine leaving the carbonyl group unreacted.

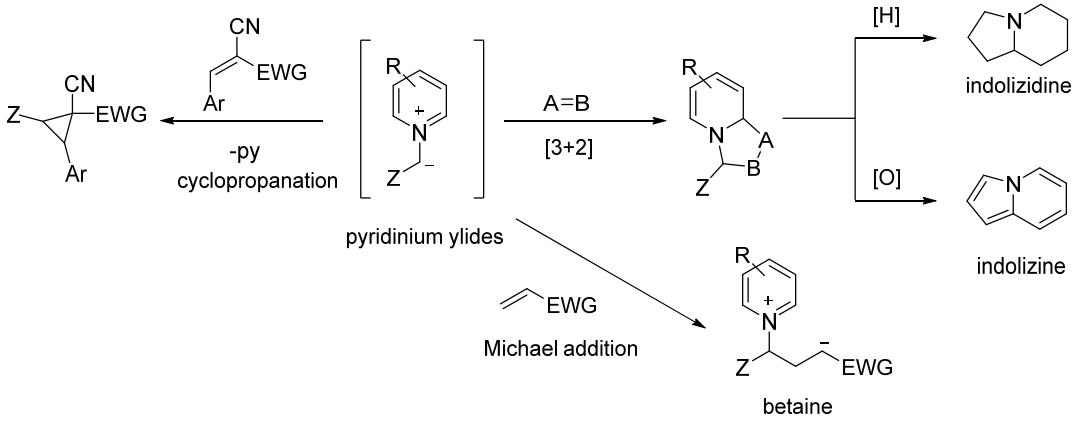


Scheme 23. Dearomatization of *N*-alkylpyridinium salts with aldehydes, catalyzed by chiral NHCs. Conditions: (**a**) $NaBH_4$, CH_2Cl_2/EtOH, 0 °C and (**b**) $Pd(OH)_2$, H_2, MeOH, rt.

5. Pyridinium Ylides

Azomethine ylides, consisting of an iminium ion adjacent to a carbanion, are allyl-anionic-type dipoles that can be applied to dipolar cycloaddition reactions (for reviews see [68–71]). Since their discovery by Kröhnke in 1935 [72], the properties and reactions of pyridinium ylides, a special subclass of azomethine ylides, have been intensively studied (for reviews see [11,73,74]).

These compounds, albeit unstable and not isolable, react with various electrophiles to form a variety of products. They can be successfully engaged in 1,3-dipolar cycloadditions, Michael additions, or cyclopropanations, depending on the nature of the employed electrophile. In the case of 1,3-dipolar cycloadditions, the obtained products, displaying partially reduced indolizine backbones, may then be converted to proper indolizines by oxidation, or into indolizidines by reduction or other types of functionalization (Scheme 24).

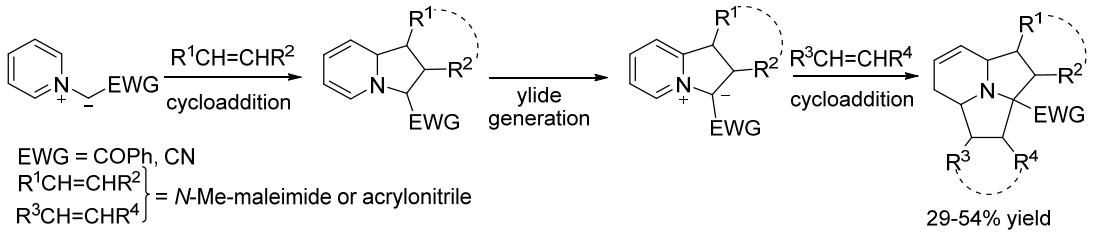


Scheme 24. Reactivity of pyridinium ylides.

Mayr and co-workers [75] have studied the nucleophilicity parameters [76] of pyridinium ylides and have found that they are approximately a million times more reactive than analogously substituted triphenylphosphonium ylides and about a thousand times more reactive than the corresponding dimethylsulfonium ylides.

When 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient olefins or alkynes is followed by oxidative aromatization (spontaneous or chemically induced) a convergent and straightforward access toward functionalized indolizines is arranged. Many excellent examples of this synthetic sequence (cycloaddition/aromatization) have been published (for examples see [75,77–82]) as indolizine is an important skeletal structure present in many natural and synthetic bioactive molecules (for examples see [83–93]) and in material with photochemical properties [94–102]. Pivina and co-authors recently reported quantum chemical calculations on the spatial and electronic structure of pyridinium ylides, as well as the modelling of their1,3-dipolar cycloadddition reactions. The results of computer modelling were in agreement with the experimental results [103]. However, as stated previously, this chapter will mainly report examples of the dearomatization reactions that allowed the formation of stable dihydropyridine derivatives.

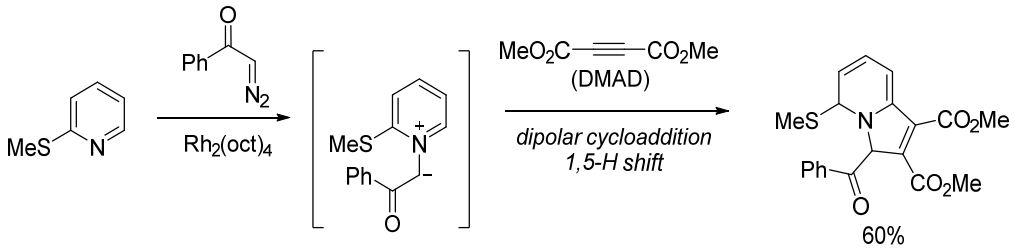
Kanemasa and Tsuge in 1989 [104] reported a tandem 1,3-dipolar cycloaddition of pyridinium methylides with olefinic dipolarophiles to produce cyclo[3.2.2]azine derivatives in a highly regioselective, stereoselective, and face-selective manner, and in good yields. The second cycloaddition involved a new azomethine ylide generated by a thermal tautomerization of dienamines or enamines. Two identical or two different olefins can be used in the two cycloaddition steps (*N*-methylmaleimide or acrylonitrile) enlarging the scope of the reactions (Scheme 25).



Scheme 25. The tandem 1,3-dipolar cycloaddition of pyridinium methylides to olefinic dipolarophiles.

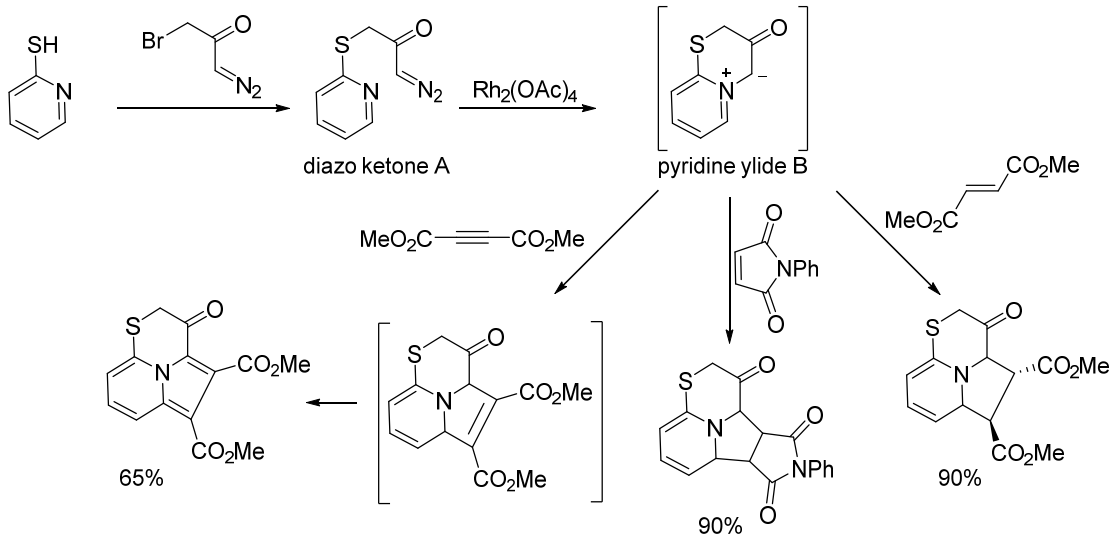
Padwa and co-workers in 1993 [105] studied the behaviour of various pyridinium ylides in [3 + 2] cycloadditions with different alkynes and alkenes as dimethyl acetylenedicarboxylate (DMAD), *N*-phenylmaleimide, and dimethyl fumarate.

Thus, 2-(methylthio)pyridine was reacted with α-diazoacetophenone in the presence of catalytic rhodium(II) octanoate, to generate pyridinium ylides, and dimethyl acetylenedicarboxylate affording the corresponding dihydroindolizine in a 60% yield via a [3 + 2] cycloaddition and a 1,5-H shift (Scheme 26).



Scheme 26. The [3 + 2] cycloaddition reaction of pyridinium ylides to dimethyl acetylenedicarboxylate (DMAD).

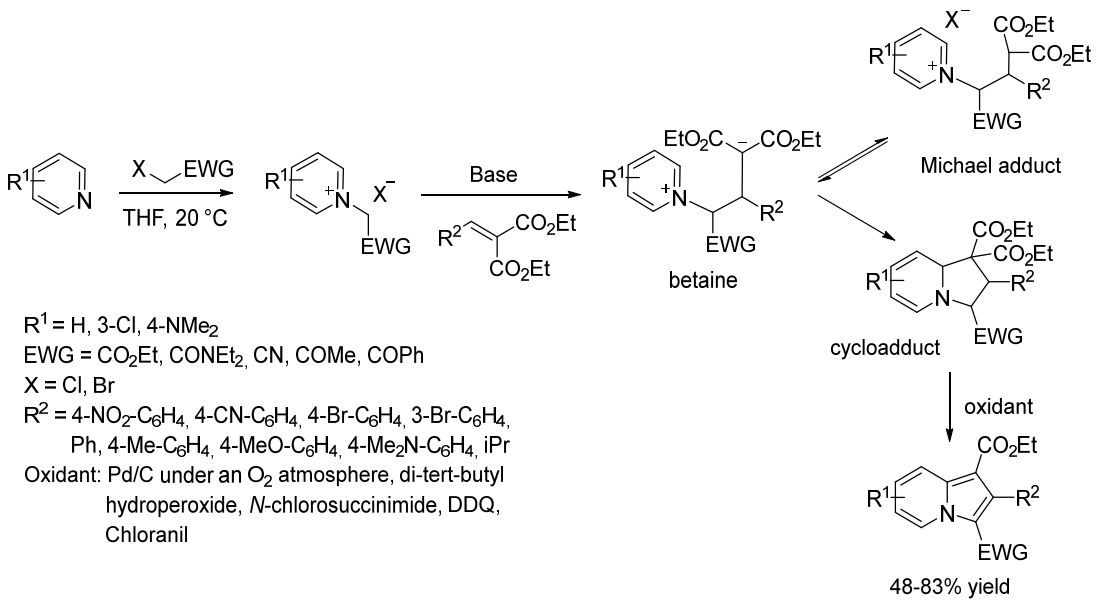
An intramolecular version of this reaction has also been reported, thus the α-diazo ketone A (Scheme 27, compound A) was obtained by the nucleophilic substitution of 2-mercaptopyridine with l-bromo-3-diazo-2-propanone. Afterwards, rhodium(II) acetate catalyzed the intramolecular formation of the pyridine ylide B (Scheme 27, compound B) that was reacted with different olefins, affording the depicted cycloadducts in good and very good yields. All the obtained compounds proved to be difficult to isolate in pure form due to the presence of a reactive ketene *N*,*S*-acetal moiety.



Scheme 27. [3 + 2] Cycloaddition reaction of pyridinium ylides with different olefins.

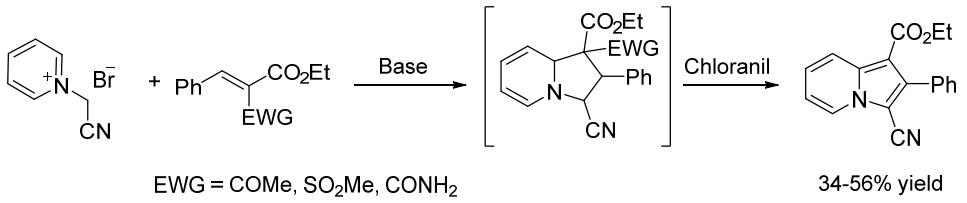
In 2013, Mayr and co-authors [75,78] presented their results concerning the [3 + 2] cycloaddition of pyridinium ylides. As depicted in Scheme 28, treatment of pyridinium salts (in turn obtained from the corresponding pyridine by nucleophilic substitution) with a base in the presence of arylidene-malonates, acting as acceptors, afforded a mixture of Michael adducts and cycloadducts in a ratio depending on the solvent and the base used.

The use of KOtBu (1.1 equiv.) in tetrahydrofurane (THF) or of NaOH (32% aq.) under biphasic conditions allowed the formation of the cycloadduct, only slightly contaminated by the Michael adduct (ratio >98:2). The cycloadducts are labile compounds and for this reason were not isolated but were converted into the corresponding indolizines by oxidation (dehydrogenation and elimination of the acceptor group of the Michael acceptor). After a careful screening of different oxidants (Pd/C under an O_2 atmosphere, di-tert-butyl hydroperoxide, *N*-chlorosuccinimide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and tetrachloro-1,4-benzoquinone (Chloranil)), Chloranil was selected as the most satisfactory. The scope of the reaction was evaluated by varying the substituents on the pyridine and on the arylidene-malonate. The presented indolizine synthesis had a high tolerance of electron-withdrawing and electron-donating groups on the phenyl ring of the electrophile. It was even possible to replace the aryl ring in the arylidene-malonates with an isopropyl group and to obtain the corresponding indolizine in 83% yield, which indicates that this method is not restricted to aromatic Michael acceptors.



Scheme 28. The [3 + 2] cycloaddition of pyridinium ylides to alkylidene malonates.

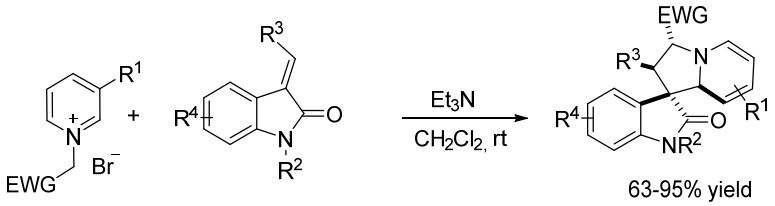
Moreover, it was possible to engage different Michael acceptors in this reaction, as reported in Scheme 29, in which one ester group of the benzylidene-malonates is replaced by an acetyl, methylsulfonyl, or amidocarbonyl group. These acceptors behaved similarly, and yielded the same indolizines upon treatment with Chloranil, as the second EWG group was eliminated faster than the ethoxycarbonyl group.



Scheme 29. The [3 + 2] cycloaddition of pyridinium ylides to various Michael acceptors.

This peculiar behavior is particularly interesting, since arylidene-malononitriles and other cyano substituted Michael acceptors are cyclopropanated by pyridinium ylides [106] through an intramolecular S_N2 reaction that results in the formation of cyclopropanes and the elimination of the pyridine ring. Mayr has also investigated the kinetics of the reaction of pyridinium ylides with diarylcarbenium ions, quinone methides, arylidene malonates and substituted chalcones.

The 1,3-dipolar cycloaddition of pyridinium ylides with electrophilic alkenes was recently applied by Dowden and co-authors [107,108] to the synthesis of tetrahydroindolizidines. In the first paper [107], pyridinium ylides were generated in situ by a reaction of the corresponding pyridinium salt, using triethylamine as the base in dichloromethane (DCM), and then reacted with 3-alkenyloxindoles, obtaining the desired products in good or very good yields (Scheme 30). The resulting cycloadducts showed the same relative stereochemistry of biologically active oxindole alkaloids, especially isorhynchophylline and strychnofoline.

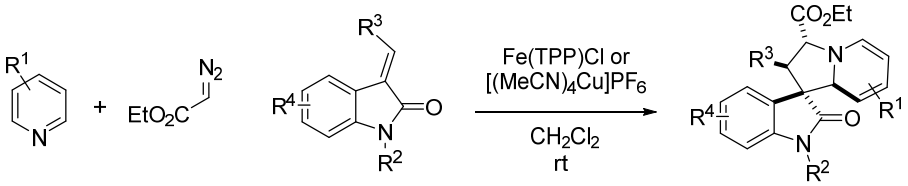


EWG = CO_2Et, COMe
R^1 = Br, CN, F, H, $CONH_2$, COMe
R^2 = H, COMe, propargyl,
R^3 = CO_2Et, H
R^4 = H, 5-Br, 5-NO_2, 5-OMe,

Scheme 30. The 1,3-Dipolar cycloaddition of pyridinium ylides to 3-alkenyloxindoles.

Shortly after [108], the same group reported the generation of pyridinium ylides via metallocarbenes instead of the typically employed methodology, namely the deprotonation of the corresponding salts, avoiding the production of a stoichiometric amount of the conjugate-acid waste and the alkylation step of the pyridine derivatives.

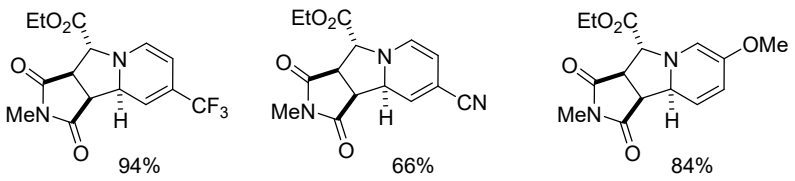
Two different catalysts were utilized by the authors for the preparation of pyridinium ylides, explicitly 1 mol% of Fe(TPP)Cl (TPP = tetraphenylporphyrin) or 5 mol% $(MeCN)_4CuPF_6$. The catalytically generated in situ pyridinium ylides were reacted with electrophilic alkenes producing the corresponding cycloadducts in good and very good yields and with generally excellent diastereoselectivity (Scheme 31).



R^1 = 3-Br, 3-I, (3-Br-4-Me), (3-Br-5-MeO),4-CF_3,
3-CN, 3-CO_2Me
R^2 = Ac, H
R^3 = CO_2Et, COPh
R^4 = H, 5-NO_2, 5-OMe, 6-OMe

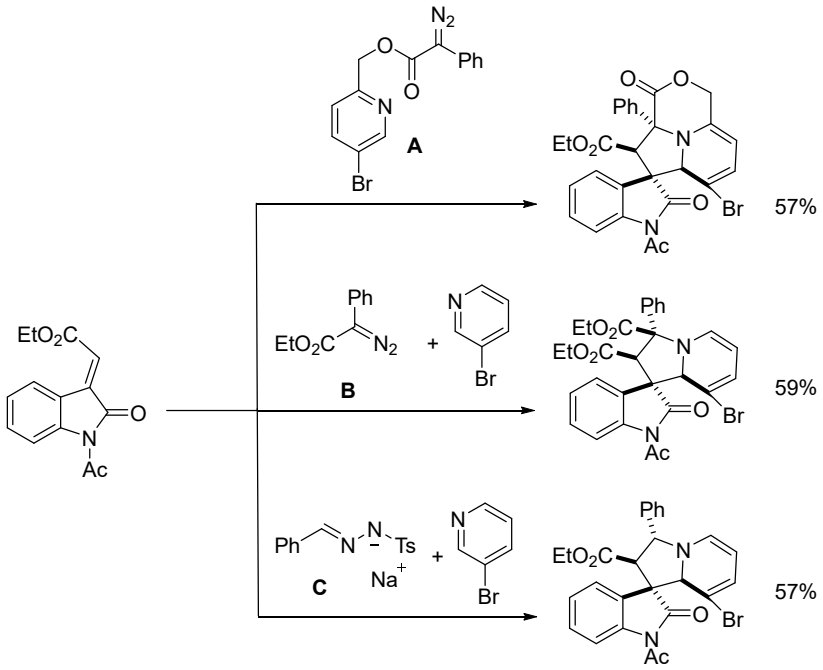
Scheme 31. The 1,3-Dipolar cycloaddition of pyridinium ylides to 3-alkenyloxindoles.

The catalytically generated in situ pyridinium ylides were also reacted with a different electrophilic alkene in an equally productive way. Thus, cycloadducts were obtained in good yields as single diastereoisomers from reactions of *N*-methylmaleimide with 4-trifluoromethylpyridine (94%), 4-cyanopyridine (66%), and 3-bromo-5-methoxypyridine (84%), respectively (Scheme 32).



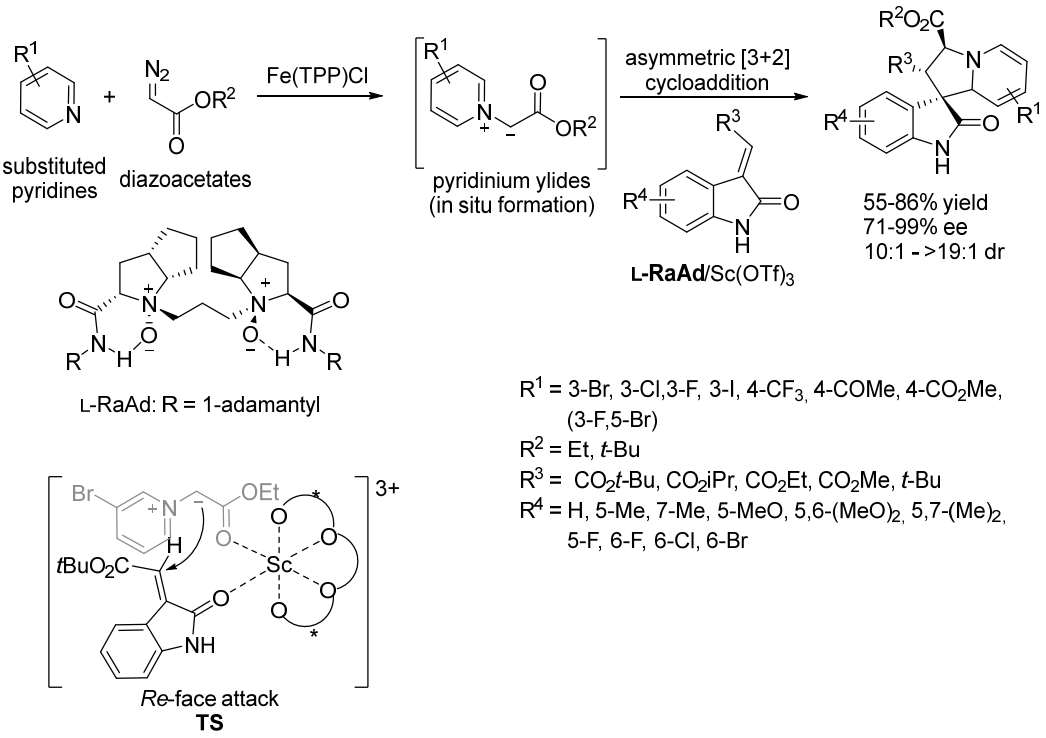
Scheme 32. 1,3-Dipolar cycloaddition of pyridinium ylides to *N*-Me-maleimide.

Moreover, alternative diazo precursors were investigated by the authors, with the aim of broadening the range of alpha-substituted pyridinium ylides available (Scheme 33). A diazo-substituted pyridine (Scheme 33, compound A), , ethyl diazophenylacetate (Scheme 33, compound B), and the in situ generated diazo compound from a tosylhydrazone salt (Scheme 33, compound C) [109] were reacted successfully with model 3-alkenyloxindole.



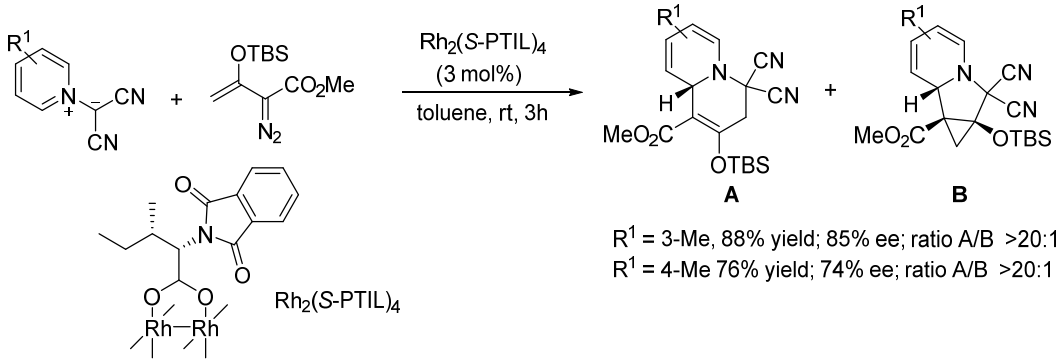
Scheme 33. The 1,3-Dipolar cycloaddition of 3-alkenyloxindoles, a variation of diazo precursors.

Building upon these results, Feng and co-authors [110] recently presented a highly efficient asymmetric cascade reaction of alkenyloxindoles with pyridinium ylides, under relay catalysis, involving an achiral iron(III) catalyst and a chiral *N*,*N*′-dioxide-scandium(III) complex. Pyridinium ylides were prepared in situ from pyridines and diazoacetates, in the presence of 1 mol% of Fe(TPP)Cl (TPP = tetraphenylporphyrin). Then, the catalytic asymmetric reaction was performed with 10 mol% of the chiral L-RaAd/Sc(OTf)$_3$ complex (Scheme 34). The use of MeOAc as the solvent of 4 Å molecular sieves (MS) at 0 °C was judged as the best reaction condition by the authors. The tetrahydroindolizidines were obtained in a good to excellent diastereo- and enantioselective manner. Oxindole substrates with electron-withdrawing substituents provided the corresponding products with lower yields and ee, with respect to the ones with electron-donating substituents on the phenyl ring of the oxindole. The ee values decreased when the steric bulk of R^3 decreased, implying that a bulky R^3 is essential for stereocontrol. Halogen moieties including fluoro, chloro, and iodo substituents as well as trifluoromethyl, acetyl and ester substituents on the pyridine unit were well tolerated, affording good yields and high ee values for the desired products. The authors have obtained X-ray crystal structures of the L-RaAd/Sc(OTf)$_3$ complex that showed how the two amine oxide oxygen atoms and two amide oxygen atoms in the *N*,*N*′-dioxide ligand bind to the Sc^{III} cation to form a six-coordinate octahedral geometry. The remaining two coordination sites were occupied by the two trifluoromethyl sulfonate anions. A plausible mechanism for the bimetallic relay catalysis is thus proposed: at first, achiral Fe^{III} induces the diazo compound to form a metal carbene, this iron carbene species is then attacked by the pyridine to generate the intermediate pyridinium ylide. Both the oxindole and the pyridinium ylide coordinate to the chiral Sc^{III} complex, with dissociation of two trifluoromethyl sulfonate anions. The addition of the carbanion of the ylide takes place only from the β-Re face of the oxindole.



Scheme 34. Asymmetric cascade reaction of alkenyloxindoles with pyridinium ylides.

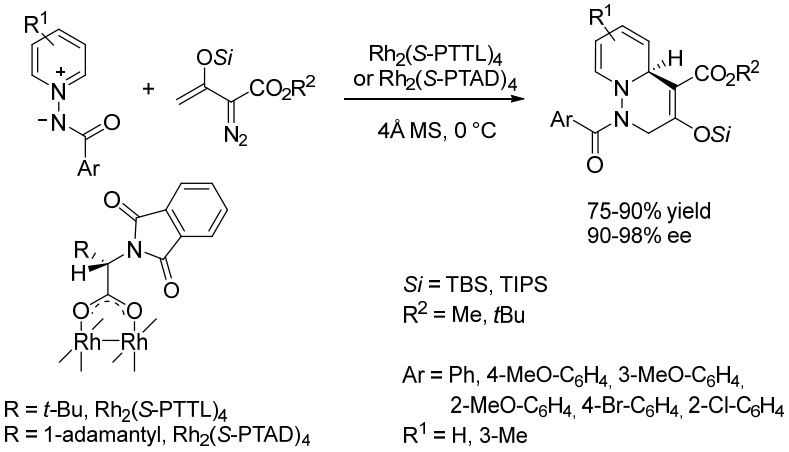
Dearomatization of pyridines, via pyridinium ylide reactivity, was also briefly explored by M. P. Doyle [79]. In this paper (mainly dealing with isoquinolinium methylides), pyridinium methylides were treated with enoldiazoacetate in the presence of a chiral dirhodium catalyst [Rh_2(*S*-PTIL)$_4$] offering easy access to high yields and to highly enantioenriched, substituted quinolizidines via a formal [3 + 3] cycloaddition (Scheme 35). The reaction outcome was solvent, catalyst, and temperature dependent with a competing process that formed an apparent product from a [3 + 2] cycloaddition that could be suppressed by increasing the catalyst loading.



Scheme 35. The [3 + 3] cycloaddition of catalytically generated enolcarbene reactive dipoles to pyridinium methylides.

Shortly after, M P. Doyle [111,112] thoroughly investigated the dearomatization of pyridinium substrates via *N*-acyliminopyridinium ylides (Scheme 36). These stable dipoles reacted with enoldiazoacetates catalyzed by dirhodium (II) catalysts giving [3 + 3] cycloaddition products in high isolated yields and with exceptional enantiocontrol when catalyzed by Rh_2(*S*-PTTL)$_4$ or Rh_2(*S*-PTAD)$_4$ in fluorobenzene or toluene as solvent.

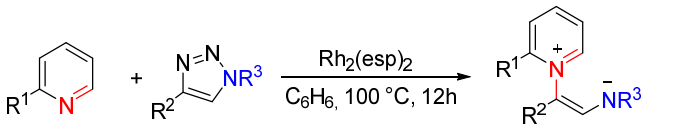
In this transformation, steric effects have an important influence on the control of selectivity, since dirhodium catalysts with bulky ligands, such as Rh_2(*S*-PTTL)$_4$ or [Rh_2(*S*-PTAD)$_4$, dramatically improve the selectivity control.



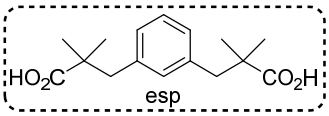
Scheme 36. The [3 + 3] cycloaddition of catalytically generated enolcarbene reactive dipoles to *N*-iminopyridinium ylides.

6. Pyridinium Zwitterions

In 2014, Yoo and co-authors reported on the preparation of unprecedented pyridinium zwitterions that could be unexpectedly isolated and that exhibited patterns of charge distribution different from those exhibited by typical pyridinium ylides (Scheme 37). These air-stable and very unusual azomethine ylides could be efficiently prepared via a rhodium-catalyzed reaction between pyridines and 1-sulfonyl-1,2,3-triazoles [113,114].



R^1 = 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-*t*Bu-C_6H_4, 4-F_3C-C_6H_4, 4-Cl-C_6H_4, 4-Acetyl-C_6H_4, 2-naphthyl, 3-Me-C_6H_4
R^2 = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-*t*Bu-C_6H_4, 4-F_3C-C_6H_4, 4-Br-C_6H_4, 3-Me-C_6H_4, 3-MeO-C_6H_4, 3-F-C_6H_4
R^3 =SO_2-C_6H_4-Me, SO_2-C_6H_4-OMe, SO_2-C_6H_4-CF_3, SO_2-C_6H_5



Scheme 37. Efficient route for synthesizing an azomethine ylide.

Yoo reported that a wide range of reactants smoothly underwent the process necessary to produce the desired azomethine ylides in high yields, independently from the substituent present (either electronic or steric variation). These ylides were isolable by flash column chromatography and could be crystallized and fully characterized, including by X-ray crystallography. An important feature of these ylides (isolable 1,5-dipoles—pyridinium 1,5-zwitterionic structure) was the geometry of the dipole unit and planarity of the azomethine in contrast to the typical azomethine ylides. In addition, the pyridine backbone formed a torsion angle of 74.2° with the enamide moiety;

hence, the two components were arranged in an almost orthogonal manner (Figure 1). The stability of the pyridinium zwitterions was ascribed to the aromaticity of the pyridinium core.

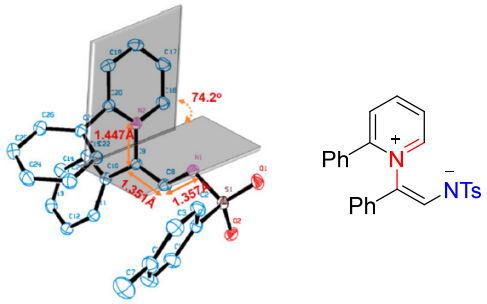
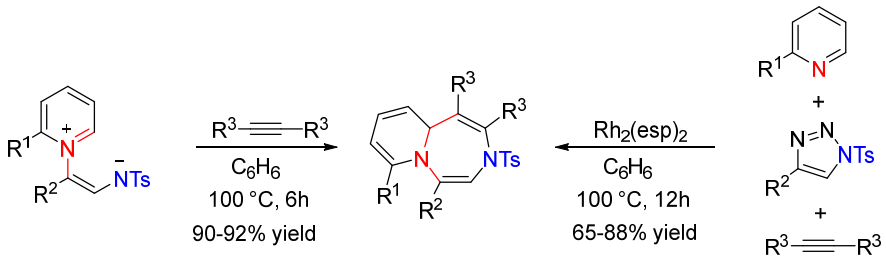


Figure 1. Molecular structure azomethine compound.

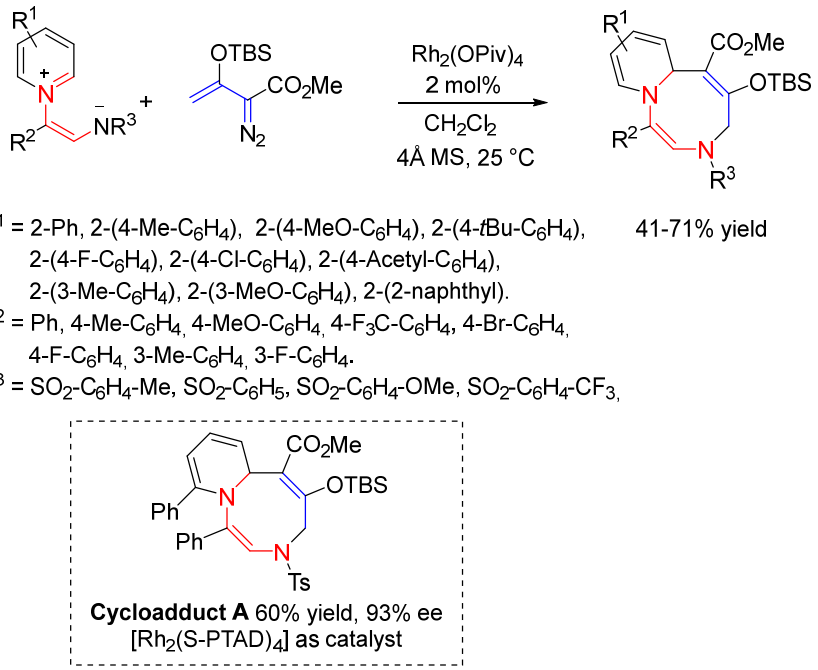
Since azomethine ylides are known to undergo dipolar cycloaddition with π bonds, Yoo [113,114] investigated the [5 + 2] cycloaddition of the isolated ylides to dimethyl acetylenedicarboxylate (DMAD) obtaining the desired, biologically active 1,4-diazepines with excellent yields. Moreover, a one pot version of the presented [5 + 2] cycloaddition reaction of pyridines presented, 1-sulfonyl-1,2,3-triazole and activated alkynes via in situ generated azomethine ylides, were successfully achieved (Scheme 38).



R^1 = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4,4-Acetyl-C_6H_4, 3-Me-C_6H_4, 3-MeO-C_6H_4, 2-naphthyl
R^2 = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-F_3C-C_6H_4, 3-MeO-C_6H_4, 3-F-C_6H_4
R^3 =CO_2Me, CO_2Et

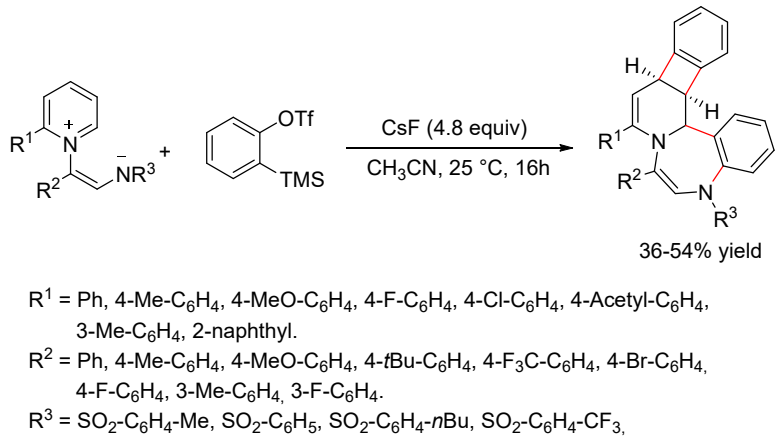
Scheme 38. The [5 + 2] cycloaddition of azomethines and multicomponent [5 + 2] cycloaddition reaction.

Later, Yoo explored the reactivity of pyridinium zwitterion 1,5-dipole equivalents with rhodium (II) enolcarbenes, generated following the Doyle methodology from enol diazoacetates and developing a new [5 + 3] cycloaddition to afford eight-membered heterocyclic compounds [115]. The optimized cycloaddition occurred efficiently under mild conditions, with a wide range of pyridinium zwitterions and a high functional group tolerance (Scheme 39). This cycloaddition enabled the facile construction of eight-membered heterocyclic compounds that were otherwise difficult to access.To demonstrate the synthetic utility of the proposed methodology, a stereoselective version of the [5 + 3] cycloaddition of tert-butyldimethylsilyl (TBS)-protected enol diazoacetate was optimized using [Rh_2(*S*-PTAD)$_4$] as the catalyst in toluene at 0 °C. The corresponding cycloadduct A (Scheme 39 cycloadduct A, R^1 = 2-Ph, R^2 = Ph, R^3 = Ts) was obtained in good yield and with 93% ee.



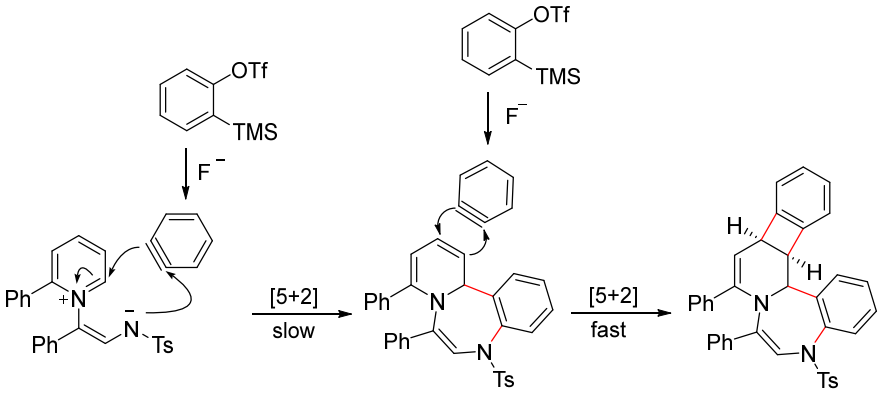
Scheme 39. The Rh^{II}-catalyzed [5 + 3] cycloaddition of pyridinium zwitterions.

As part of their interest in the cycloadditions of pyridinium zwitterions for the preparation of heterocyclic compounds, Yoo and co-authors [116] developed an efficient and metal-catalyst-free synthetic protocol that provided fused 1,4-benzodiazepine derivatives via cascade [5 + 2]/[2 + 2] cycloadditions of 1,5-dipoles with arynes (Scheme 40). All the processes resulted in the one-pot formation of four new bonds, namely one C–N bond and three C–C bonds.



Scheme 40. Cascade [5 + 2]/[2 + 2] cycloadditions—synthesis of multifused 1,4-benzodiazepines.

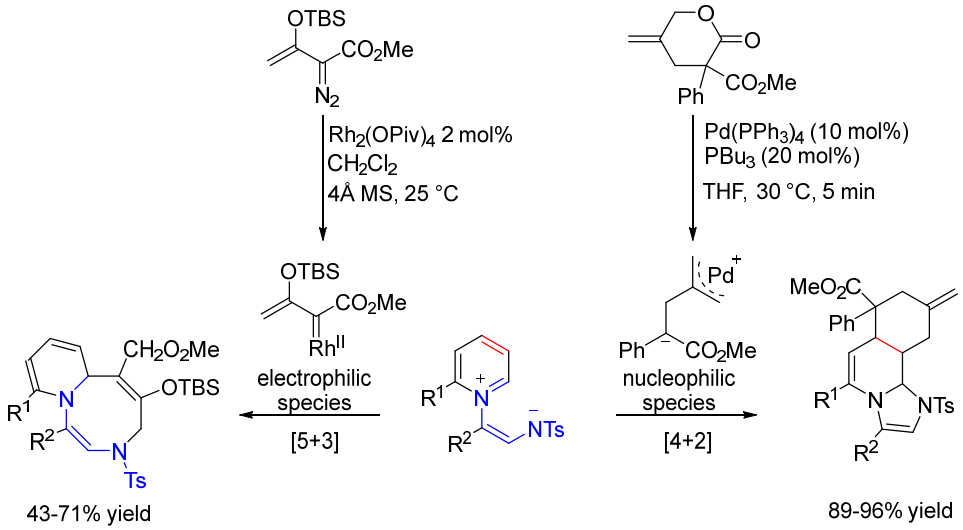
A mechanistic rationale for this cascade reaction was proposed by the authors. The pyridinium zwitterion reacted with the benzyne (for related benzyne-promoted, dearomatization of pyridine derivatives see [117,118]) generated in situ from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and led to the formation of 1,4-benzodiazepine; this first [5 + 2] cycloaddition seemed to be the rate-determining step because it involved the dearomatization of the pyridinium zwitterion. Then, the intermediate immediately cyclized with another molecule of benzyne, leading to the formation of polycyclic 1,4-benzodiazepines (Scheme 41).



Scheme 41. Proposed mechanism via domino cycloadditions.

Very recently, Yoo and co-authors [119] realized that the intrinsic and permanent charge polarization in the pyridinium zwitterion could lead to dipole-controlled divergent cycloadditions in a rational and predictable manner. They reported the first example of divergent cycloadditions of pyridinium zwitterions controlled by the electronic properties of the metal-bound reaction partners (Scheme 42).

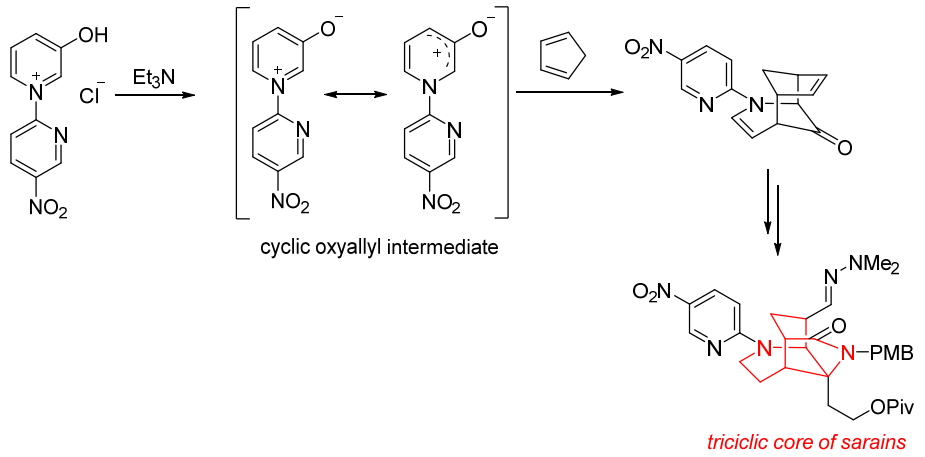
The pyridinium zwitterion had multiple reaction sites and the chemoselectivity was determined by the electronic demand of the catalyst–substrate complex. The reaction with electrophilic rhodium (II) enol carbenoids resulted in a [5 + 3] cycloaddition to afford eight-membered *N*-heterocyclic compounds, whereas the reaction with nucleophilic Pd-reagents afforded fused *N*-heterocyclic compounds via regioselective [4 + 2] cycloadditions. The rhodium species were prepared from enol diazoacetates, as previously described, whereas the palladium-bound zwitterionic species was readily generated from γ-methylidene-δ-valerolactone. The positive charge of the zwitterion was delocalized over the pyridinium skeleton and, in the presence of a Pd-bound nucleophile, the initial attack was directed at the C-4 position. Subsequent ring closure gave a [4 + 2] cycloaddition product.



Scheme 42. Dipole-controlled divergent cycloadditions.

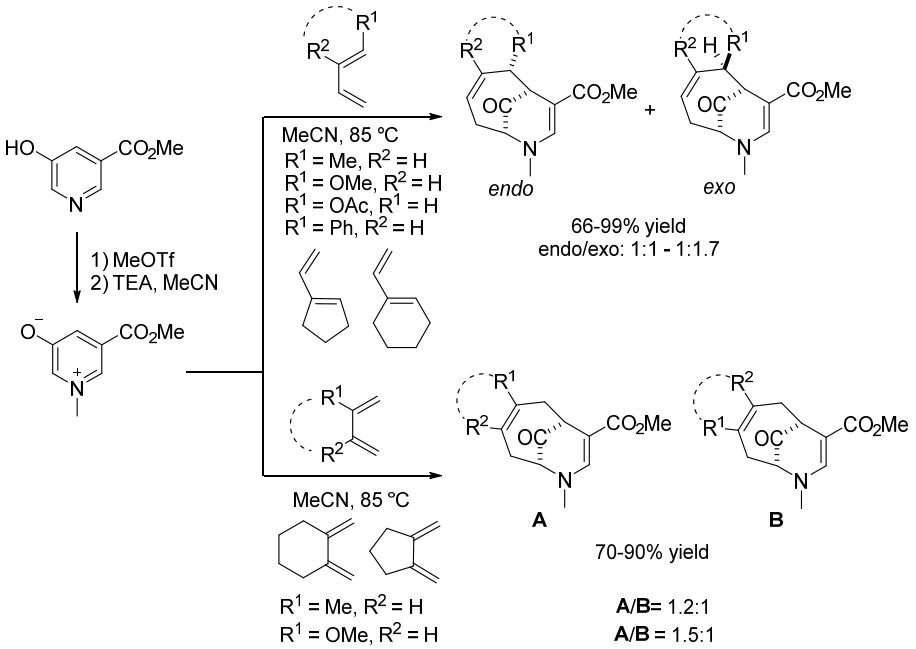
The frontier molecular orbitals of the pyridinium substrate and the activated catalyst complex were calculated and revealed that the pyridinium zwitterion could act both as a nucleophile and as an electrophile, depending on the reaction partner, in a much more defined manner than that of conventional substrates, leading to the observed regiodivergent chemical reactivity.

Another class of pyridinium zwitterions, namely 3-oxidopyridinium ions (3-oxidopyridinium betaines) were used extensively in the cycloaddition reactions of olefinic compounds for the construction of various heterocyclic derivatives in the 1980s and 1990s. [120]. Following the 3-oxidopyridinium betaine cycloaddition approach of Katritzky and Dennis, Cha and co-authors [121,122] developed a new synthetic procedure to suitably functionalize the tricyclic core of sarains. The cornerstone of the proposed synthetic plan was a quick assembly of the central azabicycle of sarains by the [4 + 3] cycloaddition of the six-membered cyclic oxyallyl intermediate with cyclopentadiene, which resulted in the diastereoselective formation of the corresponding endo-like cycloadduct (Scheme 43).



Scheme 43. The [4 + 3] cycloaddition of 3-oxidopyridinium ion to cyclopentadiene.

More recently, Krenske and Harmata [123] developed a [4 + 3] cycloaddition reaction of *N*-alkyl oxidopyridinium ions (substituted with an electron-withdrawing group at the 5-position) with a diene, in the presence of trimethylamine, that successfully produced the corresponding cycloadducts with good to excellent yields. The reactions were often completely regioselective, though generally not endo/exo selective (Scheme 44). The process provided rapid access to bicyclic nitrogenous structures (7-azabicyclo[4.3.1]decane ring system) resembling natural alkaloids. The DFT calculations indicated that the cycloaddition involved the concerted addition of the diene onto the oxidopyridinium ion.



Scheme 44. The [4 + 3] cycloaddition reactions of oxidopyridinium ion to dienes.

7. Conclusions

In this article, by complementing and updating previous reviews published in the early 2010s and covering differing aspects of pyridine chemistry, we collected and described the nucleophilic dearomatization reactions of pyridines to hydropyridines, reported in the literature produced between 2010 and mid-2018. To better focus our work, we excluded reductions and addition-rearomatization reactions from our selection.

In general, due to its relative inertness, activation of the pyridine by *N*-functionalization is required to effect a nucleophilic addition. Coordination of the pyridine nitrogen to metals and metalloids, *N*-acylation, *N*-sulfonylation or *N*-alkylation affords (transient) electron-deficient pyridinium salts. These are more prone to suffer a nucleophilic addition, compared to the parent pyridine. Ultimately, suchapproach resulted in useful synthetic platforms for the direct installation of a large variety of nucleophiles (organometallics, enolates, electron-rich heteroaromatics, umpoled aldehydes, etc.) onto the pyridine. The regioselectivity (C-2/C-6 vs. C-4) of the additions was variable and depended on the nucleophile, the promoter, and the activation strategy, as well as the substitution pattern on the pyridine ring. Sometimes, in relation to previous studies dealing with less demanding dearomatization of benzo-fused pyridines (quinolines and isoquinolines), catalytic enantioselective protocols were developed. Accordingly, several efficient entriesto highly valuable and structurally diverse enantioenriched hydropyridine compounds are currently available.

Conversely, functionalization of pyridine nitrogen with groups, capable of stabilizing a negative charge, results in pyridinium ylides. In these dipolar species, which could also be accessed via insertion of the pyridine nitrogen into a metal-carbene bond, the enhanced electrophilicity of the pyridine nucleus was flanked by the nucleophilicity of the negatively charged function. Accordingly, cycloadditions of a variety of electron-deficient dipolarophiles have been developed, rendering polycyclic frameworks and embedding partially unsaturated pyridine moiety in their structures. To date, only a few examples of catalytic asymmetric processes have been reported dealing with such reactivity, although more work in this area can be expected in the near future.

Overall, the works summarized here demonstrate that the synthesis of hydropyridines via the addition of nucleophiles to pyridines has been heavily studied in recent years. On the other hand, the recent literature is witnessing a constant flow of publications describing direct oxidative functionalizations of the pyridine nucleus (that is, affording substituted pyridine derivatives), occurring via radical chemistry (i.e., Minisci-type and photocatalytic reactions), or via

N-activation—substitution. Altogether, these works demonstrate a current and significant interest in pyridine chemistry, which we expect to last for the next several years.

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Conflicts of Interest: The authors declare no conflicts of interest.

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