CHEMICAL REVIEWS

Review

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Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to *N*-Activated Pyridines

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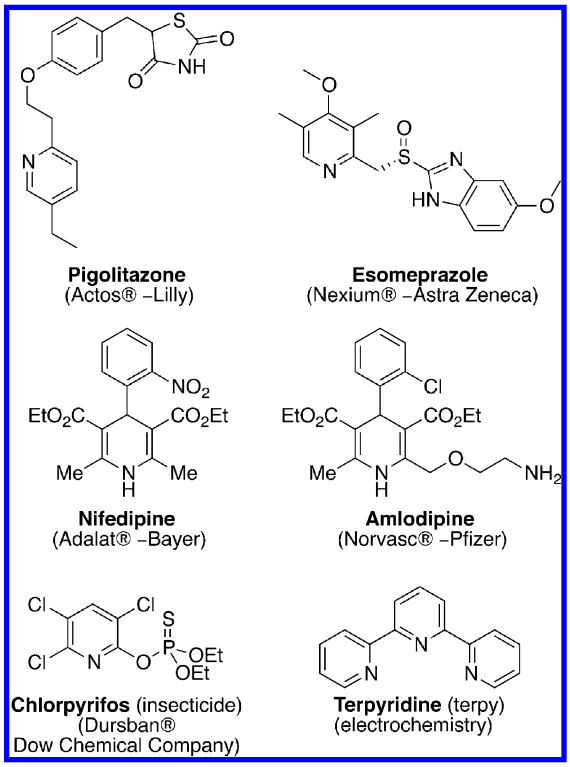

Figure 1. Examples of commercialized pyridine or dihydropyridine derivatives.

1. INTRODUCTION

Pyridines are among the most prevalent heterocyclic structural units in pharmaceutical and agrochemical targets, as well as in materials science (Figure 1).[1] Pyridines also provide convenient synthetic precursors to chiral dihydro- and tetrahydropyridines, as well as piperidines, which continue to be of interest as intermediates in alkaloid synthesis,[2,3] in NADH models,[4,5] and as important biologically active structures.[6−10] Dihydropyridines in turn may also be converted to substituted pyridines through oxidation. Similarly, pyridines, dihydropyridines, and tetrahydropyridines are important building blocks in the preparation of piperidine scaffolds via reduction or nucleophilic additions (Figure 2).[11−13]

The chemistry to directly functionalize pyridine remains a significant challenge due to poor chemoselectivity and the

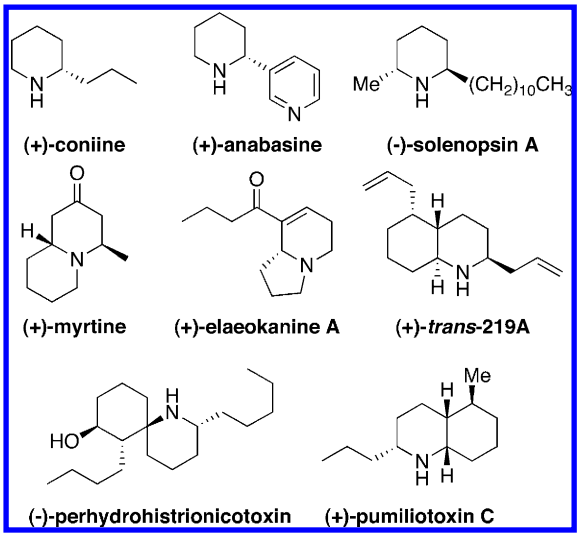

Figure 2. Piperidine-containing natural products.

lower energy of the π-system relative to benzene.[14] As a result, electrophilic aromatic substitution is not effective without the inclusion of substituents to activate the pyridine ring.[15,16] Additionally, pyridine derivatives that do not contain a good leaving group are generally unreactive toward aromatic nucleophilic substitution.[17] Organometallic nucleophiles can attack the heterocyclic ring directly, but this often lead to low yields in the absence of an external oxidant.[18] Furthermore, organometallic species derived from pyridine, particularly at the 2-position, have traditionally been unstable and difficult to access.[19,20] These factors have led to the use of pyridines functionalized at nitrogen to generate cationic pyridinium salts or neutral, but similarly activated, pyridinium ylides. The resulting pyridinium species can be both more electrophilic and/or more nucleophilic than the unactivated parent heterocycle. Furthermore, the acidity of the α-C−H bond is increased in the pyridinium reagents, enabling more facile deprotonation and associated chemistries, compared to reacting pyridine derivatives with strong bases.[21]

This review examines the functionalization of *N*-activated pyridinium species by the addition of nucleophiles and electrophiles, as well as by transition metal-mediated functionalization (Figure 3). The issues of regioselectivity, stereoselectivity, and the mechanisms of the additions will be addressed.

Sections 2−4 are concerned with nucleophilic additions to pyridinium species forming dihydropyridines, which may be progressed to substituted pyridines or piperidines. These sections are divided according to the nature of pyridine activation: *N*-C (acyl, imidate, alkyl) and *N*-heteroatom. The following two sections (5 and 6) are concerned with the synthesis of substituted pyridines without the disruption of the aromaticity, via pyridinyl metal species. Section 5 examines electrophilic addition to *N*-heteroatom pyridinium species following deprotonation adjacent to the nitrogen to afford substituted pyridines. The last section is concerned with transition metal-mediated C−H functionalization of pyridinium species.

This review covers a substantial time period of the literature, from the 1940s to the current day, and state-of-the-art methodologies, and as such reflects some of the changing approaches and challenges in organic chemistry. Publications

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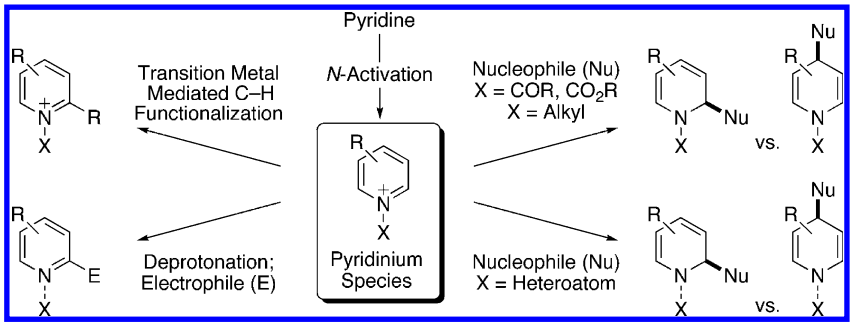


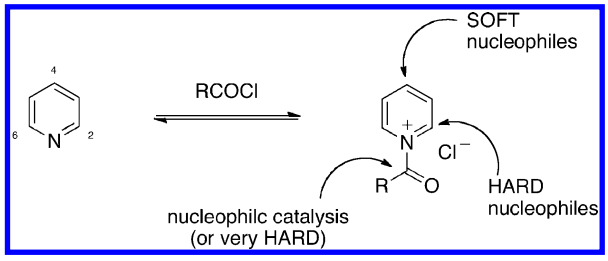
Figure 3. Functionalization of *N*-activated pyridinium species.

up to the end of 2010 have been included. This review will concentrate on the bimolecular (intermolecular) addition of nucleophilic and electrophilic reagents directly to the ring of *N*-activated pyridinium species, which has not previously been reviewed as a whole. The broad chemistry of dihydropyridines has been previously reviewed[22−24] and is outside the scope of this review. To provide a complete picture of the additions to activated pyridines, in the context of regio- and stereoselective synthesis of dihydropyridines, we will include here some material covered in previous reviews and in other major works on the chemistry of nitrogen heterocycles.[25−29] The chemistry of benzopyridine derivatives (such as quinolines), intramolecular rearrangement, cycloaddition reactions, reductions (including addition of hydride), electrophilic aromatic substitution, and radical reactions, though important, will not be considered in this review.

2. NUCLEOPHILIC ADDITION OF ORGANOMETALLIC REAGENTS TO *N*-ACYL PYRIDINIUM SALTS

The addition of nucleophiles to *N*-acyl pyridinium salts has been investigated systematically since the 1970s and provides an effective method for the synthesis of dihydropyridines, 2,3-dihydro-4-pyridones, and substituted pyridines by subsequent oxidation. Frequently, the reactions are performed via the addition of the activating reagent to a mixture of the pyridine and organometallic reagent. This forms the pyridinium salt in situ, providing perhaps the most straightforward method for the synthesis of dihydropyridines. As well as not requiring a preactivation step, *N*-acyl pyridinium salts are also more electrophilic than *N*-alkyl pyridiniums salts due to increased activation of the π-system. Furthermore, the stability of the dihydropyridine products is improved by the acyl "protection" of the nitrogen.

Scheme 1. Pyridine/Pyridinium Equilibrium and Electrophilic Sites



In the presence of acyl chlorides or chloroformates, pyridine exists in equilibrium with the *N*-acyl pyridinium salt that contains reactive electrophilic sites at the 2-, 4-, and 6-positions of the heterocyclic ring as well as at the carbonyl carbon (Scheme 1). Upon addition of an organometallic nucleophile, mixtures of substituted 1,2- and 1,4-dihydropyridines are frequently obtained, rather than addition at the 1-acyl carbon, as is common in nucleophilic catalysis (e.g., with 4-dimethylaminopyridine (DMAP)).

Despite the fact that the equilibrium can often sit to the side of the uncomplexed pyridine, depending on the nature of the reagents and conditions,[30,31] pyridines themselves react only slowly with organometallic nucleophiles, and it is addition to the pyridinium salts that is responsible for formation of the desired product.[32] Wanner and co-workers have investigated methods to improve the position of the equilibrium in favor of the *N*-acyl pyridinium salts to enhance the reaction rates/yields. For example, changing the nature of the counterion from chloride to the less-nucleophilic triflate has been demonstrated to significantly increase the amount of pyridinium species in solution and lead to improved yields.[30] Although in some cases premixing of the activating reagent has been advantageous, particularly with more sterically hindered pyridines, the organometallic reagent is often added prior to the acylating agent. The reaction of the acyl chloride with the pyridine must be very rapid to prevent significant competition from the addition of the organometallic species to the activating agent. In cases with more activated pyridines containing stabilizing electron-withdrawing groups, nucleophilic addition has been proposed to occur to the uncomplexed pyridine followed by the trapping of the resulting anion. This is often considered in the case of the addition of 4-selective nucleophiles to nicotinic derivatives carrying electron-withdrawing groups at the 3-position,[33,34] although in similar examples addition to the *N*-acyl pyridinium salts has also been proposed.

The hard/soft acid/base (HSAB) model has been used to rationalize the regioselectivity of addition of organometallic nucleophiles,[35−37] and the judicious choice of nucleophile, acyl chloride, and reaction conditions can afford selective 1,2- or 1,4-additions. As discussed in the next section, softer organometallics, such as organocuprates, generally add to the 4-position, whereas harder nucleophiles add at the 2-position. Only very hard nucleophiles such as alkyl lithium reagents undergo addition at the acyl carbon. The use of chiral and enantioenriched substrates has led to diastereoselective additions at the 2- or 4-positions, and recently catalytic enantioselective additions to the 2-position have been described. In all cases, the combination of the nucleophile and the acylating agent are important in determining regio- and stereoselectivity, as are the nature and position of pyridine substituents.

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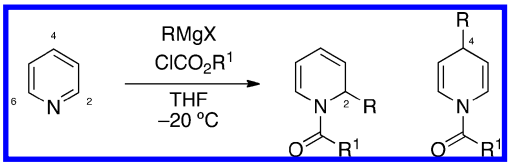
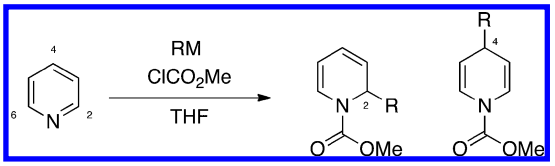
Table 1. Regioselectivity of Grignard Reagent Addition to *N*-Acyl Pyridine with Various Steric Demands in the Activating Group



entry	RMgX	R^1	yield (%)	ratio C-2/C-4
1	EtMgBr	Me	76	70:30
2	EtMgBr	EtO	73	64:36
3	EtMgBr	*t*-Bu	73	52:48
4	PhMgCl	Me	70	93:7
5	PhMgCl	EtO	80	93:7
6	PhMgCl	Ph	77	73:27
7	PhMgCl	*t*-Bu	66	52:48

Table 2. Regioselectivity of the Addition of Varying Organometallics to *N*-Acyl Pyridine



entry	R	M	temp (°C)	yield (%)	ratio C-2/C-4
1	Me	MgI	0	54	92/8
2	Bu	MgBr	0	41	78/22
3	Bu	MgBr	−78	99	67/33
4	*i*-Pr	MgBr	−78	99	37/63
5	Bu	ZnCl	0	99	19/81
6	Bu	Li	−78	not observed	
7	CH_2=CH−	MgBr	−78	81	>99/1
8	PhC≡C−	MgBr	−78	85	>99/1
9	TMSC≡C−	MgBr	−78	99	>99/1
10	CH_2=$CHCH_2$−	$SnBu_3$	0	87	94/6
11	CH_2=$CHCH_2$−	MgBr		57	79/21

2.1. Regioselective Additions to *N*-Acyl Pyridinium Species and Their Derivatives

The C-2 versus C-4 regioselectivity of nucleophilic additions to *N*-acyl pyridinium salts is highly dependent upon the nature of the organometallic reagent due to the inherent HSAB duality of the pyridinium electrophile. This is best illustrated in examples using unsubstituted pyridine, as the steric and electronic features of functional groups on the pyridine ring can influence the position of attack (vide infra). Early investigations indicated that hard organometallic reagents, generally Grignard reagents but also organocadmium nucleophiles, displayed a strong preference for addition at the 2-position. However, several of these studies were performed with substituted pyridine derivatives.[38−40] Comins and Abdullah examined the addition of Grignard reagents to unsubstituted pyridiniums salts with a variety of activating agents. It was demonstrated that although alkyl Grignard reagents afforded poor regioselectivity, the corresponding arylmagnesium reagents displayed higher 2-selectivity (Table 1, entries 1 and 4).[41] The extent of addition to the 4-position was clearly dependent upon the degree of steric hindrance at the 2-position, with larger activating reagents leading to an increased 1,4-addition versus 1,2-addition (compare entries 1−3 and 4−7).

The regioselectivity of addition to pyridines activated by methyl chloroformate was investigated systematically by Yamaguchi and co-workers, who compared the nature of the nucleophile.[42,36] Alkyl Grignard reagents gave 1,2- and 1,4-addition in variable ratios depending on the alkyl moiety, whereas the harder MeMgBr afforded higher selectivity for the 2-position (Table 2). Varying the metal to the softer butylzinc chloride (*n*-BuZnCl) gave increased 4-addition. The use of the harder *n*-butyllithium was proposed to add at the carbonyl moiety when using methylchloroformate as the activating reagent, with none of the ring addition observed. Alkenyl and alkynyl Grignard reagents underwent 1,2-addition exclusively (entries 7−9), and addition of alkynyl Grignard reagents to 2-alkylpyridines gave very high levels of 6-selectivity. This feature was applied to the synthesis of piperidine alkaloids (±)-solenopsine A[43] and (±)-monomorine I,[44] as well as to ene−diyne derivatives containing tetrahydropyridine moieties.[45] Other metalloalkynes have been shown to add to *N*-acyl pyridiniums at the 2-position as the magnesium,[46] silver,[47] or zinc species,[48] or with an amine base in the presence of a catalytic quantity of copper salt.[49,50] In all cases, the addition to the 2-position is favored, rather unusually for organocopper species as these reagents are considered as soft nucleophiles. Beveridge and Arndtsen recently exploited this approach using copper iodide followed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation in a one-pot synthesis of substituted 2-alkynyl pyridines.[51]

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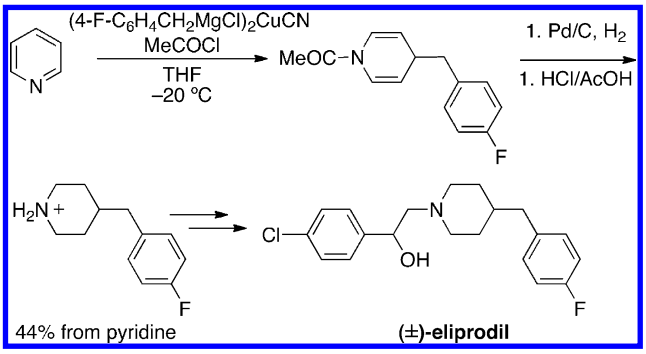
Yamaguchi et al. developed the 2-selective addition of allyltin reagents (Table 2, entry 10), which showed improved regioselectivity over allyl Grignard reagents (entry 11).[52,53] The S_E2' addition of substituted methallyl and crotyltin reagents gave unstable products, which required perhydrogenation over Rh−Al_2O_3 to allow further characterization. However, in these cases low regioselectivity was observed, with a preference for addition at the 4-position. Furthermore, prenyltributyltin attacked at the 4-position of the pyridinium salts exclusively. This trend could also be explained through the HSAB principle with the hardness of the reagents classified as allyl > methallyl/crotyl > prenyl, which is in good agreement with the regioselectivity observed, although the increase in steric bulk of the reagents would compliment this effect. Allylation using indium reagents formed from various substituted allyl bromides has also been observed displaying similar regioselectivity effects.[54]

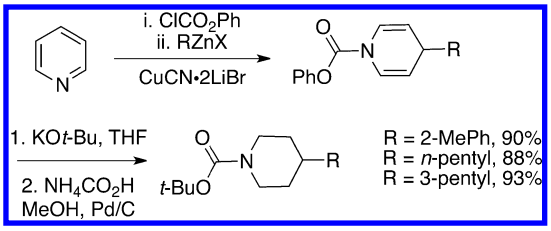
Piers and Soucy showed that the use of organocopper reagents as soft nucleophiles enabled the synthesis of 1,4-dihydropyridine derivatives. Alkyl and aryl cuprates in the presence of methyl chloroformate were shown to give high yields and reliable 4-selectivity (Me_2CuLi, 98% 4-selectivity, 81% yield; Ph_2CuLi, 90% 4-selectivity, 70% yield).[32] This was further developed by Comins and Abdullah using Grignard reagents with catalytic CuI (5%) to achieve very high levels of

Scheme 2. Synthesis of Eliprodil by 4-Selective Cuprate Addition



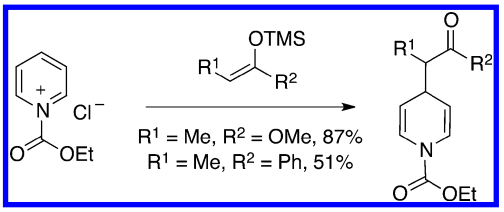
selectivity although with reduced yields (EtMgCl, 100% selective, 27% yield; PhMgCl, 98.8% selectivity, 55% yield).[41] A similar method was recently used in the synthesis of *N*-methyl-D-aspartate (NMDA) receptor antagonist Eliprodil (Scheme 2).[55] Cuprates formed from 3-pyridyllithium[56] and benzyl Grignard reagents[57] have also been shown to add effectively. Akiba et al. used RCu·BF_3 reagents to achieve high selectivity and yields (R = Bu, 89% yield, 99.5% 4-selectivity).[58] Softer mixed Cu−Zn species have been derived from alkyl and arylzinc reagents with copper sources.[59,60] These have been

Scheme 3. 4-Selective Addition of Cu−Zn Nucleophiles under Parallel Synthesis Conditions



employed to achieve high-yielding 4-selective addition, for example, in the synthesis of 4-substituted piperidine derivatives under parallel synthesis techniques, which used alkyl zinc halides or dialkyl zinc reagents with catalytic CuCN·2LiBr (Scheme 3).[61] Recently, Arndtsen and co-workers reported that mild organoindium reagents add to pyridinium salts formed in

Scheme 4. Selective Addition of Silyl Enol Ethers to 4-Position



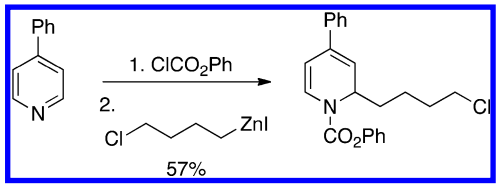
situ in the presence of chloroformates under copper catalysis with moderate to good C-4 selectivity.[62]

Silyl enol ethers generated from ketones and silyl ketene acetals, which are soft nucleophiles, add with high regioselectivity to the 4-position in the presence of ethyl chloroformate (Scheme 4).[63] 2,2,2-Trichloroethyl chloroformate was also employed with silyl enol ethers prepared from acetone or acetophenone to afford high yields and excellent 4-selectivity by increasing the steric demand at C-2. Titanium enolates also gave good 4-regioselectivity in some cases.[64]

Other nucleophiles that add selectively at the 4-position include benzylic tin reagents[65] and $P(OR)_3$, which provided high yields of 4-phosphonates.[66] The addition of trialkylalkynylborates to *N*-acetylpyridine also provided a 4-selective addition.[67] Initially this formed an *E*/*Z* mixture of vinylborane-substituted dihydropyridines, which could be oxidized to a mixture of vinyl pyridines or directly to the pyridine-containing ketone.

2.1.1. Influence of Pyridine Ring Substituents on Regioselectivity of Addition. The presence of substituents on the ring can influence the regioselectivity of nucleophilic additions by blocking electrophilic sites or by directing nucleophiles to adjacent sites. Groups at the 4-position generally only allow addition at the 2-position. This section presents the directing effects of pyridine substitutents and their

Scheme 5. Addition of Functionalized Alkyl Zinc Reagents at C-2 (C-4 Blocked)



influence on the regioselectivity of addition to *N*-acylpyridinium salts.

Alkyl zinc reagents afforded low regioselectivity with unsubstituted pyridines, but the use of 4-substituted pyridines with PhOCOCl provided a method to introduce functionalized alkyl chains at the 2-position (Scheme 5).[68] Acyl pyridiniums are sufficiently reactive so that addition occurs chemoselectively in the presence of other reactive functional groups such as esters, ketones, and halides. The addition of Grignard reagents

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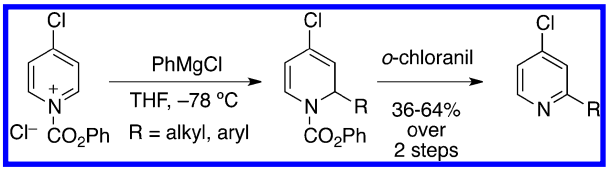
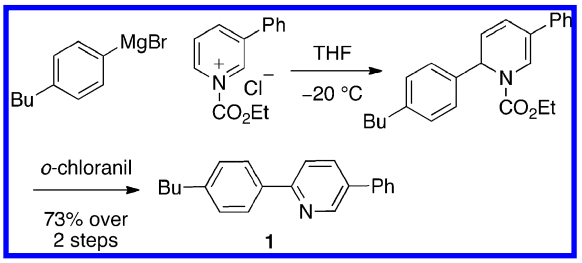
Scheme 6. C-2 Selective Addition to 4-Chloropyridine



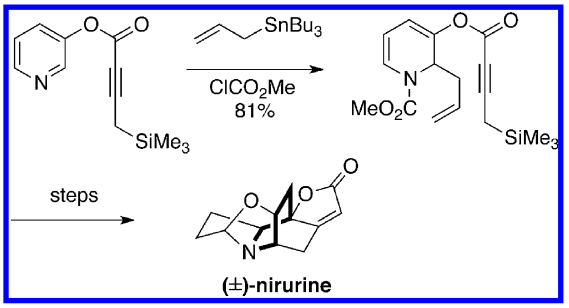
Scheme 7. Addition of Grignard Reagents at C-6 due to a Bulky C-3 Group



to 4-chloro- and 4-bromopyridines provides a direct synthesis of 2-substituted 4-halopyridines following oxidation of the dihydropyridine with *o*-chloranil (Scheme 6).[69,70]

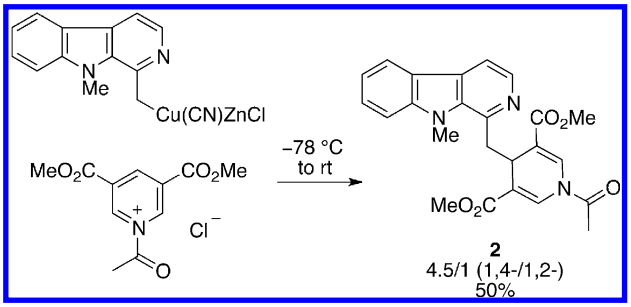
Substituents at the pyridine C-3 differentiate the 2- and 6-positions. The presence of bulky groups in the 3-position can block the adjacent positions, providing a regioselective addition at C-6,[41] e.g., in the synthesis of pyridine-containing liquid crystalline compound **1** (Scheme 7).[71] Alternatively, 3-substituents may *direct* hard nucleophiles to the 2-position. This was observed in early studies for 3-methyl groups providing an ortho-directing effect by agostic interactions causing organometallic reagents to preferentially add at the more-hindered 2-position of pyridines and activated pyridinium species.[72,39] However, significantly increasing the bulk of the nucleophile or the acylating reagent, as for phenyl chloroformate, overturns this effect.[39] The directing effect of a 3-Me group was also observed for the 2-selective addition of allyl tin reagents (Table 3, entry 1).[53] Other 3-substituents provided more powerful directing effects for the same system (entries 2−5), presumably via coordination to the incoming nucleophile. Allyl tin reagents have been used in 2-selective additions in the synthesis of pentacyclic alkaloid (±)-nirurine, directed to C-2 by a functionalized exoester (Scheme 8).[73,74] Alkynyl tin reagents have also been shown to be well directed to the 2-position by 3-carbonyl groups.[75,76]

Scheme 8. Synthesis of Pentacyclic Alkaloid (±)-Nirurine Using Allyl Tin Reagents and a Directing C-3 Substituent



Soft nucleophiles continue to add with high 4-selectivity in the presence of nonbulky 3-substituents. For example, high 4-selectivity has been shown for the addition of organocuprates derived from Grignard reagents to pyridinium salts bearing a range of substituents at the 3-position (3-Me, Br, OMe, CO_2Me, COR, and $OCONEt_2$), generally achieving good yields.[77−81] Cuprates derived from zinc species have successfully provided high 4-regioselectivity in additions to nicotinic

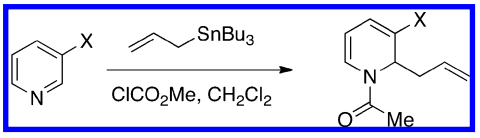
Scheme 9. Selective Cuprate Addition on Hindered Pyridiniums Towards Alkaloid Structures



acid derivatives and other 3-substituted pyridines.[82−84] In some examples using sterically hindered 3,5-substituted pyridines and more complex nucleophiles, a lower regioselectivity has been observed. However, addition to the 4-position is still favored, e.g., in the synthesis of dihydropyridine **2**, prepared during the synthesis of the proposed structures of alkaloid natural products lyaline and ladine (Scheme 9).[85] Trialkylsilyl cuprate reagents $(R_3SiLi)_2CuCN$ have also been added to the 4-position of methyl nicotinate.[86]

Silyl ketene acetals have also shown highly regioselective additions to nicotinic esters and amides activated by methyl chloroformate,[87,88] which was used in the synthesis of (±)-sesbanine (Scheme 10).

Table 3. C-2 Directing Effect of 3-Substituents in Allyl Tin Additions



entry	X	α-selectivity (%)	ratio C-2/C-6	yield (%)
1	Me	89	75/25	74
2	Cl	93	100/0	87
3	Br	94	100/0	87
4	OAc	91	100/0	94
5	CHO	86	76/24	86

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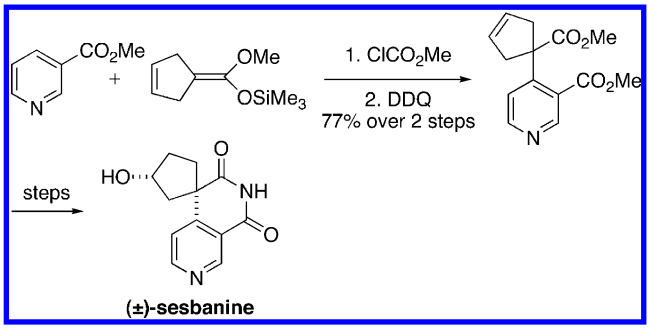
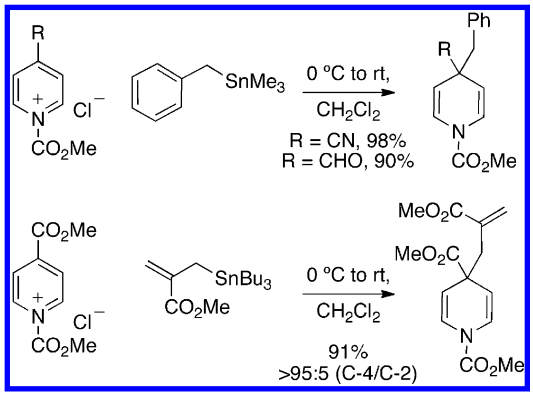
Scheme 10. Synthesis of (±)-Sesbanine by 4-Selective Silyl Ketene Acetal Addition



Similar to benzyl tin reagents,[65] benzylic zinc bromides undergo highly regioselective additions to 1-(phenoxycarbonyl)pyridinium salts formed from methyl nicotinate.[89,90] Isocyanides have also been added to the 4-position of nicotinic amide, providing access to 3-cyano-4-carbamoyl-1,4-dihydropyridines by an intramolecular dehydration−rearrangement from the starting amide, effectively introducing a carbamoyl group at the 4-position.[91] In exceptional cases, naturally 4-selective reagents have been shown to add to the 4-position when the pyridinium salt is substituted with electron-withdrawing groups, in spite of the steric repulsion. Benzyl tin reagents[65] and some allyl tin reagents substituted with ester and cyano groups[92] have thus afforded 4,4-disubstituted products (Scheme 11).

Scheme 11. Unusual 4-Selective Addition to C-4 Substituted Pyridinium Species



2.1.2. Control of Regio- and Diastereoselectivity by the Introduction of Removable Blocking Groups. The introduction of a temporary, easily removable bulky group can control the regioselectivity of addition, by blocking otherwise competing reactive sites. Subsequent removal of the blocking group can reveal the desired unsubstituted dihydropyridine. Adding a blocking group to the 4-position ensures addition to the 2-position. Chloride has been used for this purpose and removed by hydrogenation to allow access to (±)-solenopsine A and (±)-dihydropinidine,[70] as well as alkaloids from the quinolizidine family.[68] The bulky trimethylstannyl group has been used to "*direct*" Grignard reagents[93] and zinc ester enolates[94] to the 2-position, which would otherwise give poor regioselectivity. The trialkyl tin group could then be removed under mild conditions by treatment with oxalic acid.

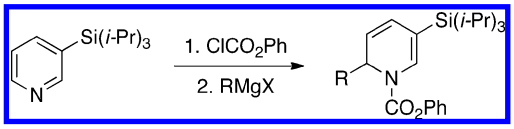
Trialkyltin[95] and trialkylsilyl[96] groups at the 3-position have been used as blocking groups to afford 6-selective additions. 3-Triisopropylsilylpyridine in combination with phenyl chloroformate was shown to be optimal, resulting in the addition of alkyl and aryl Grignard reagents exclusively at the 6-position (Table 4).[97] This was used in the preparation of indolizidine alkaloid (±)-elaeokanine A. The blocking group may be removed or replaced to install other functionality, e.g., in the synthesis of (±)-tylophorine, where the silyl group was replaced by bromide (using pyr·HBr_3), which was then used in a cross-coupling reaction.[98]

The use of a large blocking group at the 3-position permitted the diastereoselective addition of Grignard reagents by using a chiral nonracemic acyl group (see section 2.2.1 for further discussion). Chiral menthyl chloroformate derivatives were used with 3-triisopropylstannylpyridine to achieve diastereoselectivities of 88:12 to 96:4 diastereomeric ratio (dr) (Table 5).[99] The triisopropylstannyl group was chosen to allow removal under mild conditions, because the 1,2-dihydropyridines are sensitive to acid. However, removal of the auxiliary was also difficult due to the sensitive nature of the dihydropyridine, although it could be removed following reduction to the enantioenriched piperidine, which was used in the synthesis of (−)-*N*-methylconiine.[99]

Wanner and co-workers developed a chiral acyl group to allow diastereoselective addition to 3-trialkylsilyl pyridines.[100] The use of acyl chloride/bromide **3** derived from a bicyclic lactone provided excellent diastereoselectivity, albeit in modest yield, for the addition of alkyl Grignard reagent **4** (Scheme 12). Improved yields, but slightly reduced selectivity, were achieved by changing the Br^- or Cl^- counterion of the *N*-acyl pyridinium to triflate with TMSOTf (TMS = trimethylsilyl). This technique was applied to other substituted pyridine derivatives, which achieved poor to good selectivities.[31]

Aside from these examples, the diastereoselective synthesis of 1,2-dihydropyridines using chiral nonracemic acyl chlorides is not well developed when the 4-position is not substituted. However, the use of trialkylsilyl blocking group has been used extensively, particularly by Comins, to enable highly effective

Table 4. 6-Selective Additions to *N*-Carbamoyl 3-Triisopropylsilylpyridinium Salt



entry	R	ratio (C-6/C-4/C-2)	yield (%)
1	Me	100:0:0	96
2	Bu	100:0:0	98
3	*c*-Hex	100:0:0	98
4	Ph	100:0:0	93

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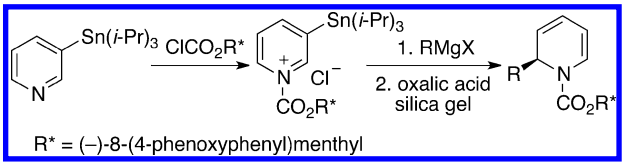
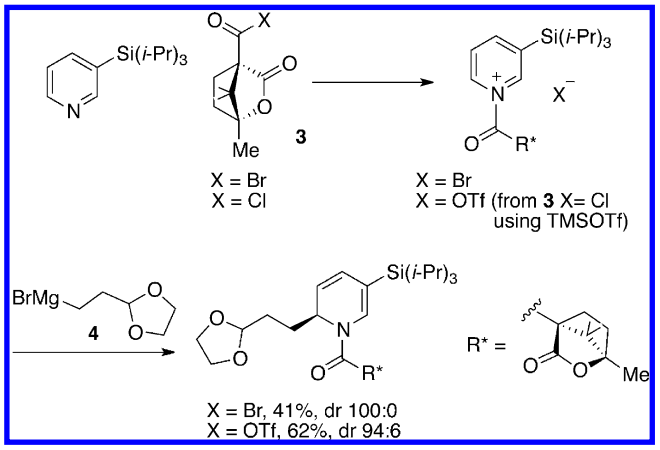
Table 5. Diastereoselective Addition to 3-Triisopropylstannylpyridine with Menthyl Auxilliary



entry	RMgX	dr	yield (%)
1	PrMgCl	91:9	72
2	*c*-HexMgCl	96:4	81
3	BnMgCl	88:12	58
4	VinylMgBr	95:5	71
5	PhMgBr	95:5	85

Scheme 12. Diastereoselective Addition to 3-Triisopropylsilylpyridine



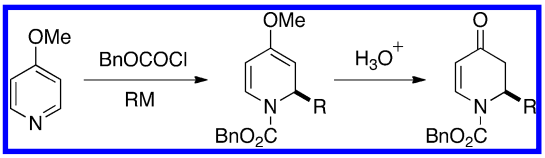
diastereoselective addition to 4-methoxypyridines (see section 2.2.1).

As an alternative approach to blocking addition at undesired sites, activated pyridinium species coordinated η-2 to tungsten complexes have been employed (Table 6).[101,102] Addition occurred to the bound pyridinium salt with high regio- and diastereoselectivity at C-2 on the opposite face to the complexing metal species (>10:1 dr). The acetyl pyridinium salt was stable to water, and various nucleophiles could be added in moderate to good yields. Subsequent reductive transformations yielded a variety of substituted piperidines.[103]

2.2. Synthesis of 4-Pyridones: 1,2-Addition to 4-Methoxypyridines

The addition of a wide variety of nucleophiles to *N*-acyl-4-methoxypyridines has been extensively studied, providing 2-substituted *N*-acyl-2,3-dihydro-4-pyridones as versatile heterocyclic building blocks (Scheme 13).

Scheme 13. Synthesis of *N*-Acyl-2,3-dihydro-4-pyridones from 4-Methoxypyridine



The presence of the 4-methoxy group forces nucleophiles, such as Grignard reagents, to add exclusively at the 2-position, giving the 1,2-dihydropyridine.[104] This intermediate is generally not isolated, but readily undergoes hydrolysis under a mild acidic workup to unmask the carbonyl group. The 2,3-dihydro-4-pyridone products are more stable than 1,2-dihydropyridines,

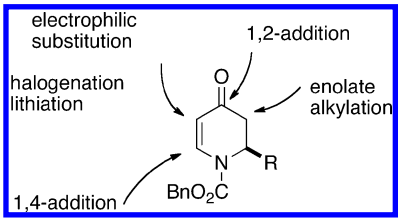
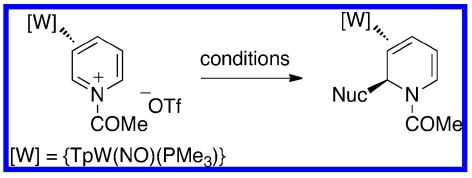


Figure 4. Derivatization of stable 2,3-dihydro-4-pyridones.

and they provide numerous points for potential derivatization, making this particularly applicable for natural product synthesis.[105] Furthermore, dihydropyridones are precursors to *N*-acyl-1,2-dihydropyridines,[99,106] or the 4-oxygen can be subsequently removed to provide the piperidine (using common reducing conditions such as Luche or Wolff–Kishner

Table 6. Coordination of a Tungsten Complex to *N*-Acyl Pyridines to Promote Addition to the 2-Position



entry	conditions	Nuc	yield (%)
1	TMSCN, DABCO	CN	88
2	indole, 2,6-lutidine	3-indolyl	61
3	Et_2Zn	Et	88
4	MeMgBr	Me	57
5	Zn, allylBr	allyl	89

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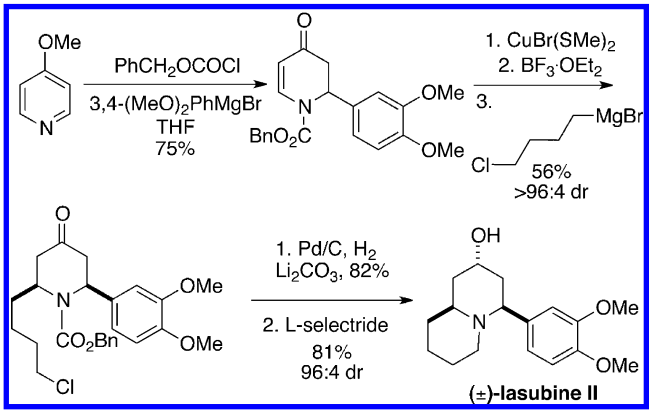
reduction),[107] thus acting as a removable blocking group. Methods to derivatize the *N*-acyl-2,3-dihydro-4-pyridones have been extensively developed (Figure 4), including enolate alkylations,[108] conjugate additions,[109,110] halogenation/transition metal-mediated couplings,[111,112] and lithiation/trapping of

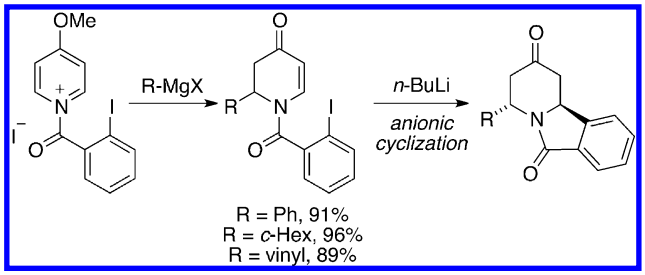
Scheme 14. Synthesis of (±)-Lasubine II from 4-Methoxypyridine



electrophiles;[113] however, this will not be exhaustively covered in this review.[105] As a result, these dihydropyridone products have been employed as useful building blocks, being selectively transformed into a wide range of functionalized 6-membered heterocyclic systems.

The largest application of this technology has been in the preparation of alkaloid natural products, such as in the short synthesis of (±)-lasubine II (Scheme 14).[114] This approach to the synthesis of alkaloid structures with bicyclic cores, involving the addition of a functionalized Grignard nucleophile that will subsequently allow cyclization, has been widely exploited.

Scheme 15. Cyclization Through Functionalized Acyl Groups

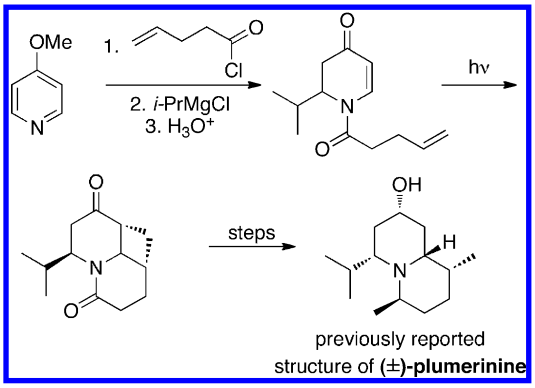


Examples include the synthesis of (±)-pumiliotoxin C,[115] synthetic studies toward the lycopodium alkaloids,[107,116] and the synthesis of indolizidine alkaloid (±)-209B.[117]

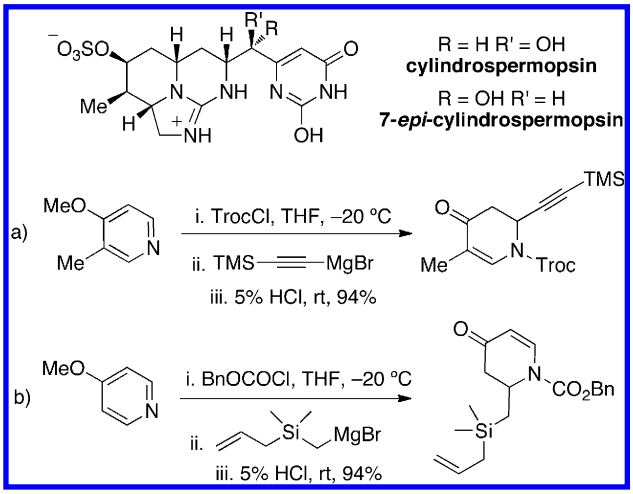
Benzo-fused *trans*-indolizidine structures have been prepared by an alternative approach, involving the use of a functionalized acyl group, and an intramolecular cyclization, by anionic means[118] or by a Heck reaction,[119] to form the fused ring systems (Scheme 15). A range of Grignard nucleophiles were incorporated, including a selection of heteroaryl anions.[120] Other functionalized acyl chlorides have been employed, for example, to allow a facially selective intramolecular [2 + 2]-photocycloaddition leading to the synthesis of the putative structure of (±)-plumerinine (Scheme 16).[121]

Notable uses of this methodology are the syntheses of (±)-cylindrospermopsin natural products by Snider and co-

Scheme 16. Intramolecular [2 + 2]-Photocycloaddition from Functionalized Acyl Group

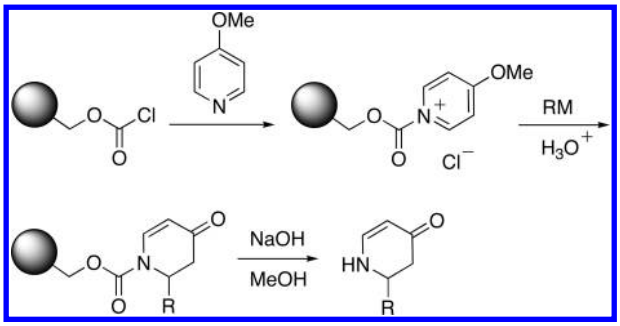


Scheme 17. Syntheses of Cylindrospermopsin Natural Products



workers, using 3-methyl-4-methoxypyridine (Scheme 17a),[122] and then by Weinreb and co-workers (Scheme 17b), resulting in revision of the C-7 stereochemistry.[123] The dihydropyridone

Scheme 18. Resin Activation and Capture Approach to Dihydropyridines Allowing Facile Purification



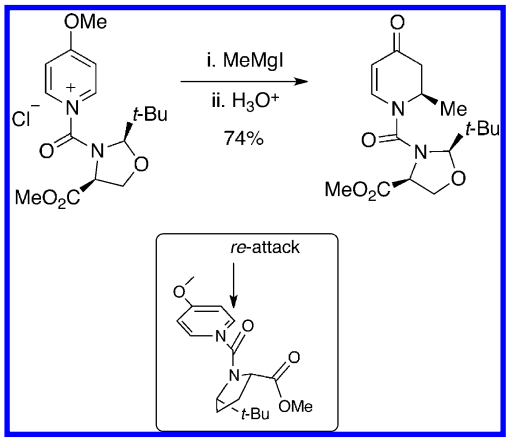
building blocks have also been used as precursors for the preparation of chiral acyclic amino alcohols[124] and *β*-amino acids[125,126] by ring-opening/cleavage.

The general approach to the synthesis of dihydro-4-pyridones has been transferred to a solid support using resin activation/capture (REACAP).[127] The reactive intermediate was generated by reacting 4-methoxypyridine with a chloroformate linked to a polystyrene resin (Scheme 18). Reaction

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642–2713

with Grignard reagents afforded a resin-bound *N*-acyl dihydropyridone, allowing facile purification. Cleavage with NaOH liberated the free product with modest yields, 31−67%, but high purity, 85−98%. Additionally, further functionalization could be performed prior to release.[128] *N*-Acyl-protected dihydropyridones have also been prepared by REACAP technology in which the resin was linking through the 4-oxy-position and, hence, was cleaved in the hydrolysis step using trifluoroacetyl (TFA).[129]

Scheme 19. Diastereoselective Addition to 4-Methoxypyridine by Streith and Co-workers



By introducing a chiral nonracemic acyl chloride, Streith and co-workers achieved a diastereoselective addition to 4-methoxypyridine (Scheme 19).[130,131] For the addition of MeMgI, an initial diastereomeric excess (de) of 95% was obtained and recrystallization afforded a single diastereoisomer in 74% yield. The addition of PhMgBr also gave a moderate yield with high stereoinduction (93% de). High levels of stereoinduction were believed to be achieved by chelate control from the preferred ground-state conformation.[131] Unlike Comins' methodology (see section 2.2.1), this approach did not require a large blocking group at C-3. However, few examples have been reported and the harsh conditions required to remove the auxiliary, involving treatment with 50% HCl followed by aqueous sodium hydroxide, have prevented its further use.

2.2.1. Diastereoselective Addition to 3-Trialkylsilyl-4-methoxypyridines. By combining the use of 4-methoxypyridines, a large C-3 blocking group, and chiral nonracemic acyl chlorides, Comins and co-workers achieved a robust methodology for preparation of dihydropyridones with high stereoselectivity. This involved the diastereoselective addition of Grignard reagents to chiral *N*-acyl pyridinium salts, formed from 4-methoxy-3-(triisopropylsilyl)pyridine **5** and the chloroformates of menthyl derivatives (**6**−**8**) followed by hydrolysis of the 4-methoxy-1,2-dihydropyridine (Scheme 20).[132,133]

The optimized triisopropylsilyl substrate **5** requires preparation from 4-methoxypyridine, but its use offered two key advantages:

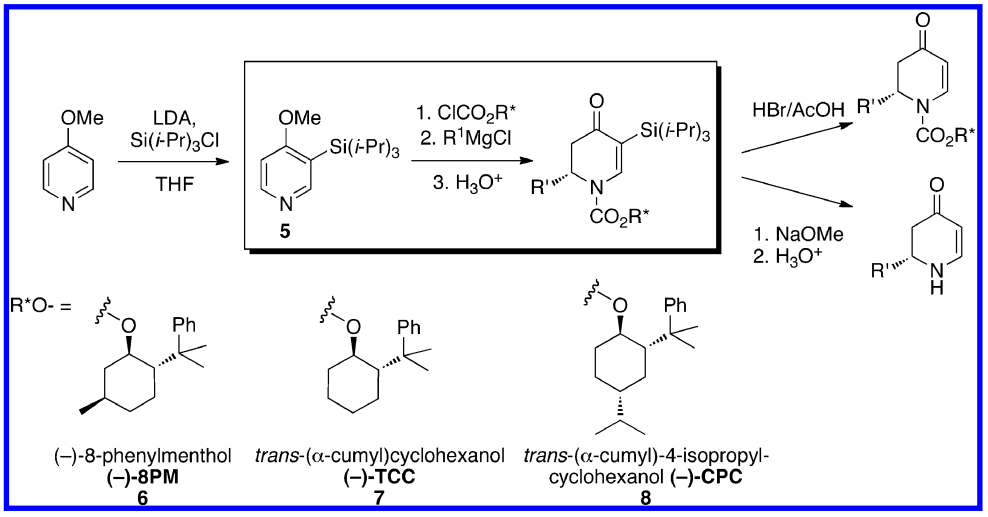
(1) With these substituents in place, addition occurred only at C-6, where the chiral auxiliary is effective at inducing a highly diastereoselective addition.

(2) The formation of the dihydropyridone affords a stable product, allowing the facile removal of both the blocking group and the auxiliary without affecting the newly created chiral center.

The reaction variables were examined, with the nature of the C-3 blocking group and the chiral auxiliary exerting the largest influence over the diastereoselectivities.[133] A low dr (65:35) was obtained with 4-methoxypyridine in combination with (−)-8PM **6** for the addition of PhMgCl. The addition of a bulky group in the 3-position reduced the number of reactive positions on the intermediate pyridinium salt, which led to an increase in the diastereoselectivity (e.g., for $SiMe_3$, 83:17 dr). The large triisopropylsilyl group was optimal, which provided up to 97:3 dr for the synthesis of 2-(*S*)-phenyldihydropyridone. In some cases, auxiliaries derived from (−)-8-(4-phenoxyphenyl)menthyl achieved higher diasteroeoselectivities than (−)-8PM, but the preparation was inconvenient. A study into alternative auxiliaries identified other practical chloroformates,[134,135] particularly *trans*-(α-cumyl)cyclohexanol (TCC **7**), which is available as either enantiomer.[136]

This methodology has been widely used in the preparation of stereochemically enriched dihydropyridines and piperidines (see section 2.2.2 for a wide range of examples in natural product synthesis). Single diastereoisomers could be obtained

Scheme 20. Diastereoselective Addition to 4-Methoxy-3-(triisopropylsilyl)pyridine



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by chromatography or crystallization, and the pyridone moiety may then be further derivatized as discussed above. Because of the stability of the dihydropyridone, the auxiliary and the

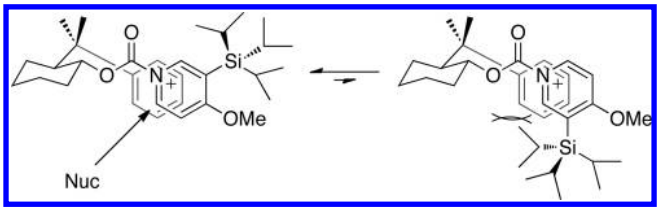


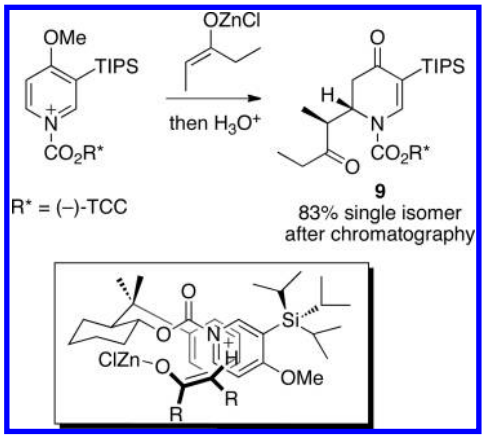
Figure 5. Origin of stereoselectivity using (−)-TCC auxiliary **7**.

triisopropylsilyl (TIPS) group could be removed together in a one-pot procedure using NaOMe/MeOH followed by treatment with aqueous acid. The auxiliary could possibly be recovered and recycled (Scheme 20).[133]

The asymmetric induction is believed to arise due to the aryl substituent of the chiral auxiliary, which undergoes $\pi-\pi$ interaction as shown in Figure 5. In this case, one face of the pyridinium salt is blocked, favoring nucleophilic attack from the opposite face. Rotation about the O_2C-N^+ bond disfavors the π-stacking due to steric interactions with the bulky TIPS group.[133]

The addition of metallo-enolates to chiral *N*-acyl pyridinium salts has also been investigated.[137] Zinc or magnesium enolates gave high yield and de, providing the same sense of induction as

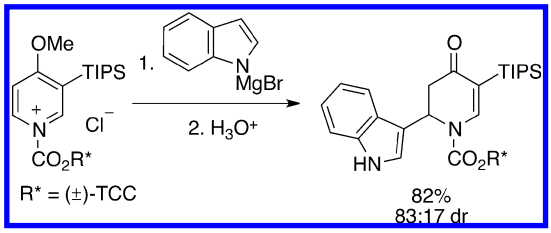
Scheme 21. Enolate Addition with Control of Two Stereogenic Centers



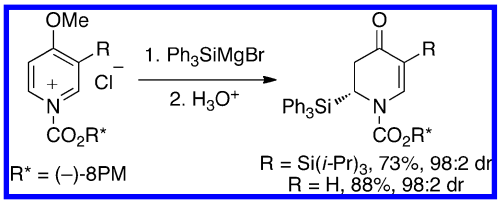
the Grignard reagents. The addition of prochiral zinc enolates proceeded highly stereoselectively, introducing two new stereogenic centers in high yields.[138] The stereochemistry of the second center was determined by the enolate geometry; for example, the addition of the zinc *E*-enolate of 3-pentanone to the pyridinium salt provided dihydropyridone **9** in high yield and diastereoselectivity (Scheme 21). The *E*-enolate provided the anti-isomer with high stereocontrol. This facial selectivity was explained by an acyclic transition state to reduce nonbonded interactions with the pyridinium ring and an attractive electrostatic interaction between pyridinium "*N*" and enolate "*O*" atoms.

As well as aryl, vinyl, and alkyl Grignard reagents, other nucleophiles have been examined. Various indolyl and pyrrolyl Grignard reagents have been used for the addition with good yields but moderate diastereoselectivity (Scheme 22).[139] Silyl

Scheme 22. Addition of an Indole Grignard Reagent



Scheme 23. Addition of Silyl Nucleophiles with High Diastereoselectivity



Grignard reagents have been demonstrated to add successfully with very high dr (Scheme 23).[109] Interestingly, with bulky (triphenylsilyl)magnesium bromide as the nucleophile, the large blocking group was not required to achieve high selectivity, with addition to 4-methoxypyridine occurring with 98:2 dr.

2.2.2. Application in the Synthesis of Natural Products Containing Chiral Piperidine Units. Comins' technology described in the previous section has been employed in the stereoselective synthesis of numerous alkaloid natural products.[140,105] These natural products include the preparation of piperidine (Table 7, entries 1−5), indolizidine (entries 6−10), and decahydroquinoline alkaloids (entries 11−14), as well as quinolizidines and other bi- and tricyclic alkaloids (entries 15−19; also see Figures 2 and 6).

In the synthesis of (+)-allopumiliotoxin 267A, a C-5 methyl substituent was present in the *N*-acyl pyridinium (Scheme 24).[160] The addition proceeded at the C-6 position in high yield and diastereoselectivity (70%, >98:2 dr). Very recently, Comins and co-workers reported a general approach to the phlegmarine alkaloids.[161]

This well-developed methodology has been proven to be both powerful and versatile, as illustrated by the previous examples. However, the preparation of unsubstituted 2-alkyl- or 2-aryldihydropyridines required the removal of both TIPS and OMe groups.

2.3. Diastereoselective 1,2-Addition to *N*-Imidoyl Pyridinium Salts

The addition to *N*-imidoyl pyridinium salts developed by Charette and co-workers provided a conceptually similar approach that provided the highly 2-selective addition of nucleophiles without the need for additional ring substituents. This relied on the formation of electrophilic *N*-imidoyl pyridinium salts by reacting pyridine derivatives with amides activated in situ by triflic anhydride, although the mechanistic details vary depending on the nature of the pyridine and the amide (Scheme 25).[162,163]

Pyridinium *N*-imidoyl salts preformed from *N*-methylbenzamide were treated with various organometallic nucleophiles (Table 8).[164] Grignard reagents generally gave highly regioselective C-2 addition to form 1,2-dihydropyridine **10** (entries 1−4, 6, and 7). The regiocontrol was explained by the

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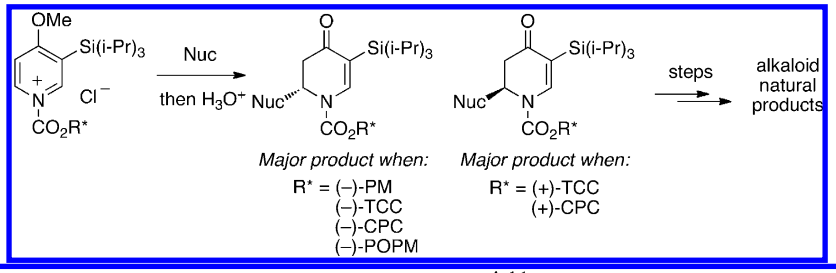
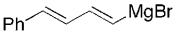
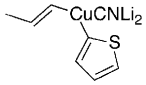
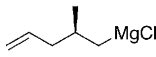
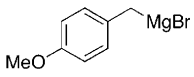
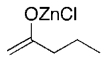
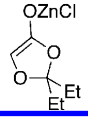
Table 7. Approach to Alkaloid Natural Product Synthesis



entry	Nucleophile (Nuc^-)	R* [a]	dr[b]	yield (%)[c]	alkaloid natural product	ref
1	PrMgCl	(–)-PM	96:4	88	(–)-coniine	141
2	$CH_3(CH_2)_{10}MgBr$	(–)-TCC	95:5	85	(–)-solenopsin A	142
3	VinylMgBr	(–)-TCC	93:7	78	(2*S*,4*R*)-4-hydroxypipecolic acid	143
4		(+)-TCC	96:4	78	(+)-α-conhydrine	144
5		(+)-TCC	93:7	81	(+)-dienomycin C	145
6	*n*-HexMgCl	(+)-CPC	96:4	87	(+)-indolizidine 209D	118
7	CH_2=$CH(CH_2)_2MgBr$	(–)-TCC	95:5	91	(–)-septicine, (–)-tylophorine	146
8		(+)-TCC	95:5	91	indolizidines (–)-205A, (–)-207A, (–)-235B,	147
9	$EEO(CH_2)_3MgBr$	(–)-POPM	97:3	82	(+)-elaeokanine A and C	148
10		(–)-TCC	94:6	61	(–)-slaframine	149
11	CH_2=$CH(CH_2)_3MgBr$	(+)-TCC	97:7	81	*trans*-decahydroquinoline (+)-219A	150
12		(–)-TCC	94:6	76	N_a-acetyl-N_b-methylphlegmarine	151
13		(–)-TCC	93:7-95:5	80	(+)-luciduline	152
14	$Cl(CH_2)_4MgBr$	(–)-PM	93:7	71	(+)-myrtine, (–)-lasubine I, (+)-subcosine I	153
15	*n*-PentMgCl	(–)-CPC	95:5	91	(–)-perhydrohistrionicotoxin	154
16		(+)-TCC	95:5	89	(+)-metazocine	155
17		(–)-PM	96:4	89	(–)-porantheridine	156
18		(+)-TCC	97:3	72	(+)-hyperaspine	157
19		(+)-TCC	>98:2	85	(+)-cannabisativine	158 159

[a]POPM, (phenoxyphenyl)menthyl; PM, phenylmenthyl; EE, ethoxyethyl. [b]dr from original addition observed by crude ^{1}H NMR. [c]Yield of major isomer after treatment with acid.

pyridinium *N*-imidoyl salt adopting an *E*-conformation (*E*)-**12** to minimize the $A^{1,3}$-strain between the *N*-methyl of the imidate and the proton at the C-2 position (Figure 7). This hypothesis was supported by ^{1}H and NOESY NMR studies on the pyridinium salt intermediate formed between *N*-methylbenzamide and pyridine. In the (*E*)-**12** conformation, the imidate lone pair is oriented toward the C-2 position of the pyridinium, enabling delivery of the organometallic species to C-2 through chelation with the nitrogen lone pair.[164] Surprisingly, for primary alkyl reagents, slightly higher 2-selectivity was observed

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642–2713

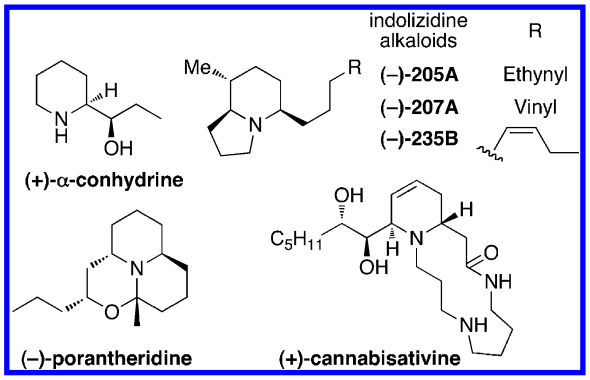
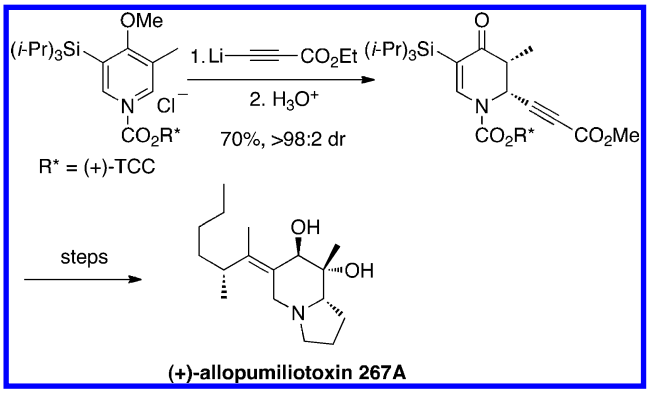
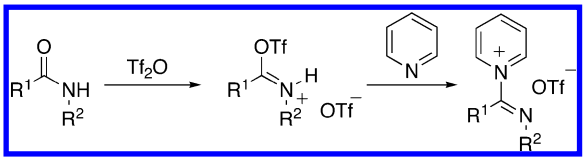


Figure 6. Examples of the alkaloid natural products synthesized with Comins' methodology.

Scheme 24. Stereoselective Synthesis of (+)-Allopumiliotoxin 267A



Scheme 25. Formation of *N*-Imidoyl Pyridinium Salts

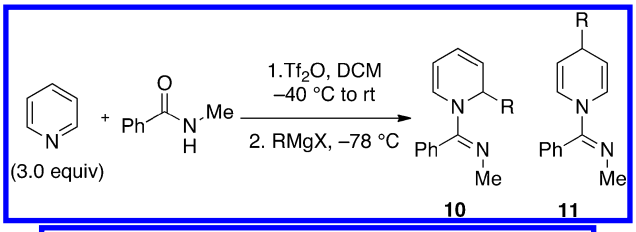


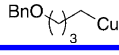
for the corresponding organocuprate reagents, which commonly afford 4-selectivity in the absence of such a chelation effect (Table 8, entries 4, 5 and 7, 8; see section 2.1). It was demonstrated that lactams 2-pyrrolidinone and 2-piperidinone could be used to activate pyridine under these conditions.[165] The synthesis of (±)-tetraponerine T4 was designed to incorporate 2-pyrrolidinone, the activating amide, into the natural product structure.[165]

Highly diastereoselective and regioselective additions were achieved when enantiopure (*S*)-valinol-derived amide **13** was employed as a chiral auxiliary (Table 9).[164] Bidentate chelation of the auxiliary with the nucleophile (the imidate *N*-lone pair and ether oxygen) directed organometallic reagents to the C-2 position of the corresponding pyridinium salt with excellent regio- and diastereoselectivies (Table 9, entries 1 and 5–7). As observed with the achiral amide, EtMgBr afforded lower regiocontrol (C2/C4 ratio of 75:25, entry 2). In this case, alkylcuprates gave slightly better regioselectivities but with decreased diastereoselectivity, whereas diorganozinc reagents such as Et_2Zn provided both high regio- and diastereoselectivity (entry 3).

Elaboration of the resulting dihydropyridine structure and removal of the auxiliary provided efficient access to diverse

Table 8. Formation of 2-Substituted 1,2-Dihydropyridines from *N*-Methylbenzamide



entry	RMgX	ratio C-2:C-4	yield (%)
1	MeMgBr	>95:5	83
2	PhMgBr	>95:5	84
3		>95:5	86
4	EtMgBr	90:10	82
5	EtCuCNMgBr	92:8	65
6	2-FurylMgBr	>95:5	96
7		90:10	70
8		94:6	76

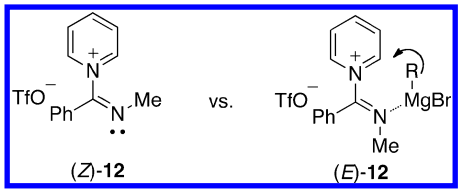


Figure 7. Regioselective addition of Grignard reagents to (*E*)-imidate pyridinium salts via chelation.

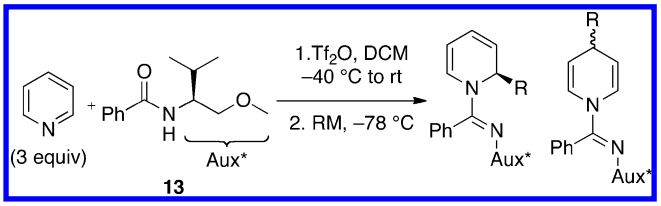
nitrogen-containing scaffolds such as *trans*-2-substituted 3-amino-1,2,3,6-tetrahydropyridines,[166] 2,5-*cis*-disubstituted piperidines,[167,168] and indolizidines.[169] This methodology was employed in the synthesis of several natural products such as (*R*)-(−)-coniine,[164] (+)-julifloridine,[170] (+)-lepadine B,[171] and L-pipecolic acid.[172] Furthermore, the procedure was translated onto tetraaryl phosphonium solubility-control groups, linked through the auxiliary, to facilitate workup and purification.[173]

Removal of the auxiliary could be performed under several conditions. Deprotection of the methoxy ether of the chiral auxiliary using an excess of a strong Lewis acid such as BBr_3 liberated a free alcohol, which then cyclized in situ to yield the free piperidine and 1 equiv of the corresponding oxazolidine.[173] The chiral and achiral amidine auxiliaries have also been deprotected using reductive conditions such as $AlCl_3$/$LiAlH_4$,[172] Li/NH_3 in EtOH/tetrahydrofuran (THF) at −34 °C,[170] or $Pd(OH)_2$ (cat.) with H_2/cyclohexene in AcOH/EtOH.[164] Alternatively, the amidine nitrogen has been removed by hydrolysis (aqueous 6 N HCl in MeOH at reflux)[172] or by methylation (MeI, K_2CO_3), followed by a basic hydrolysis of the amidinium quaternary salt (aqueous 2.5 N NaOH in Et_2O system). This latter example was exemplified in the synthesis of 2,3,4,5-pentasubstituted piperidines, indolizidines, and quinolizidines.[174,169]

The effect of pyridine substituents on the regioselectivity of addition to *N*-imidoyl salts was examined using *N*-methylbenzamide and various 3-substituted pyridines.[175] The addition of PhMgBr or MeMgBr to 3-methoxypyridine afforded

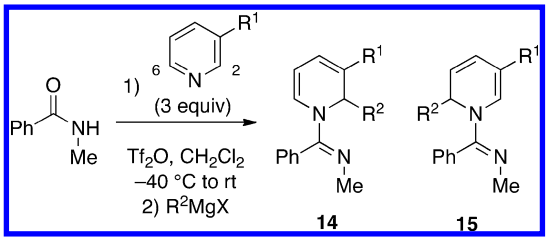
dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642–2713

Table 9. Diastereoselective Addition of Grignard Reagents to Chiral Pyridinium *N*-Imidate Salts



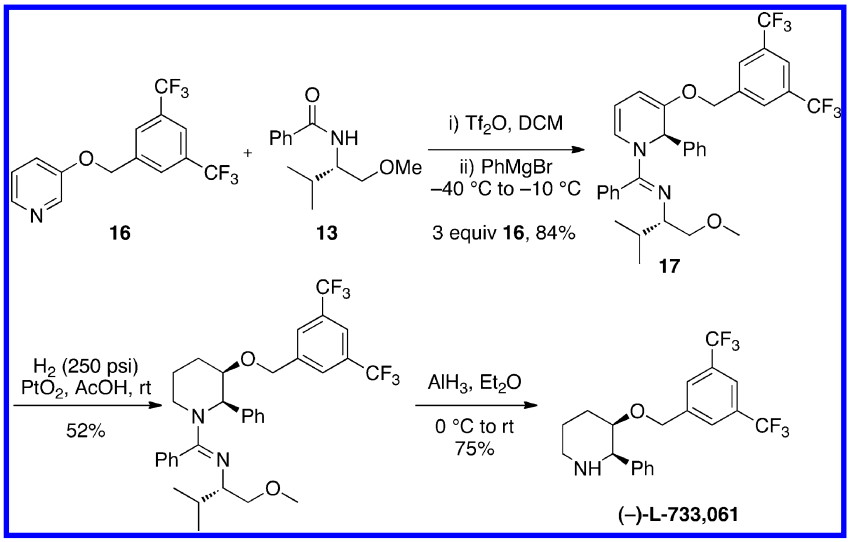
entry	RM	ratio C-2/C-4	dr	yield (%)
1	MeMgBr	>95:5	>95:5	77
2	EtMgBr	75:25	>95:5	79
3	Et_2Zn	>95:5	>95:5	73
4	PhMgBr	90:10	>95:5	74
5	PhMgBr·LiCl	>95:5	>95:5	89
6	2-FurylMgBr	>95:5	>95:5	68
7	1-HexynylMgBr	>95:5	>95:5	65

Table 10. Regioselective Addition of Grignard Reagents to 3-Substituted Pyridinium *N*-Imidate Salts



entry	R^1	R^2 MgX	ratio C-2/C-6	yield **14** (%)
1	Me	MeMgBr	89:11	80
2	Me	PhMgBr	79:21	72
3	OMe	MeMgBr	>95:5	100
4	OMe	PhMgBr	>95:5	94
5	Cl	MeMgBr	95:5	85
6	Cl	PhMgBr	78:22	66
7	Br	MeMgBr	92:8	80

Scheme 26. Total Synthesis of (−)-L-733,061



excellent regioselectivity, exclusively at the more hindered C-2 position, to afford dihydropyridine **14** (Table 10 entries 3 and 4). Slightly lower selectivity was observed in the addition of MeMgBr or PhMgBr to 3-picoline, 3-chloropyridine, and 3-bromopyridine imidate salts with the minor pathway providing dihydropyridine **15** (entries 1−2 and 5−7). Although the selectivities observed for the addition of MeMgBr were comparable to those observed with *N*-acyl pyridinium salts, the addition of PhMgBr gave much higher regiocontrol than previously reported with other pyridinium systems.[176] The products resulting from addition to the C-4 position of the activated pyridinium were not observed in any case.

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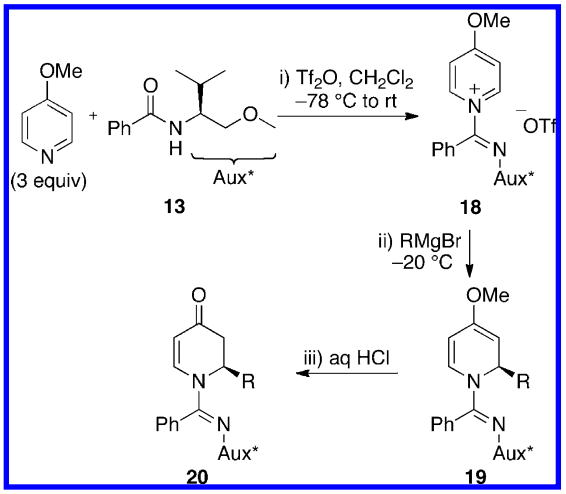
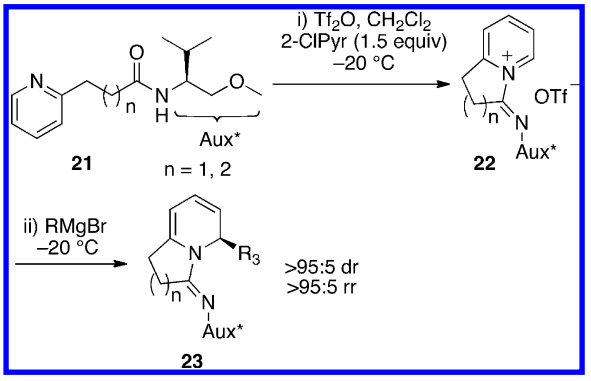
Table 11. Diastereoselective Additions of Grignard Reagents to Activated 4-Methoxypyridine



entry	RMgBr	dr	yield **20** (%)
1	MeMgBr	95:5	85
2	EtMgBr	93:7	76
3	*n*-BuMgBr	>95:5	71
4	*t*-BuMgBr	93:7	61
5	2-FurylMgBr	95:5	65
6	CH_2=$CH(CH_2)_5MgBr$	93:7	84

Table 12. Intramolecular Activation/Cyclization to Form Bicyclic Pyridinium Salts and Dihydropyridines



entry	*n*	RMgBr	yield **23** (%)
1	1	MeMgBr	94
2	1	*t*-BuMgBr	83
3	1	vinylMgBr	85
4	2	vinylMgBr	83
5	2	2-thiophenylMgBr	86

The diastereoselective variant of this method was applied in the rapid total syntheses of two biologically active substituted piperidines, (−)-L-733,061 and (−)-CP-99,994, potent Substance P antagonists.[175] For the synthesis of (−)-L-733,061, the use of 3 equiv of pyridine **16** led to an 84% yield of dihydropyridine **17** (Scheme 26). Introducing 1.5 equiv of 2,6-di-*tert*-butyl-4-methylpyridine as a proton scavenger additive allowed reduction of the amount of **16** to 1.5 equiv maintaining a 70% yield. In the synthesis of (−)-CP-99,994, the use of a modified chiral amide was essential to cleave the *N*-imidoyl auxiliary. In this case Ph_2Zn was required to maintain a high diastereoselectivity in the formation of dihydropyridine.

The electrophilic pyridinium **18** generated from 4-methoxypyridine, and chiral amide **13** was reacted with various Grignard reagents to afford the C-2 addition product **19** with excellent diastereoselectivities (Table 11).[177] As in Comins' methodology (see section 2.2), the dihydropyridine intermediate **19** containing a methyl enol ether was subjected to hydrolysis prior to isolation as the 4-pyridinone **20**. This approach was applied to the barrenazine natural products.[177]

Combining the amide auxiliary on the 2-position of a pyridine allowed an intramolecular reaction to access bicyclic dihydropyridine moieties (Table 12).[169] The activation step required an external base to ensure complete stability of the pyridinium intermediates **22**, and 2-chloropyridine was found to be suitable because it was not activated under these conditions. The addition of Grignard reagents to pyridinium salts **22** furnished excellent regioselectivities (>95:5) and diastereoselectivities (>95:5) and produced high yields for a

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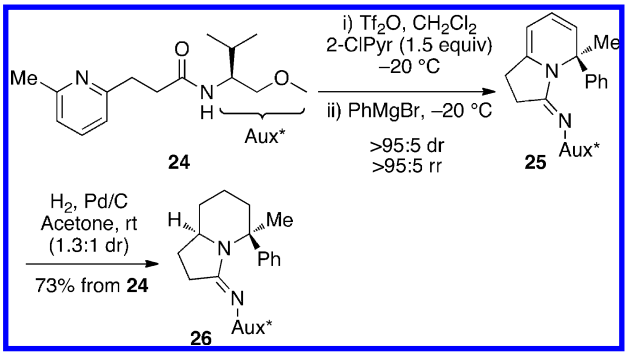
Scheme 27. Formation of a Quaternary Center via Addition of PhMgBr



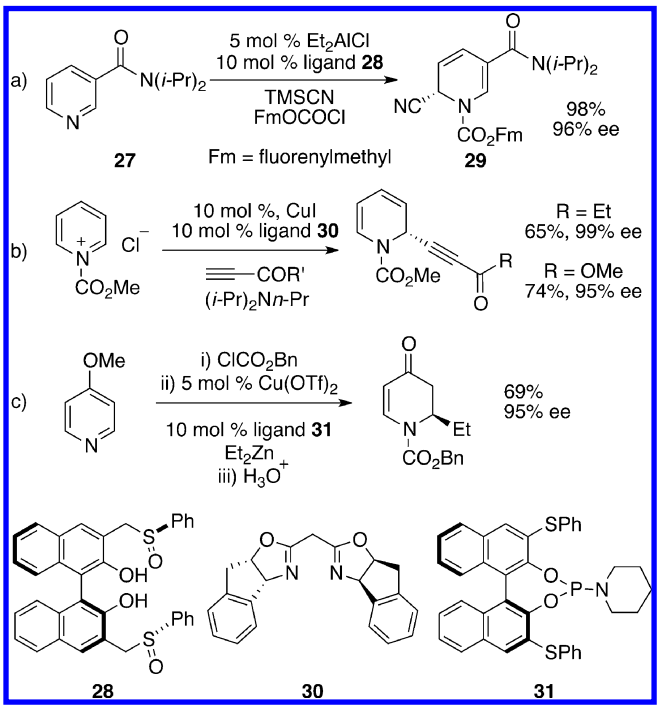
variety of dihydroindolizidines (n = 1) and dihydroquinolizidines (n = 2).

When 2,6-disubstituted pyridine **24** was subjected to the intramolecular activation/cyclization conditions and reacted with PhMgBr, the formation of the C-6 quaternary center was observed (Scheme 27). Excellent regio- and diastereoselectivity (>95:5) was obtained, but unstable dihydropyridine moiety **25** required reduction to **26** prior to isolation. This provided a rare example of stereoselective quaternary center formation following the addition of an organometallic species to a C-2 position of a pyridinium salt (see sections 3.1 and 4.2.2).[178,179]

2.4. Enantioselective 1,2-Addition Controlled by a Chiral Catalyst

The development of catalytic enantioselective additions to the 2-position of activated pyridines has been a significant advance in recent years.[180] In 2004, Shibasaki and co-workers reported a catalytic enantioselective Reissert reaction for pyridine derivatives[181] that had previously not been achieved in synthetically useful yields for *N*-acyl pyridines.[182] The addition of cyanide to achiral nicotinic amide **27** employing a bifunctional catalyst derived from a BINOL (1,1′-bi-2-naphthol) ligand **28** (10 mol %) and Et_2AlCl (5 mol %) achieved excellent yields, regioselectivity, and enantioselectivity (up to 96% ee) (Scheme 28a). The catalytic system was proposed to act by providing dual activation of the *N*-acyl pyridinium and the TMSCN by the Lewis acid (Al) and Lewis base (sulfoxide) positions, respectively. The sulfoxides may also play a role in the stabilization of a highly enantioselective bimetallic complex, as suggested by electrospray ionization mass spectrometry (ESI-MS) studies. The use of the bulky isopropyl amide aided the achievement of high enantioselectivities. High levels of enantioselectivity were also obtained for substrates bearing a chloride or bromide at the 4-position by using a similar ligand containing phosphine oxides as the Lewis basic sites.

Scheme 28. Catalytic Enantioselective Additions to *N*-Acyl Pyridinium Salts



A further advance came in 2007 as Ma and co-workers developed a highly enantioselective addition of 1-alkynes to *N*-carbamoyl pyridinium salts catalyzed by copper–bisoxazoline complexes (CuI with ligand **30**, Scheme 28b).[183] Unsubstituted pyridines were successfully employed, and activated alkynes bearing a carbonyl group (ynones and ynoates) gave high enantioselectivities when using smaller "R" groups. This allowed the rapid preparation of two indolizidine natural products.[183] Unactivated alkynes also added smoothly but with poor enantioselectivity. Other studies by Arndtsen and co-workers demonstrated that a Cu-QUINAP system enables the addition of tetramethylsilyl (TMS)-acetylene to pyridine activated with ethyl chloroformate in 80% ee and 33% isolated yield.[184]

A study by Feringa and co-workers appeared in 2009 for the catalytic enantioselective addition of dialkylzinc reagents to 4-methoxypyridines in the presence of benzyl chloroformate (Scheme 28c).[185] This constituted the first example of the catalytic enantioselective addition of alkyl organometallic reagents to *N*-acyl pyridinium salts and used a copper catalyst in conjunction with phosphoramidite ligand **31**. High levels of enantiomeric excess were reported with primary dialkyl zinc reagents (up to 97% ee) under well-optimized conditions.

Despite these advances, the range of nucleophiles that may be added remains limited. The development of catalytic enantioselective additions of a wider range of nucleophiles to pyridinium salts constitutes a significant synthetic challenge for the future.

2.5. Diastereoselective 1,4-Addition Controlled by Pyridine 3-Substituents

In the synthesis of nonracemic 1,4-dihydropyridines, chiral substituents on the pyridine ring have been exploited. Chirality in the *N*-activating group is too distant from the 4-position to induce stereocontrol, and because substitution on the ring is necessary for the product to be chiral, substituents at the 3-position have been used to bear a chiral auxiliary. To date, enantioselective additions to the 4-position of substituted pyridinium salts have not been developed.

Meyers used pyridines carrying an oxazoline auxiliary at the 3-position (derived from 3-CN pyridines) to achieve highly diastereoselective additions of organometallic species to C-4 in the presence of methyl chloroformate.[186,187] High levels of diastereoselectivity were accessed in the 4-selective addition of MeLi to substituted pyridines **32** to provide dihydropyridine **33** (Scheme 29). The diastereoselectivity conformed to the usual

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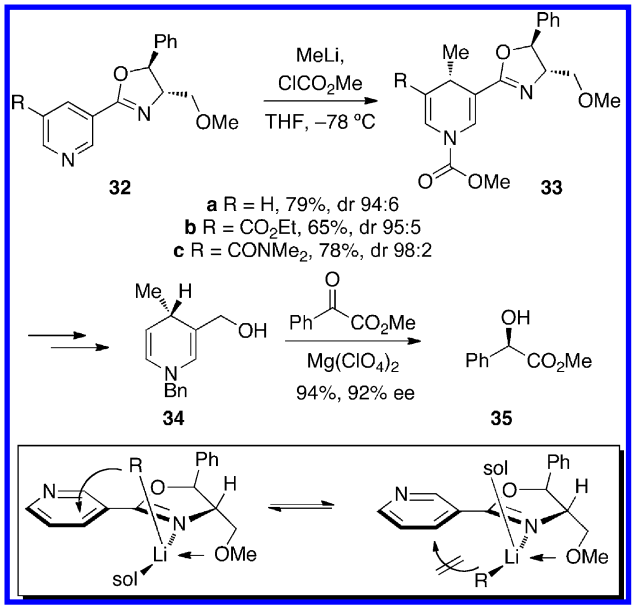
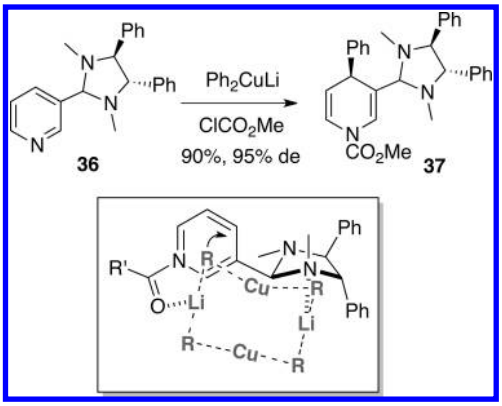
Scheme 29. Diastereoselective Addition to 4-Position of Pyridine-3-oxazolines in the Synthesis of a NADH Mimic



model of addition to alkenyl oxazolines, involving delivery of the nucleophile by chelation to the auxiliary.[188] Building on the work of Ohno et al.,[189] Meyers and Oppenlaender developed the chiral 4-methyl-1,4-dihydropyridines as efficient, albeit slow, NADH (reduced nicotinamide adenine dinucleotide) mimics.[33] Subsequent removal of the auxiliary, and optimization of the peripheral groups, led to highly enantioenriched dihydropyridine **34**, which transferred the stereochemically defined

Scheme 30. Diastereoselective Addition Controlled by a Chiral Aminal Derived from Pyridine-3-carboxaldehyde

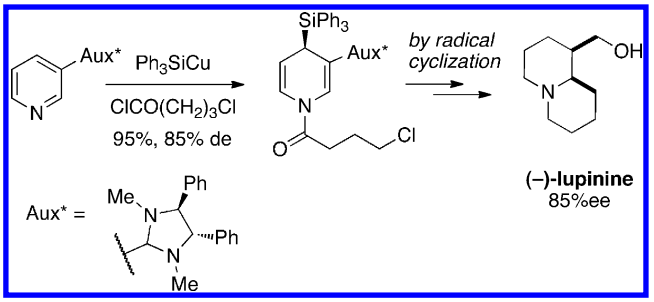


hydrogen atom to benzoyl formic ester to provide methyl mandelate **35** with chirality transfer of up to 95%.

Mangeney, Alexakis, and co-workers developed a diastereoselective addition of organocuprates to the 4-position of *N*-acyl pyridinium salts **36** using chiral aminal auxiliaries derived from C_2-symmetric chiral diamines (Scheme 30).[190−192] The auxiliary could be introduced efficiently from pyridine-3-carboxaldehyde and removed by treatment with 5% HCl to regenerate the aldehyde. In the transition state, a steric difference between the two faces of the pyridinium salt is created by the *N*−Me substituents of the aminal, adopting a trans relationship with the Ph groups. Coordination to the nitrogen of the aminal directs the dimeric cuprate nucleophile by coordination to provide **37** in high yield and stereocontrol. This proposed arrangement includes coordinating interactions between the dimeric cuprate and both the acyl carbonyl and the aminal nitrogen, providing a preferred conformation for nucleophilic attack. Low diastereoselectivity was observed with *N*-alkyl pyridinium salts due to the increased rotational freedom of the pyridinium ring in the absence of the coordinating carbonyl group.[192]

A range of nucleophiles was examined, generally providing high stereoselectivity (up to 95% de) and excellent regioselectivity in the cases of alkyl-, aryl-, and vinylcopper reagents. A study into the addition of various enolates gave much poorer regioselectivity.[193] The reagent $CuCH_2CO_2Et$ afforded the 6-adduct exclusively regardless of the acylating agent, but 2-ethoxy vinylcopper gave good 4-selectivity in the presence of benzoyl chloride. Alkynylcopper reagents again appear to be anomalous, providing 6-selective addition (discussed in section 2.1).[192] A range of functionalized acyl chlorides were used as activating agents, allowing short asymmetric syntheses of indoloquinolizine and benzoquinoline frameworks via an acid-promoted cyclization from indole moieties on the acyl group to the 6-position of the dihydropyridine (see section 3.3 for further discussion).[194,192] Alternatively, the use of activating groups bearing haloalkyl

Scheme 31. Access to Alkaloid Frameworks by the Use of Functionalized Acyl Chlorides in the Diastereoselective Addition of Cuprate Reagents



functionality enabled a radical cyclization from the functionalized acyl group onto the dihydropyridine to access alkaloid natural products. For example, the addition of a silyl group provided a stereochemical marker for the synthesis of (−)-lupinine and set up a selective radical cyclization from the chloroalkyl activating group (Scheme 31).[195,196]

Davies and co-workers reported the use of an iron acyl auxiliary $[\eta^5\text{-}(Cp)Fe(CO)(PPh_3)]$ at C-3, which gave high levels of stereoinduction due to a postulated $\pi-\pi$ interaction involving the triphenylphosphine ligands.[34] Complete regio- and stereoselective additions were obtained with alkyl- and aryllithium reagents. In the latter system the addition was proposed to occur to the pyridine prior to trapping with an acyl or alkyl electrophile in good yields. Indeed, treatment with methanol instead of the acyl electrophile afforded the unsubstituted 1,4-dihydropyridine.

Nicotinic amides bearing various chiral auxiliaries have been shown by Yamada and co-workers to undergo face-selective 1,4-additions. π-Stacking interaction of the auxiliary with the cationic pyridinium salt led to the remote asymmetric induction by hindering one of the pyridinium faces. Initial reports used an oxazolidinone and thiazolidine-2-thione auxiliaries, which provided moderate levels of regio- and diastereoselectivity for

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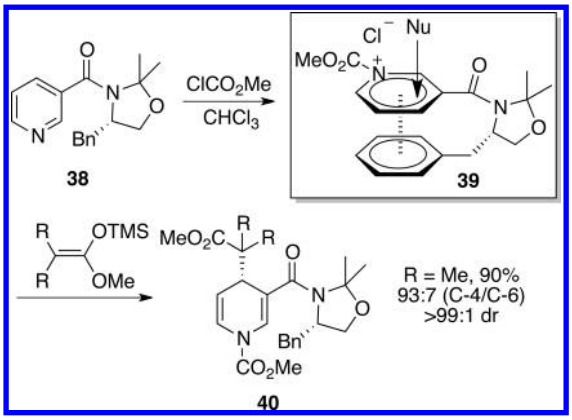
cuprate and silyl ketene acetals.[197,198] Complete diastereoselectivity was obtained by establishing an intramolecular cation-π

Scheme 32. Addition to Chiral Cation-π Complexes of Pyridinium Salts

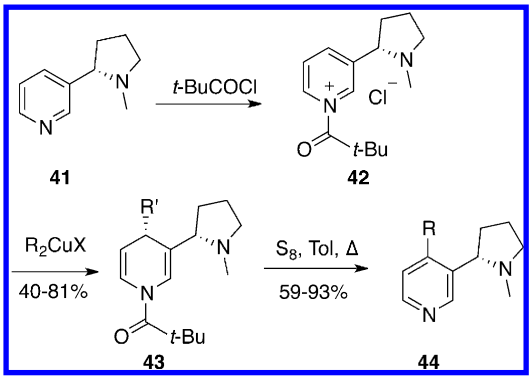


interaction between the pyridinium cation and a phenyl moiety on the auxiliary.[199] For example, the addition of silyl ketene acetals to **38** in the presence of methyl chloroformate gave >99% diastereoselectivity with good regioselectivity, providing dihydropyridine **40** (Scheme 32). The nucleophiles were successful in the system as chelation control was not necessary to achieve stereoinduction. The proposed interaction in intermediate **39** was supported by NMR studies, ab initio calculations, and crystal structures. Hypothesis for orientation of the pyridinium is not well developed, but the preferred conformation of the intermediate as indicated was supported by calculation. The auxiliary was removed using Schwartz's reagent ($Cp_2Zr(H)Cl$) to give the corresponding aldehyde without reduction of the other functionality in the 1,4-dihydropyridine products.

The same system achieved high stereoselectivity for the 2-selective addition of allyl metal nucleophiles.[200] Generally high diastereoselectivity was achieved for the major product, but the regioselectivity was less predictable. Allyltributyltin provided 92% selective addition at C-2 (92:8 dr) with 8% of C-6 addition. Allyl indium afforded a ratio of up to 70/30 for the 2-/6-selective addition, but under similar conditions prenylindium gave 94% 4-selectivity, being a softer nucleophile (see section 2.1).

(*S*)-Nicotine **41** is a viable substrate for the 4-selective addition of cuprate reagents that proceeded in high yield and generally high diastereoselectivity.[201] Previously, nicotine has proved to be a problematic substrate because of the competing nucleophilicity of the pyrrolidine nitrogen. Indeed, in the presence of phenyl chloroformate, the pyrrolidine nitrogen is acylated, which can lead to the nucleophilic opening of the pyrrolidine ring.[202] Comins and co-workers demonstrated that a successful 4-addition could be achieved by the use of the hindered pivaloyl chloride, which reacted selectively to give the desired pyridinium salt **42**. The addition of alkyl and aryl cuprates occurred with complete 4-selectivity and with high diastereofacial selectivity, presumably due to complexation with the chiral pyrrolidine ring. The dihydropyridines **43** were subsequently rearomatized with elemental sulfur to access a range of nicotine derivatives **44** for investigation of potential biological application in the treatment of central nervous system (CNS) diseases (Scheme 33).

Scheme 33. Addition to Nicotine: Synthesis of Nicotine Derivatives



3. NUCLEOPHILIC ADDITION TO *N*-ALKYL PYRIDINIUM SALTS AND THEIR DERIVATIVES

N-Alkyl pyridinium salts are comparatively less electrophilic than their *N*-acyl counterparts; hence, the addition of nucleophiles generally requires harsher conditions to have comparable high conversions.[192] The regioselectivity obtained in nucleophilic additions to these activated heterocycles is inherently dependent upon the structure and size of the pyridine *N*-substituent, as well as the nature of the nucleophile.[203] Additionally, in some circumstances, the C-2/C-6-to-C-4 regioisomeric ratio can be governed by a thermodynamic equilibration of the 1,2-dihydropyridine to the 1,4-dihydropyridine. However, by modulating temperature of addition, nitrogen substituent, and nature of the nucleophile, it is possible to induce good site selectivity.

Dihydropyridines accessed by the nucleophilic addition to *N*-alkyl pyridinium salts are generally less stable than those formed by acyl activation because they include a reactive enamine functionality. Consequently they are generally not isolated but are subjected to additional reactions in situ. Electron-withdrawing substituents located at the C-3 position of the pyridine moiety are commonly found.[2,204] This additional polarization of the pyridinium moiety renders the pyridinium ring more reactive toward nucleophilic attack and, with these substrates, stabilizes the resultant dihydropyridine product.

Typically, *N*-alkyl pyridinium salts are preformed or purified following an electrophilic alkylation reaction between an alkyl halide (or pseudohalide) and pyridine (the Menschutkin reaction). Alternatively, *N*-alkyl pyridinium salts can be synthesized via the Zincke reaction, which will be discussed in more detail in section 3.2.

3.1. Regioselective Additions to *N*-Alkyl Pyridinium Salts—Nature of the Nucleophile

This section covers the nucleophilic addition to *N*-alkyl pyridinium salts reported from the early 1940s to recent publications. To compare the regioselectivity obtained by each method, the studies are categorized by the type of nucleophile.[22−24,205]

3.1.1. Organometallic Reagents as Nucleophiles. The earliest accounts relating regioselective additions of nucleophiles to *N*-alkyl pyridinium salts were mainly aimed toward the synthesis of benzomorphan and morphinan analgesics and their analogues (Figure 8).[206−213] These reactions were limited to the addition of benzyl Grignard reagents to *N*-methyl pyridinium salts **45** (Table 13). The resultant 1,2-dihydropyr-

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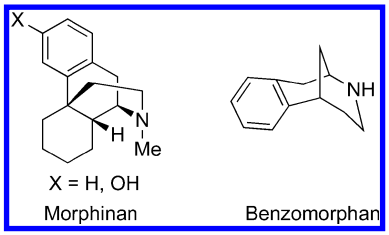


Figure 8. Benzomorphan and morphinan targets.

idines **46** were often unstable species and, thus, were commonly reduced by catalytic hydrogenation to the corresponding 1,2,5,6-tetrahydropyridine or piperidine derivatives **47**.

The addition of other Grignard reagents to *N*-alkyl pyridinium salts resulted in the formation of dihydropyridines that were either too unstable for isolation or polymerized upon treatment with base. For example, only a very small quantity of a 2-substituted piperidine (~6%) could be isolated from the addition of PhMgBr or PhLi to *N*-benzylpyridinium chloride following a PtO_2/H_2 reduction.[214−216] Indeed, there are few examples of regioselective organomagnesium additions to these pyridinium salts that provide synthetically useful yields of dihydropyridines: MeMgI adds efficiently to *N*-phenyl-3,5-diethyl-2-propylpyridinium iodide at the C-6 position;[217] BnMgCl adds selectively at C-4 of the hindered *N*-methyl-2,4,6-triphenylpyridinium perchlorate;[218] and PhMgBr and EtMgBr react at the C-2 position of *N*-methyl-4-picolinium iodide.[219] Lyle and co-workers undertook a more thorough study into the regioselective additions of various organometallic nucleophiles to *N*-alkyl pyridinium salts **48** bearing an electron-withdrawing substituent (EWG) at the C-3 position (Table 14).[220,221] The authors were also interested in the chemoselectivity of organometallic nucleophilic addition to the pyridinium versus the electrophilic carbonyl C-3 substitutent. With alkyl Grignard or organocadmium reagents, a mixture of C-2 (**49**) and C-6 (**50**) addition was usually observed (Table 14, entries 1 and 4). Comparatively, the addition of aryl nucleophiles was only achieved in modest yield at the C-6 position (Table 14, entries 2−3 and 5). Organocadmium reagents attacked the pyridinium moiety exclusively, providing a means for the synthesis of functionalized pyridine derivatives. Phenyl lithium reacted violently with *N*-benzyl-3-cyanopyridinium bromide without isolation of the product, whereas Ph_2Hg proved unreactive. Interestingly the resultant dihydropyridines in these accounts were stable and could be isolated. Pyridinium salts bearing additional methyl groups at C-2, C-4, or C-5 positions were also shown to undergo addition of organomagnesium nucleophiles at the C-2 or C-6 positions.

Addition at the C-4 position was observed only when a triphenylmethyl group was attached to the pyridine nitrogen, presumably due to the fact that the bulkiness of the activating group blocked addition at the 2- and 6-sites. A 35% yield was obtained for 4-phenylpyridine after the thermal decomposition of the 1,4-dihydropyridine intermediate **52** derived from the addition of PhMgBr to *N*-triphenylmethylpyridinium tetrafluoroborate **51** (Scheme 34). In comparison, high C-4 regioselectivity was previously obtained in the hydride reduction of pyridinium salts containing a bulky *N*-substituent.[222]

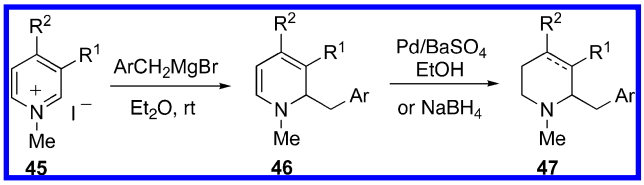
Concomitantly to Lyle and Comins' work on *N*-acyl pyridinium salts discussed in section 2,[32,40,58] Wenkert et al. described the addition of lithium dimethylcuprate exclusively to the C-4 position of *N*-alkyl pyridinium salts. This afforded the corresponding unstable 1,4-dihydropyridines, which were treated with HBr/benzene to yield the tetracycles **53a−c** as single regioisomers (Scheme 35).[223] These cascade one-pot reactions are related to the "Wenkert procedure", which is reviewed in section 3.3.

In 2000 Hilgeroth and Baumeister disclosed the high yielding regioselective C-4 addition of PhMgCl, in the presence of catalytic amounts of CuI, to *N*-methyl (**54**) and *N*-benzyl (**55**) pyridinium salts in the synthesis of 6,12-diazatetrakishomocubane analogues **56** and **57** (Scheme 36).[224] Independently, Bennasar et al. studied the interaction of diphenyl cuprate with *N*-alkyl pyridinium salts containing a C-3 electron-withdrawing substituent (Scheme 37**A**).[225] Using the higher-order heterocuprate $Ph_2Cu(CN)Li_2$, high C-4 regioselectivity was achieved in good yields. The resultant dihydropyridine compounds were treated with 1,1,1-trichloroacetic anhydride (TCAA) to ensure their stability via the installation of an additional electron-withdrawing substituent at the C-5 position.

The scope of nucleophile was extended to functionalized aryl Grignard reagents using Knochel's protocol with a catalytic amount of a copper salt (Scheme 37**B**).[226−230] The application of aryl Grignard reagents bearing an electron-withdrawing substituent gave lower C-4 regioselectivities. To circumvent this problem, similar to Lyle's approach,[220] the pyridinium *N*-methyl group was replaced by the hindered *N*-benzhydryl substituent. Consequently, improved isolated yields and exclusive C-4 regioselectivity were achieved. In this case the same 1,4-dihydropyridine product and only slightly reduced yields were obtained without the CuI additive.

For the addition of nonaromatic organocuprate reagents to *N*-methyl pyridinium salts, the situation was more complex

Table 13. Additions of Benzyl Grignard Reagents Aimed Toward Benzomorphan and Morphinan Syntheses



entry	R^1	R^2	$ArCH_2MgBr$	yield (%)	reference
1	$-(CH_2)_4-$		BnMgBr	83% (**46**)	206
2	$-(CH_2)_4-$		*p*-$MeOC_6H_4MgBr$	30% (**46**)	207
3	Me	Me	*p*-$MeOC_6H_4MgBr$	25% (**47**)	208−210
4	Et	Et	*p*-$MeOC_6H_4MgBr$	30% (**47**)	211

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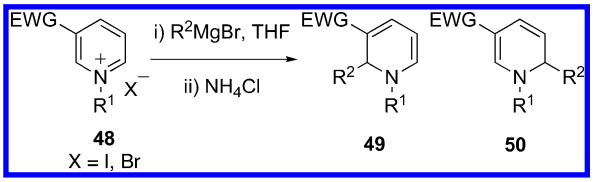
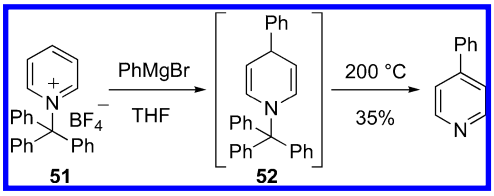
Table 14. Addition of Organometallic Species to *N*-Alkyl Pyridinium Salts Containing a C-3 EWG

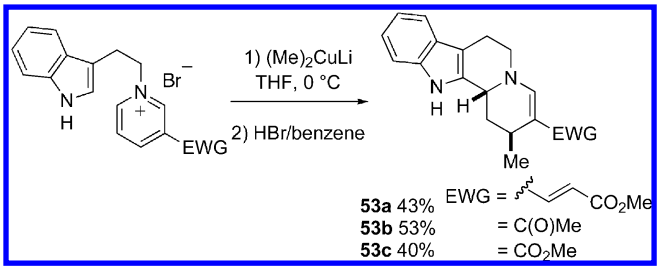


entry	R^1	EWG	R^2 MgBr	isolated product	yield (%)
1	Me	CN	MeMgBr	**49** + **50**	(14 + 26)
2	Me	CN	*p*-TolylMgBr	**50**	40
3	Bn	CN	*p*-TolylMgBr	**50**	42
4	Me	CO_2Me	MeCdCl	**49** + **50**	(10 + 26)
5	Me	CO_2Me	PhCdCl	**50**	45

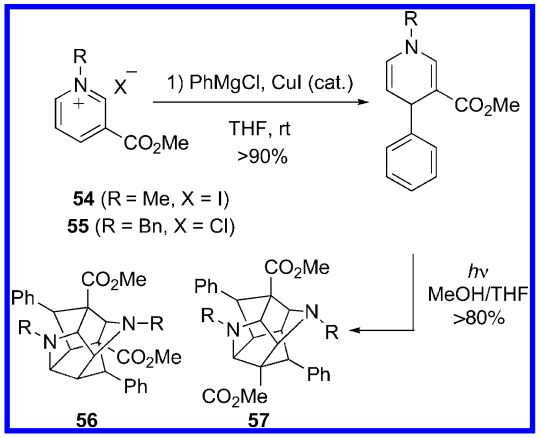
Scheme 34. Addition of PhMgBr to a Hindered *N*-Alkyl Pyridinium Salt



Scheme 35. Regioselective Additions of Organocuprate Reagents to *N*-Alkyl Pyridinium Salts



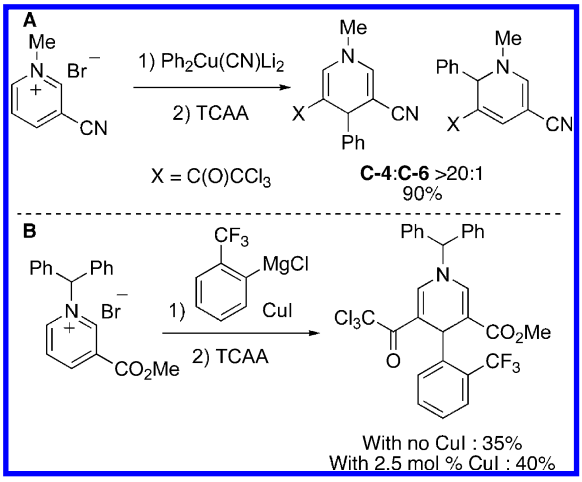
Scheme 36. Regioselective Addition of PhMgCl Using a Catalytic Amount of CuI



(Table 15).[231] Dialkylcuprates showed preferential addition at the C-4 position, whereas harder alkynyl/alkenyl cuprates displayed higher C-2/C-6 selectivity. It was concluded that lower basicity of the organocuprates could be correlated with higher C-6 selectivity, although the yields were significantly lower with these reagents (compare entries 2–6).

To access natural products containing a 2-vinylindole moiety such as (±)-uleine, (±)-apparicine, and (±)-ngouniensine,

Scheme 37. Addition of Aryl Cuprates to *N*-Alkyl Pyridinium Salts



mixed organocuprate reagents derived from vinylstannane **59** were explored (Table 16).[232] The regioselectivity of the reaction was somewhat dependent on the method of cuprate generation. When the vinylstannane **59** was directly subjected to transmetalation with the high-order $Me_2Cu(CN)Li_2$, the addition of the mixed organocuprate occurred preferentially to the C-6 position (entries 1 and 2). When the vinylstannane **59** was first treated with MeLi, then converted to its corresponding divinylcuprate by treatment with $MgBr_2{\cdot}OEt_2$ followed by CuI, and then reacted with the pyridinium salt **58**, the regioselectivity was switched for the C-4 addition. A precomplexation of the magnesium atom with the C-3 carbonyl group is believed to direct the attack of the nucleophile to the less-hindered C-4 position.

Donohoe et al. recently reported a highly regioselective addition of various Grignard reagents to the *N*-methyl or *N*-allyl pyridinium salts (**60** and **63**) derived from methyl 4-(methyloxy)-2-pyridinecarboxylate (Scheme 38A) or its analogous methyl-6-(methyloxy)-2-pyridinecarboxylate (Scheme 38B).[179] This methodology represents rare examples whereby a quaternary carbon center was formed through a C-2 selective addition of a nucleophile to a pyridinium salt bearing a C-2 substituent. The high regioselectivity observed was explained by the favorable hard–hard interaction between the electron-deficient C-2 position and more electrophilic C-2 position with Grignard reagents. A wide variety of nucleophiles were employed to readily access 4- and 2-pyridones after the hydrolysis of the enol ether. When diorganozinc reagents, generated in situ, were added to the same pyridinium systems,

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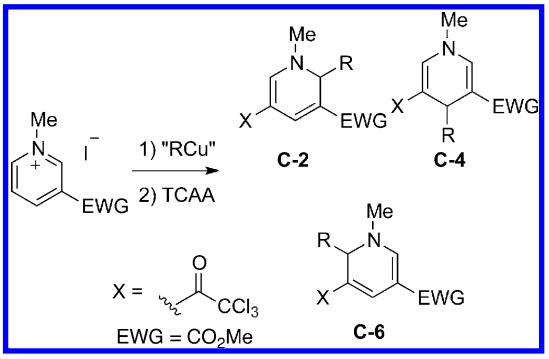
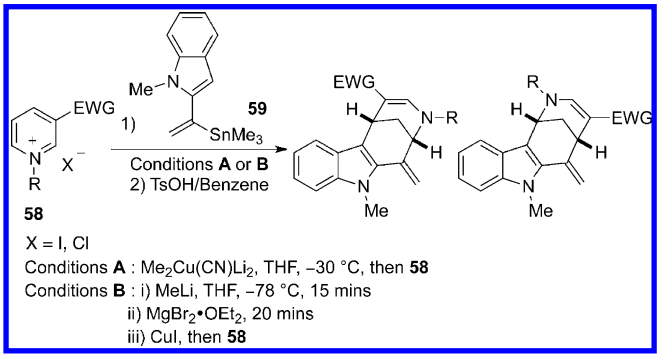
Table 15. Addition of Nonaromatic Organocuprate Reagents to *N*-Alkyl Pyridinium Salts



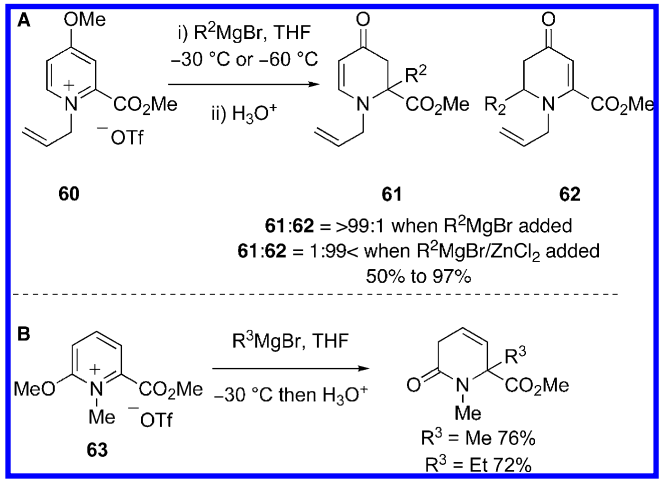
entry	"RCu"	ratio C-2/C-4/C-6	combined yield (%)
1	Bu_2CuLi	0:90:10	77
2	$(PhC{\equiv}C)_2Cu(CN)Li_2$	50:0:50	68
3	$(PhC{\equiv}C)Cu(CN)Li$	40:0:60	30
4	$(PhC{\equiv}C)_2Cu(CN)(ZnCl)_2$	20:0:80	18
5	$(PhC{\equiv}C)Cu(CN)(ZnCl)$	0:0:100	<10
6	$(PhC{\equiv}C)MgBr/CuI$ (cat.)	100:0:0	65

Table 16. Addition of 2-Vinylindole Cuprates to *N*-Alkyl Pyridinium Salts



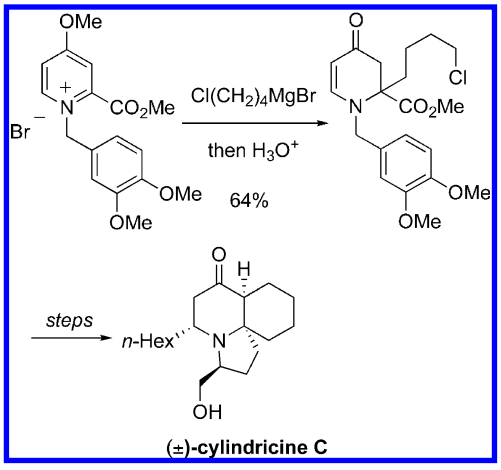
entry	R	X	EWG	cuprate generation	ratio C-6/C-4	yield (%)
1	Me	I	CO_2Me	**A**	6:1	45
2	Bn	Cl	C(O)Me	**A**	>20:1	35
3	Me	I	CO_2Me	**B**	6:5	60
4	Bn	Cl	C(O)Me	**B**	>1:20	40

Scheme 38. Regioselective Addition of Grignard or Zinc Reagents to *N*-Methyl or *N*-Allyl Pyridinium Salt Forming 2- or 4-Pyridones



addition was observed at the softer C-6 position, also with excellent regioselectivity (Scheme 38A with $ZnCl_2$). A modified

Scheme 39. Total Synthesis of (±)-Cylindricine C by Donohoe et al.



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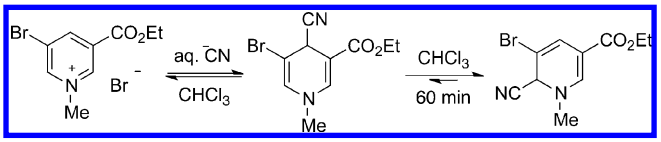
version of the regioselective Grignard reagent addition methodology was used by Donohoe in the total synthesis of (±)-cylindricine C and formal synthesis of (±)-cylindricine A (Scheme 39).[233]

3.1.2. Cyanide as Nucleophile. Cyanide nucleophiles are much less reactive toward pyridinium salts relative to Grignard or organolithium reagents and are much less studied. Preactivation of the pyridine ring through *N*-alkylpyridinium salts formation is mandatory for the addition of $^{-}$CN to occur, and efficient reactivity is often only observed with an electron-withdrawing substituent at the C-3 position of the pyridinium.

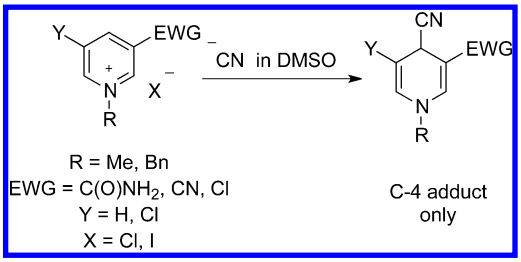
Foster and Fyfe initially reported that a Reissert-type cyanide addition occurred with unsubstituted *N*-methyl pyridinium iodide or *N*-(*p*-dinitrobenzyl)pyridinium iodide, affording a 3:2 mixture of C-4 to C-2 addition.[234] Lyle and Gauthier also

Scheme 40. Lyle and Gauthier's Regioselectivity Study on the Additions of Cyanide to 3,5-Disubstituted Pyridinium Salts



observed poor regioselectivity while reacting 1-methyl-3-bromo-5-ethoxycarbonylpyridinium bromide in ethanolic solution or chloroform with an aqueous cyanide source (Scheme 40).[235] The major product observed after crystallization in CCl_4 was assigned to be the C-6 adduct. The latter dihydropyridine could then be gradually converted to the 1,4-dihydropyridine in chloroform over 60 min. This equilibration was also reported

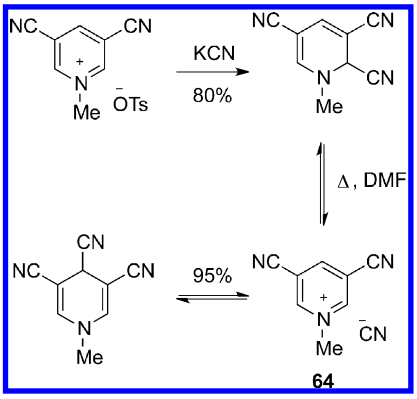
Scheme 41. Regioselective Additions of Cyanide to Various Pyridinium Salts Containing an Electron-Withdrawing Substituent on the 3-Position



by Foster and Fyfe with the same substrate, but a different behavior was noted when the reaction was performed in dimethylsulfoxide (DMSO) or with other pyridinium salts (Scheme 41).[234]

In Foster and Fyfe's study, the reaction of *N*-benzyl-3-carboxamidopyridinium chloride, *N*-methyl-3,5-dichloropyridinium iodide, or *N*-benzyl-3-cyanopyridinium bromide with a cyanide ion in DMSO showed the exclusive addition of the cyanide to the C-4 position. The position of the $^{-}$CN attack was made evident by preparing the corresponding 2,6-dideuterated pyridinium salts[236] and reacting them in the same conditions. One general conclusion made by the authors was that the observed C-4 regioselectivity of the cyanide addition can be correlated to solvent effects and not to the structure of the pyridinium salt.[237−239] However, the authors suggested that it could be possible to favor the formation of the C-2 or C-6 isomers by stabilizing the dihydropyridine intermediate sufficiently with two strongly electron-withdrawing substituents at the 3,5-positions. This was made

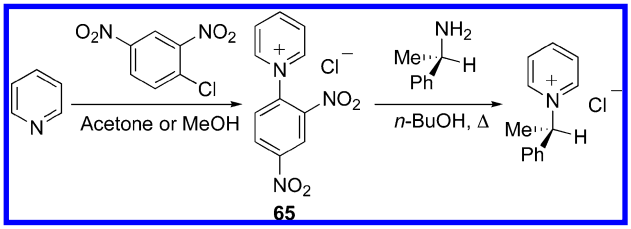
Scheme 42. Reversible Addition of Cyanide to *N*-Methyl-3,5-dicyanopyridinium Tosylate



evident by Wallenfels and co-workers with the reaction of cyanide anion with *N*-methyl-3,5-dicyanopyridinium tosylate, which gave exclusively 1,2-addition and a stable adduct in 80% isolated yield (Scheme 42).[240,241]

The 2-isomer was then converted to the 1,4-isomer in 95% yield by heating it to 150−160 °C in dimethylformamide (DMF), demonstrating the reversibility of cyanide addition via reformation of the pyridinium salt **64** through attack at the C-4 position. Substituents at the 4-position of pyridinium salts disfavored addition of cyanide at that site and thus favored addition at the C-2 or C-6 positions. It was reported that the addition of $^{-}$CN to 4-Me-NAD^{+} was very slow and poorly regioselective, and little addition of $^{-}$CN was observed on more-hindered pyridinium salts.[242−245] However, a 43% yield was observed for the addition of cyanide at the C-4 position only with the more reactive 3,5-dicyano-1,2,4,6-tetramethylpyridinium tosylate.[246]

Scheme 43. Formation of a Chiral *N*-Alkyl Pyridinium Salt Using the Zincke Reaction



3.2. Diastereoselective Additions of Organometallic Reagents to *N*-Alkyl Pyridinium Salts

The Marazano group reported the first efficient diastereoselective and regioselective addition of an organometallic reagent to enantioenriched *N*-alkyl pyridinium salts.[247] The generation of these pyridinium salts relied on a chiral auxiliary installed via a Zincke reaction (Scheme 43).[248−252] This reaction could be effectively performed by mixing an enantioenriched chiral amine with the highly electrophilic *N*-2,4-dinitrophenylpyridinium chloride (**65**). The Zincke reaction is an efficient

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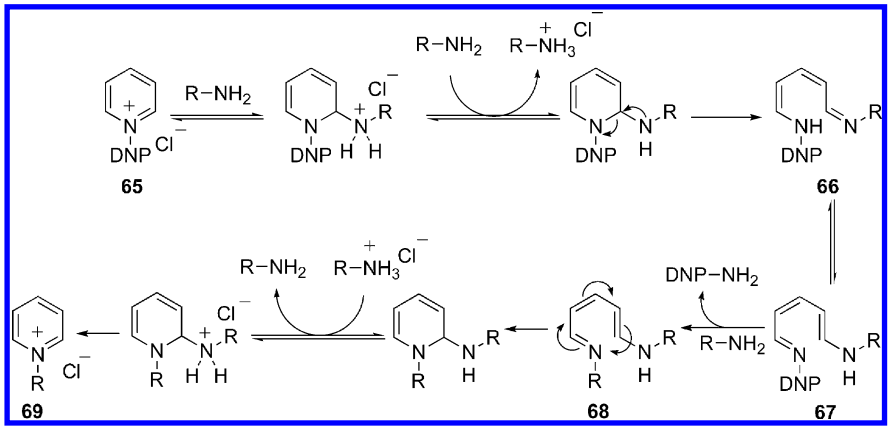
Scheme 44. General Mechanism of the Zincke Reaction

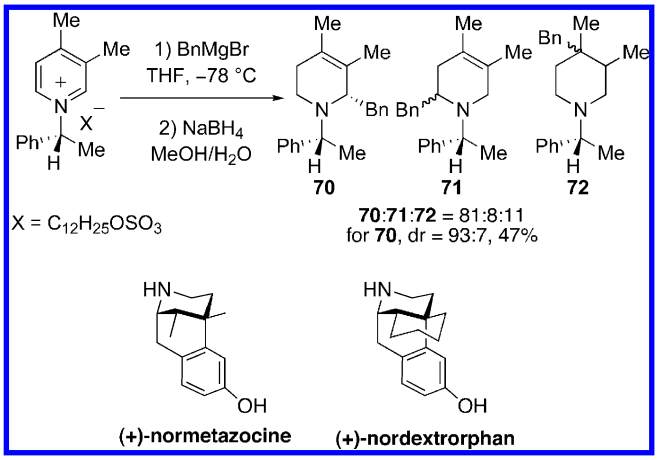


alternative to the direct alkylation using chiral secondary halides, where the stereochemical information is sometimes partially lost due to a competitive S_N1 displacement pathway. Alternatively, as found by Katritzky and co-workers, the reaction between a pyrilium salt equivalent and an amine can yield directly the desired *N*-alkyl pyridinium salts.[253,254]

The mechanism of the Zincke reaction has been extensively studied and has been postulated to proceed by the addition of an amine equivalent to the C-2 position of *N*-2,4-dinitrophenylpyridinium chloride **65** and ring-opening to form the dianil salts **66** and **67**, which are in equilibrium (Scheme 44).[255] The addition of 1 equiv of amine to the dianil salts forms an intermediate **68** by expulsion of 2,4-dinitroaniline, which ring-closes back to the desired *N*-alkyl pyridinium salt **69** through a 6π-electrocyclization.[256]

Genisson and Marazano used these salts in the rapid stereoselective syntheses of (+)-normetazocine and (+)-nordextrorphan, which are important precursors to benzomorphan

Scheme 45. Addition of Benzylmagnesium Bromide to Chiral *N*-Alkyl Pyridinium Salts



and morphinan analgesics.[247] The addition of substituted benzyl Grignard reagents to the 3,4-dimethyl pyridinium salt derived from (*R*)-(+)-1-phenethylamine with a lipophilic sulfonate counterion afforded unstable dihydropyridines, which were reduced in situ to the tetrahydropyridines (Scheme 45). The diastereoselectivity was generally high; however, the isolated yields for the tetrahydropyridine were only modest (47% for **70** in Scheme 45). Grewe and Mondon reported a similar behavior with BnMgBr on an achiral *N*-methyl pyridinium salt during synthetic studies toward the same natural benzomorphan analogues (see entry 1, Table 13).[206,257,258]

The high diastereoselectivity achieved by Marazano was unexpected considering the freedom of rotation of the chiral auxiliary. In analogous nucleophilic additions to iminium

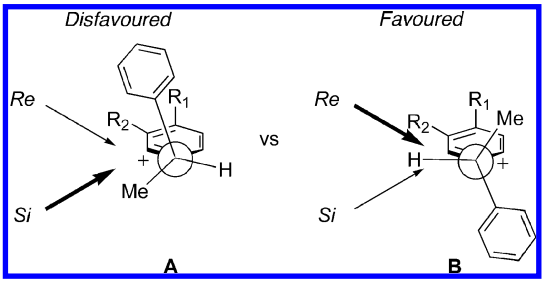


Figure 9. Stereochemical models to explain the face-selectivity in Marazano's system.

compounds containing a chiral *N*-alkyl auxiliary, good stereoselectivities are obtained when chelation or allylic 1,3-strain favor a certain conformation.[259−261] In the case of pyridinium salts, Newman projections of two possible conformers **A** and **B** can be drawn to explain the stereoinduction of the reaction (Figure 9). To account for the major isomer where the benzyl adds preferentially to the *Re* face of conformation **B**, the favored attack in **B** can be closely compared to the analogous Felkin−Anh model for nucleophilic addition to carbonyl compounds where chirality is α to the side of attack.[262,263]

The latter methodology was extended to unsubstituted *N*-alkyl pyridinium salts to form enantioenriched 2-substituted and 2,6-disubstituted 1,2,5,6-tetrahydropyridines.[264] Using the pyridinium salt derived from pyridine and (*R*)-(+)-1-phenethylamine using the Zincke procedure, the regioselectivity of the reaction was found to be dependent upon the size of the Grignard reagent. Small nucleophiles added exclusively to the C-2 position (MeMgBr, vinylMgBr) and bulky alkyl chains added preferentially to the C-4 position (*i*-PrMgBr, BnMgBr) due to steric hindrance from the chiral activating group. The modest diastereoselectivity was similar to that achieved through the addition of nucleophiles to chiral *N*-alkyl isoquinolinium salts.[265] To increase the diastereoselectivity, Marazano modified the chiral auxiliary by installing a (*R*)-(−)-phenylglycinol protecting group on the pyridinium salt. The addition of

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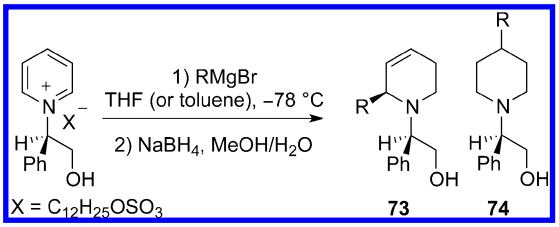
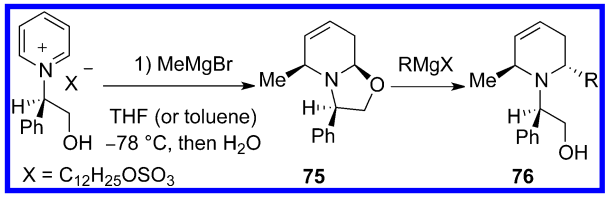
Table 17. Addition of Various Grignard Reagents to a Second Generation of Chiral *N*-Alkyl Pyridinium Salts



entry	RMgBr	dr for **73**	ratio C-2/C-4	yield **73** (%)
1	MeMgBr	90:10	100:0	45
2	VinylMgBr	90:10	100:0	27
3	*n*-PrMgBr	85:15	100:0	53
4	*i*-PrMgBr	91:9	79:21	35
5	BnMgBr	76:24	34:66	21

organomagnesium reagents gave significantly improved stereoselectivity with the (*R*)-(−)-phenylglycinol auxiliary (Table 17).

Scheme 46. Isolation of a Cyclic Aminal



Also, this auxiliary led to improved stability of the dihydropyridine intermediates. For example, when a (*R*)-(−)-phenylglycinol auxiliary was employed, the diastereoselective reaction could be stopped at the formation of a stable bicyclic aminal compound **75** when the $NaBH_4$ reduction step was omitted (Scheme 46). This aminal intermediate was then used in the diastereoselective synthesis of various *trans*-2,6-substituted tetrahydropyridines (**76**) via the addition of another equivalent of Grignard reagent.[266,267]

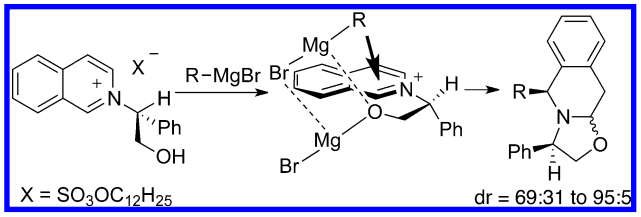
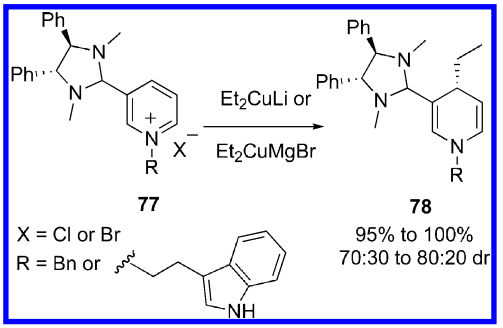


Figure 10. Stereochemical model explaining the high selectivity obtained in additions to *N*-alkyl isoquinolium salts.

The selectivity enhancement was explained by a precomplexation between the organometallic reagent and the magnesium alkoxide of the chiral auxiliary. This hypothesis was first examined in the *N*-alkyl isoquinolium series where the auxiliary again gave better selectivity (dr from 69:31 to 95:5) compared to the (*R*)-(+)-1-phenethylamine system (from 62:38 to 90:10) (Figure 10).[265]

Mangeney, Alexakis, and co-workers examined cuprate additions to the C-4 position of *N*-alkyl pyridinium salts such as **77** bearing a chiral aminal functional group at the C-3 position (Scheme 47).[192] However, only 70:30 to 80:20 dr's were obtained for the C-4 regioselective addition of Et_2CuLi to

Scheme 47. Addition of Et_2CuLi to Chiral Aminal-Containing *N*-Alkyl Pyridinium Salts



the pyridinium salts **78**. It was found later that *N*-acyl pyridinium salts afforded significantly higher diastereoselectivities for the same transformation (see section 2.5).

More recently, Kunz reported that *N*-(2,3,4,6-tetra-*O*-pivaloyl-*β*-D-galactopyranosyl)pyrid-4-one (R^1 = CH_2OPiv) and *N*-(2,3,4-tri-*O*-pivaloyl-*α*-L-arabinopyranosyl)pyrid-4-one (R^1 = H) could be transformed in situ into their corresponding *N*-glycosyl-4-triisopropylsilyloxypyridinium triflate salts (Table 18).[268,269] These reacted diastereoselectively with Grignard reagents to form enantioenriched 2-substituted dihydropyrid-4-ones **79**. No reaction occurred in the absence of the silyl activating reagent.

The 2-pivaloyl group on the chiral glycosyl auxiliary was proposed to control the selectivity of the reaction (Figure 11). The front face of pyridinium ring **A** was shielded by the steric interaction between the nitrogen heterocycle and the pivaloyl group, leaving the back face available. The Lewis basic oxygen atom of the 2-pivaloyl carbonyl group is thought to share electronic density with the upper side of the pyridinium salt, thereby limiting the attack of the nucleophile to the lower back face of the heterocycle. These results were supported by X-ray diffraction from one of the addition products (**79**) and by previous experiments on similar systems.[270−272]

Kunz and co-workers extended the scope of the reaction to pyridones by replacing the starting heterocycle by an *N*-galactosyl-2-pyridone compound, which reacted with Grignard reagents or organocopper reagents to yield **80** as the major isomer.[269,273] The 2-pyridones were activated with TMSCl or TIPSOTf and the addition of the nucleophile occurred selectively at the C-4 position of the pyridinium ring with excellent diastereoselectivities (Table 19).

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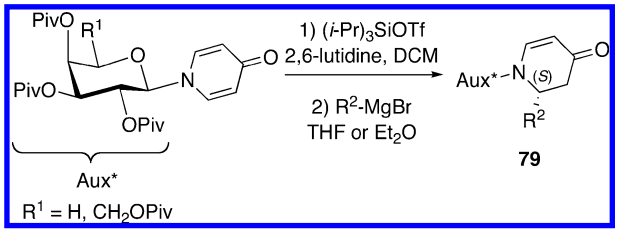
Table 18. Diastereoselective Synthesis of 2-Substituted Dihydropyrid-4-ones Using *N*-Glycosyl Pyridinium Salts



entry	R^2 MgX	dr (*S*)	yield (%)
1	MeMgCl	>95:5	74
2	*n*-PrMgCl	90:10	84
3	PhMgCl	0:100	83
4	*i*-PrMgCl	8:92	89
6	vinylMgBr	0:100	51
7	1-butenylMgBr	100:0	19

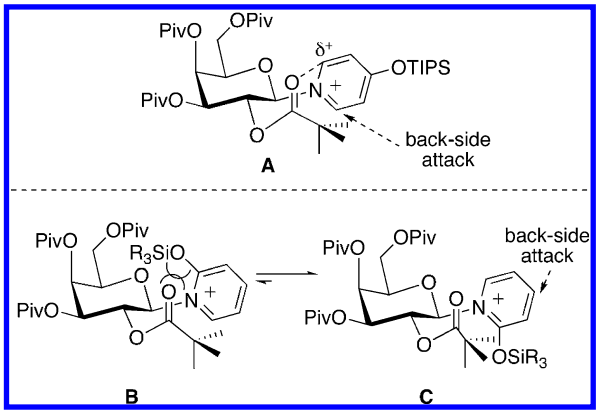


Figure 11. Stereochemical models proposed for the controlled addition.

The excellent regioselectivity and diastereoselectivity obtained can be accounted for by examining the two possible rotamers of the pyridinium such as in Figure 11. The stability of both rotamers is differentiated by an unfavorable steric repulsion observed in the rotamer **B**. This methodology was applied in the synthesis of benzomorphan derivatives by using substituted benzyl Grignard reagents.[274]

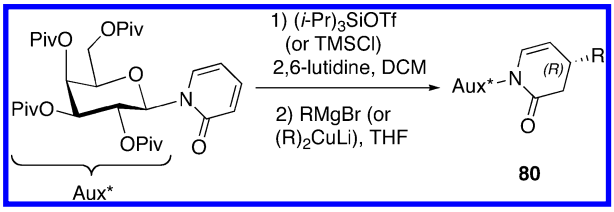
Planar chirality has been used by Ohno et al. to direct Grignard reagents reacting at the C-4 position of *N*-methyl NAD(P)$^+$ analogues.[275] The addition of various Grignard reagents to the pyridinium salt **81** gave exclusively the product **83**. In contrast, the addition of Grignard reagents to the pyridinium salt **82** furnished the opposite diastereoisomer (Table 20).

3.3. Regioselective Additions of Enolates to *N*-Alkyl Pyridinium Salts

The addition of stabilized nucleophiles, in particular enolates and their equivalents, constitutes an important class of reactions with *N*-alkyl pyridinium salts.[2,22−24,276,277] The seminal examples reported in this field were published by the Kröhnke group in the 1950s.[278,279] The authors intended to react alkyl pyridinium salts with aryl nitroso compounds in basic conditions to form nitrones **85** (Scheme 48).[280] Instead, they discovered one of the first examples of a regioselective addition of a stabilized nucleophile to the pyridinium ring moiety. Early reports by Kröhnke illustrated a reaction between acetone and *N*-(2,6-dichloro)benzylpyridinium bromide exclusively at the C-4 position forming **86**. The aryl nitroso equivalent was believed to aid the oxidation of the 1,4-dihydropyridinium salt. Other nucleophiles such as acetophenone, *p*-ethylacetophenone, *p*-bromoacetophenone, methylvinyl ketone, methylbenzyl ketone, and nitromethane were also shown to add to the pyridinium salt at the C-4 position.

Concomitantly to Kröhnke, early reports on the C-4 reduction of a *N*-benzylnicotinamidinium salt with sodium dithionite ($Na_2S_2O_4$) acting as the stabilized nucleophiles were disclosed.[281−283] The addition of sodium dithionite, a soft nucleophile, occurred at the C-4 position preferably to afford the more stable 1,4-dihydropyridine sulfinate adduct (Scheme 49).[284] Later, the products from this reduction were shown to be activated chemoselectively by protonation of the enamine *β*-

Table 19. Diastereoselective Synthesis of 4-Substituted Dihydropyrid-2-ones Using *N*-Glycosyl Pyridinium Salts



entry	RMgX	dr (*R*)	yield (%)
1	EtMgCl	>99:1	54
2	PhMgCl	>99:1	76
3	*i*-PrMgCl	1:99<	88
4	1-butenylMgBr	>99:1	86

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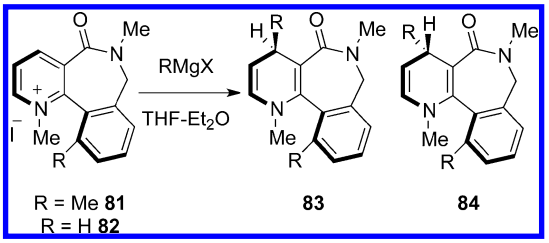
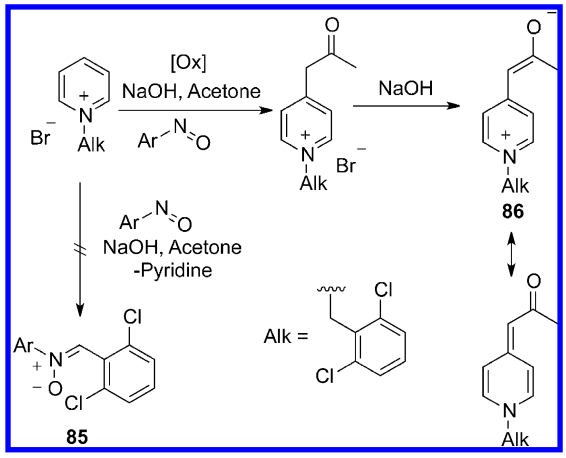
Table 20. Diastereoselective Additions of Grignard Reagents to Analogues of NAD(P)$^+$

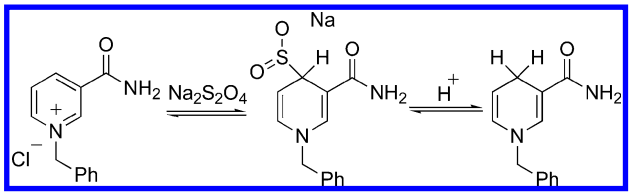


entry	pyridinium	RMgX	ratio 83/84	yield (%)
1	**81**	MeMgI	98:2	67
2	**81**	EtMgI	98:2	75
3	**81**	*i*-PrMgBr	97:3	72
4	**82**	MeMgI	2:98	60
5	**82**	*i*-PrMgBr	2:98	62

Scheme 48. Addition of Acetone to *N*-Alkyl Pyridinium Salt



Scheme 49. Addition of Sodium Dithionite to *N*-Benzylnicotinyl Chloride Salt



carbon and subsequent addition reactions with various nucleophiles at C-6 (vide infra).[285−289]

Also, the presence of C-3 electron-withdrawing groups on *N*-alkylpyridinium salts influences the reactivity of the enamines formed by C-4 selective additions and has been exploited in cascade cyclization processes to form 1,2,3,4-tetrahydropyridines **87** (Scheme 50). The nonconjugated enamine, formed by addition at C-4, may readily react with external electrophiles to form a 3,4-dihydropyridinium ion. A second nucleophile may then undergo an intra- or intermolecular addition to the reactive iminium. The overall process known as the "Wenkert procedure" has been extended to various carbon-based nucleophiles and often involves an indole moiety as the second nucleophile reacting through a Pictet−Spengler-like mechanism.[290−292] This strategy has been applied to access readily to various natural products such as alkaloids of the yohimboid series, (±)-vinoxine, (±)-geissoschizoline, (±)-ervitsine, and natural products derived from the *Strychnos* family (Figure 12).[293−298]

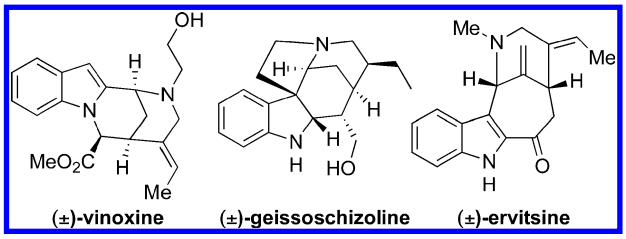
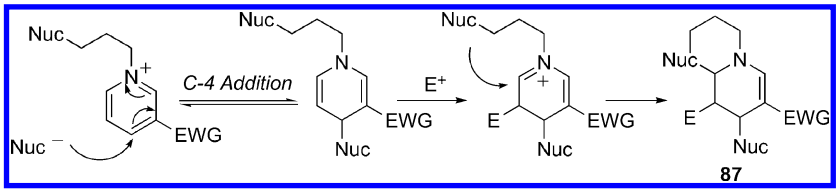


Figure 12. Synthesis of alkaloids approached via the "Wenkert procedure".

The following section will discuss the regioselectivity issues and synthetic outcome of reactions involving various stabilized carbon nucleophiles mainly employed in the "Wenkert procedure" introduced in section 3.1. Because many reviews have been published on this field, readers should refer to the previous publications for additional insights.[2,24,276,277,292]

3.3.1. Wenkert Procedure: Seminal Work. The first contemporary example of this concept was reported by the Wenkert group in a model study toward (±)-vallesiachotamine.[290] Later on, the same group revisited this target using a similar strategy, with a different stabilized nucleophile (Scheme 51).[299,300] Silicon-stabilized nucleophiles were screened, and the addition of the sodium anion of ethyl trimethylsilylacetate resulted in a completely regioselective C-4 addition to

Scheme 50. Chemoselective Protonation of 1,4-Dihydropyridines



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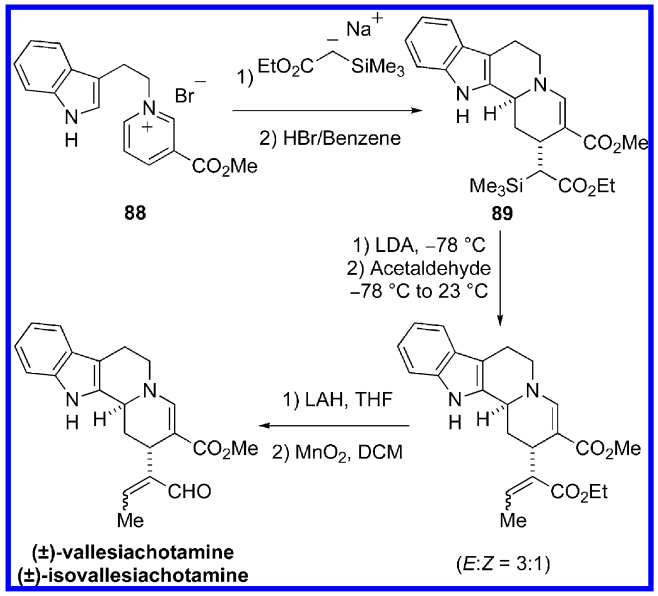
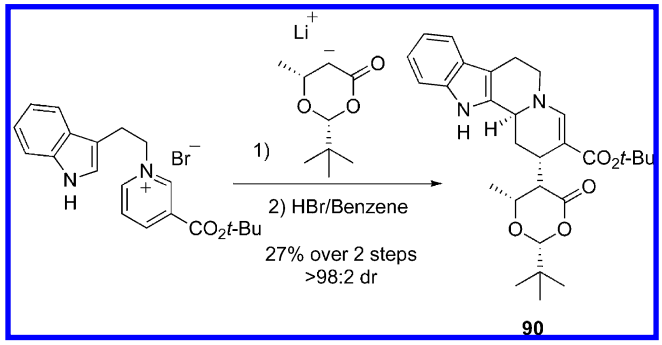
Scheme 51. Revisited Synthesis of (±)-Vallesiachotamine by Wenkert



pyridinium salt **88**. The resultant 1,4-dihydropyridine was cyclized to yield **86** as a single diastereoisomer with HBr in benzene. It was proposed that the indole moiety added preferentially in the axial position of the 3,4-dihydropyridinium intermediate, affording the anti-product **89**.

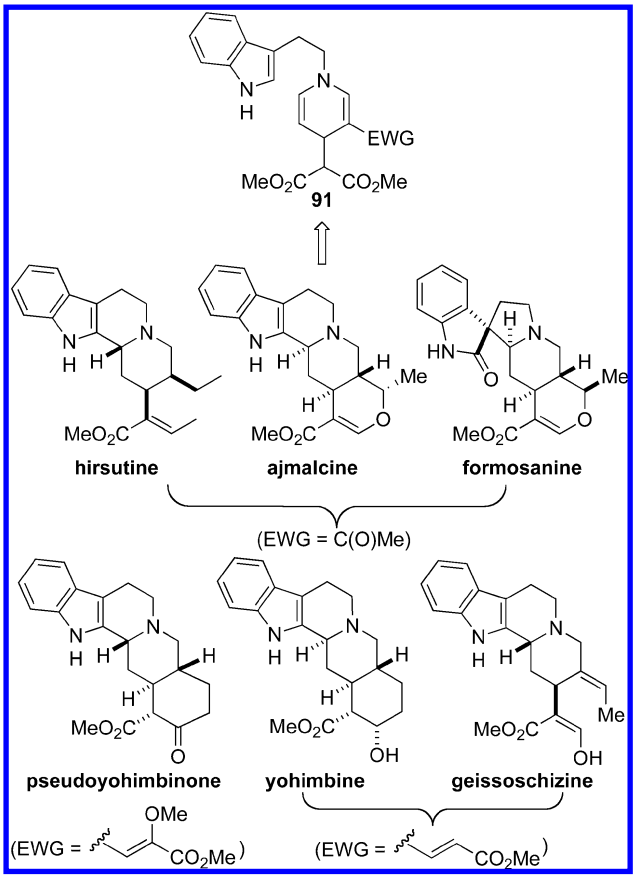
Scheme 52. Key Step in Synthesis of (+)-Vallesiachotamine by the Spitzner Group



The stereoselective syntheses of (+)-vallesiachotamine and (−)-isovallesiachotamine using the "Wenkert procedure" were undertaken in 1991 by Spitzner and co-workers.[301−303] The addition of a chiral enolate occurred exclusively at the C-4 position of an indole-tethered *N*-alkyl pyridinium salt, and cyclization occurred in HBr/benzene in 27% yield over two steps and excellent diastereoselectivity (>98:2 dr) to give the alkaloid **90** (Scheme 52).

The seminal discoveries demonstrated the high versatility of the Wenkert procedure in the preparation of indoloquinolizidine alkaloids. For example, the stable sodium salt of dimethyl malonate was reported to add exclusively to the C-4 position of pyridinium salts.[292,293,304−306] This led to the formal or total syntheses of various alkaloids using dihydropyridine intermediate **91** bearing different C-3 electron-withdrawing substituents as a common intermediate (Scheme 53). Various substituted enolates have been shown to undergo effective addition with excellent C-4 regioselectivity (Table 21).

Scheme 53. Synthesis of Various Alkaloids from the Addition of $NaCH(CO_2Me)_2$ to *N*-Alkyl Pyridinium Salts



In contrast to previous examples, addition of the potassium salt of Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane) to alkylated pyridinium salt **92** did not result in the expected C-4 addition.[312] Instead, a mixture of products **94** and **95** in a 2.5:1 ratio were observed following HCl/MeOH-mediated hydrolysis with an overall yield of 24% (Scheme 54). This was rationalized by a formal C-6 addition of the anion of Meldrum's acid to give the kinetic product **93**, which reduced another equivalent of pyridinium reactant **92** at the C-4 position to yield the observed derivatives after treatment with HCl/MeOH. The absence of the expected C-4 addition product was explained by a rapid oxidation of **93** before equilibration to the more stable 1,4-dihydropyridine derivative. The unusual isolation of the product of a formal C-6 addition (**94**) highlighted the thermodynamic equilibration of the regioisomeric products.

Both C-4 and C-6 addition products were also observed through the decomposition of a 1,2-dihydropyridine adduct through an irreversible ring-opening sequence similar to the formation of Zincke aldehydes to form a conjugated triene derivative (Table 22).[223,313] This was reported by Wenkert while studying the interaction of the indole-tethered pyridinium salt with a mixture of lithium diisopropylamide (LDA) and ethyl (methylthio)acetate. The mechanism of this ring-opening side-reaction was believed to involve the addition of the nucleophile to the C-6 position of the *N*-alkyl pyridinium salt. The resulting 1,2-dihydropyridine underwent ring-opening on treatment with 1 equiv of base to form the vinylogous amides or pyridone (Table 22 and Scheme 55).[313]

Generally the formation of dihydropyridines via the addition of a stabilized nucleophile is viewed as an ionic mechanism;

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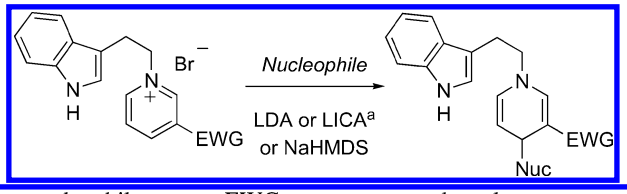
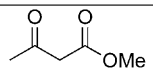
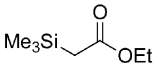
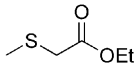
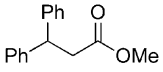
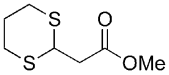
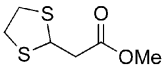
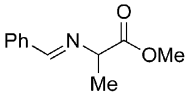
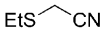
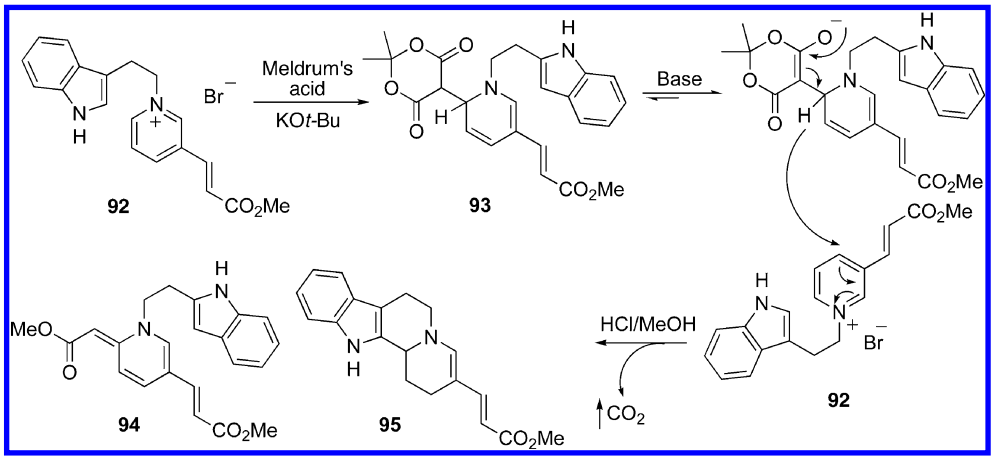
Table 21. Addition of Various Stabilized Nucleophiles to the C-4 Position of *N*-Alkyl Pyridinium Salts



entry	nucleophile	EWG	natural product	references
1		CHO	(±)-yohimbine	307
2		CO_2Me	(±)-vallesiachotamine (±)-isovallesiachotamine	300
3		CO_2Me	tetracyclic indoloquinolizidine	223
4		$C(O)NH_2$	naphtyridine derivatives	308
5		$C(O)NH_2$	naphtyridine derivatives	308
6		C(O)NHR	(±)-nauclefine	308
7		$C(O)NH_2$	naphtyridinedione derivatives	308, 309
8		CO_2Me	vinylogous urethanes derivatives	310
9		CO_2t-Bu and CO_2Me	(±)-antirhine	311

[a]LICA = Lithium isopropylcyclohexylamide.

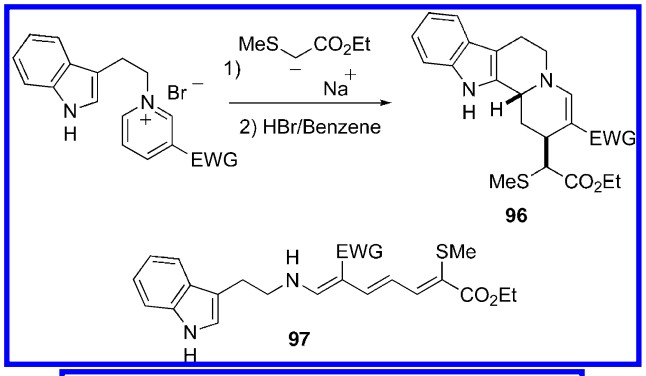
Scheme 54. Mechanistic Rationale for the Observation of Products 90 and 91

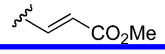


however, a radical pathway has also been postulated in few cases via a single electron transfer (SET) from the nucleophile to the pyridinium salt and radical termination between both partners.[223] For example, dimer **100** was formed from the pyridinium salt **99** under basic conditions (Scheme 56). Further reaction of **100** occurred in a mixture of chloroform/DMSO, forming a 1:1 mixture of 1,2-dihydropyridine **101** and 1,4-dihydropyridine **102** in 95% combined yield after 8 days. After an additional 3 days at room temperature, a 52% yield of cyclized product **103** and 33% yield of **101** were obtained.

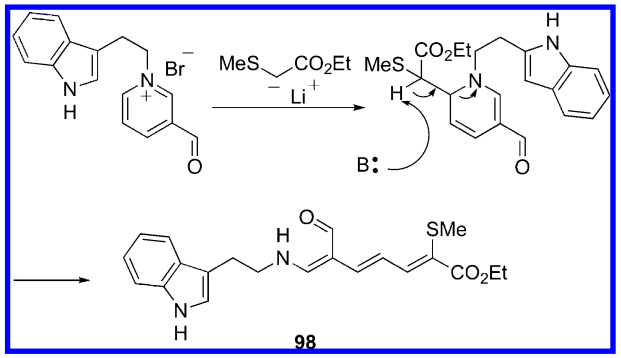
dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642–2713

Table 22. Ring-Opening of 1,2-Dihydropyridine Derivatives



entry	EWG	ratio **96**:**97**	combined yield (%)
1	CHO	0:100	43
2	C(O)Me	0:100	35
3		58:42	36

Scheme 55. Ring-Opening Mechanism under Basic Conditions



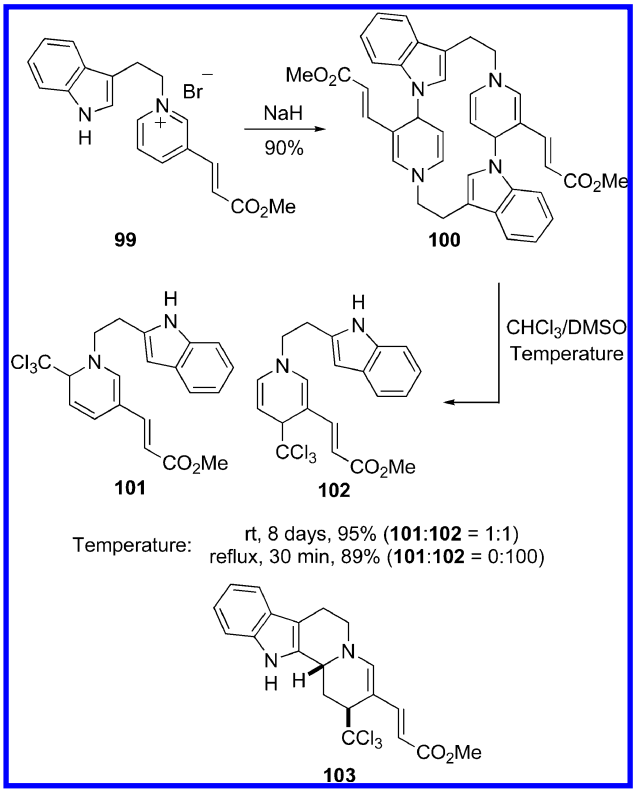
However, when the dimer was heated under reflux in chloroform/DMSO for 30 min, **102** was formed exclusively in 89% yield.

The proposed explanation for these observations involved the homolytic cleavage of the C−N bond between the indole nitrogen and the dihydropyridine carbon of the dimer followed by further reaction with chloroform, forming **101** and **102** where **102** is the most stable isomer.[314]

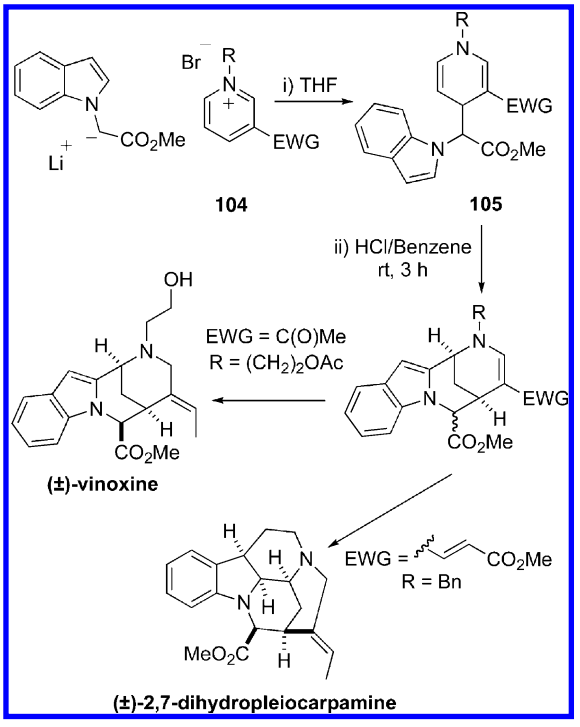
3.3.2. Wenkert Procedure: Addition of Nucleophiles Positioned at the Nitrogen of Indole Derivatives. Complementary to the work of Wenkert, Bosch, Bennasar, and co-workers independently reported a class of stabilized nucleophiles that incorporated an indole moiety in its structure rather than being tethered to the alkyl substituent of the pyridinium ring.[2,24,276,277] The first example of this process involved the addition of the anion of methyl 1-indoleacetate to *N*-alkyl pyridinium salt **104** as the key step in the rapid total synthesis of (±)-vinoxine and (±)-2,7-dihydropleiocarpamine (Scheme 57).[296,315−317] Moreover, in a revised synthesis of (±)-vinoxine, it was determined that an acetyl group substituent at the C-3 position of the pyridinium salt was optimal for the introduction of the (*E*)-ethylene substituent stereoselectively.

Following these results, the authors sought to modify the nature of the nucleophile to an acetyl or methyl propionate group linked to the indole *N*-1 position, to provide access to

Scheme 56. Addition of Chloroform to Dimer 100



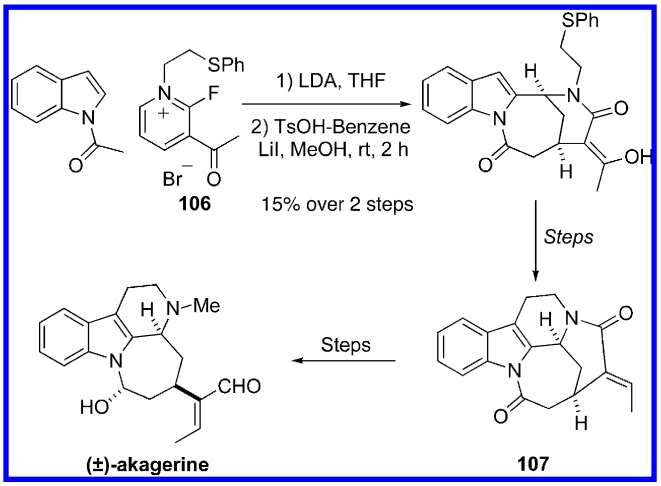
Scheme 57. Addition of the Anion of Methyl 1-Indoleacetate to *N*-Alkyl Pyridinium Salts



indoloquinolizidine alkaloids such as (±)-apogeissoschizine.[318−323] A more recent example of this was illustrated by the incorporation of a fluorine atom to the C-2 position of the pyridinium salt **106**, permitting the oxidation of the resulting vinylogous amide and cleavage of the C−F bond in the same manner (Scheme 58).[324−326] By using the enolate of 1-

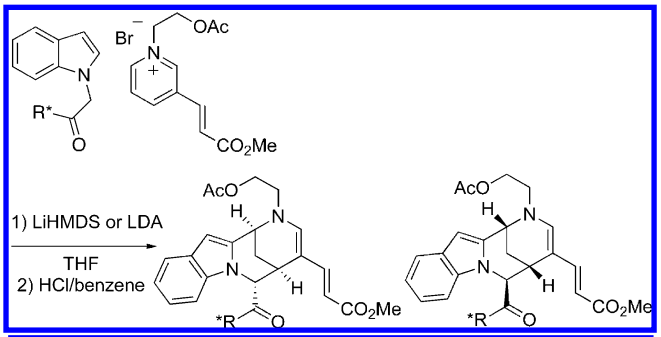
dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642−2713

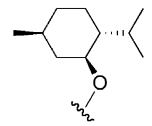
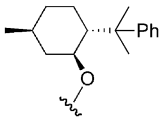
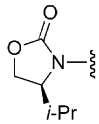
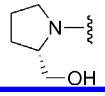
Scheme 58. Employing an *N*-Alkyl 3-Acetyl-2-fluoropyridinium Salt in the Wenkert Procedure



acetylindole as the nucleophile and by performing the Wenkert procedure using a mixture of TsOH/Benzene, LiI, and MeOH,

Table 23. Diastereoselective Addition of Various Chiral Enolates

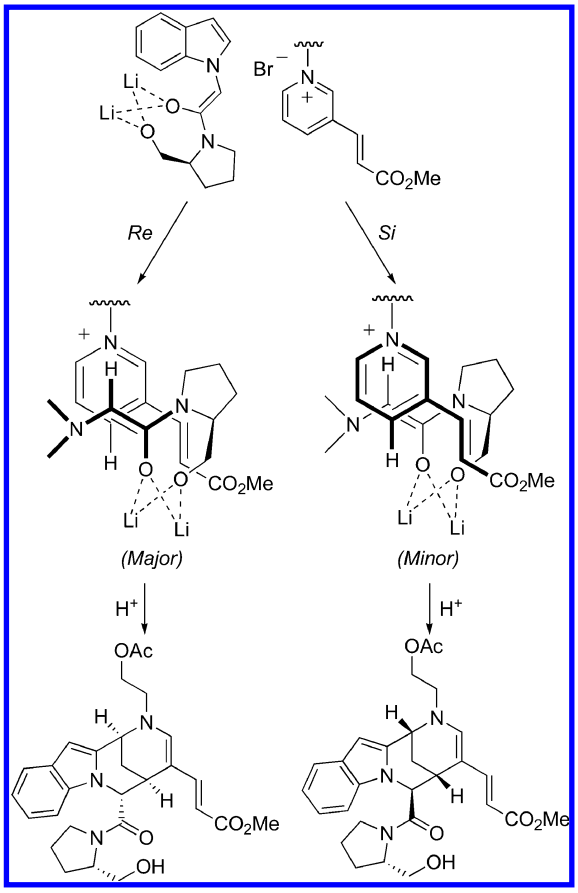


entry	R*	dr	separable mixture	combined yield (%)
1		2.5:1	No	28
2		2:1	No	28
3		1.4:1	Yes	31
4		3:1	Yes	25

they were able to synthesize an advanced 2-piperidone intermediate **107** needed for the synthesis of (±)-akagerine by exclusive C-4 addition of the nucleophile.[327,328]

In 2002, Bennasar et al. examined the stereoselective addition of the enolate of methyl 1-indoleacetate bearing various chiral

Scheme 59. Stereochemical Models Used to Explain the Diastereoselectivity of the Reaction



auxiliaries (Table 23).[329] In the stereoselective syntheses of (+)-16-epivinoxine and (−)-vinoxine, the chiral enolate of a prolinol derivative was required to achieve an optimal dr of 3:1 (entry 4). The stereochemical outcome of the reaction could be rationalized by the formation of a (*Z*)-enolate adding preferentially to the *Re*-face of the pyridinium salt (Scheme 59). The synthesis of (+)-16-epivinoxine was completed after hydrolysis/decarboxylation with aqueous 4 N HCl and removal of the chiral auxiliary by transesterification with MeOMgBr. A 1:2 mixture of (−)-vinoxine and (+)-16-epivinoxine could be accessed via epimerization of (+)-16-epivinoxine under basic conditions using *t*-BuOK in MeOH.

3.3.3. Wenkert Procedure: Addition of Enolates Located at the C-2/C-3 Position of Indoles. To access additional bicyclic alkaloids following the Wenkert procedure, stabilized nucleophiles have also been located at the C-2 or C-3 position of the indole core. In an approach to the synthesis of alkaloids from the *Strychnos* family, Alvarez et al. reported the addition of the lithium enolate of methyl 2-indole acetate to a *N*-alkyl pyridinium salt that was submitted to the Wenkert procedure (Scheme 60).[330,331] With an unprotected indole moiety, nucleophilic addition occurred exclusively at the C-4 position of the pyridinium salt, leading to a 50% yield of the tetracycle **108** as a single diastereoisomer, after treatment with HCl/benzene. Cyclized product **110** was also observed in <5% yield, derived from the addition of the indole nitrogen to the in situ generated dihydropyridinium ion. In comparison, using an *N*-methyl-substituted indole, an inseparable 3:1 epimeric mixture of tetracycles **108** and **109**, respectively, was observed.

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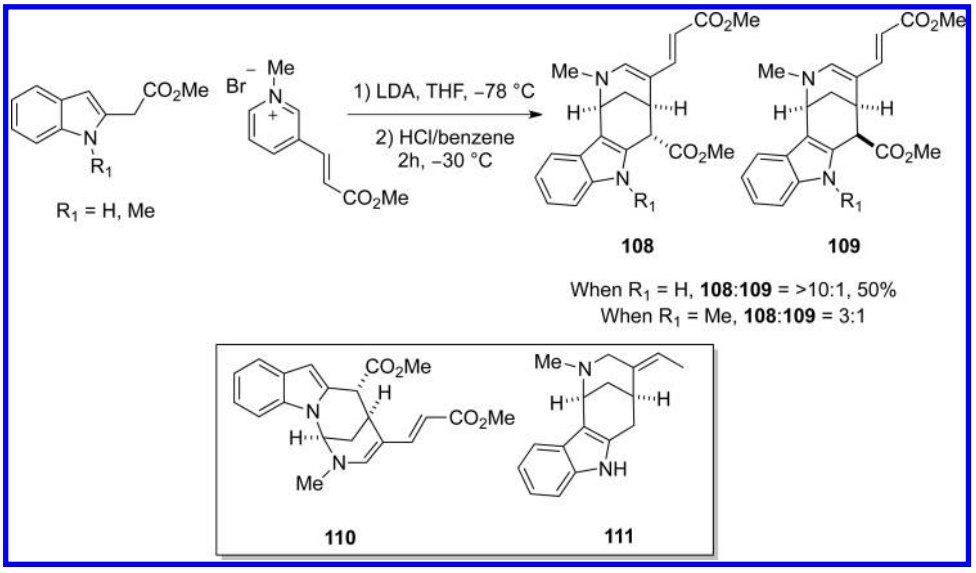
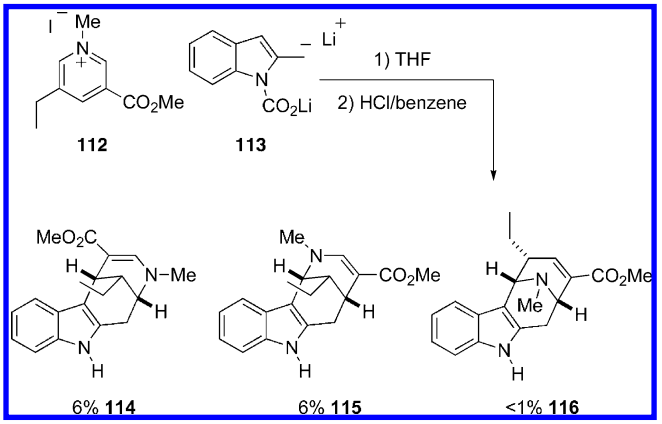
Scheme 60. Wenkert Procedure with the Anion of Methyl 2-Indole Acetate



When R_1 = H in **108**, decarboxylation of both the C-6 methyl ester and acrylate carbonyl moieties under the acidic conditions led to the formation of side-product **111**.

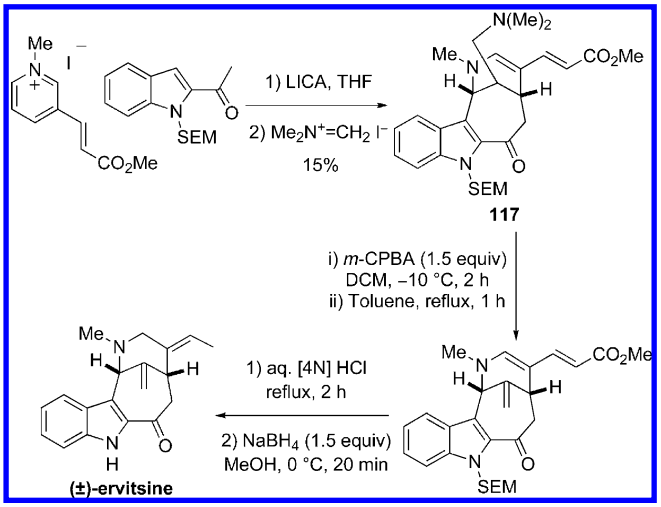
Scheme 61. Addition of a Lithiated Nucleophile to 3,5-Disubstituted Pyridinium Salts



To broaden the scope of *Strychnos* alkaloids accessible by this approach (such as aspidospermatan, tubotaiwine, or ervitsine), Lavilla, Bosch, and co-workers studied the interaction of various nucleophiles with 3,5-disubtituted *N*-alkyl pyridinium salts.[332−334] However, only the hard lithiated bisanion **113** added to a significant extent to pyridinium salt **112** to furnish a complex mixture of tetracycles **114**−**116** in low yields (Scheme 61). It is noteworthy that the addition of CuBr·DMSO to the nucleophile did not improve the selectivity or the efficiency of the reaction.

The Wenkert procedure was revisited to introduce an *exo*-methylene observed in the (±)-ervitsine structure (Scheme 62).[298,334−336] The seminal accounts by Bosch on the total synthesis of the alkaloid describe the regioselective addition of the lithium enolate derived from the SEM-protected 2-acetylindole generated with lithium isopropylcyclohexylamide (LICA) to the *N*-methyl pyridinium salt. The resultant 1,4-dihydropyridine adduct was treated with Eschenmoser's salt (Me_2NCH_2I) instead of a proton source to form the reactive

Scheme 62. Total Synthesis of (±)-Ervitsine

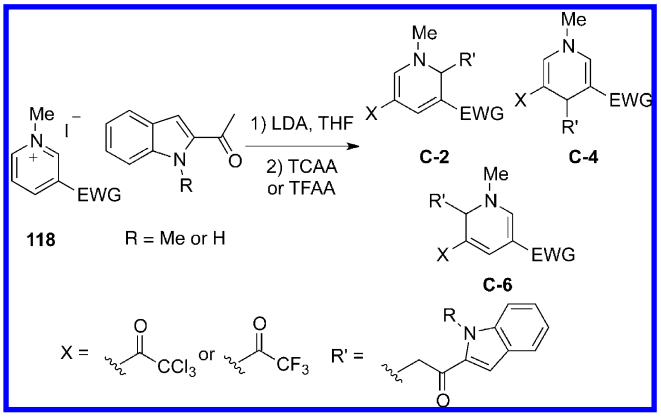


iminium species, which directly cyclized to tetracycle **117** in 15% yield. The synthesis was completed after installation of the methylene bond by Cope elimination of the oxide of the tertiary *N*,*N*-dimethylamine and formation of the (*E*)-ethylidene bond.[337]

In a different context, Bennasar , Vidal, and Bosch noted that certain 1,4-dihydropyridines did not cyclize to the desired tetracycles when using a trifluoroacetic acid anhydride (TFAA) or trichloroacetic acid anhydride (TCAA) quench (Table 24).[338] To understand this behavior, the regioselectivity of the addition of enolates to pyridinium salts **118** was surveyed. In general, the ratio of C-6 and C-4 addition was in sharp contrast to those obtained when the reaction was treated with acid. Indeed, instead of observing C-4 addition as the main product, a mixture of dihydropyridines was obtained (C-4 and C-6 addition) as well as the addition at the more-hindered C-2 position in some cases. Additionally, the yields obtained were slightly higher than those observed in the acid-mediated cyclizations. The dramatic changes made to the nature of the electrophile unraveled the poor regiocontrol of the addition of stabilized nucleophiles to pyridinium salts and revealed that the ratio of products obtained from the reaction was dependent

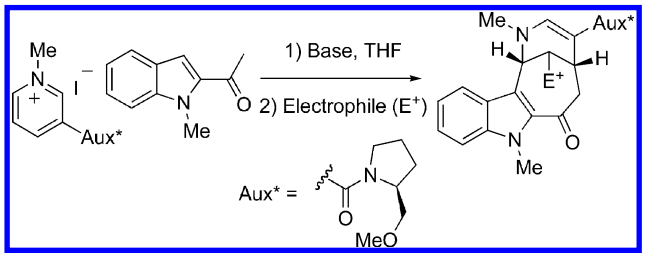
dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642−2713

Table 24. Addition of 2-Acetylindole Followed by a TCAA or TFAA Quench



entry	EWG	electrophile	ratio C-2/C-4/C-6	combined yield (%)
1	C(O)Me	TCAA	0:1:2	20
2	C(O)Me	TFAA	0:2:1	15
3	CO_2Me	TCAA	1:2:1	60
4	CO_2Me	TFAA	0:5:4	45
5	Et	TCAA	0:0:1	20

Table 25. Addition of an Enolate Nucleophile to a *N*-Alkyl Pyridinium Salt Possessing a Chiral Auxiliary



entry	base	electrophile	dr	combined yield (%)
1	LDA	HCl/benzene	3:1	25
2	LDA	PhSeCl	2:1	40
3	LICA	$Me_2N^+{=}CH_2\ I^-$	2:1	40

upon the method used to trap the intermediate as addition of acid supported the reversibility of the addition of the enolates. Nevertheless, this TCAA-modified procedure was used for numerous syntheses of various ring systems of natural silicine and methuenine alkaloids[339] such as (±)-6-oxo-16-episilicine[340] and (±)-6-oxosilicine[341] as well as (±)-ervatamine[342] and other alkaloids from the ervatamine series.[336]

The introduction of an (*S*)-prolinol auxiliary to the C-3 position of the pyridinium salt permitted rapid and stereoselective synthesis of (−)-*N*-methylervitsine by quenching the

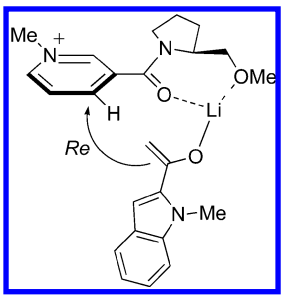


Figure 13. Stereochemical model to rationalize the diastereocontrol.

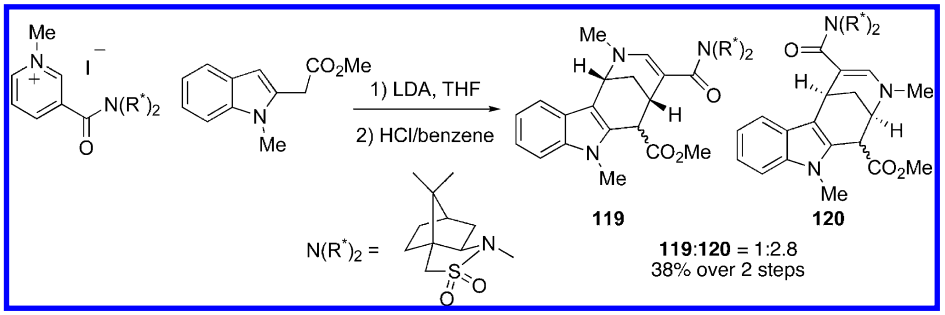
1,4-dihydropyridine intermediate with various electrophiles,[343] yielding tetracycles in modest efficiency and diastereocontrol (Table 25). The diastereoselectivity of the reaction was rationalized by the precomplexation of the lithium enolate to both the carbonyl oxygen and the methoxy group of the auxiliary before the nucleophile was delivered to the *Re*-face of the pyridinium ring (Figure 13). Prior to this work, modest diastereocontrol had been observed in the addition of lithium carbanions to an activated pyridine moiety bearing a chiral oxazolidinone auxiliary.[33,186,344]

Other chiral functional groups at C-3 have been investigated to improve the diastereoselectivity of the addition to *N*-alkyl pyridinium salts.[345] *N*-Methyl and *N*-benzyl nicotinyl salts derived from Oppolzer's (2*R*)-bornane-10,2-sultam[346] proved to be the most efficient for the diastereoselective addition of the anion of methyl 2-indolylacetate preceding a Wenkert procedure (Scheme 63). A modest ratio of 1:2.8 for products **119** and **120**, respectively, was obtained originating from unfavorable steric interactions between the chiral sulfonamide auxiliary and the incoming nucleophile.

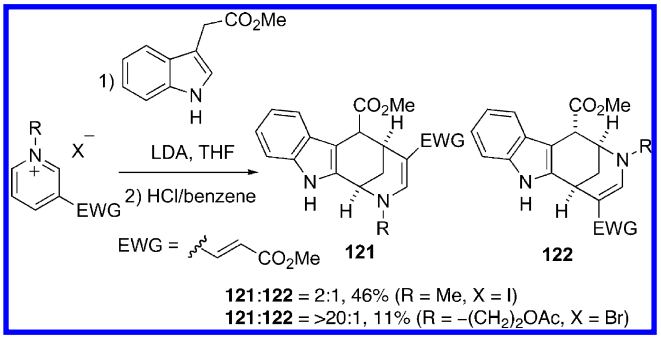
In their approach toward the akuammiline alkaloids, the Bosch group studied the addition of nucleophiles located at the C-3 position of indoles to *N*-alkyl pyridinium salts.[347−349] The addition of the lithium salt of methyl 3-indoleacetate to the pyridinium ring yielded the hexahydro-l,5-methanoazocino[3,4-*b*]indole **121** and **122** with modest regiocontrol and yields (Scheme 64).

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642−2713

Scheme 63. Addition of Methyl 2-Indolylacetate to a Chiral Sulfonamide Pyridinium Salt



Scheme 64. Addition of Methyl 3-Indoleacetate to *N*-Alkyl Pyridinium Salts



However, access to the akuammiline alkaloids required installation of a quaternary center on the indole moiety.[350] Various synthetic routes have been explored to achieve this, and the problem of finding a convenient approach to this family of alkaloids remains unresolved. Nevertheless, using a similar procedure as the one depicted in Scheme 64 led to the formation of different 3,4-secoakuammilian derivatives via the ring-opening of the piperidine moiety and installation of the indole quaternary center using a Pummerer reaction.[351,352] The Wenkert procedure could be envisioned in a synthesis of (±)-3,4-secocabucraline derivatives (Figure 14).[353]

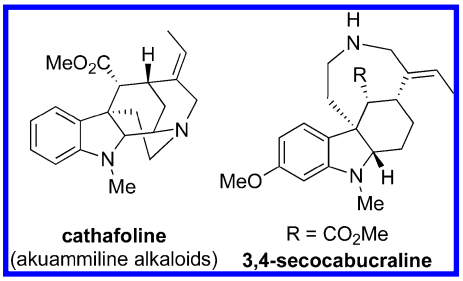
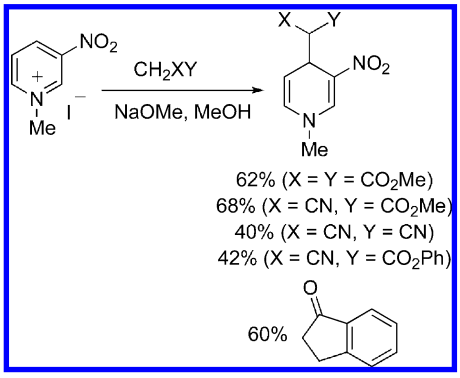


Figure 14. Formation of 3,4-secoakuammilian derivatives.

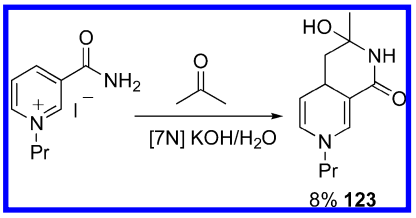
3.3.4. Addition of Miscellaneous Nucleophiles to *N*-Alkyl Pyridinium Species. There are many reports of the addition of stabilized nucleophiles to *N*-alkyl pyridinium salts that do not contain an internal nucleophile for cyclization. Following the pioneering work of Kröhnke et al.,[278] Severin et al. studied the addition of various stabilized nucleophiles to *N*-methyl-3-nitropyridinium iodide (Scheme 65).[354] The addition of sodium salts of dimethyl malonate, malonitriles, indanone, and methyl/phenyl cyanoacetate occurred exclusively to the C-4 position of the pyridinium salts.

The addition of an acetone enolate to *N*-propyl nicotinamide iodide was also regioselective for the C-4 position, giving **123** after intramolecular hemiaminal formation (Scheme 66).[355,356] Additionally, a C-4 addition of nitromethane to a common nicotinamidium salt was shown to be regioselective but reversible.[357]

Scheme 65. Addition of Stabilized Nucleophiles to *N*-Methyl-3-nitropyridinium Iodide



Scheme 66. Addition of Acetone to *N*-Propyl Nicotinamide Iodide



Following their work on the addition of nucleophiles to *N*-*N* linked pyridinium salts (see section 4),[358] Sammes, Lee, and Katritzky reported an improved method to synthesize 4-substituted pyridines **124** through the addition of various enolates of nitriles or esters to *N*-trityl pyridinium or picolinium salts (Table 26).[359] The additions were found to be C-4 selective with low to moderate yields of the pyridine product formed by the rapid oxidation of the unstable 1,4-dihydropyridine intermediate. Similarly, Lounasmaa and Koskinen reported the regioselective addition of dimethyl malonate anion to the pyridinium salt in connection with their studies toward quinuclidine alkaloids.[360]

The regioselectivity of addition of a silyl ketene acetal to *N*-benzyl pyridinium salts was disclosed by Yamada et al. (Table 27).[198] It was found that in MeCN treatment of these *N*-benzyl pyridinium salts bearing a thioxazoline or oxazoline functional group at C-3 afforded high C-4 regioselectivities and yields for **125** (entries 1 and 2), unlike the *N*-benzyl nicotinic amide salt (entry 3). An important solvent effect was noted for these reactions when changing from MeCN to DMSO-d_6, as the

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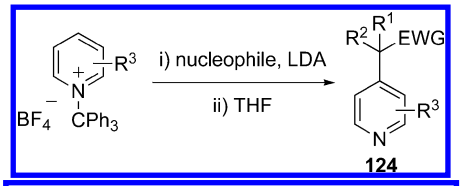
Table 26. Addition of Stabilized Enolates to *N*-Trityl Pyridinium Salts



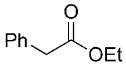
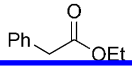
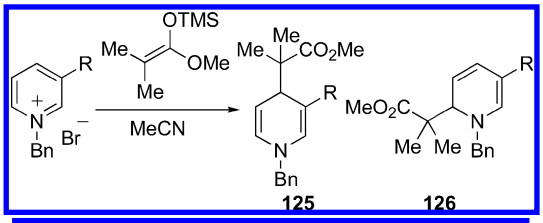
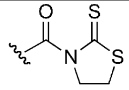
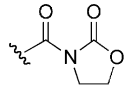
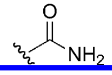
entry	nucleophile	R^3	yield **124** (%)
1		H	60
2		H	29
3		H	63
4		2-Me	19
5		3-Me	60

Table 27. Addition of Ketene Silyl Acetals to *N*-Benzyl Pyridinium Salts

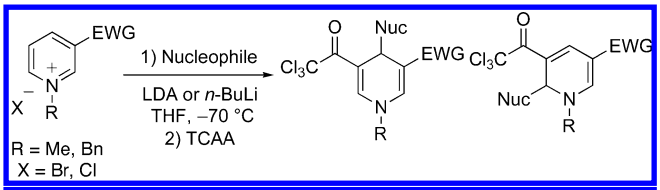


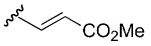
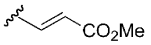
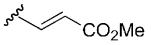
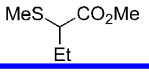
entry	R	ratio C-4:C-6	combined yield (%)
1		96:4	77
2		94:6	93
3		35:56	73

regioselectivity dramatically decreased to about 1:1 for the C-4/C-6 additions.

Bennasar et al. explored the interaction of various stabilized nucleophiles with *N*-alkyl pyridinium salts under conditions similar to those depicted in Table 24.[361] Various sulfones, thioacetals, and esters were screened, and the stable dihydropyridines were quenched by the addition of TCAA (Table 28). The combined addition and TCAA quench strategy permitted the expedient synthesis of (+)-camptothecin and (±)-20-deoxycamptothecin starting from a *N*-(2-bromo-3-quinolylmethyl)-2-fluoropyridinium salt **127** (Scheme 67).[362,363] When the lithium enolate of methyl α-(methylsulfanyl)acetate was added regioselectively to 3-acetyl-1-benzydrylpyridinium bromide, the monoterpene alkaloid

Table 28. Addition of Various Stabilized Nucleophiles to *N*-Alkyl Pyridinium Salts Followed by TCAA Quench



entry	EWG	nucleophile	ratio C-4/C-6	combined yield (%)
1	CO_2Me	$MeSCH_2SMe$	0:100	34
2	CO_2Me	CH_3CO_2Me	15:85	60
3		$PhSO_2Me$	0:100	20
4		Butyrolactone	50:50	60
5		CH_3CO_2Me	40:60	60
6	C(O)Me		100:0	57

(±)-jasminine could be accessed following TCAA quench and oxidation of the 1,4-dihydropyridine intermediate (Scheme 68).[364]

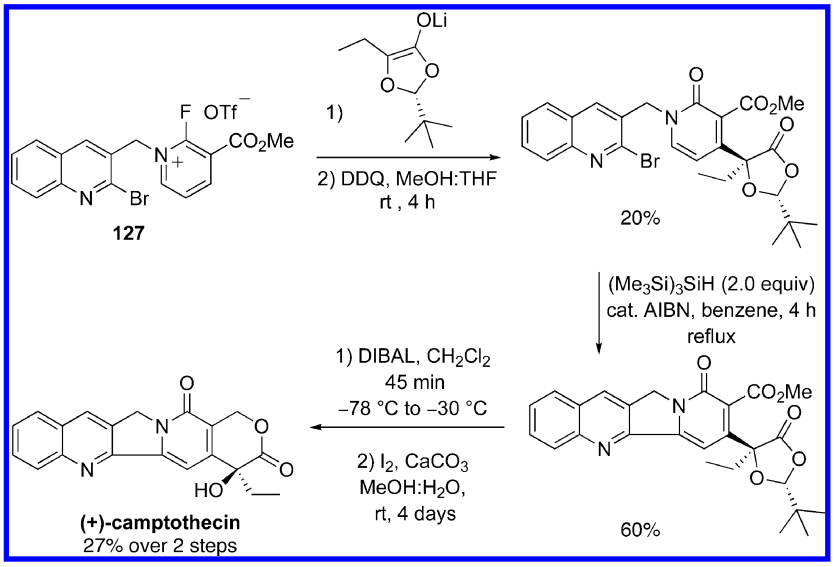
In contrast to the enolate additions illustrated above, Wilson and Eberle reported the addition of cyclic nitrones **128a–c** to *N*-(2,6-dichloro)benzyl pyridinium salts to give stable 1,2- and 1,4-dihydropyridines (Scheme 69).[365] The ratio observed between the 1,2- and 1,4-dihydropyridine products was dependent upon the structure of the nitrone. Using nitrone **128a**, only C-4 addition was observed, affording 53% of **129a**, whereas nitrones **128b–c** resulted in a mixture of dihydropyridines **129b–c** and **130b–c**. Interestingly, when nitrone **128c** was used, the addition occurred through the methyl substituent instead of the cyclic carbon. Because the reaction was not performed in basic conditions, the authors proposed that nitrone **128c** itself provided the base to buffer the reaction.

For the addition of indole derivatives to *N*-alkyl pyridinium salts, modifying the base produced dramatic changes in selectivity (Scheme 70).[366] If 3-methylindole was employed, addition occurred exclusively to the C-4 position of the pyridinium via the free nitrogen position, giving **133** in 51% yield. However, if 2-substituted indoles were added to the pyridinium salt, C-6 regioselectivity was observed through the addition of indole via the available carbon position, providing dihydropyridines **131** in 50–91% yield. Altering the base/solvent to NaH in DMSO reversed the selectivity of the addition with 2-substituted indoles.[367] Preferred selectivity was obtained for the C-4 addition of indole derivatives to *N*-alkyl pyridinium salts bearing a C-3 electron-withdrawing substituent or 3,5-disubtituted pyridinium salts. A similar behavior was reported for *N*-acyl pyridinium salts by Bergman and Deubel and co-workers.[368,369]

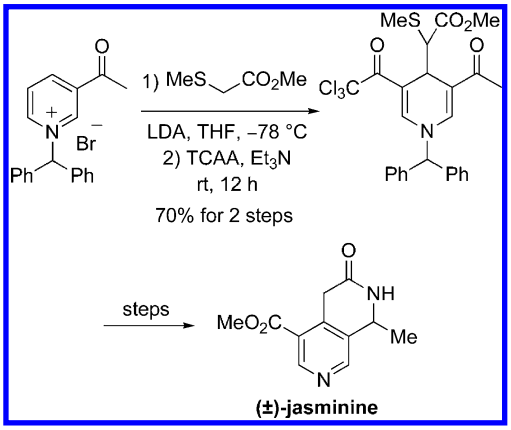
Lavilla et al. applied a phase-transfer catalysis (PTC) strategy to the nucleophilic addition of indoles and pyrroles to various *N*-alkyl pyridinium salts, affording the desired products in modest to high yields (Table 29).[370] Regioselectivity was greatly influenced by the nature of the solvent: 1,2-dihydropyridines **134** were the favored products when dichloromethane was used, whereas 1,4-dihydropyridines **135**

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642–2713

Scheme 67. Stereoselective Synthesis of (+)-Camptothecin



Scheme 68. Synthesis of (±)-Jasminine Via the Addition of Methyl α-(Methylsulfanyl)acetate



were isolated as the major regioisomers when using toluene as solvent.

In an attempt to induce asymmetry in the addition of indole to pyridinium salts **136** and **137**, *N,O*-dibenzylcinchonidium bromide **138** was employed as a chiral phase-transfer catalyst (1 mol % in toluene/50% NaOH; Scheme 71).[371] The C-4 addition products were obtained in moderate to good yields with low enantiomeric excesses (<5% ee and 11% ee, respectively).

More recently, Kostyuk and co-workers reported that various nitrogen-containing heterocycles could be added regioselectively to the C-4 position of *N*-benzyl-3-cyanopyridinium chloride through the available nucleophilic carbon of the heterocycles (carbons circled in Table 30).[372] In general, moderate to good yields were obtained for the stable 1,4-dihydropyridines, which could be isolated after recrystallization.

4. NUCLEOPHILIC ADDITIONS TO *N*-HETEROATOM PYRIDINIUM SPECIES

The use of oxygen, nitrogen, silicon, and other heteroatoms to activate pyridine constitutes a vast body of work. Similar to the work described in the previous sections, these *N*-activated pyridines lower the lowest unoccupied molecular orbital (LUMO) of the heterocycle, facilitating attack by various nucleophiles to generate substituted azines.[18] The formation of the *N*-heteroatom bond is generally facile and importantly may in many cases offer a more facile cleavage or further synthetic options than the N–C bonds in the preceding sections. The section will focus on the attack of nucleophiles onto *N*-heteroatom pyridinium species and will discuss both the mechanistic and regioselective outcomes of these transformations.

4.1. Nucleophilic Additions to Pyridine *N*-Oxides and *N*–*O* Salts

4.1.1. Properties, Synthesis, and Deprotection of Pyridine *N*-Oxides. Pyridine *N*-oxides have been widely applied in the activation and functionalization of pyridine. Their popularity lies in their high reactivity, ease of synthesis, and inexpensive commercial availability. By using pyridine *N*-oxides to activate the aromatic ring, various mesomeric moments are accessed, thereby permitting both nucleophilic and electrophilic attack due to the σ-electron-withdrawing and π-back-donating character of the *N*-oxide moiety (Figure 15).[373,374]

As described ealier in this review, the regioselectivity of the substitution on the activated pyridine often relies on the nature of the nucleophile or electrophile. Nucleophilic substitutions typically occur in the 2- and 4-positions with 4-selectivity preferred with bulky nucleophiles (Figure 16). This will be considered in greater detail in subsequent sections. Alternatively, hard electrophiles react at the 4-position whereas soft electrophiles have a preference for the 2-position.[373] Under extremely acidic conditions electrophilic substitution can occur at the 3-position.[373] Electrophilic addition to pyridine *N*-oxides will not be further discussed as it is outside the scope of this review (see section 5 for the reactions of pyridine *N*-oxide anions).

Several methods have been reported for the *N*-oxidation of pyridine. Hydrogen peroxide is remarkably efficient but suffers from the potential overoxidation of the substituents of functionalized pyridines.[373,375] Sharpless' conditions using a $MeReO_3/H_2O_2$ couple have been reported to be a reliable and mild method to effect the oxidation,[376] and dimethyldioxirane displays similar reactivity.[377,378] However, peracids are perhaps the most common reagents employed.[379–381] A nonexhaustive summary can be seen in Figure 17. It should be noted that

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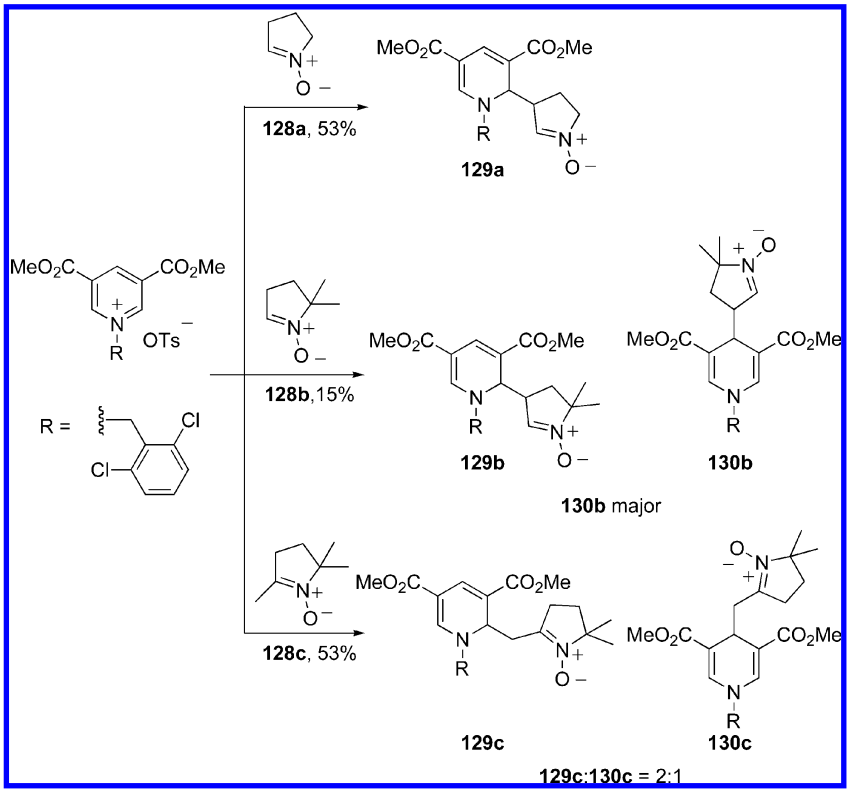
Scheme 69. Addition of Various Cyclic Nitrones 128a−c to *N*-Alkyl Pyridinium Salts



Scheme 70. Addition of 2- and 3-Methyl Indole to *N*-Alkyl Pyridinium Salts

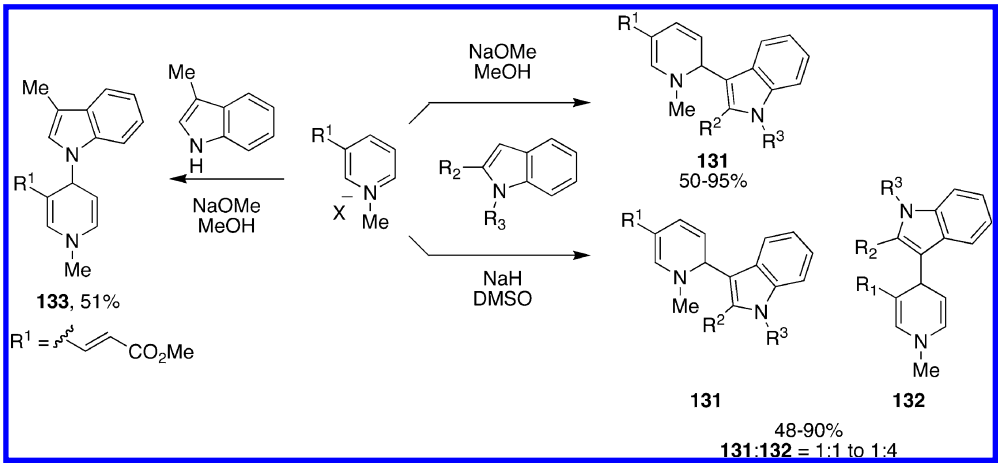
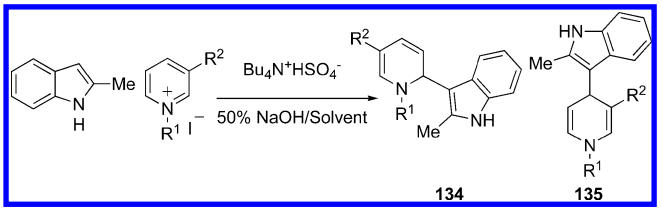


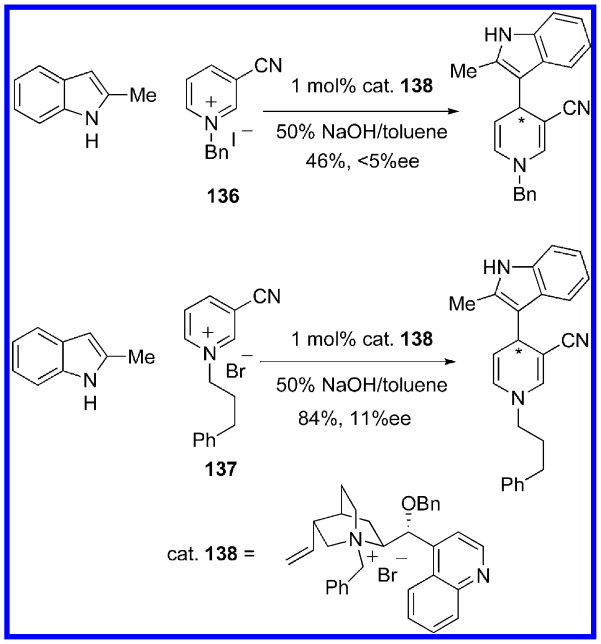
Table 29. Addition of Indoles to *N*-Alkyl Pyridinium Salts Using Phase-Transfer Catalysis



entry	R^1	R^2	solvent	ratio C-6/C-4	combined yield (%)
1	Bn	CN	CH_2Cl_2	50:50	26
2	Bn	C(O)Me	CH_2Cl_2	100:0	20
3	Bn	CO_2Me	CH_2Cl_2	88:12	75
4	Bn	CN	toluene	0:100	99
5	Bn	CO_2Me	toluene	50:50	90

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642−2713

Scheme 71. Asymmetric Phase-Transfer Catalysis (PTC) on *N*-Alkyl Pyridinium Salts



pyridine *N*-oxides have also been prepared through ring-closing techniques.[373]

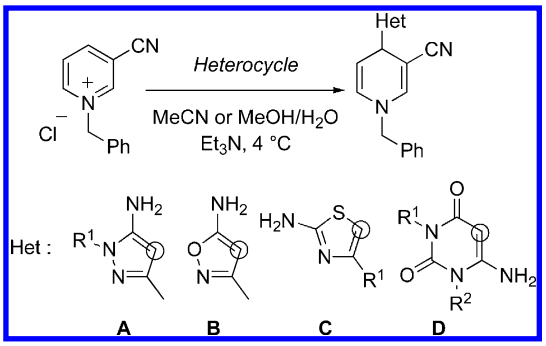
Deoxygenation (or deprotection) of the *N*-oxide has been widely explored (Figure 17). Reductive techniques using Pd/C[382,383] or Zn[384] dust are known, as well as the use of several acids,[377,385] including Lewis acids[377,385,386] and peracids.[377] Radical-based deoxygenation can also be employed with Al,[387] Re,[388] and Mo[389] reagents.

4.1.2. Addition of Grignard Reagents to Pyridine *N*-Oxides. In 1965 Kato and Yamanaka described the addition of PhMgBr to pyridine *N*-oxides in THF.[390] The proposed 2-phenyl-*N*-hydroxydihydropyridine intermediate was isolated in 60−80% yield, and 2-phenylpyridine could be obtained upon treatment with Ac_2O in 43% yield (Scheme 72). In a later account Kato et al. described the use of NaOH and BzCl to obtain 2-phenylpyridine, as well as several other adducts resulting from ring-opening reactions that are outside the scope of this review.[391] Later van Bergen and Kellogg undertook mechanistic investigations providing evidence that the reaction proceeded through a ring-opening/ring-closing sequence,[392] and not via the dihydropyridine intermediate.[390,391] Through the judicious isolation of intermediates, synthesis of standards for comparison, and by studying ^{1}H NMR coupling constants as well as IR spectral analysis, it was concluded that Kato et al. had not isolated the *N*-hydroxydihydropyridine intermediate but the Δ^2-*cis*,Δ^4-*trans*-pentadienal-*syn*-oxime (Scheme 73).[391] The increased conjugation in the linear system, relative to the dihydropyridine intermediate, favors this product. It was reasoned that the ring-opening may proceed through a disrotatory electrocyclic opening and that the Ac_2O promoted ring-closing to the 2-phenylpyridine occurred through a Beckmann-type rearrangement with the loss of acetic acid.[391] This finding explained Kato's later results whereby the ring-opened product was isolated.[391,393,394]

Kato and Kellogg's work lay largely dormant for 40 years before being revisited by Almqvist, Olsson, and co-workers.[395,396] Reacting pyridine *N*-oxide with phenylmagnesium chloride at rt, followed by the addition of Ac_2O and heating in a microwave at 120 °C for 4 min, provided the desired 2-phenylpyridine in 63% yield. The reaction was found to tolerate a wide range of *sp* and *sp*^{2} hybridized Grignard reagents in high yields (Table 31).[395] Alkyl Grignard reagents gave only modest yields presumably due to α-metalation of the pyridine ring. In the case of 3-picoline, *N*-oxide substitution occurred at the more-hindered 2-position. Unsymmetrical 2,6-substituted pyridines were prepared in moderate to good yields through regenerating the pyridine *N*-oxide by oxidation in air after the first addition, followed by the addition of a second nucleophile and then treatment with Ac_2O.

In a further application of this methodology, Almqvist, Olsson, and co-workers described the regio- and stereospecific synthesis of *trans*-2,3-dihydropyridine *N*-oxides by the sequential addition of a Grignard reagent and an electrophile to pyridine *N*-oxide.[397] The formation of the dienal oxime could be suppressed by replacing H_2O in the workup with

Table 30. Addition of Aminoheterocycles to *N*-Benzyl-3-cyanopyridinium Chloride



entry	heterocycle	R^1	R^2	yield (%)
1	A	H		52
2	A	$-(CH_2)_2CN$		79
3	B			25
4	C	Me		32
5	C	Ph		60
6	D	Bn	H	57
7	D	Me	Me	51

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642−2713

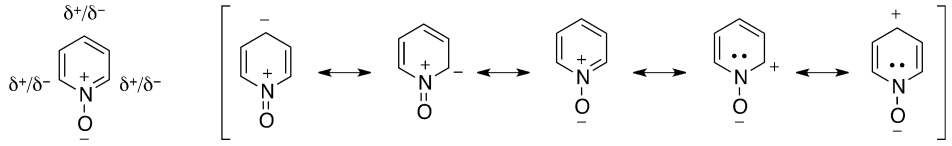


Figure 15. Electronic properties of pyridine *N*-oxides.

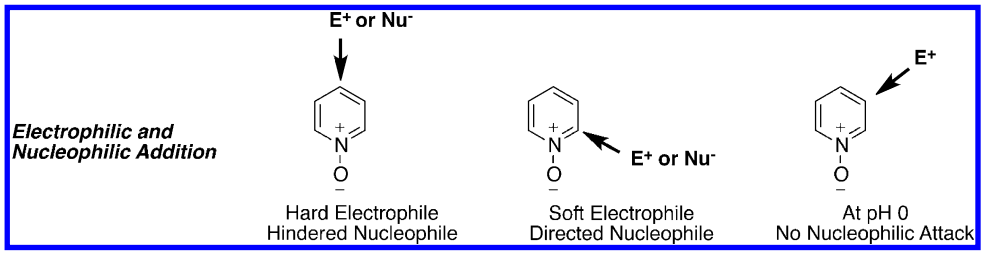


Figure 16. Substitution tendencies of pyridine *N*-oxides.

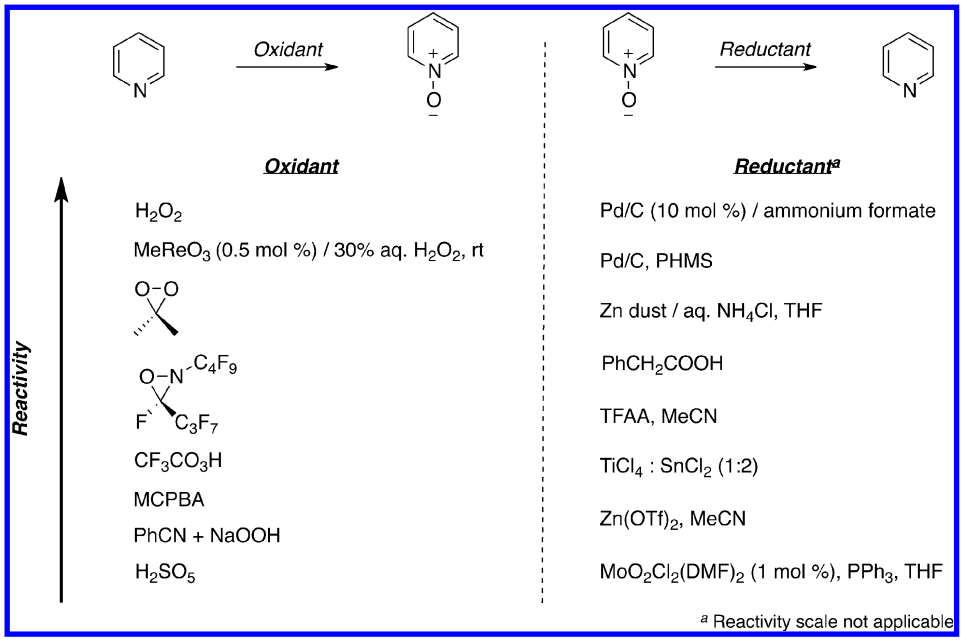
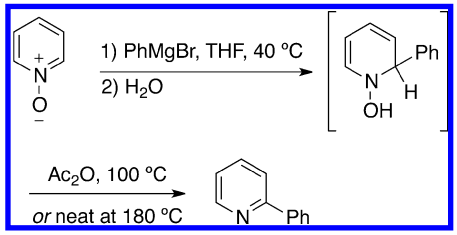


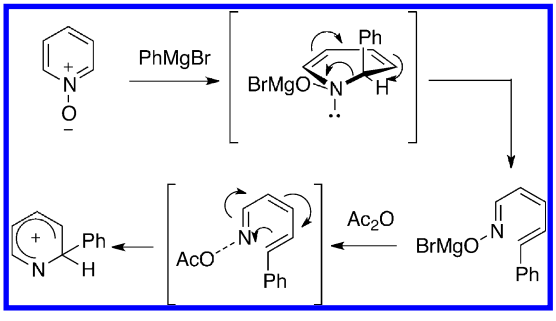
Figure 17. Common methods to oxidize and reduce pyridine and pyridine *N*-oxides.

Scheme 72. Kato's Hypothesis of Grignard Addition to Pyridine *N*-Oxide



MeOH followed by a $NaBH_4$ quench to give 2-phenyl tetrahydropyridine *N*-oxide. Isolation of the product suggests the formation of a cyclic vinylogous enamine that in turn could attack an electrophile. Consequently, the addition of aldehydes following the Grignard addition was found to give the 2,3-dihydropyridine *N*-oxides in good yields with trans selectivity (Scheme 74). The scope of the reaction was found to be general with aliphatic and aromatic aldehydes being operative, as were cyclic ketones. In addition, substitution at all positions on the pyridine moiety was tolerated.[397]

Scheme 73. Mechanistic Rationale for the Formation of 2-Phenylpyridine



Pyridine *N*-oxides have also been applied in addition-elimination reactions. Pentachlorobenzene is not susceptible to attack by Grignard reagents, but methylmagnesium iodide can be added to pentachloropyridine *N*-oxide to give a 66% yield of a mixture of 2-methyl-3,4,5,6-tetrachloro- and 2,6-dimethyl-3,4,5-trichloropyridine-*N*-oxide.[398] Ethyl- and phenyl-

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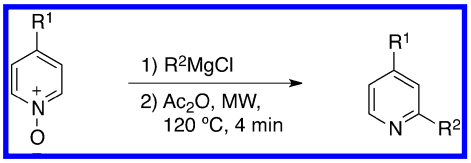
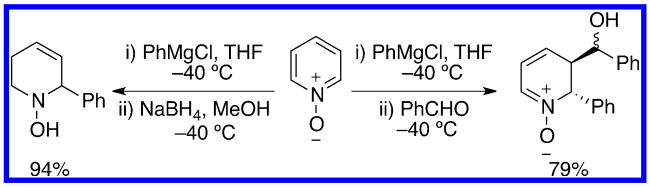
Table 31. Scope of the Addition of Grignard Reagents by Almqvist, Olsson, and Co-workers



entry	R^1	R^2	yield (%)
1	H	Ph	63
2	H	*p*-MeOPh	83
3	H	Bn	38
4	Ph	*c*-PrC≡C−	86
5	Ph	thiophen-2-yl−	73
6	BnO	Ph	82
7	Cl	Ph	74

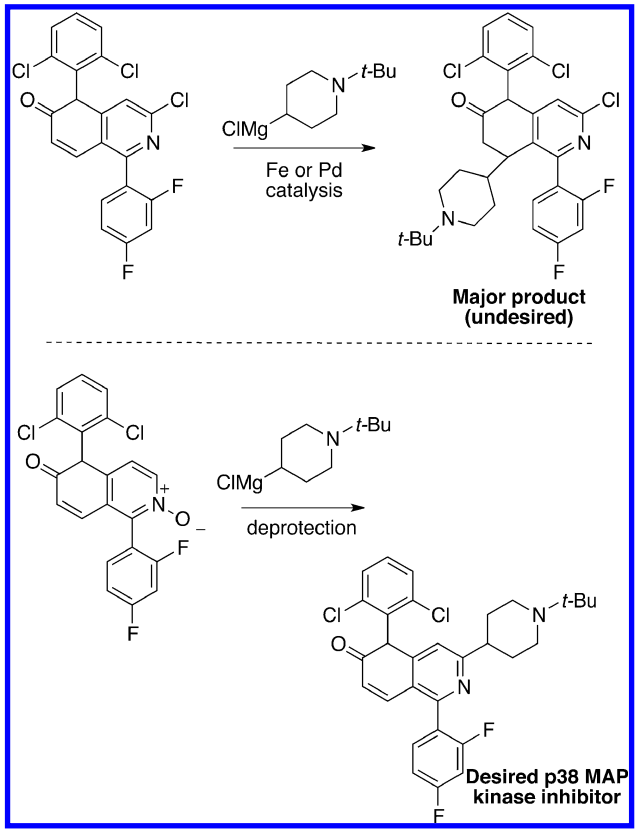
Scheme 74. Synthesis of *trans*-2,3-Dihydropyridine *N*-Oxide



magnesium bromide are also possible partners, but organolithium compounds were found to be unreactive.

The addition of Grignard reagents to pyridine *N*-oxides has been applied by the Process Group at Merck in the end game of

Scheme 75. Application of a Pyridine *N*-Oxide Derivative in the Preparation of a p38 Kinase Inhibitor



the synthesis of a Naphthyridone p38 MAP kinase inhibitor (Scheme 75).[399] Several attempts for the addition of the *N*-*tert*-butylpiperidine moiety as a Grignard reagent to the unactivated pyridine moiety invariably furnished 1,4-addition to the enone. The use of TMSOTf or PhOCOCl to activate the pyridine was unsuccessful due to the presence of the electron-withdrawing 2,4-difluorophenyl group, thereby decreasing the nucleophilicity of the nitrogen atom. Consequently, conditions were developed to prepare the pyridine *N*-oxide in 97% yield on a 2-kg scale using *m*-CPBA in toluene at rt.[399] The *N*-oxide was then subjected to addition using conditions similar to those described by Kato followed by deoxygenation with isobutyl chloroformate, giving the desired inhibitor in 92% yield.

4.1.3. Addition of Cyanide Nucleophiles via Reissert-Type Reactions. The Reissert–Henze reaction involves the cyanation of quinoline through activation of the azacycle by acyl chlorides. The resulting "Reissert compound" can be readily rearomatized and hydrolyzed to afford 2-quinaldic acid. However, a similar reaction had not been successful with pyridines due to the increased aromaticity of the heterocycle,[400] leading to much interest in developing an analogous reaction. The interest in the Reissert–Henze reaction is highlighted by a literature survey: in early 2010, no less than 225 publications and 180 patents utilizing a modified Reissert–Henze reaction to cyanate pyridines were disclosed. The remainder of this section will focus on seminal reports of such reactions and highlight the principle reactions in use today.

Feely and Beavers described the cyanation of *N*-alkoxypyridinium salts as a method to access 2-cyanopyridines (Scheme 76). Methylation of the pyridine *N*-oxide using dimethyl sulfate, followed by directly dissolving the crude hygroscopic salts in an aqueous solution with excess of KCN, gave cyanide addition to the pyridinium salt. Rearomatization with the loss of methanol yielded a mixture of 2- and 4-cyanopyridine.[400] A year later, Okamoto and Tani independently reported the same reaction involving methylated pyridine *N*-oxides, describing similar reaction yields and selectivities.[401,402] In 1969 Kobayashi and Kumadaki published the addition of cyanides to benzyloxy pyridinium salts bearing CF_3 groups.[403] When the trifluoromethyl group was located at the 2- or 3-position, addition of the cyanide occurred exclusively at the less-hindered 6-position. Kobayashi and Kumadaki described the double electron-withdrawing effects by the CF_3 and the benzyloxy groups as a main driving force for selectivity.[403]

Issues of selectivity in these reactions were not addressed until the 1980s. Shioiri and co-workers applied diethyl phosphorocyanidate (DEPC) as both an activating and directing reagent for *N*-oxide derivatives (Scheme 76).[404] Although the scope of the reaction was attenuated on quinoline

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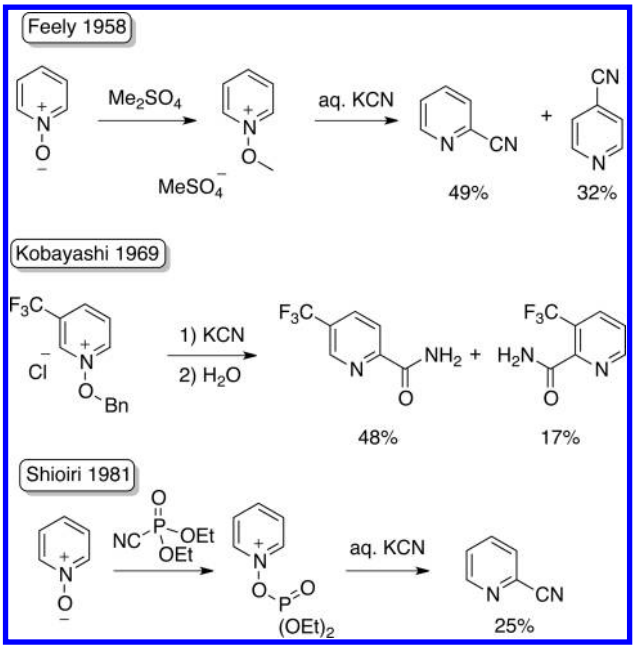
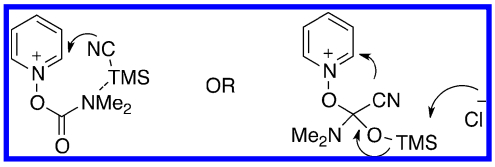
Scheme 76. Progression of the Modified Reissert–Henze Reaction



and isoquinoline derivatives, an example involving pyridine *N*-oxide afforded the 2-cyanopyridine exclusively in 25% yield. A few years later, Fife further developed this approach using TMSCN as the cyanide source. Several acyl chlorides were explored. Dimethylcarbamyl chloride provided the 2-CN product in nearly quantitative yield, presumably because the carbamyl chloride was less susceptible to cyanide attack. The 2- and 3-picoline *N*-oxides also afforded excellent yields (Table 32, entries 2–4), as did 4-picoline *N*-oxide. This method has perhaps become the most popular method of the generation of cyanopyridines.[405] In the case of 3-picoline *N*-oxide, Fife observed addition at the more-hindered 2-position as the major product, explained to be the result of α-electronic stabilization of the Reissert intermediate (entries 3–6).[406] The lack of addition at the 4-position was postulated to be the result of a directed intramolecular delivery of the cyano group by the Lewis basic dimethyl carbamate (Scheme 77).[407] Furthermore it was demonstrated that the formation and isolation of the acyloxypyridinium salt provided a more reactive intermediate than the formation of the activated pyridinium in situ.

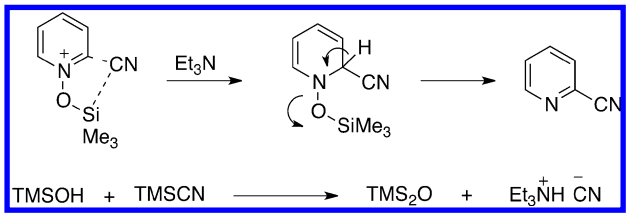
Simultaneously Vorbrüggen and Krolikiewicz reported a similar method for the preparation of 2-cyanopyridines that is also widely used.[408] Reacting pyridine *N*-oxide with TMSCN

Scheme 77. Delivery of the Cyano Group in Fife's System



directly, without the inclusion of an additional acyl activating/directing group, permitted the cyanation at the 2-position in

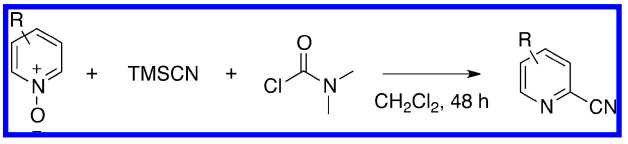
Scheme 78. Vorbrüggen and Krolikiewicz's System



good to excellent yields (Scheme 78). Excess TMSCN was required to quench the TMSOH generated in the reaction, in the presence of triethylamine to neutralize the HCN formed. The scope of the reaction was general, except in the case of less-reactive pyridine *N*-oxides, where the addition of both TMSCN and NaCN provided improved results.[408] Several groups have exploited this, such as Pagani, Facchetti, and co-workers in the synthesis of lanthanide contrast agents,[409] as well as Schäfer and co-workers in the scale synthesis of a thrombin inhibitor (Scheme 79).[410]

4.1.4. Addition of Hetero Nucleophiles to Pyridine *N*-Oxides and *N*–*O* Salts. *Nitrogen-Based Nucleophiles.* The 2-aminopyridyl group is widely present in pharmacologically active compounds.[1,10,14,20] The first accounts of the addition of nitrogen nucleophiles to pyridine *N*-oxides involved the addition of azides. Azide addition to pyridine itself was known, but the reaction suffered from poor regioselectivity and chemical yields. Reddy and co-workers reported the addition of arenesulfonyl azides to pyridine *N*-oxides in the early 1980s.[411] The resulting product was a tetrazolo[1,5-*a*]pyridine, in equilibrium with the 2-azidopyridine (Scheme 80).[411] In 2006 Keith revisited the scope of the reaction by exploring the efficiency of various sulfonyl activating groups.[412] The generation of the activated pyridinium salt with TsCl in the presence of pyridine *N*-oxide followed by the addition of $TMSN_3$ afforded the resulting product in 73% yield. Moreover,

Table 32. Fife's Directed Cyanation of Pyridine *N*-oxides



entry	R	product	yield (%)
1	H	2-CN	94
2	2-Me	2-CN, 6-Me	100
3	3-Me	2-CN, 3-Me	90
4	3-MeO	2-CN, 3-MeO	87
5	3-OH	2-CN, 3-OH	86
6	3-CO_2Me	2-CN, 5-CO_2Me	42

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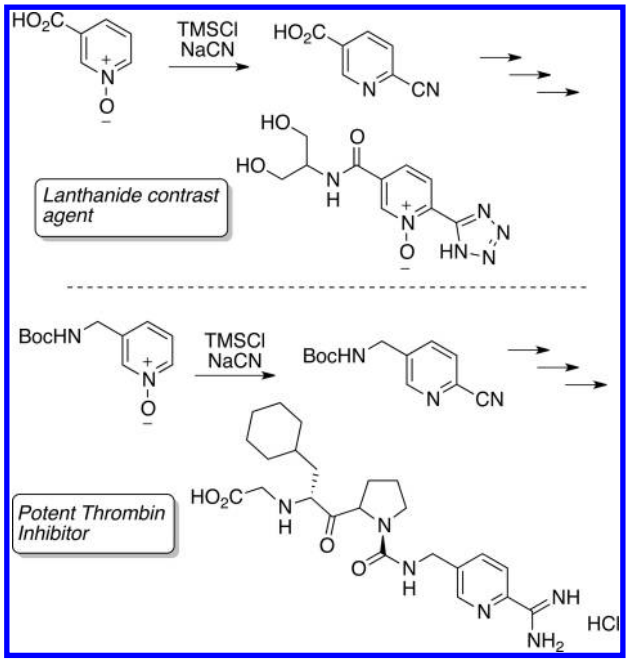
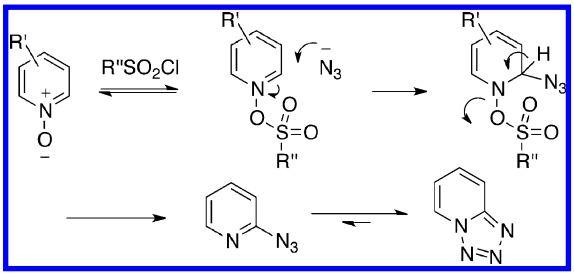
Scheme 79. Some Applications of the Modified Reissert Reaction



Scheme 80. Addition of Azides to Pyridine *N*-Oxides

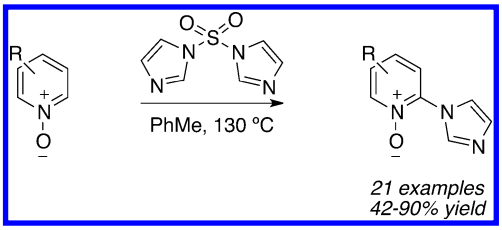


the use of diphenylphosphoryl azide (DPPA) as both activating agent and azide source gave a quantitative yield of the product.

In 2007 the Process Group at Merck Rahway described a direct amination of pyridine *N*-oxides.[413] Although this reaction was previously reported for quinoline *N*-oxides, difficulties were reported in the transition to pyridine *N*-oxides due to a dimerization side reaction, along with the preferential attack of the amino group with the tosyl activating group.[413] Furthermore, the traditional route using the Chichibabin reaction suffers from low yields and site selectivity. Through control of the addition of the reagents, Yin and co-workers were able to add *tert*-butylamine to pyridine *N*-oxide in the presence of Ts_2O with excellent selectivity for addition at the C-2 position (Table 33).[413] The *tert*-butyl group could be removed in situ through the addition of TFA at 70 °C following the completion of the addition step. The methodology was later applied in the synthesis of potent non-nucleoside reverse transcriptase inhibitors.[414]

In an analogous reaction, Keith reported a one-step conversion of pyridine *N*-oxides to 2-imidazolopyridines. By the reaction of pyridine *N*-oxide with sulfuryl imidazole in toluene at 130 °C, the products were obtained in good to

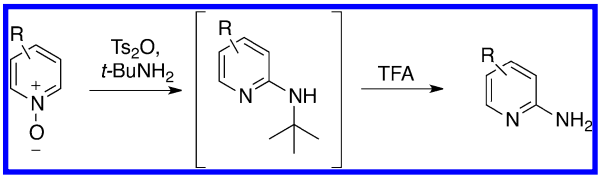
Scheme 81. Synthesis of 2-Imidazolopyridines from Pyridine *N*-Oxides



excellent yields with substitution occurring at the 2-position almost exclusively (Scheme 81).[415] With electron-donating groups at the 3-position, the reaction occurs at the more-hindered site, whereas a mixture of regioisomers is obtained when 3-electron withdrawing groups are present.

The addition of amides to the 2-position of pyridine *N*-oxides was disclosed by Medley and Movassaghi. This work builds on the initial report from Abramovitch and Singer whereby amidations of pyridine *N*-oxides occur through thermal rearrangements.[416] The recent work was accomplished by first activating the amide with Tf_2O in the presence of a non-nucleophilic pyridine source and then subjecting the reactive intermediate to pyridine *N*-oxide in the presence of a base (see section 2.3).[417] 2-Fluoropyridine was found to be optimal for the amide activation, though a range of pyridines with electron-withdrawing groups at the 2-position was found to be effective. The need for fluorine on the pyridine ring was thought to be a result of the decreased nucleophilicity of the pyridine

Table 33. Amination of Pyridine *N*-Oxide



entry	pyridine *N*-oxide	yield (%)
1	H	84
2	4-Me	88
3	3-Me	83 (1.7:1 3-Me vs 5-Me)
4	4-Cl	71
5	4-MeO	90
6	2-CO_2Me	80
7	2-Pyr	81
8	2-Me, 3-MeO, 4-Cl	82

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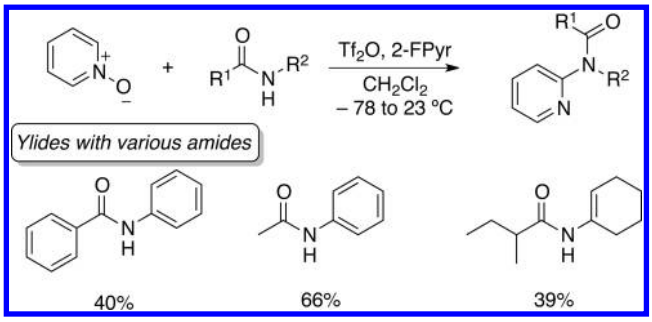
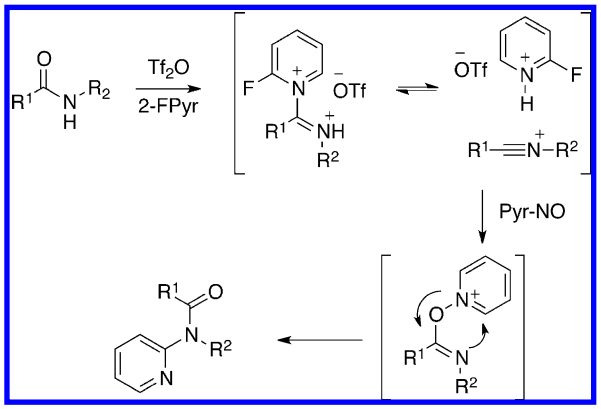
additive.[417] A range of amides could be added, but both quinoline and isoquinoline *N*-oxides displayed superior reactivity compared to pyridine *N*-oxides, presumably due to

Scheme 82. Deoxgenative Amidation of Pyridine *N*-Oxides: Selected Scope



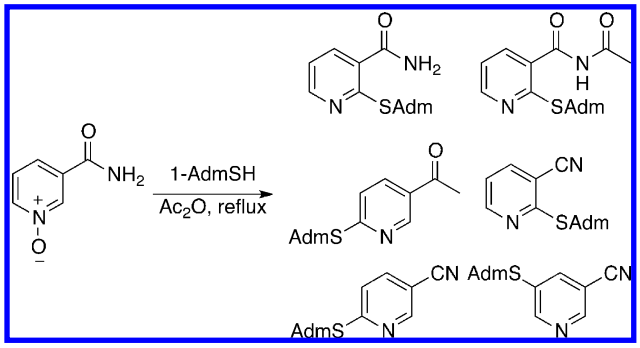
Scheme 83. Deoxgenative Amidation of Pyridine *N*-Oxides: Mechanism



the decreased degree of aromaticity of these systems (Schemes 82 and 83).

Sulfur-Based Nucleophiles. The addition of thiols to pyridine can be achieved through a displacement of a halide (typically chlorine). Although the latter method is often used, it suffers from two main drawbacks: (i) the need for the halogenation of pyridine, which has regioselectivity/purification issues (vide infra), and (ii) moderate yields in the subsequent addition of the sulfur nucleophile. Initial studies involved the addition onto *N*-acyl pyridinium species, and later studies were made on the addition of thiols onto pyridine *N*-oxides. The first account involved the addition of 1-adamantanethiol onto nicotinamide *N*-oxide.[418] The reaction was found to be mostly selective for the 2-position, although in total six products were observed, many of them being formed as a result of side-reactions following the amide activation with Ac_2O (Scheme 84).[418] The reaction was simultaneously studied on 3-picoline *N*-oxide using *tert*-butyl mercaptan and 1-adamantanethiol, which also led to a mixture of regioisomers.[419] The formation of the 3-thio derivatives was postulated to occur as a result of the formation of bridged sulfur intermediate that could be opened by the addition of acetate at the 2-position. The $^-$OAc was subsequently eliminated during rearomatization. Interestingly, the inclusion of triethylamine led to improved selectivities for the addition at the 2-position. This was due to increased proton abstraction at C-2, favoring rearomatization over the formation of the sulfur bridge. The scope of the reaction was found to be extremely general with a wide range of alkyl thiols

Scheme 84. Thiol Addition to 3-Amido Pyridine *N*-Oxide



being operative in the transformation (Table 34), but with the compromise of incomplete selectivity when triethylamine was not included and decreased yields when it was.[420] Exploration of the role of the activating agent for the *N*-oxide determined that, in addition to anhydrides, several acyl chlorides, carbamoyl chlorides, sulfonyl chlorides, and sulfonamide chlorides were operative.[420] The 2- and 3-regioselectivity with these agents was comparable to that observed with Ac_2O (Table 34); again this was improved upon addition of triethylamine, but in contrast, this also improved the yield. Lastly, the substitution on the pyridine *N*-oxide ring was also considered, and as can be expected a mixture of 2- and 3-thiopyridines was observed, with the 2-thiopyridines being the major products.[421] More recently, some of the latter 2-thiopyridines were found to have modest antimicrobial activity.[422]

The Sato group studied the addition of 4-methoxytoluene-α-thio when using diethylcarbamoyl chloride as an additional activating reagent for the pyridinium.[423] In particular, the electronic effects of substituents at the 3-position of pyridine *N*-oxides were investigated. Instead of using Et_3N to aid in the deprotonation, the addition of $ZnBr_2$ was added to stabilize the anionic Meisenheimer intermediate, which can still be deprotonated, affording the desired product.

Chloride Nucleophiles. The halogenation of pyridines may be achieved through the deprotonation of an activated pyridinium species followed by a quench by an electrophilic halide source (see section 5). It is also possible to add a chlorine anion directly to pyridine *N*-oxides using $POCl_3$ as the activating reagent. Okuda and Robison first reported this transformation in 1959 on 3-cyanomethylpyridine *N*-oxide, with the major product being the more-encumbered 2-Cl product (37%).[424] Over 30 years later, the reaction was revisited to use the chloropyridines generated from pyridine-*N*-oxides in the preparation of thiopyridines (vide supra).[425,426] Yamanaka et al. explored the site-selectivity of the reaction with 3-substituted pyridine *N*-oxides (Table 35). The yield of the chlorination was not affected by the electronics or the sterics of the substituent on the pyridine *N*-oxide.[427] However, the selectivity of addition was substituent-dependent, with potential electron-rich groups yielding a mixture of regioisomers.

4.2. Nucleophilic Addition to *N*–*N*-Pyridinium Salts and Ylides

Relative to pyridine *N*-oxides, pyridinium species activated by means of an *N*–*N* bond have been less explored for the structural elaboration of pyridine. However, they offer the ability to tune the reactivity of the pyridinium by varying the electronics of the *N*-substituent. As an indication, the pK_a of the azo-activating group can be varied significantly from ~13 in the

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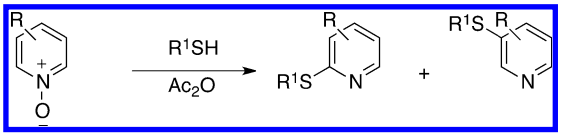
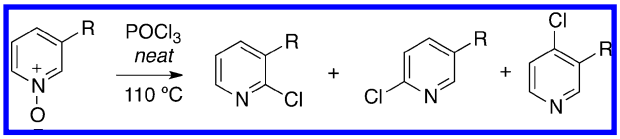
Table 34. Selected Scope of Thiol Addition onto Pyridine *N*-Oxides



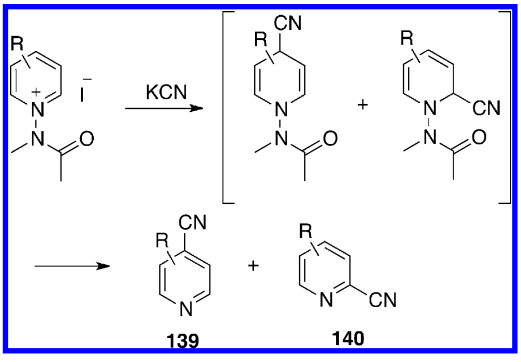
				site of thiol addition				
entry	R	Et_3N	R_1	C-2	C-6	C-3	C-5	combined yield (%)
1	H	no	*t*-Bu	70		30		62
2	H	yes	*t*-Bu	90		10		41
3	H	no	Me	52		48		38
4	4-Me	no	*n*-Pr	50		50		31
5	2-Ph	no	1-Adm		76		24	81
6	2-Ph	yes	1-Adm		98		2	78
7	3-Me	no	*t*-Bu	45	19		36	66
8	3-Me	yes	*t*-Bu	61	34		5	20

Table 35. Selectivity of Chlorination of 3-Susbstituted Pyridine *N*-Oxides



		product ratio			
entry	R	C-2	C-3	C-4	overall yield (%)
1	H	70		30	82
2	CN	88	10	2	83
3	$CONEt_2$	80	20	0	93
4	CO_2H	86	14	0	75
5	NO_2	73	27	0	68
6	Br	46	46	8	77
7	Me	30	27	43	77
8	NMe_2	34	47	19	80

Table 36. Cyanation of *N*-Acylaminopyridinium Salts



		product yield (%)	
entry	R	**139**	**140**
1	H	89	3
2	2-Me	88	0
3	3-Me	92	0
4	4-Me	0	13

case of *N*-aminopyridium salts to ~3 in the case of the *N*-protonated *N*-iminopyridinium ylides (cf pK_a protonated pyridine *N*-oxide = 0.8).[428] The emphasis of the present section will be the nucleophilic addition to *N*–*N*-pyridinium species.

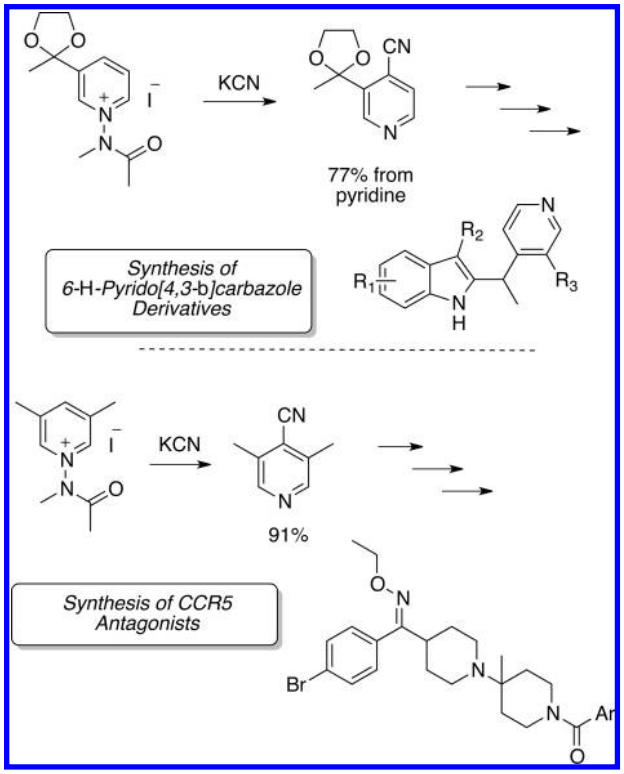
4.2.1. Addition of Cyanide to *N*–*N*-Pyridinium Salts. As with the modified Reissert reaction with pyridine *N*-oxides, the addition of cyanide anions constitutes perhaps the largest class of reaction for *N*–*N* pyridinium salts. The first report was released by Ohsawa and co-workers in 1963 involving the addition of aqueous KCN to 1-(*N*-acylalkylamino)pyridinium derivatives, giving primarily the 4-cyanopyridine.[429] Although traces of the 2-cyanopyridine product were observed, it was found that the regioselectivity was dependent on the

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642–2713

concentration of the KCN employed. At 12.5 M a 1.4: 1 ratio of the 4-CN (**139**) to the 2-CN (**140**) product was observed, although when the concentration was lowered to 6.2 M, the 4-CN product was isolated in 89% yield with little 2-CN product obtained.[430] The products were formed through an addition/elimination mechanism whereby elimination of the amide from a cyano dihydropyridine intermediate afforded the observed products. The scope of substituted pyridines was explored, and high regioselectivity was observed for the 4-position, regardless of the substitution on the ring, with the exception of 4-methyl-1-(*N*-acylmethylamino)pyridinium salt, which furnished the 2-CN compound in 13% yield (Table 36).[430]

Subsequently, Sainsbury et al. applied this methodology to the synthesis of 6*H*-pyrido[4,3-*b*]carbazole derivatives.[431] In their account, *N*-acylaminopyridinium ylides were *N*-methylated to generate the corresponding pyridinium salts. Applying Ohsawa's obervations led to the 4-CN pyridines, which were converted to the corresponding carbazoles (Scheme 85). Also,

Scheme 85. Application of Cyanation of *N*-Acylaminopyridinium Salts Toward the Synthesis of Biologically Active Compounds



a research group at Schering-Plough applied this methodology in the synthesis of CCR5 antagonists.[432]

In the 1970s Katritzky and Sammes disclosed the preparation of 1-pyridinio-4-pyridone cations through the condensation of 1-aminopyridine salts with chelidonic acid (Scheme 86).[433] These *N*-*N*-activated pyridinium compounds were found to be reactive toward KCN addition, affording the cyanated pyridine in 87% yield. Initially, the reaction was determined to be selective for the 2-position of the pyridine;[433] however, later studies also found a dependency on the concentration of the cyanide anion.[434] A decrease in KCN concentration in the reaction mixture furnished improved substitution at the 4-position, leading the authors to postulate that 2-cyanopyridine was the kinetic product, whereas 4-cyanopyridine is the result of a thermodynamic control.[434] The isolation of the dihydropyridine intermediate was described and was found to have a half-life of 14−75 h, with elimination occurring to give the corresponding cyanopyridine.[434] Finally, the use of blocking groups on the 2- and 6-position of the pyridone group provided the 4-cyanopyridine exclusively.[435] Structural studies on these salts demonstrated a large amount of *p*-character to the *N*−*N* bond, concomitantly increasing the *s*-character of the methyl *N*−*C* bonds with the C-2 and C-6 positions of the pyridone moiety, thus shortening the *N*−*C* bond length (Bent's rule). Consequently, the interactions between the pyridine and the two methyl groups of the pyridone component were found to be even more significant (Scheme 86, **141**).[436] A distance of only 0.17 Å was observed between the methyl hydrogen atoms and the hydrogen atoms at the C-2 and C-6 of the pyridinium, despite the fact that the two rings are located in perpendicular planes.[436] These findings supported the explanation of the excellent selectivity observed.

Dinitrogen pentoxide, prepared in situ from concentrated nitric acid and trifluoracetic anhydride, could be used to activate pyridine via the generation of *N*-nitropyridinium salts (Table 37).[437] These pyridinium derivatives readily underwent selective 2-cyanation in low to very good yields, for a range of substituents.

Lastly, 1-aminopyridinium salts also readily undergo selective addition of cyanide to the 4-position of the pyridinium ring (Scheme 87). However, these 4-cyanopyridines are unstable and spontaneously react in a [3 + 2]-cycloaddition with another equivalent of the 1-aminopyridinium salt to give 2-(4-pyridyl)-*s*-triazolo[1,5-*a*]pyridines.[438,439]

4.2.2. Addition of Grignard Reagents to *N*−*N*-Pyridinium Compounds. Katritzky, Sammes, and co-workers also applied the strategy of using 2,6-dimethyl blocking groups in the addition of Grignard reagents to *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts (Scheme 88, **142**).[440−442] The resulting 4-substituted pyridine could previously only be prepared in multistep syntheses,[440] and the method proved to be complementary to that previously reported with pyridine *N*-oxides. The resulting crude reaction mixtures consisted of both the dihydropyridine intermediate and the 4-substituted

Scheme 86. Synthesis of Cyanopyridines from 1-Pyridinio-4-pyridones

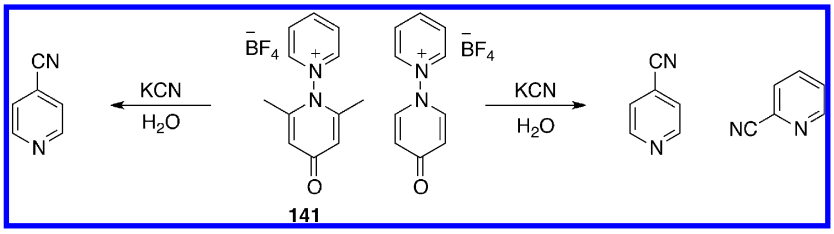


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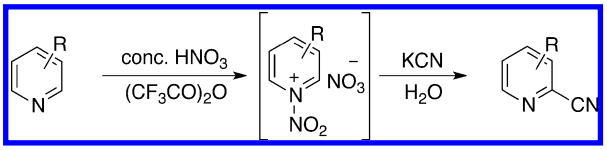
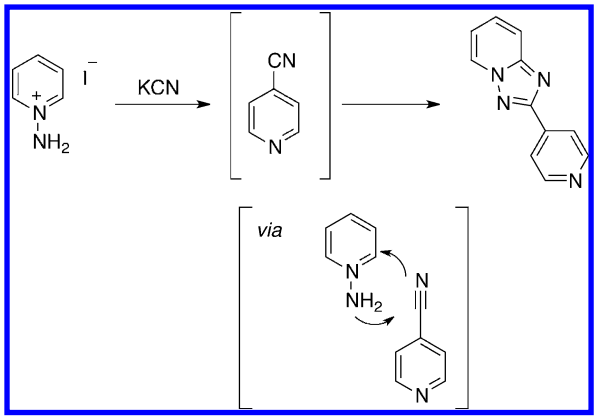
Table 37. Cyanation of *N*-Nitropyridinium Salts



entry	R	yield (%)
1	H	72
2	3-Me	75
3	3,6-Me	45
4	3-Et	78
5	3-Cl	55
6	3-Br	81
7	4-COMe	53
8	5-CO_2Et	20

Scheme 87. Cyanation of 1-Aminopyridinium Salts

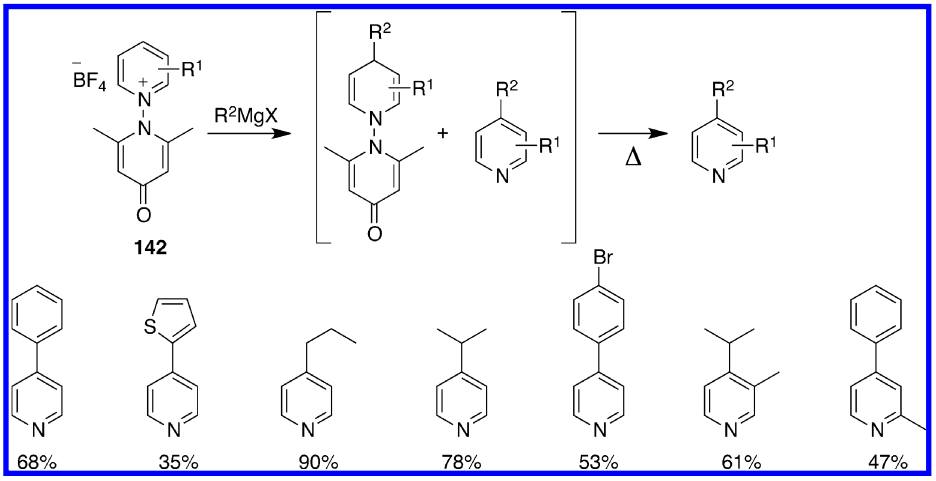


pyridine. The dihydropyridine proved too unstable for clean isolation, but heating the crude oil to 200 °C or refluxing in MeCN effected the rearomatization of the heterocycle.[442] A wide range of alkyl, aryl, and heterocyclic Grignard reagents were operative. Additionally, 2- and 3-picolinium salts were well tolerated. The last results were impressive considering the high acidity of the methyl protons and the basicity of the organomagnesium nucleophile. Attempts to add organolithium reagents were unsuccessful, and neither the dihydropyridine nor the pyridine could be isolated following pyrolysis.[442]

Legault and Charette disclosed the addition of Grignard reagents to *N*-benzoyliminopyridinium ylides.[178] These ylides were readily prepared in a one-pot procedure involving the amination of pyridine by *o*-(2,4-dinitrophenyl)hydroxylamine followed by treatment with BzCl and aqueous NaOH.[443] The Lewis basic *N*-imino group complexed to the Grignard reagent directs the attack to the 2-position of the pyridine.[178] In this case, elimination of benzamide to form the pyridine did not occur rapidly. The dihydropyridine itself was unstable but could be treated with $NaBH_4$ to yield the *N*-protected 1,2,5,6-tetrahydropyridine. Furthermore, by the inclusion of a camphoric anhydride-based chiral auxiliary at the *N*-component of the ylide (**143**), a diastereoselective addition could be achieved (Scheme 89, 84:16 dr).

4.2.3. Addition of Enolate Equivalents to *N*–*N*-Pyridinium Salts. The addition of enolates to *N*–*N*-pyridinium salts is well documented. Lithium enolates of ketones add selectively at the 4-position of *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts due to the blocking effect of the methyl groups (Table 38).[358,441] Unlike what is observed with the addition of Grignard reagents, the target pyridine was not obtained and the 4-substituted dihydropyridine intermediate could be readily isolated and purified on Al_2O_3.[441] The addition of LDA to the mixture of the pyridinum and ketone gave selective addition of the kinetic enolate. Importantly, even α,α-disubstituted enolates were reactive enough to add, forming

Scheme 88. Selected Substrate Scope for the Addition of Grignard Reagents to *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts



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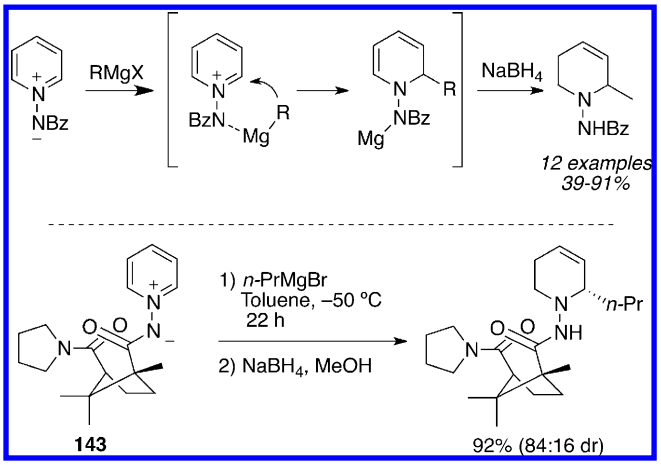
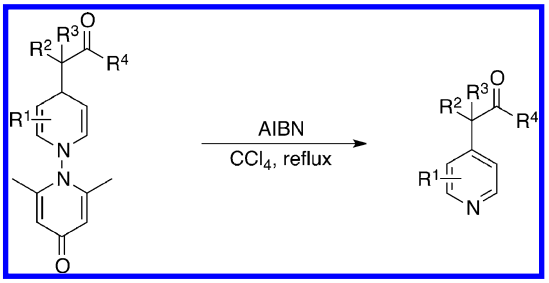
Scheme 89. Complexation-Promoted Grignard Additions to *N*-Benzoylpyridinium Ylides



an all-carbon quaternary center in 52% yield.[441] Picoline derivatives of the *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-pyridinium salts were also operative. Elimination from the dihydropyridine to provide the desired pyridine to could be accelerated in the presence of 2,2′-azobisisobutyronitrile (AIBN) in CCl_4 at reflux or could proceed thermally by refluxing in toluene (Scheme 90).[441]

The scope of the reaction was expanded to include enolates of esters and nitriles. As with the ketone analogues, the carbanions were prepared using LICA at −78 °C and added to the corresponding *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-pyridinium salt. However, this method of activation only afforded limited amounts of the 4-substituted pyridines (10−30% yield).[359] The dihydropyridine intermediate was found to be very unstable and was immediately converted to the pyridine under reflux with CCl_4 and AIBN; otherwise, decomposition was observed. The authors reasoned the decreased yield to be due to self-condensation between the enolate equivalents.[359] In fact, only ethyl phenylacetate provided acceptable results. Concidentally, the pK_a of this substrate was determined to be

Scheme 90. Generation of 4-Acylalkylpyridines



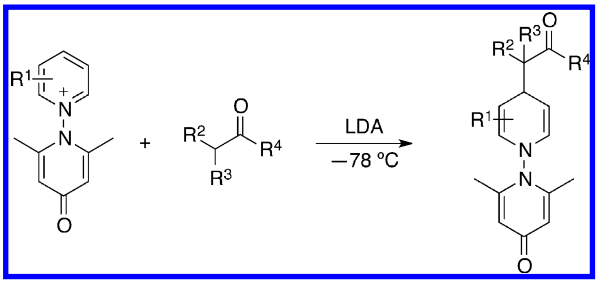
similar to that of the ketones previously reported, suggesting that the upper pK_a limit for the anion is 16−20.[359] However, the authors circumvented this problem by using *N*-triphenylmethylpyridinium tetrafluoroborates, and the desired 4-alkyl pyridines could be obtained in moderate to good yields.

Recognizing that increasing the acidity of the enolizable center appeared beneficial for the reaction, Sammes, Leung, and Katritzky explored the addition of malonate derivatives to *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salt **141**. The enolates were generated in the presence of alkoxide bases and provided the 4-substituted tetrahydropyridines in moderate to good yields (Table 39).[444] Of note, malononitrile and ethyl cyanoacetate afforded a 1:1 mixture of the 4-substituted dihydropyridine and a ring-opened product (Scheme 91).[444] This was due to competition with addition at the 2-position of the pyridinium followed by electrocyclic ring-opening, although no further explanation was provided for this observation.

The addition of nitroalkanes provided 4-nitroalkylpyridines in moderate to good yields.[441,445] The desired pyridine product was obtained by photolysis of the stable dihydropyridine in chloroform in the presence of benzoyl peroxide (Scheme 92).[445]

4.2.4. Addition of Other Nucleophiles to *N*–*N*-Pyridinium Salts. The first example of the addition of amino groups to activated pyridines was provided by Katrizky and co-workers in 1970 by addition of a 4-methoxy-*N*-aminopyridinium salt to the 4-position of another *N*-amino-

Table 38. Selected Scope for the Addition of Ketone Enolates to *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts



entry	R^1	R^2	R^3	R^4	yield (%)
1	H	H	Ph	Ph	70
2	H	H	—$(CH_2)_3$—		72
3	H	H	H	Et	92
4	H	H	H	Me	23
5	H	H	Ph	Me	70
6	H	H	H	*t*Bu	86
7	H	Me	Me	*i*Pr	52
8	H		camphor		80
9	2-Me	H	Ph	Me	80
10	3-Me	H	Me	Et	89

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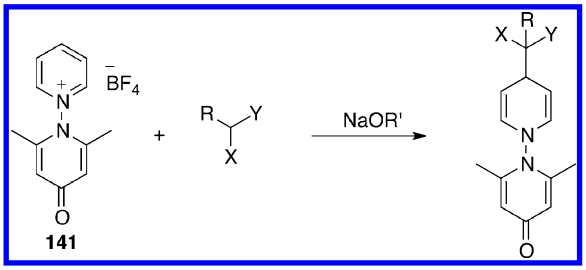
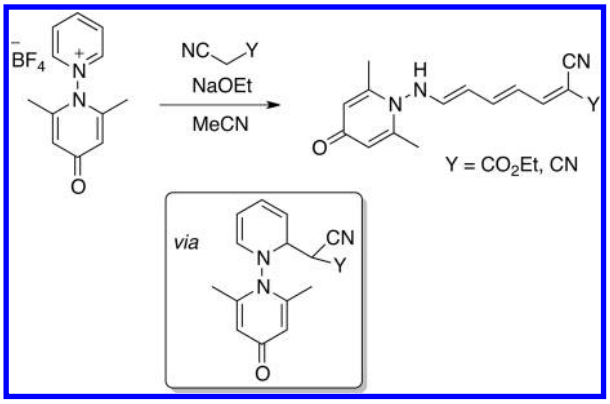
Table 39. Selected Scope for the Addition of Malonate Derivatives to *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts

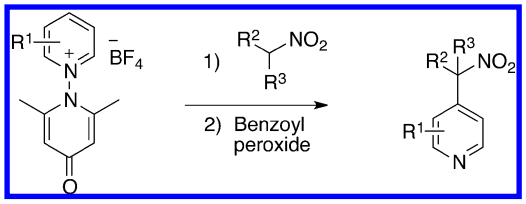


entry	NaOR′	R	X	Y	yield (%)
1	NaOEt	H	COMe	COMe	43
2	NaOEt	*n*-Pr	COMe	COEt	28
3	NaOEt	$PhCH_2$	COMe	COEt	65
4	NaOEt	Me	CN	COEt	78

Scheme 91. Ring-Opening of *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts



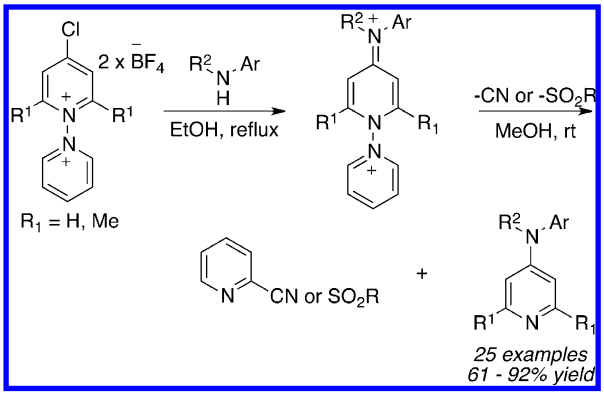
Scheme 92. Generation of 4-Nitroalkylpyridines



pyridinium salt to provide the corresponding product in 87% yield.[428] It was later determined that aniline derivatives could be readily added to 4-chloro-1-pyridiniopyridinium salts to generate a variety of iminium salts in good to excellent yields.[446] These salts were then subjected to attack by cyanide or sulfinate anions to liberate the 4-amino pyridine, along with a 2-cyano or 2-sulfonyl pyridine (Scheme 93). In addition, *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts have been shown to be effective substrates on which to add various imidazolo and triazolo nucleophiles.[441]

Katritzky and Sammes described the addition of chloride to 1-pyridinio-4-pyridones to generate a highly activated dicationic pyridinium species.[433,434] These compounds could be reacted with sulfinates to give the 2,4-disulfinyl pyridines in moderate yields. Later they reported the addition of alkyl and aryl thiols to *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts to provide 4-thiopyridines in good to excellent yields following cleavage by AIBN in CCl_4 (Table 40). The initial addition was found to be reversible in aqueous media, although it was driven to cleavage in MeCN.[447] This was presumed to be due in part

Scheme 93. Addition of Aniline Derivatives of 1-Pyridiniopyridinium Salts



to the increased pK_a of the thiol in acetonitrile, shifting the equilibrium of the reaction and favoring the formation of the thioether.

The addition of sodium metabisulfite to the 2-position of *N*-nitropyridinium salts has been reported. Although the 2-substituted dihydropyridine bisulfite was not isolated, it was used to generate 3-nitropyridines through the attack of nitric acid and subsequent eliminination of the bisulfate group to rearomatize the heterocycle (Scheme 94).[448]

Dialkylpyridin-4-yl phophonates **145** could be readily prepared from the addition of trialkyl phosphites to *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts **144** in the presence of sodium iodide and MeCN.[449] The resulting dihydropyridine intermediate, although isolable, was too unstable for characterization and readily decomposed to the 4-substituted pyridine in moderate to very good yields (Scheme 95). Curiously, when *N*-(2,5-dimethylpyrrolo-1-yl)pyridinium iodide was used in place of *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium salts, the dihydro intermediate was found to be very stable and readily isolable.[449]

4.3. Nucleophilic Additions to Pyridines Activated by Lewis Acids and Other Species

Early accounts describing the direct addition of Grignard reagents to pyridine itself are thought to proceed through the complexation of the magnesium to the heterocyclic nitrogen atom, effectively activating the pyridine in situ.[450−452] However, the seminal methods lead to low yields and are effective for more electrophilic azacycles,[453] leading to the study of the aforementioned *N*−*O* and *N*−*N* species. However, the addition

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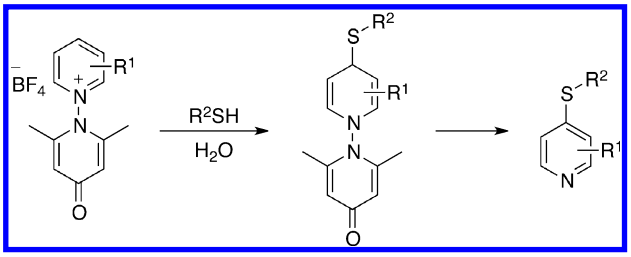
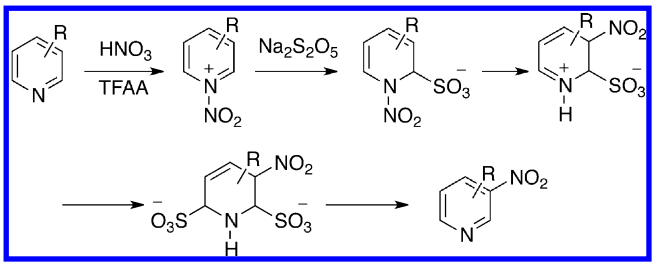
Table 40. Selected Examples for the Addition of Thiols to *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts

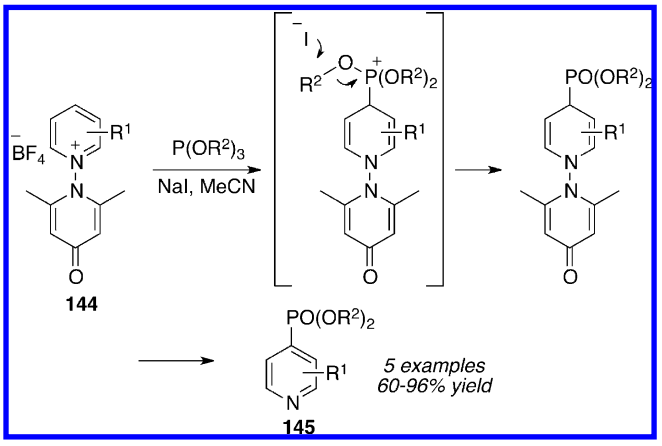


entry	R^1	R^2	yield (%)
1	H	*c*-Hex	83
2	H	Bn	90
3	H	furfuryl	80
4	H	4-Br,3-MePh	87
5	H	2-NH_2Ph	0
6	2-Me	4-ClPh	59
7	3-Me	Et	86

Scheme 94. Preparation of 3-Nitropyridines Through the Addition of Metabisulfites to *N*-Nitropyridinium Salts



Scheme 95. Addition of Trialkylphosphites to *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts



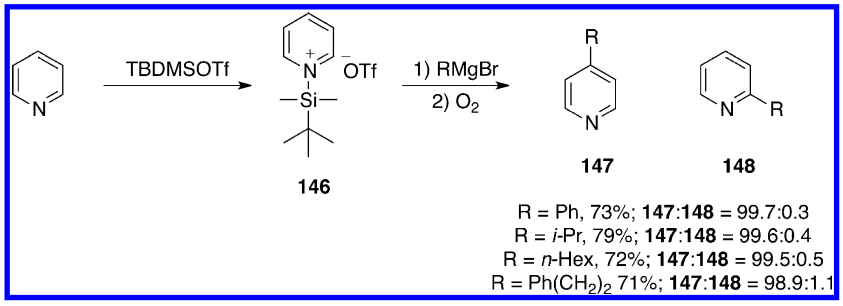
of an external Lewis acid to activate the pyridine has been explored with some success, and the following section will focus on these studies.

4.3.1. Addition of Grignard Reagents to Silyl-Activated Pyridinium Salts. Akiba et al. described the use of *t*-butyldimethylsilyl triflate to generate an *N*−Si pyridinium salt **146** that is susceptible to attack by Grignard reagents to give substituted pyridines **147** and **148** in moderate yields after oxidation.[454] The excellent 4-selectivity of the reaction is the result of the steric hindrance of the *t*-butydimethylsilyl activating group serving as a blocking group of the 2 positions.[454,455] Although a one-pot activation/addition sequence was possible, reaction yields were 10−20% lower than when the silylated pyridinium was preisolated. Facile rearomatization to the pyridine occurred under air oxidation as a result of the electropositive character of the silyl group (Scheme 96).[455,455]

Attempts to use the readily more available silyl chlorides in place of the triflates were not successful because the more nucleophilic chloride renders the activation step reversible, slowing down the overall process.[455] Anders et al. studied the formation of TMS-activated pyridinium compounds and found that silyl iodides were as effective as silyl triflates.[456] Later, Olah and Klumpp described a facile synthesis of silyl triflates with a reaction between allylsilane and triflic acid. The resulting silanes were proven to be effective in generating the corresponding silyl pyridinium species.[457]

Both hindered and nonhindered Grignard reagents were equally effective (Scheme 96). Various other nucleophiles such as cuprates, enolates, and lithiate species were also added.

Scheme 96. Addition of Grignard Reagents to Silyl-Activated Pyridinium Salts



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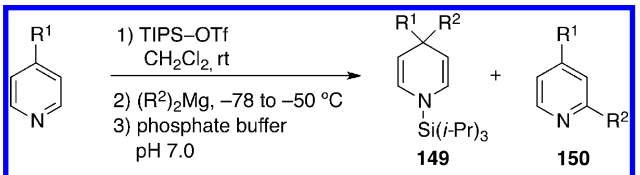
Butyllithium provided modest results, as cuprates were soft and therefore not nucleophilic enough for addition, and enolates preferentially attacked the silicon-activating group.[455]

Substitution on the pyridine ring has been explored, particularly pyridines already bearing a substituent at the 4-position using the extremely bulky TIPSOTf as the activating group.[458] Using 4-phenylpyridine with EtMgCl as the nucleophile, the stable 4,4-disubstituted *N*-silyl-1,4-dihydropyridine **149** was isolated in 28% yield and only 1% of the 2-subsituted pyridine **150** was observed.[458] This yield was improved to 78% using Et_2Mg as the nucleophile because halide anions that can displace the silyl-activating group were not present under these conditions. 2-Substitued pyridines were favored with less-hindered nucleophiles such as methyl, phenyl,

Scheme 97. Addition of Grignard Reagents to Silyl-Activated 4-Substituted Pyridinium Salts

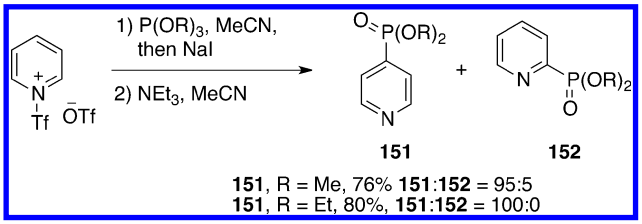


149, R^1 = Ph, R^2 = Et, 78%, **149**:**150** = 90:4
149, R^1 = Ph, R^2 = Bn, 92%, **149**:**150** = 95:2
149, R^1 = Ph, R^2 = Ph, 95%, **149**:**150** = 5:95
149, R^1 = Ph, R^2 = Me, 59%, **149**:**150** = 0:1
149, R^1 = Bn, R^2 = *i*-Pr, 78%, **149**:**150** = 1:0

and allyl (Scheme 97).[458] As previously, the desilylation/rearomatization was presumed to be effected by aerial oxygen upon workup. 3-Nicotinates were later determined to also be viable reaction substrates, albeit with poorer regioselectivity.[459] This was improved by tuning the nucleophilicity of the Grignard reagents through the addition of tetrabutylammonium iodide (TBAI; 10 mol %).

4.3.2. Addition of Nucleophiles to Triflate-Activated Pyridinium Salts. Triflate-activated pyridinium salts offer greater synthetic flexibility and consequently have garnered much interest. The first accounts described the addition of phosphines to the activated pyridine,[460,461] with pyridyl phosphanes being an important class of soft transition metal ligands.[462] Complete formation of the pyridinium triflate occurred before attack of the phosphine. A clear advantage of the method was the fact that no directing group was required in the synthesis, which is unprecedented in the preparation of these compounds. The dihydropyridine intermediate is not stable, and the product decomposes to give the 4-substituted pyridine.[461] Double addition to form potential 4,4′-products was avoided by the use of a large excess of pyridine, protecting the product from further activation.[461]

Scheme 98. Addition of Alkyl Phosphonates to Triflate-Activated Pyridinium Salts



151, R = Me, 76% **151**:**152** = 95:5
151, R = Et, 80%, **151**:**152** = 100:0

Pyridyl phosphonates **151** and **152** have also been described through this methodology (Scheme 98). Unlike with the earlier phosphine analogues, the resulting dihydropyridine intermediate was stable enough to be isolated and rearomatized upon treatment with triethylamine.[462] Again, the reaction displayed a strong preference for substitution at the 4-position, but when the pyridine already bears a phosphonate group at the 4-position, substitution occurred at the 2-position.[462] 3,5-Diphenylpyridine and 3-bromopyridine were viable substrates, although 2,6-disubstituted pyridines were not, presumably due to the inability to generate the active pyridinium species.[463] The reaction was also expanded to include quinoline analogues.[463] Amine nucleophiles have also been explored but invariably lead to ring-opened products.[464]

For the addition of enolates, Katritzky et al. demonstrated that triflate activation was more convenient and higher yielding than addition to 1-oxycarbonylpyridinium salts, *N*-benzoylpyridinium chloride, or *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-pyridinium salts.[465] Substitution was observed exclusively at the 4-position in good to excellent yields. Premixing of the pyridine with triflic anhydride to aid the formation of enol triflates was important to achieve high yields. A range of ketone enolates was operative, and the desired pyridine could be obtained after treatment with *t*-BuOK in DMSO (Table 41).[465] Interestingly, KOH in DMSO failed to give the 4-substituted pyridine, instead liberating the ketone starting material and suggesting a reverse reaction, although the authors did not describe the fate of the heterocycle.

Others have used this methodology in the synthesis of polycyclic γ- and δ-lactones **153** and **154**, which are of interest because of their biological activity and their ability to serve as scaffolds in the preparation of other complex, pharmaceutically interesting compounds.[466,467] Rudler and co-workers found that silyl ketene acetals could be readily added to pyridinium triflates to give the 4-substituted dihydropyridines containing carboxylic acids (Scheme 99).[464] Lactonization could be promoted by treatment with iodine or excess triflic anhydride, which led to the incorporation of a trifluoromethyl group (Scheme 99).[465] The addition of the CF_3 group presumably occurred by a radical mechanism, based on the work by Langlois involving electrophilic trifluoromethyl radicals.

Nucleophilic aromatic compounds were shown by Corey and Tian to add efficiently to *N*-triflyl pyridinium salts under mild conditions.[468] The products were obtained in good yields with excellent 4-selectivity, due to the steric bulk of the CF_3SO_2 group blocking the 2-position (Scheme 100). Various substitutions (both electron-rich and -poor) were tolerated at the 2- and 3-positions of the pyridine ring with little effect on the reaction yield. Rearomatization by treatment of the dihydropyridine product with *t*-BuOK was shown to occur in quantative yields.[468] Morita, Shoji, and co-workers later showed that azulene was also a viable nucleophile, giving the (4-dihydropyridyl)azulene in 72% yield.[469]

An intramolecular version of the reaction was described by Brice and Clayden to give spirocyclic 2-piperidone derivatives **155** and **156**.[470] This framework is present in several biologically active alkaloids and has been found to be an efficient scaffold for binding to G-protein coupled receptors.[470] A series of isonicotamides bearing electron-rich heterocyclic substituents were prepared and reacted with Tf_2O in a similar fashion to afford the spirocyclic compounds in moderate to good yield (Scheme 101).

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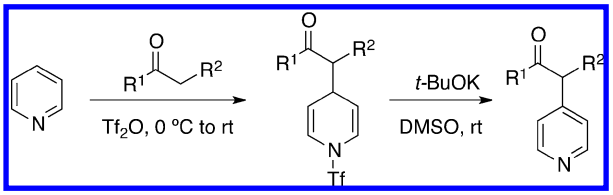
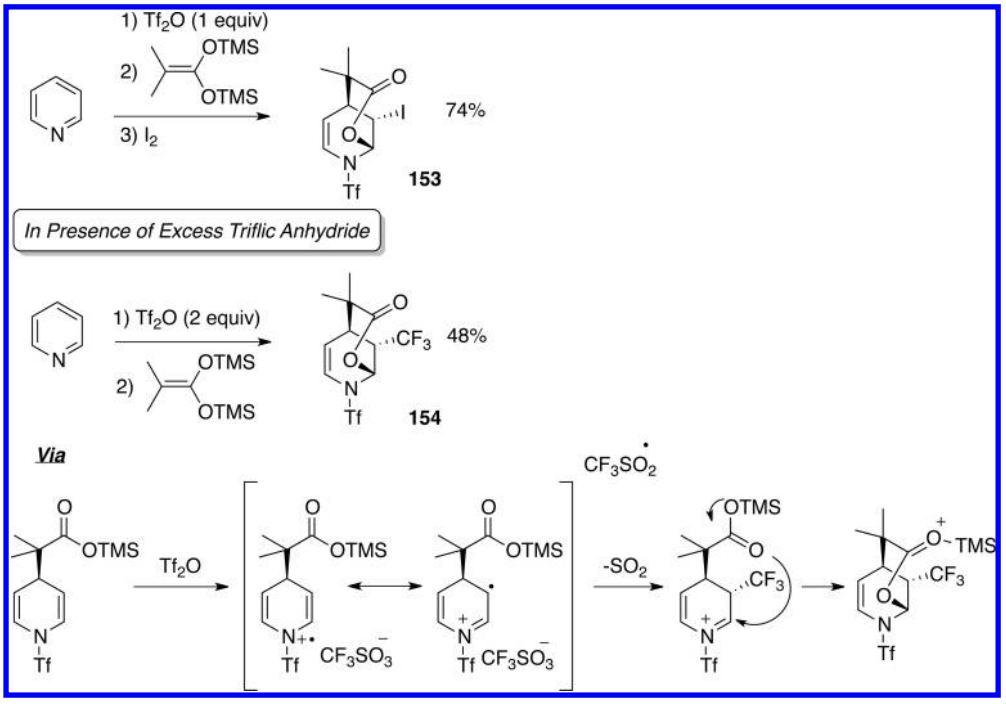
Table 41. Addition of Ketones to Triflate-Activated Pyridinium Salts

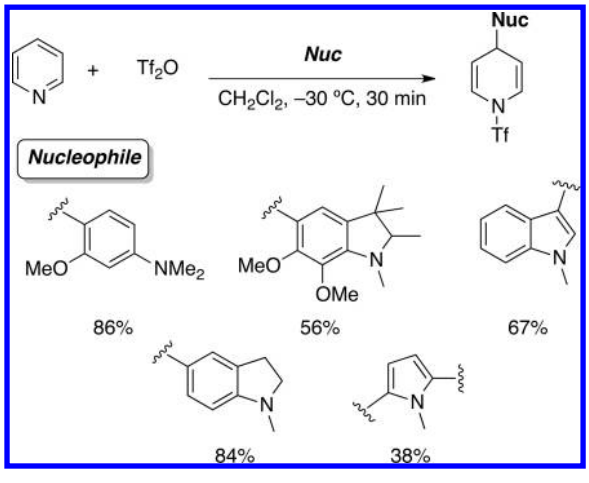


entry	R^1	R^2	yield (%)
1	*i*-Pr	Ph	91
2	Me	4-MeOPh	81
3	4-BrPh	Ph	97
4	Ph	Ph	95
5	2-thienyl	Bt	91
6	2-furyl	Bt	94
7	*t*-Bu	Bt	95

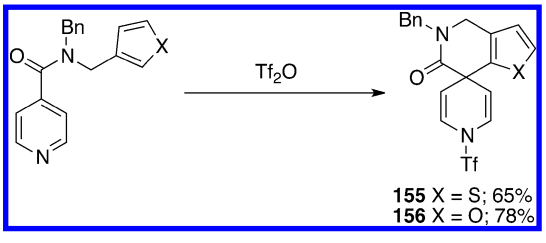
Scheme 99. Addition of Ketene Acetals to *N*-Triflyl-Activated Pyridinium Salts to form Cyclic Lactones



Scheme 100. Selected Scope for the Addition of Electron-Rich Arenes to Triflyl-Activated Pyridinium Salts



Scheme 101. Spirocyclization of *N*-Triflyl-Activated Pyridinium Salts



5. ELECTROPHILIC ADDITIONS TO *N*-HETEROATOM PYRIDINIUM SPECIES BY α-METALATION

The next section will focus on the metalation of *N*-activated pyridine species followed by the reaction with electrophiles, particularly the α-lithiation of pyridine *N*-oxides and pyridine Lewis acid complexes. Pyridines are significantly more acidic than the analogous benzenes, and the direct metalation of pyridines has been widely studied and reviewed else-

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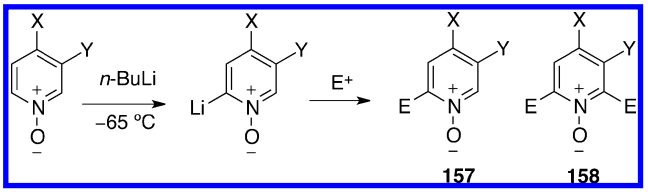
Table 42. Deprotonation of Pyridine *N*-oxides with Butyllithium



entry	X	Y	E^+	yield **157** (%)	yield **158** (%)
1	Cl	Me	CO_2	24	0
2	Cl	Me	cyclohexanone	38	0
3	OEt	H	cyclohexanone	20	12
4	Me	H	cyclohexanone	21	27
5	Cl	H	CO_2	49	0
6	H	H	CO_2	0	15
7	Me	Me	EtOAc	65	

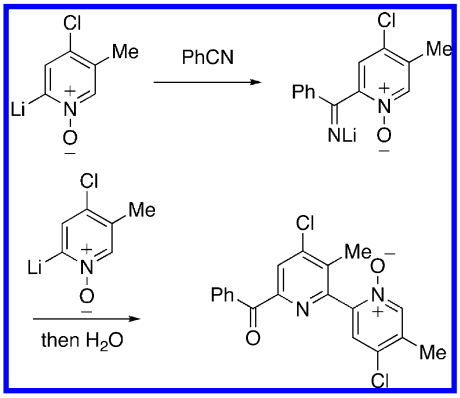
where.[471−474] Important advances have been made in this area; however, close acidities of the pyridine C−H groups make regioselectivity an issue.[475] Dimerization to the bipyridine,[476] addition of the base to the ring, or the preferential deprotonation of side chains also constitute potential limitations of the strategy. Furthermore, the regioselectivity of initial lithiation of pyridine using organolithium reagents depends on the relative acidity of the pyridine C−H bonds and a directing effect via coordination to the pyridine nitrogen.[477] 2-Pyridyllithiums may form preferentially, but because of the destabilizing interaction with the nitrogen lone pair will readily isomerize to 4-pyridyllithiums. The relative acidities of the pyridine C−H bonds are 700:72:1 for the 4-/3-/2-positions.[478,477]

As discussed in section 4, the formation of pyridine *N*-oxides activates the pyridine ring to electrophilic aromatic substitution as well as nucleophilic aromatic substitution. The use of pyridine *N*-oxides also offers several advantages for the functionalization of position C-2 as *N*-activation increases the acidity of α-protons, leading to a 2-selective deprotonation and subsequent reaction with electrophiles. It also removes the destabilizing interaction between the anion and the *N*-lone pair, providing improved control of deprotonation regioselectivity. Electrophilic aromatic substitution on these species has been reported previously and is outside the scope of this review.[377,479,480]

5.1. α-Lithiation of Pyridine *N*-Oxides

The first reports of the deprotonation of pyridine *N*-oxides were in the 1960s when Abramovitch and co-workers investigated the deprotonation at C-2 of pyridine *N*-oxides[481] and used this principle to trap the anions with various electrophilic reagents.[482] The ring was lithiated by *n*-butyllithium prior to the addition of an electrophile. Generally low yields of the pyridine derivatives were obtained, with the 2,6-disubstituted product as the major side product (Table 42). A systematic study of this reaction[483,484] demonstrated that substituents at the 3-position prevented lithiation at the 2-position through steric repulsion, leading to the C-6 substituted product **157**. This was due to steric interactions in the same plane as the C-3 methyl group and the *N*-oxide. 2-Picoline *N*-oxide was deprotonated at the C-2 methyl in preference to the ring 6-position. The anion could be trapped with ethyl acetate to form 2-acetyl pyridine *N*-oxide product **158** (entry 7).[484] However, attempts to form the phenyl ketone via treatment with PhCN afforded a dipyridine product formed by addition of the pyridyl lithium to the now more reactive 2-imino pyridine *N*-oxide (Scheme 102).[484]

Scheme 102. Unexpected Bipyridine with Nitrile Electrophiles



Since this early work, deprotonation using bulky amide bases has been successfully utilized, thereby removing the possibility of competing direct nucleophilic addition. The anions have been generated in the presence of electrophiles compatible with the amide base[485] or preformed to allow a wider range of reagents.[486] Quéguiner and co-workers studied this reaction in respect to C-2 versus C-6 regioselectivity and examined a range of possible electrophiles with various substituted pyridines using LDA (Table 43).[486] The 6-lithiation of 2-substituted pyridines gave complete regioselectivity.

More recently, Olsson, Almqvist, and co-workers demonstrated the α-deprotonation of pyridine *N*-oxides with alkyl Grignard reagents.[487] Using *n*-BuMgCl or *i*-PrMgCl avoided the disubstituted byproduct previously reported with *n*-BuLi, and a range of electrophiles could be employed. The influence of substituents at C-3 was assessed, and although 3-methyl pyridine *N*-oxide afforded only 1.5:1 C-2/C-6 selectivity when quenched with benzaldehyde, a 3-methoxy group gave exclusively the 2-substituted product (86% yield). This directing effect was also shown to be compatible with iodide, piperidone, and isocyanate electrophiles (for example, see Scheme 103). Furthermore, the intermediate Grignard species underwent palladium-catalyzed cross-coupling with diphenyliodonium triflate in the presence of zinc chloride under microwave conditions (Scheme 104).

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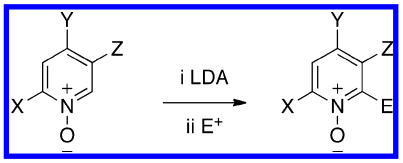
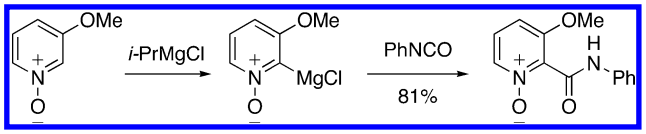
Table 43. Regioselective Pyridine *N*-Oxide Deprotonation with LDA

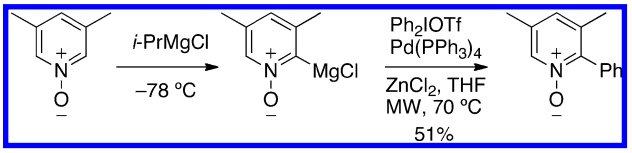


entry	X	Y	Z	E^+	yield (%)
1	CON*i*-Pr_2	H	H	EtOD	100
2	CON*i*-Pr_2	H	H	PhCHO	62
3	NHCO*t*-Bu	H	H	I_2	73
4	NHCO*t*-Bu	H	Me	MeI	83
5	NHCO*t*-Bu	H	Me	TsCN	57

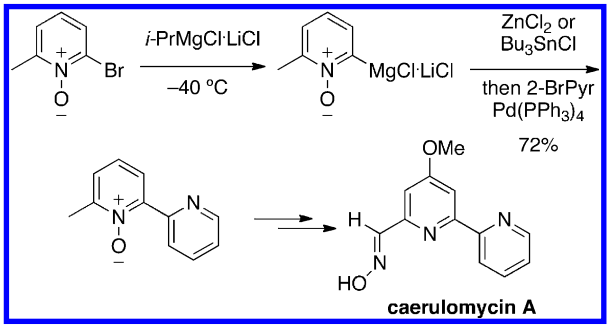
Scheme 103. Directing Effect of the 3-Methoxypyridine *N*-Oxide



Scheme 104. Magnesiation and Palladium-Catalyzed Cross-Coupling of Pyridine



Scheme 105. Synthesis of Caerulomycin A via Magnesium/Halogen Exchange

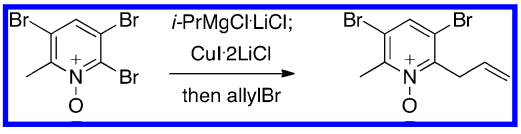


In 2009 Duan et al. reported the formation of the magnesium anions of pyridine *N*-oxides via halogen−magnesium exchange.[488] 2-, 3-, and 4-Iodopyridine as well as 2-bromopyridine *N*-oxides were selectively magnesiated with *i*-PrMgCl·LiCl and reacted with various electrophiles. The optimal temperature for the magnesiation was found to be −40 to −60 °C to prevent addition to the pyridine at higher temperatures. This methodology was used in the synthesis of two caerulomycin natural products (Scheme 105). In addition, the study showed that di- and tribromopyridine *N*-oxides could be selectively magnesiated at the 2-position under mild conditions (Scheme 106). The regioselectivity was in contrast to that obtained with 2,5-dibromopyridine, where metalation was reported at the 5-position.[489]

5.2. α-Lithiation of Preformed Pyridine−Lewis Acid Complexes

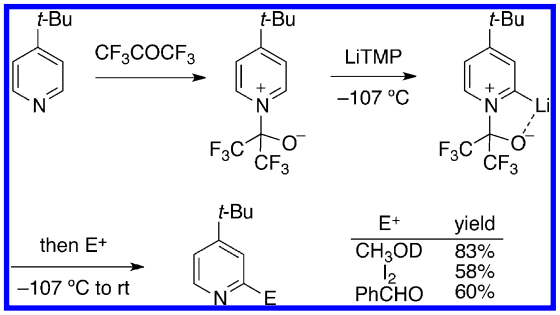
Temporary activation of pyridine has also been explored as a means to increase the acidity of adjacent protons. These

Scheme 106. Selective Metallation of 2,3,5-Tribromo-6-picoline *N*-Oxide



approaches have the advantage that the pyridine product is isolated directly from the reaction mixture. Martin and co-workers reported that the adduct of pyridine and hexafluoroacetone increased the acidity of the α-protons sufficiently to allow deprotonation, with possible chelation to aid regioselective deprotonation.[485] At very low temperature (−107 °C), the HFA−pyridine complex was stable and could be reacted with external electrophiles (Scheme 107). However, at higher

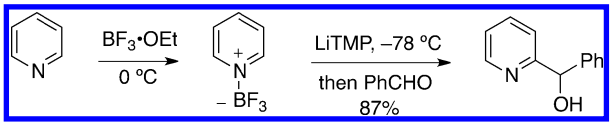
Scheme 107. Formation of HFA−Pyridine Complex to Enhance α-Acidity



temperatures, the anion was quenched by reaction with the hexafluoroacetone employed as the activating reagent.

In 1991 Kessar and co-workers reported the activation of pyridine with boron trifluoride and deprotonation of the resulting complex with LiTMP.[490,491] Trapping the intermediate with various aldehydes or ketones provided high yields of the substituted pyridine methanol (Scheme 108). The anions of

Scheme 108. Deprotonation and Trapping of Pyridine−Boron Trifluoride Complex



the pyridine−BF_3 adducts are proposed to be more reactive than the equivalent anion formed from the pyridine *N*-oxides with carbonyl electrophiles,[492] although they have not been

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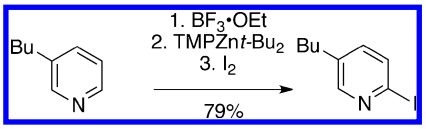
shown to be reactive toward alkyl or benzyl halides. Vedejs and Chen used acyl chlorides as electrophiles in this approach for the preparation of chiral DMAP derivatives that were used in the resolution of chiral alcohols.[493]

TMP-zincates have been used to metalate the α-position of pyridine followed by a quench with iodine.[494] Michl and co-workers demonstrated that the use of TMP-zincate to metalate 3-substituted pyridines precomplexed with boron trifluoride afforded selective 6-metalation (Scheme 109).[495]

Scheme 109. 6-Selective Metallation of 3-Substituted Pyridine−BF_3 Complexes



Knochel and co-workers recently described the metalation of functionalized pyridines using TMP magnesium and zinc amide bases following precomplexation with boron trifluoride etherate.[496] The 2-pyridyl metal intermediate was employed in Negishi cross-coupling to access 2-aryl pyridines or acylation by transmetalation with copper. A complete switch of regioselectivity was observed using the amide bases in the absence of complexation with BF_3·OEt_2 (Scheme 110). For 3-substituted pyridines, precomplexation led to metalation at the 4-position due to steric hindrance at the 2-position.

As an alternative approach, premixing BF_3·OEt_2 and TMPMgCl·LiCl also led to efficient metalation due to the unexpected high reactivity of the frustrated Lewis pair, affording the isomeric 2-pyridyltrifluoroborate **144** (Scheme 111). The intermediate could also be employed in a variety of further functionalization reactions.

6. TRANSITION METAL-MEDIATED PYRIDINIUM C−H FUNCTIONALIZATION

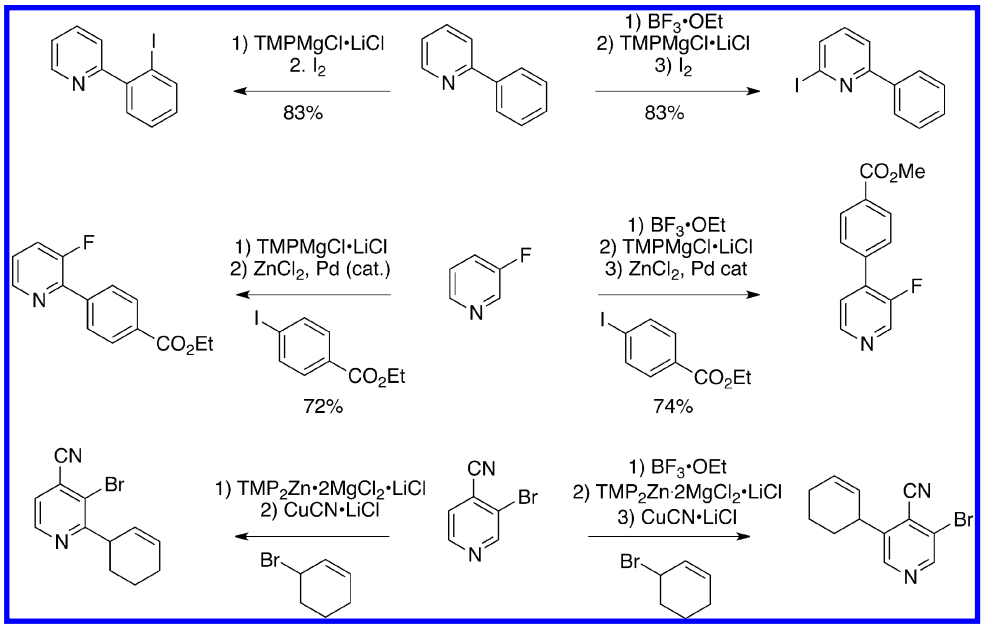
The following section will focus on processes involving the reaction of pyridine derivatives with *d*-block transition elements. Section 6.1 will outline some of the early work in the area, with the focus on early transition metals and their use to activate the pyridine ring, followed by their insertion into the pyridyl C−H bond. Several of these transformations, although requiring a stoichiometric amount of metal reagent, describe the first forays into C−H activation and functionalization. This section will be nonexhaustive, providing only a flavor of the work in the area. The remaining sections will describe the application of catalytic quantities of transition metal to the functionalization of pyridines. Early work using zirconium will be highlighted in addition to current advances with late transition metals.

6.1. Use of a Stoichiometric Amount of Transition Metal

The following section will first highlight initial work in this area and will commence with the description of various metals able to insert α to the pyridine nitrogen. Such work has already been reviewed,[497,498] but this section is intended to provide the reader with an idea of the context and synthetic possibilities. It will lead into the application of these metal complexes, particularly involving group IV and V metals, in the functionalization of pyridine and an overview of the mechanistic considerations.

6.1.1. Initial Studies of Groups III and IV and Other Metals to Form Pyridine−Metal Complexes. Group III metals were found in the mid-1980s to be able to insert into the α-position of the nitrogen of pyridine. Despite their increased bond strengths, sp^2 hybridized C−H bonds were deemed more reactive than their sp^3 counterparts. This was reasoned to be due to the initial formation of a π-complex formed with the metal. However, accessing insertion into the C−H bonds of pyridine still proved problematic due to the electron-poor nature of the azine. Consequently, it was reasoned that highly electrophilic reagents could be used to functionalize such electron-poor arenes.[499] The latter methodology was exploited by Bercaw and co-workers as they applied derivatives of permethylscandocene prepared from $ScCl_3$ in the C−H activation of various arenes, notably pyridine. The metal was thought to readily undergo metathetical reactions. Whereas

Scheme 110. Regioselective Metalation of BF_3−Pyridine Complexes



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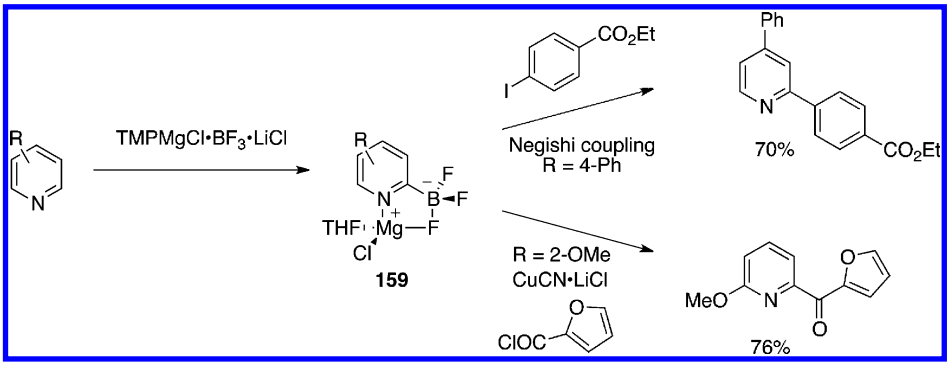
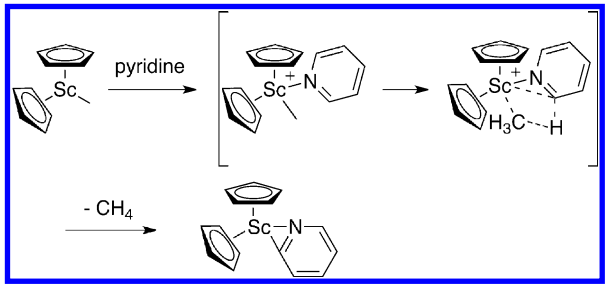
Scheme 111. Formation and Applications of 2-Pyridyltrifluoroborates



nonheterocyclic arenes formed η^1-complexes over η^3-complexes, pyridine provided an orthometalated C,N-η^2 compound as determined by X-ray diffraction (Scheme 112).[499] The

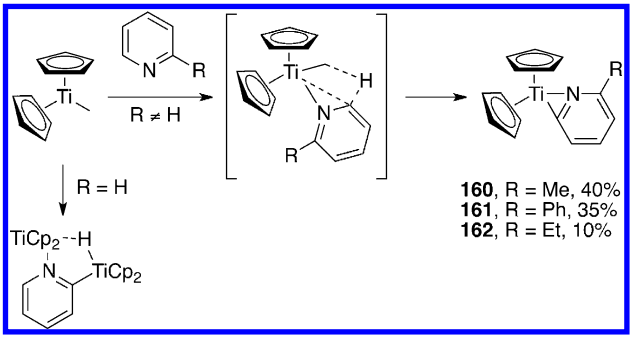
Scheme 112. Insertion of Pyridine into Cp*$_2$ScMe



formal C−H insertion involves the complexation of pyridine through its nitrogen to the Sc reagent as a reaction between Cp*$_2$ScMe and pyridine provided a Cp*$_2$ScMe(Pyr) complex that was observable by ^{1}H NMR.[499] The quarternization of the nitrogen activates the pyridine ring, further favoring the insertion into the α-C−H bond and, in the case of Cp*$_2$ScMe, liberating methane. The complexes were found to have poor affinity toward basic phosphines and aza reagents,[499] due to the crowded coordination sphere around the scandium atom, which limited further structural elaboration of the azacycle. More recently, density functional theory (DFT) studies have demonstrated that, although Sc does insert via σ-bond metathesis, this might not be the case for all group III metals, as evidence points to ionic pathways being more favorable with metals having larger ionic radii.[500]

Titanium was the first d-block transition metal believed to be involved in a direct C−H insertion into pyridine. In 1978, Klei and Teuben described the insertion of Cp*$_2$TiMe into 2-picoline to give C,N-η^2 titanocycles **160**−**162** at the 6-position of the ring, isolated as purple crystals.[501] The color change during the reaction suggested complexation of titanium to the pyridyl nitrogen, generating a *pseudo*-pyridinium species, and the insertion was observed via the evolution of methane gas.[502] Substitution at the 2-position was found to be mandatory for the reaction to occur, and a small substrate scope was explored (Scheme 113). The α-substitution is thought to be required to move the pyridine ring out of plane, forcing an interaction with the π-system, favoring σ-bond metathesis (Scheme 113).[502] In 2005, it was found that unsubstituted pyridine did indeed undergo C−H insertion with Cp*$_2$TiCl but formed a compound bearing two titanium atoms separated by a hydride bridge as determined by X-ray crystallography (Scheme

Scheme 113. Insertion of Pyridine into Cp*$_2$TiMe



113).[503] The complex, although thermally stable, was extremely air-sensitive. Curiously, Cp*$_2$TiCl was found to be even more effective in inserting into C−F bonds, as competition studies between pyridine and pentafluoropyridine showed preferential insertion into the latter substrate. This is in contrast with what is currently observed with late transition metals, and it has been reasoned that this effect is due to the thermodynamic preference of the resulting fluorine bridge.[503]

The other group IV metals (Zr, Hf, and Th) have also been demonstrated to insert α to the nitrogen of pyridine. A common feature is the electrophilic nature of the reagents, permitting attack of the electron-poor arenes on the metal center for initial activation. Zirconium has been the most applied, in particular with the direct functionalization of pyridine (vide infra). Halfnium has been seldom reported,[504] whereas thorium, although in the same group, exhibits unique properties in part due to its large atomic radius, with its reactivity governed by sterics and the access to 5f orbitals.[504] Unlike Ti, Zr, and Hf, thorium does not have a tendency to complex to sp^2 and sp hybridized systems. Whereas $(C_5Me_5)_2ZrMe_2$ and $(C_5Me_5)_2HfMe_2$ have been shown not to insert into the α-C−H bond, $(C_5Me_5)_2ThMe_2$ readily inserts, forming a C,N-η^2 metallacycle similar to that reported with Sc and Ti, while also liberating methane.[504] Additionally, the thorium reagent could also insert into the α-site of pyridine *N*-oxide, generating an η^1 organometallic species.[504] Thorium has not been applied in the derivatization of pyridine.

Zirconium complexes have been isolated in many cases.[505] In all the cases, a C,N-η^2 metallocycle was formed, often under mild conditions. The use of zirconium to activate pyridine for direct functionalization will be discussed further in the following section.

Several late transition metals have been known to form pyridinium-like complexes that permit functionalization of the heterocycle. For example, Cp*$(CO)_2$FeSiMe$_2$NPh$_2$ is known to

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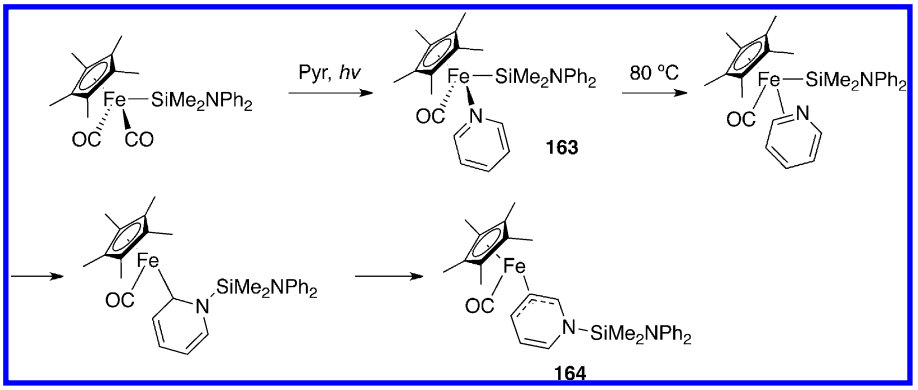
Scheme 114. Insertion of Pyridine into $Cp^*(CO)_2FeSiMe_2NPh_2$



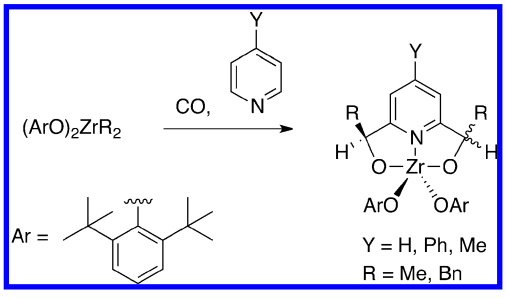
undergo metalation via the insertion of pyridine into the Fe−Si bond.[506,507] Irradiation expelled CO to enable the complexation of pyridine to the iron reagent via dissociative substitution. Upon heating to 80 °C, the activated Fe−Pyr complex **163** underwent silylation through an η^1-σ-allyl complex, which following isomerization gave the observed η^3-(*C,C,C*) Fe−Pyr product **164** (Scheme 114).[506]

As mentioned, several other metals including Ta, Cr, Mn, Re, Os, and U are known to activate pyridine and insert to give α-metalated C,N-η^2 complexes.[497,508] The following section will describe the use of stoichiometric quantities of Zr, Ti, Ru, and other reagents to activate and further functionalize the pyridine ring.

6.1.2. Application of Metal Complexes Toward Further Functionalization of Pyridine. *Zirconium Activation/Functionalization.* Zirconium was one of the first metals reported in the activation/functionalization of the pyridine ring. This group IV metal had long been known to be able to activate and insert into molecular hydrogen via a four-centered transition state following initial coordination of the H−H σ-bond. It was reasoned that a similar metathecal pathway should be possible for C−H bonds on molecules complexed to the metal center,[509] to allow direct functionalization.[509] Such 18-electron complexes were made through the oxidative addition of the metal into the C−H bond, and the resulting compounds were resistant to insertion and β-hydride elimination chemistry.[509]

In the mid-1980s Rothwell and co-workers described the use of Zr(2,6-di-*tert*-butylphenoxide)$_2$Me$_2$ in the synthesis of α,α-disubsituted-2,6-pyridinedimethoxide compounds from pyridine and carbon monoxide (Scheme 115).[510] The resulting

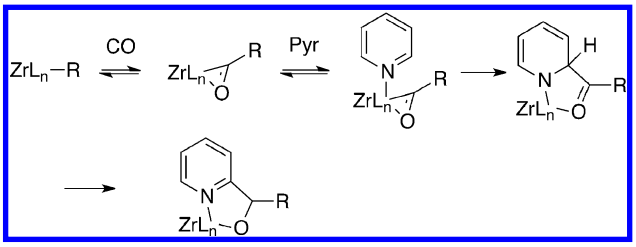
Scheme 115. Zirconium-Mediated Synthesis of Bisalkoxy Pyridine Derivatives



products are an important class of ligands and have been applied as metalloenzyme models.[511] It was found that the methyl groups of the Zr complex could be replaced with benzyl groups without an appreciable drop in yields (50−75%).[511] The presence of a substituent at the 4-position was found to be required, acting as a blocking group, even though the site was outside the coordination sphere of the metal. Bipyridine could be directly alkylated with a similar Zr reagent,[512] where CO was found to be essential. The 2,6-di-*tert*-butylphenoxide ligand was also required, and although its role was unclear, the steric hindrance suggested it functioned as a nontransferable group. The metallopyridine complex was diastereomeric due to the formation of two chiral centers, although with the exception of 4-phenylpyridine, the diastereomers had the tendency to cocrystallize.[511] It was possible to liberate the bis-substituted pyridine product from the metal through hydrolysis.

The reaction was postulated to proceed via the migratory insertion of CO into the Zr−alkyl bond, generating a η^2-complex. Pyridine then complexes to the zirconium atom, followed by insertion of the pyridine C═N bond into the Zr−COR bond (Scheme 116). The N−Zr bond length was found

Scheme 116. Potential Mechanistic Pathway

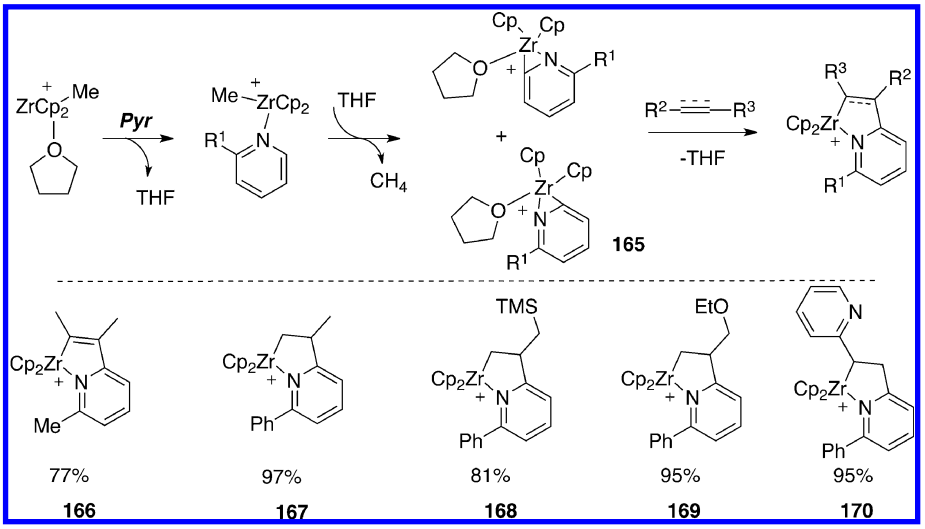


to be 0.18 Å shorter than expected, indicating a strong interaction and the likelihood of the pyridine ring being activated by the metal center.[510] The primary kinetic isotope effect was found to be 1, suggesting that the rate-limiting step was the complexation of the pyridine ring and not insertion into the C−H bond. The acyl group was thought to have carbene-like character, and thus the electrophilicity of the carbonyl carbon affects its reactivity.[510,511] As only the 2,6-disubstituted pyridine was observed, the formation of the C,N-η^2 complex observed with other group III and IV metals was ruled out, as congestion would yield only a single addition to the azine.[511] Addition at the 2,6-position exclusively and not at the 4-position was a result of the intramolecular nature of the final step of the trasnformation.

Jordan and co-workers applied cationic zirconium complexes to the functionalization of pyridine derivatives. The authors found that a highly Lewis acidic $Cp^*_2ZrMe(THF)$ species

dx.doi.org/10.1021/cr200251d | *Chem. Rev.* 2012, 112, 2642−2713

Scheme 117. Selected Zirconium-Mediated Insertion of Propene into 2-Picoline



rapidly complexed and inserted into 2-picoline ($t_{1/2}$ = 6 min) in chlorinated solvents to generate a stable C,N-η^2 complex as a single isomer bearing a THF ligand, while liberating methane.[513] Complex **165** was found to react with propene through migratory insertion (Scheme 117). The lability of the π-Zr−O interaction was key to the reaction with pyridine, because when the insertion was attempted in THF no C,N-η^2 Zr-Pyr complex was noticed, presumably because the pyridine cannot access the metal center. When bound, the pyridine was found to be perpendicular to the plane between the two cyclopentadiene ligands, placing the α-pyridine hydrogen atoms such that they are aligned with an empty orbital of the zirconium, initiating a weak agostic interaction.[509] Crystal structures indicated that the tetrahydrofuran ligand was not susceptible to C−H insertion because of steric factors, which forced the *ortho*-C−H bonds out of plane relative to the LUMO of the zirconium center, precluding any reaction.[509]

2-Butyne (**166**), ethylene, and propene (**167**) were all viable reagents, in decreasing order of reactivity, providing 5-membered azametallacycles in all cases (Scheme 117).[509] Propene, allyltrimethylsilane (**168**), and allyl ethyl ether (**169**) afforded 1,2-insertion products.[514,515] This was the expected insertion product as the least-encumbered metal center was formed, and the δ^+ was stabilized on the more-hindered carbon atom.[515] However, a reverse 2,1-insertion product was observed with vinyltrimethylsilane, styrene, and 2-vinyl pyridine (**170**), where the electronic effects outweighed the steric considerations. DFT studies on vinyl TMS confirmed the lower-energy transition state (TS) for 2,1-insertion due to the stabilization of both the α-positive and β-negative charges that built up in the polar transition state (Figure 18).[516]

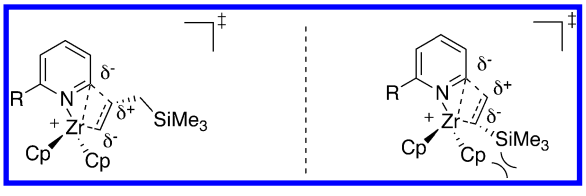


Figure 18. Site selectivity for the addition of allyl and vinyl silane to Pyr−Zr complexes.

Furthermore, the steric repulsion between the TMS group and the Cp groups was not as strong as initially thought, due to the longer C−Si bond.[515,516] The addition of alkenes to the Zr−Pyr complex was found to be thermally reversible, as demonstrated through competition studies, although the addition of alkynes was not. 2-Substituted pyridines reacted faster than pyridine itself, although the products obtained from 2-methyl pyridine were significantly more soluble than 2-phenyl pyridine and, thus, were used for most of the ^{1}H NMR and crystallographic studies.[515] The 5-membered azametallocycle could be hydrolyzed to liberate the free pyridine in several ways, including the use of catalytic hydrogen gas, which will be discussed in the next section.[513] 2-Alkenyl pyridine could be prepared through β-hydride elimination in MeCN where the nitrile was effective in trapping the Zr−H species generated.[509] Finally, hydrolysis provided the corresponding 2-alkyl pyridines.[515] The alkynyl adducts were not susceptible to hydrolysis, and although phenylsilane was reported to be effective in hydrolyzing metal−carbon bonds of group IV metals, the reagent provided only undesired side-products.[517]

The use of chiral zirconium complexes bearing either ethylenebis(indenyl) (EBI) **171** or ethylenebis(tetrahydroindenyl) (EBTHI) **172** ligands enabled moderate to excellent diastereoselectivities to be obtained with 2-substituted pyridines (Table 44).[518] The major diastereomer obtained when using propene or 1-hexene involved the alkyl group pointing toward the Cp ring. The orientation was the result of the steric interaction of the 2-position of the azine with the other Cp unit, causing a "tipping" of the pyridine ring.[519] In the case of vinyl silane and styrene, the Si and Ph group pointed away from the cyclopentadienyl ring, presumably due to favorable $\pi-\pi$ interactions. Low-temperature studies indicated that the major diastereomer formed was the kinetic product, as heating led to epimerization and isomerization.[519]

In the previous section, it was shown that pyridine can insert into Fe−Si bonds, generating N−Si species. Similar insertions are possible with Zr complexes bearing a super silyl group. Pyridine binds to these complexes, generating an activated pyridinium that is susceptible to nucleophilic attack at the 2-position by the silyl group.[520]

Activation and Functionalization by Other Metals. Titanium complexes formed by insertion into the 6-position of 2-substituted pyridine (vide infra) were found to react with

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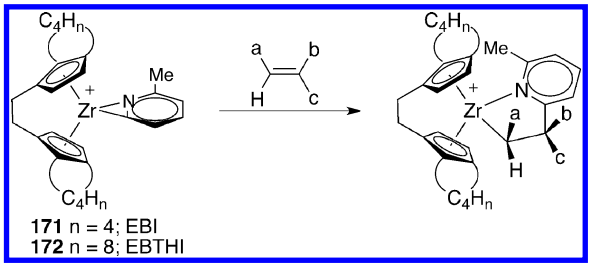
Table 44. Selected Scope for the Diastereoselective Addition of Alkenes to Zirconium-Activated Pyridines

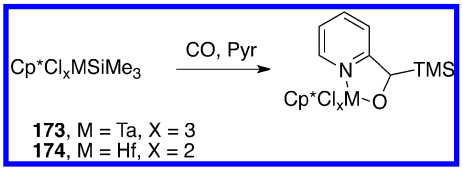


entry	ligand	a	b	c	de
1	EBI	H	H	Me	83
2	EBTHI	H	H	Me	64
3	EBI	H	H	Bu	83
4	EBTHI	Ph	H	H	>98
5	EBI	Ph	H	H	>98
6	EBTHI	Si	H	H	>98

I_2 to form 6-iodopyridine derivatives in near-quantitative yield.[502] Again, the substitution on the pyridine ring was essential, presumably to twist the heterocyclic ring out of the plane of the Cp ligands, permitting coordination of the C−H bond with the transition metal.

In the late 1980s, Tilley and co-workers demonstrated that both hafnium[521] and tantalum[522] C,N-η^2 pyridine complexes underwent silylacylation reactions (Scheme 118, **173** and **174**).

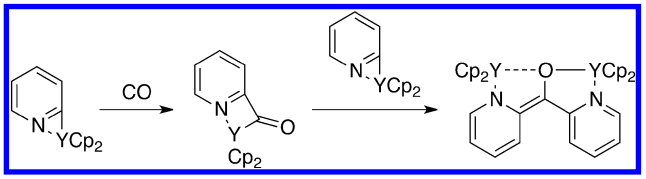
Scheme 118. Direct Functionalization of Pyridine by Hafnium and Tantalum



As was previously reported by Rothwell and co-workers with zirconium,[511] the reactions proceeded by the insertion of carbon monoxide into the M−Si bond, forming an η^2-complex.[521,522] The coordination of pyridine to this complex activated the pyridine ring to permit attack of the acylsilane moiety to the 2-position through migratory insertion. With both metals, the reaction proceeded smoothly in the absence of any substitution on the pyridine ring.

Teuben and co-workers described the cyclometalation of pyridine with $(Cp^*_2YH)_2$ to form C,N-η^2 Y−Pyr complexes, demonstrating that group III metals can be used to functionalize pyridine.[523] These Y−Pyr complexes were found to react with ethylene and propene to produce 2-alkyl pyridine adducts. In the case of propene, the 1,2-insertion product seen with Zr was observed. It should be noted that the rate of reaction with propene was much slower relative to ethylene (4 days at 60 °C vs 1 h at room temperature (rt)), as a result of the steric saturation of the yttrium center, thereby making it more difficult for the bigger propene molecule to access.[523] Propyne and 2-butyne did not insert, and only the alkynyl metal complex was observed. Curiously, 2-pentyne did successfully insert in 63% yield after 2 days at 75 °C, due to the additional steric bulk forcing the insertion.[523] A unique feature of the complexes was their reaction with CO to prepare bimetallic bispyridine compounds (Scheme 119). In all these cases, no attempts were reported to liberate the free pyridine.

Scheme 119. Yttrium-Mediated Carbonylation of Pyridine to Make Bispyridine Adducts



η^4-(Butadiene)bis(pentamethylcyclopentadienyl)thorium complexes formed from $Cp^*_2ThCl_2$ were found to attack at the 2-position of the pyridine ring.[524] Again the process is believed to occur through coordination/activation of the pyridine ring, followed by attack of the dienyl moiety into the heterocycle.

6.2. Use of a Catalytic Amount of Transition Metal

The methodologies overviewed in the previous section were essential in providing the understanding required to minimize the prefunctionalization of the pyridine moiety necessary for structural elaboration. However, the use of a catalytic amount of transition metal is usually desired. Group III, lanthanide, actinide, and late transition metals tend to be costly, as are several of the ligands needed to induce their desired reactivity, several of which must be synthesized. Additionally, the reduced environmental impact and improved atom economy of catalytic quantities of transition metal are important to enable the use of a methodology on scale. This section will highlight progress and advances toward the catalytic application of both early and late transition metals in the direct alkylation and arylation of pyridine.

6.2.1. Use of Early and Late Transition Metals in the Alkylation and Acylation of Pyridine. Jordan and Taylor's first account of zirconium-mediated alkylation of 2-picoline was developed into a catalytic reaction.[513] By performing the reaction under an atmosphere of H_2, 4 mol % of the complex **175** could be used to directly functionalize the pyridine ring with alkenes, providing 2-alkylpyridine derivatives **176**. The catalytic cycle proceeds as described in Scheme 120. First the C,N-η^2 complex undergoes insertion into propene, affording a 5-membered azametallacycle **177**. The C−Zr bond was then cleaved by hydrogenolysis with H_2. Isolation of the metallacycle and treatment with H_2 verified this mechanistic step.[513] Later, DFT calculations suggested that the process was energetically favorable as it relieved steric strain by replacing a bulky group with a hydride.[516] The sterically encumbered 2-methyl-6-

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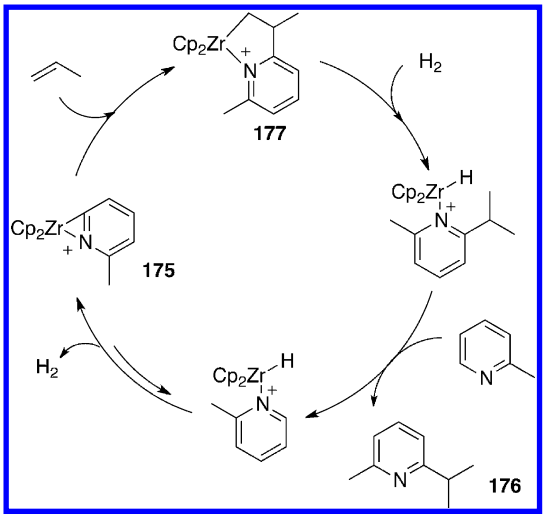
Scheme 120. Catalytic Cycle for the Zirconium-Catalyzed Direct Alkylation of Pyridine

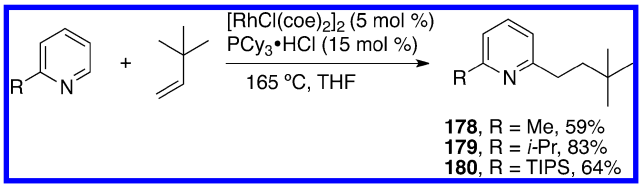


isopropyl pyridine **176** was then displaced by a less-hindered 2-picoline, liberating the intended product. Again, this was determined to be more energetically favored, and is likely driven by the tighter binding association of the 2-picoline substrate. Insertion of zirconium into the α-position of the pyridine simultaneously regenerated H_2 and the C,N-η^2 Zr–Pyr complex **175**. The stereoselective version of the reaction proceeds to afford enantioenriched 2-alkylpyridines, although only one example was provided, using 1-hexene (*R*)-2-Me-6-(2-hexyl)pyridine (58% ee).[518] The enantiomeric excess can be related to the diastereomeric excess observed for the azametallocycles prepared in the stoichiometric reactions (65% de leads to 58% ee) (Table 44).

An analogous reaction with yttrium was also reported. However, in this case hydrogen gas was not required to effect the catalytic cycle.[523] The cycle is driven by the fact that group III metals more readily undergo metathecal transformations due to their increased electrophilicity, and thus the yttrium azametallocycle could directly insert into another molecule of pyridine. It was found that 2-ethylpyridine could be prepared in 44% yield from pyridine.[523] Another advantage of the reaction was that substitution at the 2-position of the pyridine ring was not required in this case.

Lewis, Bergman, and Ellman reported an elegant $[RhCl(coe)_2]_2$-catalyzed direct alkylation of 2-substituted pyridines with 3,3-dimethyl-1-butene in the presence of PCy_3, providing the first example of a late transition metal-catalyzed reaction for such insertion into pyridines (Scheme 121).[525] Although in-

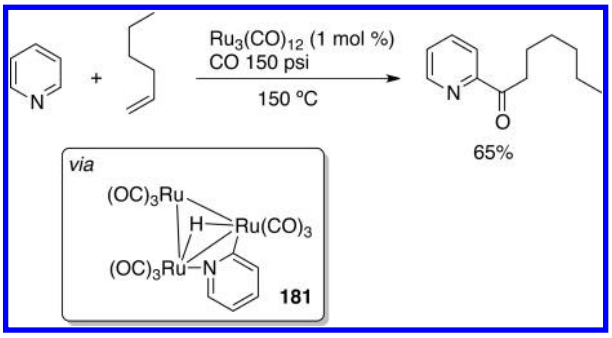
Scheme 121. Rhodium-Catalyzed Direct Alkylation of Pyridine



depth mechanistic investigations were not performed, the reaction presumably proceeds though the coordination of the Rh–phosphine complex to the Lewis basic nitrogen, activating the pyridine ring. The alkene then coordinates to the complex, possibly generating a carbene-like species that can proximally insert into the 2-position of the pyridine ring. The scope of the alkene was explored only with quinoline, as it provided superior results, but 2-isopropyl (**179**) and 2-triisopropylsilyl (**180**) pyridine were also effective partners with moderate yields.[525] The latter is of particular interest, as the TIPS could serve as a protecting group, as demonstrated though its cleavage by HF.

Triruthenium dodecylcarbonyl catalyzed the direct acylation of pyridine in the presence of terminal alkenes under a carbon monoxide atmosphere (Scheme 122).[526] The pyridine species

Scheme 122. Ruthenium-Catalyzed Direct Acylation of Pyridine



was activated as complex **181** with a trinuclear cluster of Ru atoms. The fact that the reaction was found to be first-order with regard to the catalyst and zero-order in CO led the authors to postulate that the reaction proceeded first through pyridine coordination and ortho-insertion into the heterocycle.[526] Olefin coordination and insertion into the bridging hydride, followed by alkyl to acyl migratory insertion and reductive elimination, afforded the observed product. The linear product was favored over the branched product, and when hindered alkenes such as 3,3-dimethyl-1-butene were used, a single isomer was observed, along with increased rates of reaction.[526] 2-Substitution on the ring is permitted, although electron-withdrawing groups inhibit the reaction, presumably by decreasing the ability of the basic nitrogen to coordinate to the metal center.

6.2.2. Late Transition Metal-Catalyzed Direct Arylation of *N*–*O*- and *N*–*N*-Activated Pyridinium Ylides. Although there have been very recent advances in the synthesis and cross-coupling of 2-metallopyridine derivatives, as mentioned earlier, historically this approach to the synthesis of 2-arylpyridines has been problematic.[527,528] This is due to the lack of stability of the organometallic reagents, in particular 2-pyridineboronic acids, which readily undergo protodeborylation reactions. In the mid-2000s, the direct arylation of pyridine was viewed as a solution to the problem of cross-coupling with these reagents. The following section will cover the progress and development in the area of direct arylation.

Ruthenium Catalysis. In 2005, Sames and co-workers described the cross-coupling of pyridine with iodobenzene to give 2-aryl pyridines in the presence of a ruthenium catalyst.[529] Initial screening led to the discovery that the same $Ru_3(CO)_{12}$ used in the aforementioned direct acylation provided the desired product in 36% yield in the presence of 1.2 equiv of Cs_2CO_3 in *t*-BuOH. The inclusion of PPh_3 provided improved yields, up to 70% under the optimized conditions. Mechanistic investigations suggested that the phosphine disrupted the trinuclear complex formed upon oxidative addition into pyridine, thereby giving a phosphido-bridged binuclear

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Scheme 123. Sames' Ruthenium-Catalyzed Arylation of Pyridine

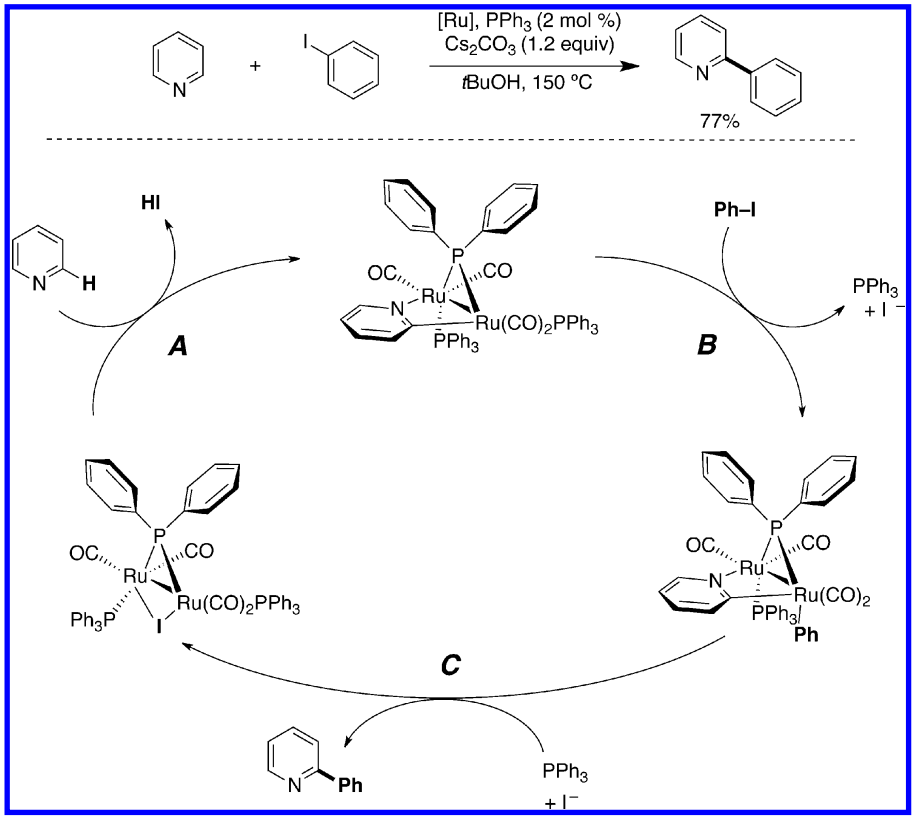
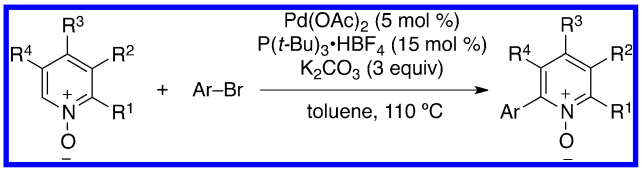


Table 45. Selected Scope for the Palladium-Catalyzed Arylation of Pyridine *N*-Oxides with Aryl Bromides



entry	Ar	R^1	R^2	R^3	R^4	yield[a] (%)
1	4-MePh	H	H	H	H	91
2	3-MeOPh	H	H	H	H	97
3	4-CF_3Ph	H	H	H	H	76
4	4-MePh	Me	H	H	H	54
5	3,5-MePh	H	Ph	H	H	80[a]
6	3,5-MePh	H	H	H	F	78[a]

[a]Yield of the major isomer.

ruthenium complex though sequential C−H and C−P bond cleavage (Scheme 123, **A**).[529] Complex **A** can in turn oxidatively insert into iodobenzene (**B**), providing the biaryl product after reductive elimination (**C**). The scope of the iodoarene was not explored.

Palladium-Catalyzed Direct Arylation of Pyridine N-Oxides. Aside from the aforementioned ruthenium-catalyzed direct arylation of pyridine by Sames and co-workers, there had been no reports of direct arylation reactions on pyridine, and only electron-rich arenes had been applied in such processes. It was thought that an S_EAr pathway was required for the arylation to proceed, which an electron-deficient arene should not be able to undertake.[382] However, around the same time as Sames' disclosure, Fagnou and co-workers reported the palladium-catalyzed direct arylation of pyridine *N*-oxides with aryl bromides.[382] The *N*-oxide offered the advantage of preventing nonproductive binding between the transition metal catalyst and the nitrogen lone pair, thus favoring productive π-binding interaction with the arene ring.[530] The *N*-oxide group also helped to increase the electron density of the pyridine ring, while increasing the Brönsted acidity of the C−H bonds at the 2-position.[530] Furthermore, their high stability, wide commercial availability, and ease of synthesis makes them attractive alternatives to 2-metallopyridines.

The conditions first reported for the coupling of aryl bromides (4 equiv) with pyridine *N*-oxide were optimized to $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_3{\bullet}HBF_4$ (15 mol %), and K_2CO_3 (2 equiv) in toluene at 110 °C (Table 45).[382] The scope of the reaction included hindered, electron-rich, and electron-poor substrates, although the latter provided slightly lower yields. Although a large excess of the pyridine reagent was needed, it was reported that 95% of the excess could be recovered. It was

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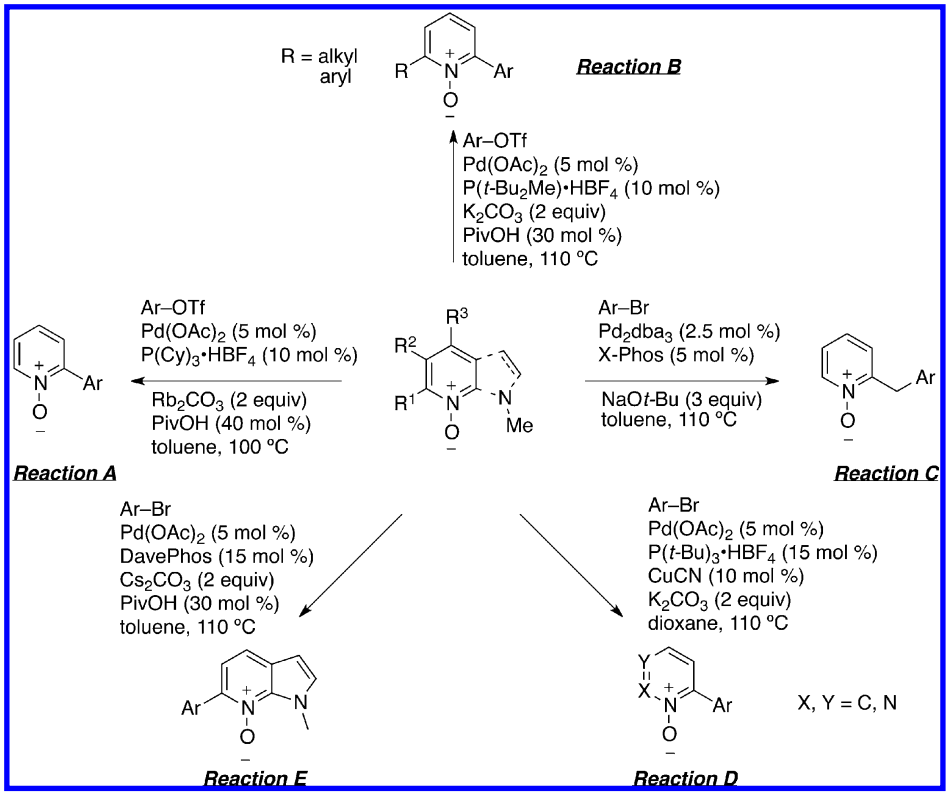
Scheme 124. Various Methods and Substrates used in the Palladium-Catalyzed Direct Arylation of Pyridine *N*-Oxide Derivatives



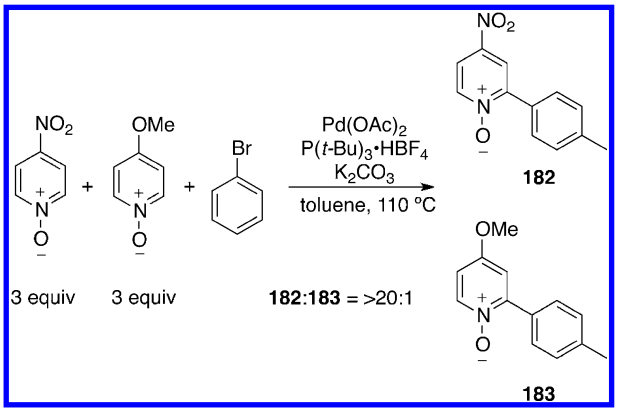
later discovered that increasing the catalyst-to-ligand ratio from 1:3 to 1:1.2 and decreasing the base loading from 2 to 1.5 equiv enabled 2 equiv of the pyridine *N*-oxide to be used while maintaining acceptable yields.[531] Similar reaction conditions allowed the scale-up of the reaction, on a 50 mmol scale.[530]

The use of aryl triflates was also considered due to their ease of synthesis from phenols and, thus, application in late-stage synthesis of complex molecules.[532] Although aryl triflates are known to undergo oxidative addition at comparable rates to aryl bromides, in this instance they proved more reactive and displayed an increased propensity for diarylated products. Two sets of optimized reaction conditions were reported depending on the pyridine substituents. Unsubstituted pyridines required $Pd(OAc)_2$ (5 mol %), bulky PCy_3 (10 mol %), Rb_2CO_3 (2 equiv), and PivOH (40 mol %) as an additive (Scheme 124, reaction **A**).[532] The scope of the reaction was found to be general, and electron-rich aryl triflates performed well with electron-poor substrates. Unlike with the aryl bromides, the coupling of aryl triflates displays a greater sensitivity to steric hindrance and led to decreased reaction yields. For 2-substituted pyridine derivatives, a separate set of conditions using $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu_2Me)\bullet HBF_4$ (10 mol %), K_2CO_3 (2 equiv), and PivOH (30 mol %) were required (Scheme 124, reaction **B**).[532] It was reasoned that the bulkier substrate required a less-hindered ligand, facilitating the insertion of palladium into the pyridine C–H bond.

In the case of aryl bromides, 2-substitution was tolerated under the standard reaction conditions, but for 2-methyl pyridine *N*-oxides decreased yields were noted, due to competing arylation at the benzylic site (Scheme 124, reaction **C**).[531] The use of a stronger base (KO*t*-Bu) and X-Phos provided excellent yield of the product where arylation occurred at the sp^3 hybridized site, i.e., conditions for the site-selective arylation of the picoline (6- vs benzylic).[531]

3-Substituted pyridines provided unsymmetrical products (Table 45, entries 5, 6), with a mixture of 2- and 6-aryl products observed. When the group at the C-3-position was a phenyl or an ethyl ester, strong preference for the least-hindered product was noted.[530] 3-Picoline *N*-oxide showed weak preference for the less-hindered substrate, possibly due to competing weak agostic interactions. Other groups such as F, CN, and NO_2 gave a strong preference for the more-hindered product.[530] This phenomenon is not unknown with palladium-catalyzed processes and may be the result of a combination of increased acidity and agostic interactions at the reaction site. Competition studies between 4-nitropyridine *N*-oxide and 4-methoxypyridine *N*-oxide showed that the electron-poor heterocycle undergoes arylation at a much faster rate (Scheme 125, **182**

Scheme 125. Competition Study for the Arylation of Pyridine *N*-oxides



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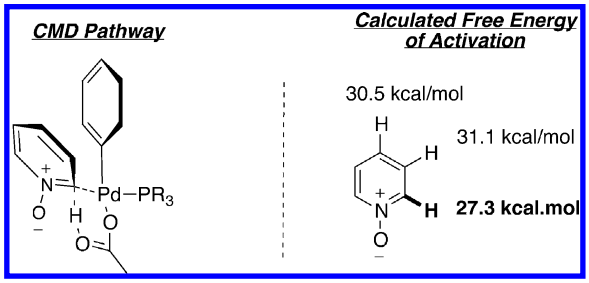
vs **183**).[382] This may be in part due to the increased Brönsted acidity of these substrates. Other heterocycles such as diazine *N*-oxides and quinoline *N*-oxides were also employed but required either the inclusion of a CuCN additive or less sterically demanding ligands (Scheme 124, reaction **D**).[530,533]

N-Methyl 6- and 7-azaindole *N*-oxides readily underwent arylation α to the pyridyl nitrogen atom using bromoarenes in moderate to excellent yields (Scheme 124, reaction **E**).[534] The optimized conditions employed 5 mol % $Pd(OAc)_2$, 15 mol % DavePHOS, 30 mol % PivOH, and 2 equiv Cs_2CO_3 in toluene at 110 °C. Under the Larrosa arylation conditions ($Pd(OAc)_2$, Ag_2O, 2-NO_2PhCO_2H), selective azole arylation was also achieved with iodoarenes, thereby offering site selectivity for the arylation process.[534]

It has been postulated that the reaction proceeds by a concerted metalation−deprotonation (CMD) sequence (Scheme 126).[535] An S_EAr pathway, although plausible, was calculated to have a prohibitively higher energy barrier, as would oxidative addition leading to Pd^{IV} intermediates.[536−538] A key feature of these reactions was the necessity for palladium acetate as catalyst and, in some cases, the use of pivalic acid as additive. Both the AcO^- and $PivO^-$ groups are known to be effective proton shuttle agents. The deprotonation step was determined to be rate-determining with a kinetic isotope effect (KIE) of 4.7. The 6-membered transition state that was postulated to be active was also energetically favored. Finally, DFT calculations have suggested that the activation energy for CMD metalation of the 2-position of pyridine *N*-oxide is ∼3 kcal/mol lower than at the 3- and 4-positions, explaining the selectivity for that site (Scheme 126).[535]

Scheme 126. Proposed CMD Pathway in the Arylation of Pyridine *N*-Oxide



An advantage of using pyridine *N*-oxides is the fact that the arylation products themselves are activated pyridinium species and are amenable to further reactions, as described in section 4. Also, the deprotection of the nitrogen to prepare the parent pyridine is possible under many reductive techniques. The application of aryl triflates in the bisarylation of pyridine *N*-oxide provided a 2,6-bisarylated pyridine derivative that was a key intermediate in the preparation of a biologically active molecule **184** known to exhibit antimalarial and antimicrobial activity (Scheme 127).[532] The described route employed three fewer steps than previously reported methodologies. The use of aryl bromides was also used to prepare a sodium channel inhibitor in only five steps with 31% overall yield.[530]

Copper-Catalyzed Direct Arylation of Pyridine N-Oxides. Daugulis and co-workers described the copper-catalyzed direct arylation of 2-phenylpyridine *N*-oxide with iodobenzene in 66% yield.[539] The obvious advantage of a Cu-catalyzed process over Pd, Rh, and Ru is the low cost of the catalytic species. The initial reaction conditions employed CuI (10 mol %) and KO*t*-Bu (2 equiv) at 140 °C in DMF and led to several issues. It was determined that the copper catalyst was not stable at the required reaction temperature, limiting the process to substrates giving fast reactions. Stability was improved through the inclusion of bathophenanthroline to stabilize the organocopper intermediates.[540] The use of KO*t*-Bu led to regioselectivity issues, as the iodoarene was found to eliminate to benzyne, and the harsh conditions enabled nucleophilic displacement of the iodide with the alkoxide base. The regioselectivity issue was remedied through the use of weaker bases such as LiO*t*-Bu and K_3PO_4.[540] When a stronger base was needed for less-reactive substrates, the very hindered Et_3COK was effective, minimizing both substitution and benzyne formation. The scope of the reaction was explored, with moderate to excellent yields obtained. 2-Picoline *N*-oxide afforded decreased yield, likely due to the acidity of the benzylic group (Table 46). For 2-iodopyridine, alkoxide bases could not be used because of the formation of the corresponding undesired 2-alkoxypyridine.[540]

Scheme 127. Application of Pyridine *N*-Oxide Arylation in the Synthesis of a Sodium Pump Inhibitor

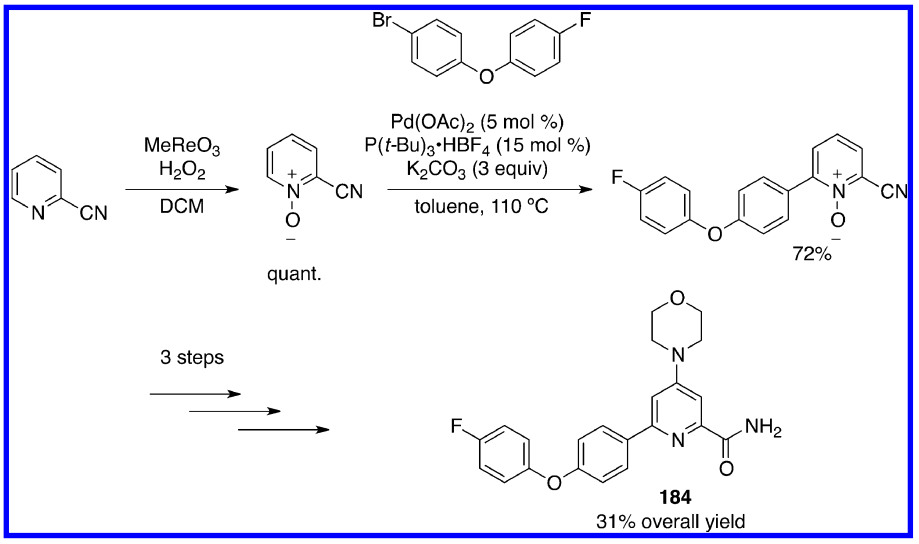


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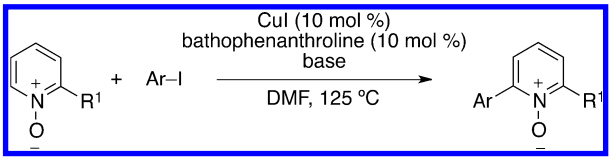
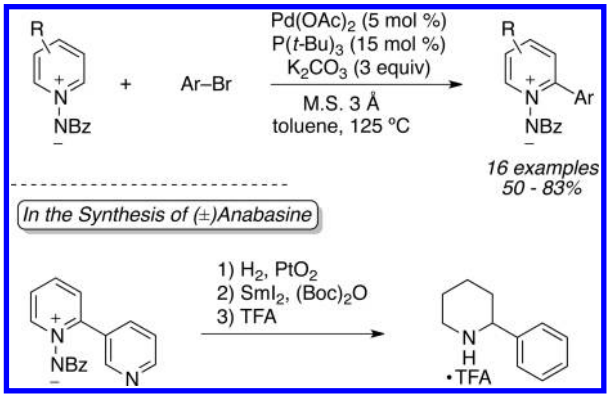
Table 46. Daugulis' Copper-Catalyzed Direct Arylation of Pyridine *N*-Oxides



entry	R^1	Ar	base	yield (%)
1	H	Ph	LiO*t*-Bu	58
2	H	Pyr	K_3PO_4	41
3	Me	Ph	LiO*t*-Bu	43
4	Ph	4-CF_3Ph	LiO*t*-Bu	80
5	Ph	naphthyl	LiO*t*-Bu	91

Palladium-Catalyzed Direct Arylation of N-Iminopyridinium Ylides. In 2008, Charette and co-workers reported the direct arylation of *N*-iminopyridinium ylides with bromoarenes (Scheme 128).[541] The *N*-iminopyridinium ylides confer a similar pKa to the α-C−H bond of the ylide to that in the pyridine *N*-oxide. However, compared to the pyridine *N*-oxide arylation reported by Fagnou, competing bisarylation was not observed so a large excess of ylide was not required. This was reasoned to be due to the out-of-plane twisting of the *N*-imino group upon monoarylation as observed X-ray crystal structure, preventing a second arylation being directed to the 6-position.[541] The strong directing group ability of the *N*-imino moiety[443] affords an increased reactivity as demonstrated through a competition study with pyridine *N*-oxide, in which none of the *N*-oxide arylation product was observed. The scope of the arylation using aryl bromides was found to be general, with no preference for electron-poor or electron-rich substrates. The methodology was used in the expedient synthesis of (±)-anabasine, demonstrating the versatility of the *N*−*N*-activation, as only the pyridinium moiety was reduced.[541] A limitation of the methodology was for 2-picolines; although selective benzylic arylation could be achieved in high yields,[542] conditions for the C-6 arylation were not developed.

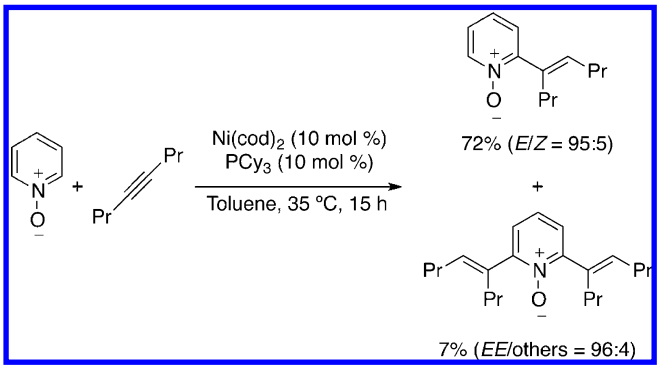
Scheme 128. Palladium-Catalyzed Direct Arylation of *N*-Iminopyridinium Ylides and Application of the Synthesis of Anabasine



6.2.3. Late Transition Metal-Catalyzed Direct Alkenylation of *N*−*O*, *N*−*N*, and *N*-Lewis Acid-Activated Pyridines. The transition metal-catalyzed direct alkenylation of pyridines has received little attention, which is a surprise given their relevance in molecules of pharmaceutical interest, their use as transition metal ligands, and the fact that the alkene can be readily reduced to prepare 2-alkyl pyridines or piperidines. Furthermore, previous methods for their syntheses either require harsh reaction conditions at a temperature of 150 °C or suffer from the drawbacks of pyridine cross-coupling (vide supra).

Murakami and Hori reported the first example of a direct pyridine alkenylation via a ruthenium-catalyzed [2 + 2]-cycloaddition of vinylidene complexes to pyridine, but as a cycloaddition process it is outside the scope of this review.[543] The next account, reported by Hiyama and co-workers, involved a reductive coupling with alkynes (Scheme 129).[544]

Scheme 129. Nickel-Catalyzed Hydroalkynylation of Pyridine *N*-Oxides



The authors had earlier shown that 5-membered electron-rich heterocycles undergo a nickel-catalyzed Fujiwara-type coupling of alkynes in the presence of PCy_3 in the synthesis of alkenyl heterocycles.[544] Although pyridine itself was unreactive in the process, they were able to take advantage of the reactivity of pyridine *N*-oxide and effect the addition of alkynes, synthesizing 2-alkenyl pyridine *N*-oxides with high regioselectivity at low temperature.[544] A wide range of symmetrical alkynes was tolerated, and unsymmetrical alkynes with significant steric differentiation could be used with complete regioselectivity. Terminal alkynes did not provide the desired product, presumably due to the rapid oligomerization of the alkyne.[544] Substitution on the *N*-oxide ring was tolerated, although reactions of pyridines bearing electron-withdrawing groups (Cl, Br, NO_2) were sluggish. The mechanism of the reaction was postulated to proceed first through coordination of the alkyne to the nickel center. The nickel species then undergoes oxidative insertion into the pyridinium C−H bond, affording a pyridyl−nickel hydride. Hydronickelation and reductive elimination complete the catalytic cycle, providing the 2-alkenyl pyridine *N*-oxide (Scheme 130).[544]

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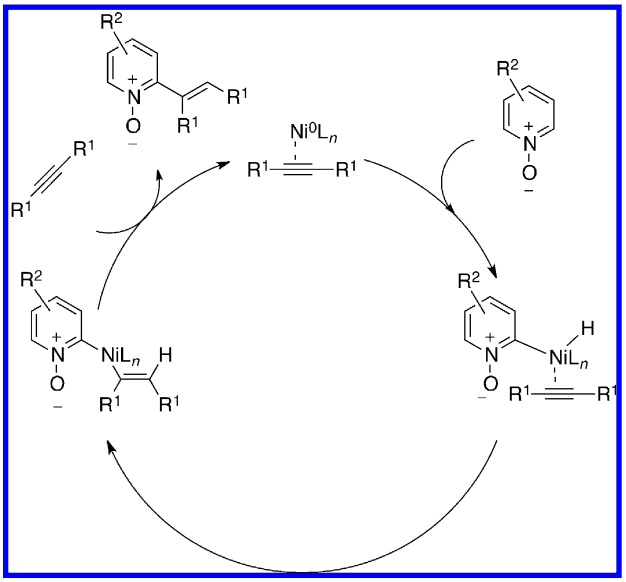
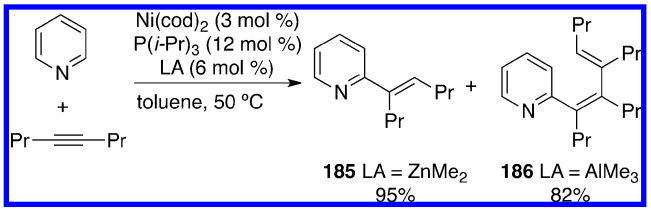
Scheme 130. Proposed Catalytic Cycle for the Nickel-Catalyzed Hydroalkynylation of Pyridine *N*-Oxides



A year later Hiyama and co-workers improved the methodology by activating the pyridine ring in situ through the addition of a catalytic quantity of a mild Lewis acid (Scheme 131).[545] The addition of 6 mol % of $ZnMe_2$, $ZnPh_2$, or $AlMe_3$

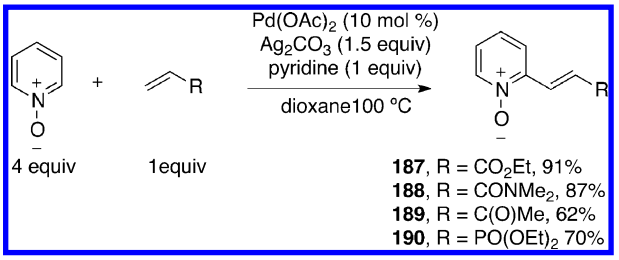
Scheme 131. Nickel-Catalyzed Hydroalkynylation of Lewis Acid-Activated Pyridines



was sufficient to generate 2-alkenyl pyridines. An excess of pyridine was needed to avoid 2,6-dialkenylation. The zinc-based Lewis acids provided monoalkenylated product **185**, where the aluminum reagents furnished the bisalkenylated **186**.[545] Not surprisingly, based on their results with the *N*-oxides, electron-poor pyridines afforded lower yields than electron-rich pyridines. The catalytic cycle is postulated to be similar to the one proposed for the hydroalkynylation of pyridine *N*-oxides.[545]

Chang and co-workers described the oxidative addition of alkenes to pyridine *N*-oxides.[546] Pyridine *N*-oxide in the presence of $Pd(OAc)_2$, Ag_2CO_3, and a pyridine additive in 1,4-dioxane at 100 °C provided the 2-alkenylated pyridine *N*-oxide in moderate to excellent yield (Scheme 132). The scope was found to be largely limited to Heck acceptors, perhaps giving insight into the reaction mechanism. The *O*-linked *N*-oxide bound palladium complex was synthesized and was found to be inactive in the reaction,[546] suggesting that the *N*-oxide group does not play a role in directing the reaction. The site selectivity is likely due uniquely to electronic activation, as reported by Fagnou and Gorelsky (vide supra). The role of the pyridine additive is not fully understood, but the fact that its replacement with K_2CO_3 leads only to a modest drop in yields suggests that it acts as a weak base. Finally, arylation with benzene was also possible under these reaction conditions,

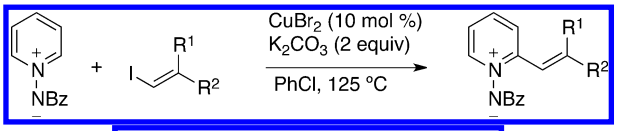
Scheme 132. Selected Scope for the Oxidative Addition of Heck Acceptors to Pyridine *N*-Oxides

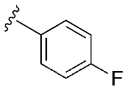
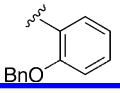


affording the 2-phenyl pyridine *N*-oxides in moderate to good yield.[546]

In 2010, Charette and co-workers disclosed a copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides with alkenyl iodides (Table 47).[547] Key features of the reaction

Table 47. Copper-Catalyzed Direct Alkenylation of *N*-Iminopyridinium Ylides



entry	R^1	R^2	yield (%)
1	H		81
2	Me		48
3	H		83
4	H		53
5	H		71

included the fact that it was insensitive to the copper catalyst employed, with most copper(0), -(I), and -(II) species operative in comparable yields. This led to the proposal that the reaction proceeded through a Cu^{I}/Cu^{III} catalytic manifold. Furthermore, the reaction proceeded in the absence of an external ligand, presumably because the *N*-imino moiety could act as an intramolecular ligand to direct the carbometalation.[547] The directing effect was highlighted through deuteration studies. The reaction was found to be stereoselective, as only *trans*-alkenyl products are observed, even when *cis*-iodides were employed.[547] The reaction was largely limited to styryl iodides, as sp^3 substitution on the double bond, with the exception of cyclopropane, led to a significant decrease in yield. However, the process was highly chemoselective, as halides (I, Br, Cl) on the aryl ring of the styryl iodide were well tolerated and no arylated products were observed.[547] It is noteworthy that the reactivity of the system could be completely altered by changing the catalytic system. When the same ylide and styryl

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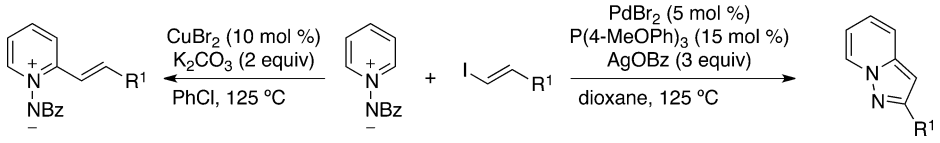
Scheme 133. Tuning the Reactivity in the Direct Functionalization of *N*-Iminopyridinium Ylides with Alkenyl Iodides



iodide are reacted in the presence of $PdBr_2$, $P(4\text{-}MeOPh)_3$, and AgOBz, 2-substituted pyrazolopyridines were accessed in moderate to high yields (Scheme 133).[548]

7. CONCLUSIONS

This review highlights the efforts directed toward the functionalization of pyridine via *N*-activation. The methods depicted throughout this review have proven to be valuable and remain of interest due to the wealth of structures that may be derived from the pyridine core with interest in medicinal, material, and agrochemical sciences. Furthermore, these approaches have been applied in the synthesis of several natural products, representing a strong reliable method for the rapid construction of biologically active nitrogen-containing heterocycles. Although seminal advances have been made, the preparation of highly substituted, functionalized pyridine derivatives still remains a challenge. We hope the present review will stimulate the continued development of new methodologies to achieve these aims, particularly in regard to the catalytic enantioselective addition of nucleophiles at the C-2- and C-4-positions, as well as methods for C−H functionalization of pyridine derivatives.

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Biographies

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James J. Mousseau was born in Montréal, Quebec, Canada, in 1981. Upon completing his B.Sc. in Honors Biochemistry in 2004 at Concordia University, he continued his M.Sc. studies at Concordia under the supervision of Professor Louis A. Cuccia and was involved in the synthesis of novel crescent-shaped urea-linked heterocyclic foldamers. In 2011 he completed his Ph.D. studies under Professor André B. Charette at Université de Montréal studying arene direct functionalization processes. He currently is an NSERC Postdoctoral Fellow at the Massachusetts Institute of Technology under Professor Timothy F. Jamison, and his current research investigates epoxide ring-opening cascade reactions.

Guillaume Pelletier was born in Pointe-Claire, Québec, Canada, in 1984. He received his B.Sc. degree in chemistry at the Université de Montréal in 2007 and is currently is pursuing his Ph.D. studies as an NSERC predoctoral fellow in the group of Prof. André B. Charette at Université de Montréal. His current research is directed towards the chemoselective functionalization of activated amides and synthesis of polysubstituted piperidines, indolizidines, and quinolizidine alkaloids.

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