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INTRODUCING A METHYL GROUP INTO PYRIDINES AND QUINOLINES: A MINI-REVIEW

Eliezer Falb[a] and Alfred Hassner[b]*

[a] Galmed Pharmaceuticals, Ltd. 16 Tiomkin St., Tel Aviv, 6578318 Israel. [b] Department of Chemistry, Bar-Ilan University, Ramat-Gan 5290002, Israel. E-mail: Hassner.Alfred@biu.ac.il

This review is dedicated to Prof. Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – Pyridines are ubiquitous N-heterocycles that are present in many natural products and synthetic drugs with important biological applications. Introduction into a pyridine of a methyl (Me) or an isotopically labeled methyl group at carbon can alter its biological properties. However, regioselective introduction of a Me group in high yield, and preferably in a green manner, is often quite challenging. In this mini-review, several methods, most of which are recent, are examined whereby a Me or CD_3 is introduced at a specific carbon in pyridines, as well as in some quinolines.

CONTENTS

1. INTRODUCTION

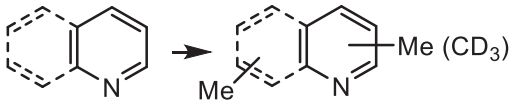
Pyridines are ubiquitous N-heterocycles with important biological and medical applications.[1] Quinolines are likewise featured in many pharmaceuticals and agrochemicals. In this mini-review we discuss some methods employed and challenges encountered during introduction of methyl (Me) groups into pyridines and some quinolines, highlighting recent efforts to introduce a Me or CD_3 group into pyridine moieties *via* C-C bond formation. A plethora of methods was reported for C-C bond formation between heteroarenes and hydrocarbon functions such as aryl, alkyl, alkenyl, alkynyl, allyl or C=O groups, but many of them do not describe methyl introduction. One may wonder why literature examples for introduction of Me groups into pyridines or other heterocycles, are much rarer than for introduction of other hydrocarbon units. Possibly researchers did not try to introduce Me because it cannot be functionalized as easily as other hydrocarbon groups such as alkenes or aromatics. Yet, methyl substituents on pyridines or quinolines are reactive and can be further functionalized. For instance, after methylation of the quinoline unit in camptothecin, the Me group was readily functionalized, leading to new antitumor agents.[2] Another reason could be that the product, a Me homolog, is difficult to separate from the starting material. This is also true in the case of trans-metalation of boron and metalation of halo-pyridines, when protodehalogenation occurs as a side reaction. In many cases the free electron pair on the pyridine nitrogen hampers C-methylation, resulting in poor yield of the desired product. Furthermore, Me species are more reactive and less discriminating and often lead to mixtures of products. Nevertheless, one should keep in mind that many reported methods for introducing alkyl or aryl groups into pyridines or quinolines also present potential approaches for obtaining methylated species.

The Me group is the smallest hydrocarbon unit, but its introduction into an existing organic molecule can alter its biological properties. For instance, an additional methyl group in an organic molecule, such as a known drug, can improve its potency–"the magic methyl effect".[3] Incorporation of a Me group, as for instance in alanine, resulting in α-methylalanine (aminoisobutyric acid, AIBA), has a pronounced effect on the lipophilicity and other properties of the amino acid and of derived peptides;[4] for example, AIBA-containing proteins are able to pass the blood-brain barrier.[4] Similarly, thymine, present only in DNA, features simply one additional Me compared to uracil, which is a component of RNA. Furthermore, once an effective method of introducing a Me group is established, it can also be applied to isotopically labeled Me, i.e. to CD_3, CT_3, $^{11}CH_3$ or $^{13/14}CH_3$. Such labeled compounds, including CF_3 analogs, are

useful for studying drug metabolism. Compounds incorporating $^{11}CH_3$ are used in positron-emission tomography (PET) as both diagnostic and clinical tools.

Introduction of deuterium (D), being the closest isostere of hydrogen, represents nowadays a new methodology in medicinal chemistry, very similar to the "old" one of substituting hydrogen with fluorine to improve the pharmacological properties of new and known drugs. The commercial availability of CD_3 derivatives, such as CD_3I and $CD_3B(OH)_2$, as well as new preparations of CD_3BF_3K[5] provides a convenient mode for isotopic labeling. Recently the food and drug administration (FDA) recognized that a CD_3 labeled drug is a distinct entity warranting complete proof of efficacy.[6]

2. APPROACHES TO C-METHYLATION OF PYRIDINES



Regioselective introduction of a C-methyl group onto a pyridine carbon can essentially be carried out in two ways:

a) by changing an existing carbon functional group into a Me.

b) by addition of a Me moiety.

Emphasis here is on the second methodology.

Pyridines and quinolines are electron-deficient heteroarenes that can react with methyl nucleophiles such as methyl Li, Mg or Cu species, some of which are not very stable at room temperature (rt). Often, such reactions take place at cryogenic temperatures, which are energy consuming and therefore not green. From an environmental point of view, it is advantageous to employ relatively stable methyl electrophiles, such as Me-I, Me-OTf, or Me-B derivatives, especially since these are also readily available in isotopically labeled form and represent relatively atom efficient reagents (boron reagents being more atom efficient than I or OTf species). The reaction partner in that case has to be a pyridine nucleophile, hence a metalated species. Electron poor pyridines can be converted to electron rich metalated derivatives by either base abstraction of a hydrogen or by halogen-metal exchange from a halopyridine. Furthermore, addition of methyl nucleophiles to pyridines or pyridinium species leads to dihydropyridine intermediates which can then be oxidized to pyridines.

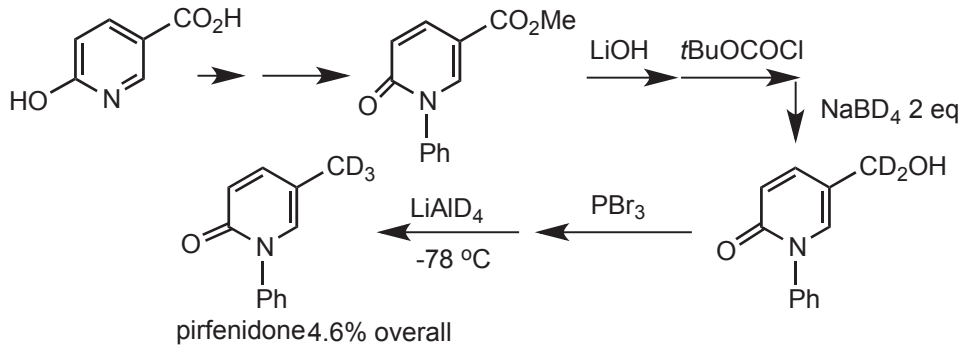
To enhance electrophilicity, pyridines were converted to pyridinium species. Thus, Me radicals, formed *in situ*, can be employed as nucleophiles with a protonated pyridine partner, allowing greener methylation at room temperature. Recently MeOH was employed as a green source of Me radicals (see below).

We consider five possible pathways leading to introduction of a C-Me group into a pyridine, although

there is often overlap among them. Most methods for C-methylation of pyridines are also applicable to quinolines and usually also to isoquinolines. For convenience and clarity, C-methylation of quinolines is treated here in a separate section.

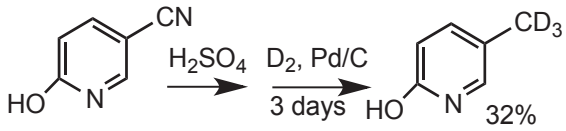
2.1 MODIFICATION OF AN EXISTING C-FUNCTIONAL GROUP INTO A METHYL GROUP

Reduction of an existing CO_2H, CN, CH_2OH and even CF_3[7] functionalities, on the pyridine framework, were utilized for introduction of a methyl group. Such transformations were of interest in cases where a deutero-methylpyridine was desired and the corresponding pyridine derivative was readily available. The conversions usually required multiple steps that were not green and purification procedures that resulted in low yields of methylated product. For example, the patented preparation of the drug pirfenidone includes a multi-step conversion of a carboxy-containing pyridine into the desired CD_3-labeled species[8] (Scheme 1).



Scheme 1

Another patent[8] reported the conversion a 5-cyano containing pyridine into an intermediate employed in the pirfenidone synthesis contains a CD_3 group (Scheme 2).

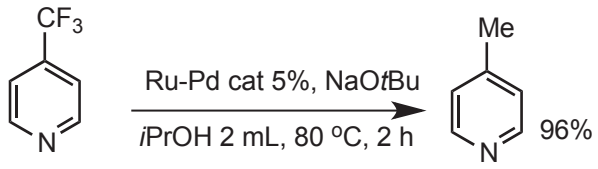


Scheme 2

Efficient introduction of a functional group that is readily convertible into a methyl or isotopically labeled methyl group into a pyridine or quinoline also constitutes a multi-step process for methylation. The good yield by which a CH_2OH group was introduced into pyridines by reaction of N-methoxypyridinium salts with MeOH-H_2O and $(NH_4)_2S_2O_8$, leading to 2-hydroxymethylpyridines (see pathway **2.5**) offers such an example.[9] Recent efficient room temperature introduction of CH_2-OH using MeOH by photoredox using

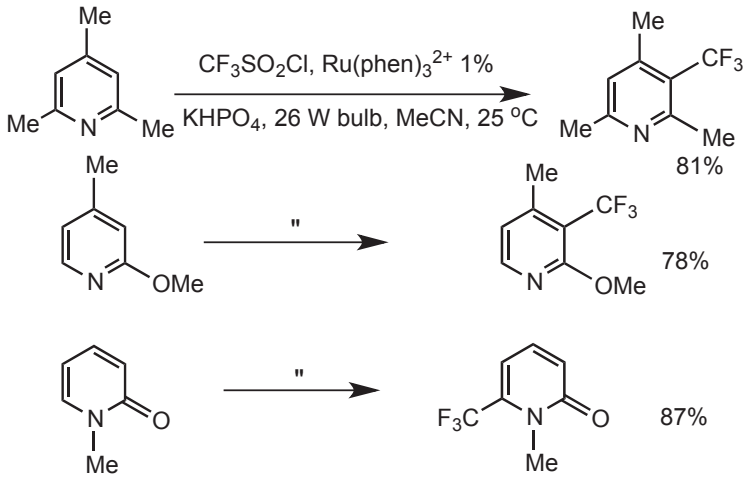
blue light and an iridium catalyst (see pathway **2.5**) can also be used to form C-methylpyridines or quinolines.

The introduction of a CF_3 group will also be considered here, as effective methods are known for inserting a CF_3 into heteroarenes. Subsequent reduction of the CF_3 provides a viable indirect pathway to C-methylpyridines or C-methylquinolines. Indeed, reduction of 4-trifluoromethylpyridine to 4-methylpyridine has recently been shown[7] to proceed in 96% yield at 80 °C within 2 h, in the presence of NaO*t*Bu and 2-propanol, mediated by a triazolyl-liganded Ru-Pd bimetallic catalyst. The reduction may involve transfer hydrogenation from isopropanol/sodium *t*butoxide of the Ru-Pd complexed CF_3 group. This method should lend itself also to reduction of a CF_3 to a CD_3 group (Scheme 3).



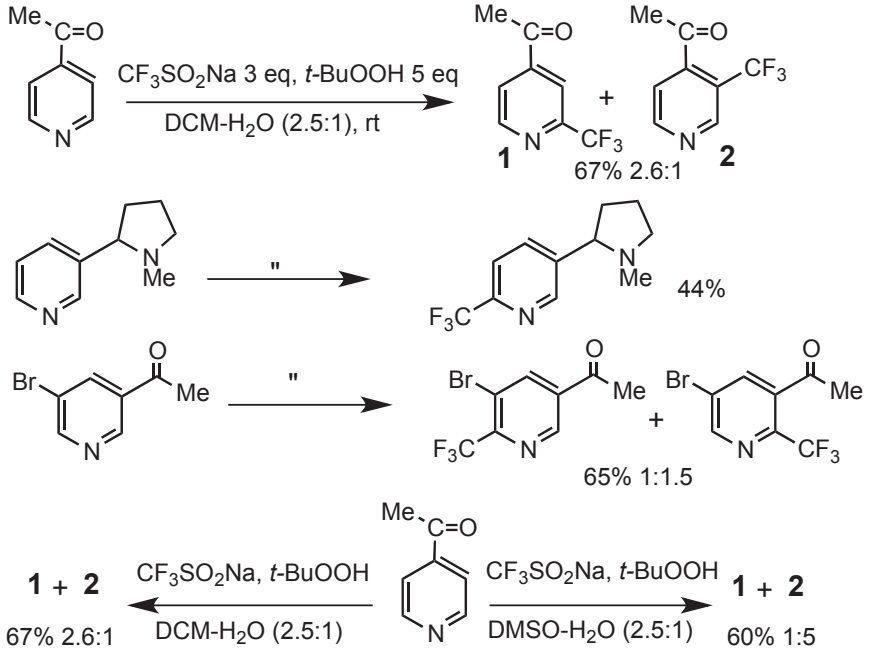
Scheme 3

CF_3 groups were introduced into arenes and heteroarenes efficiently *via* CF_3 radicals[10] generated from many sources, such as trifluoromethylsulfonyl (CF_3SO_2) or trifluoroacetoxy (CF_3CO_2) derivatives, as well as from CF_3-halogen, R_3Si-CF_3, CF_3-I(III)R and, CF_3-SAr_2, often initiated in a photoredox reaction and sometimes in the presence of transition metal catalysts. The MacMillan group was one of the first to suggest the use of trifluoromethylsulfonyl derivatives for generation of CF_3 radicals in a photoredox reaction; they applied it to trifluoromethylation at C-3 of a few electron rich pyridines.[11] Thus, 3-trifluoromethyl-2-methoxy-4-methylpyridine was generated in 78% yield by reaction of 2-methoxy-4-methylpyridine using triflyl chloride (CF_3SO_2Cl) and irradiation with a 26 W light bulb in the presence of a ruthenium-phenanthroline catalyst $Ru(phen)_3^{2+}$ and K_2HPO_4 at rt in MeCN under argon. In the same manner, 2,6-dimethyl- or 2,4,6-trimethylpyridine were trifluomethylated at the 3-position, while N-methylpyridone provided the 6-methyl derivative in high yield (Scheme 4).



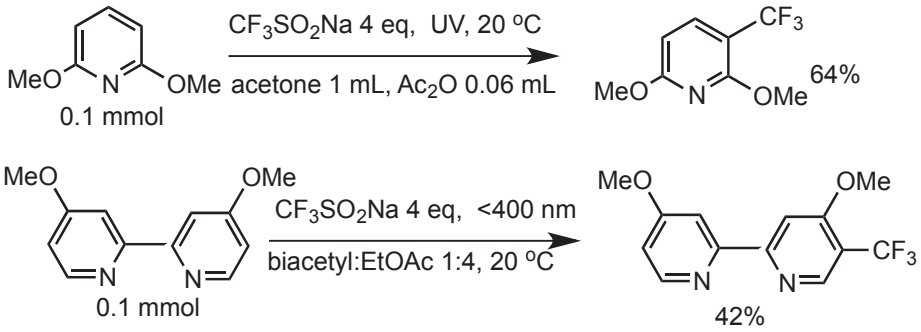
Scheme 4

An alternative to introduce the CF_3 group into electron poor as well as electron rich heteroarenes was shown by Baran and coworkers, using sodium triflinate (CF_3-SO_2Na) in the presence of *t*-BuOOH as CF_3 radical source. The reaction proceeds at room temperature in DCM-H_2O in the absence of metals. Thus 4-acetylpyridine, 4-cyanopyridine and 4-carbethoxypyridine led to introduction of CF_3 at C-2 and C-3 in different ratios and in 67, 48 or 53% yield respectively. The type of solvent also affected the regioselectivity. For instance, in DCM-H_2O the ratio of 2-CF_3:3-CF_3 pyridine (**1**:**2**) derived from 4-acetylpyridine was 2.6:1, which was reversed in DMSO-H_2O to 1:5. Nicotine afforded the C-6 CF_3 derivative (44%), while the quinoline segment of dihydroquinine led to introduction of CF_3 at C-7 in 49% yield[12] (Scheme 5).



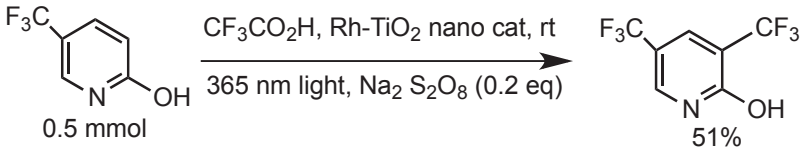
Scheme 5

Sodium triflinate CF_3SO_2Na also served as a CF_3 radical source for mono trifluoromethylation of electron rich pyridines like 2,6-dimethoxypyridine or 4,4'-dimethoxy-2,2-bipyridine in a photoredox free radical reaction in the absence of metal catalyst initiated by acetone or diacetyl[13] (Scheme 6).



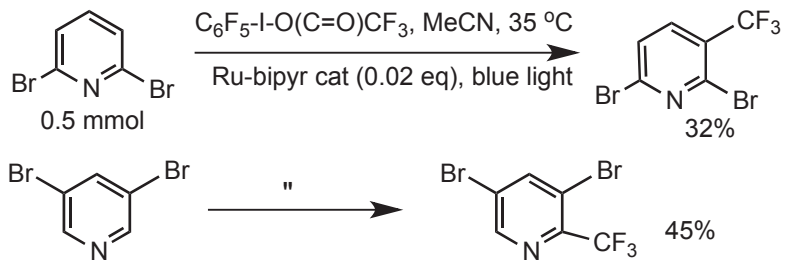
Scheme 6

CF_3 radicals were also generated by decomposition of trifluoroacetic acid (TFA) in a photoredox reaction using visible light promoted by a Rh-Ti nano-catalyst at room temperature.[14] While with pyridine as substrate this reaction led to a mixture of all three regioisomeric trifluoromethylpyridines in 55% yield (the 2-CF_3 isomer was the major product), 2-hydroxy-5-trifluoromethylpyridine furnished the 3-CF_3 derivative as the sole isolated product in similar (51%) yield (Scheme 7).



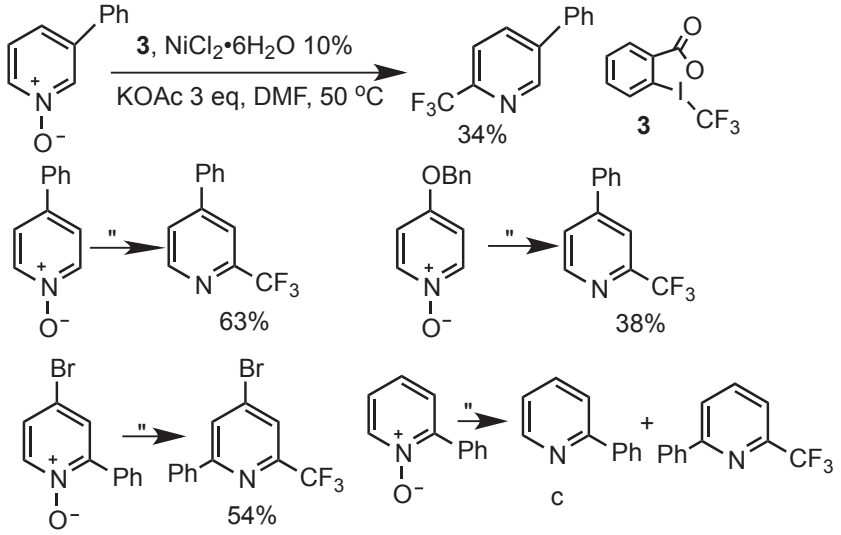
Scheme 7

The aryl periodotrifluoroacetate C_6F_5-I(III)$(TFA)_2$ also served as a source of CF_3 radicals, generated by decomposition of CF_3CO_2 radicals. In this case, CF_3 was introduced into electron deficient 2,6-dibromopyridine at C-3, or into 3,5-dibromopyridine at C-2, in modest yields in the presence of a Ru-bipyr photoredox catalyst and blue light[15] (Scheme 8).



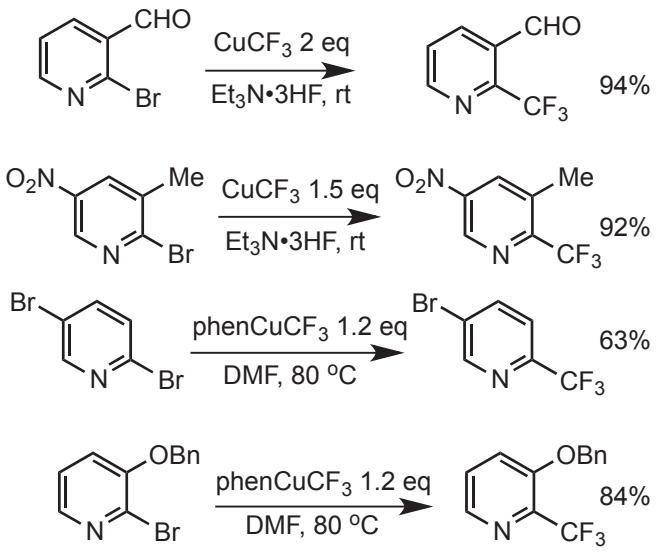
Scheme 8

About 20 substituted pyridine N-oxide examples were trifluoromethylated by means of the Togni[16] periodine reagent **3** and $NiCl_2$-(10%), KOAc (3 eq.) at 50 °C under Ar, leading to 2-CF_3 substituted pyridines with concurrent loss of the N-oxide group. Most substrates were 4-substituted pyridine N-oxides containing either electron-donating (*t*Bu, benzyl, OR) or electron withdrawing groups (benzoyl, halogen). An example of introduction of CF_3 into a 3-substituted pyridine is shown below. Also, disubstituted pyridines gave 2-CF_3 derivatives in 32–58% yield at gram scale. Quinolines, including hydroquinine, were trifluoromethylated at C-2 as well[17] (Scheme 9).



Scheme 9

Several examples for replacement of a Br substituent on pyridines by a CF_3 group, at 25–80 °C, in 73–94% isolated yield were reported by means of a $CuCF_3$ catalyst, the latter derived from reaction of CF_3H with DMF. A 2-Br or 3-I substituent was replaced much more readily than a 3-Br substituent. 2-Bromoquinoline likewise afforded the 2-CF_3 derivative in 80% yield[18] (Scheme 10).

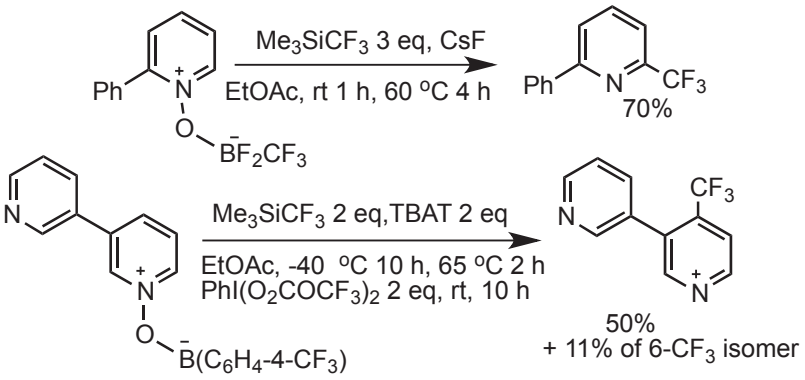


Scheme 10

Instead of $CuCF_3$, a storable complex: phenanthroline-$CuCF_3$ (phen$CuCF_3$), was introduced by Hartwig *et al.* for replacement of Br by CF_3 at 80 °C.[19] They applied the method to about 20 bromopyridines, both electron-poor and electron rich, in good yield. A few representing examples are shown in Scheme 10.

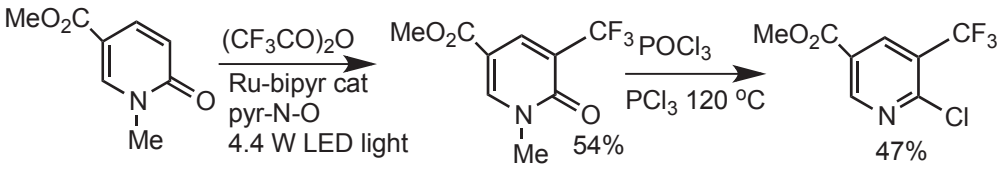
Selective introduction of 2-CF_3 groups into pyridines using Me_3SiCF_3 as a CF_3 source was reported by Kuninobu, Kanai *et al.*[20] Thus, a few 3-, 4-, and 6-substituted pyridines were converted selectively to 2-CF_3 derivatives in 27–70% yield employing 6 eq. of Me_3SiCF_3, TFA and KHF_2 (3 eq. each) and a trimethyleneurea as a Lewis base in dioxane at rt, with $PhI(OAc)_2$ as a oxidant (Scheme 11).

These authors also achieved selective 4-trifluoromethylation of pyridines *via* pyridine N-oxides by attaching to O a much bulkier B group, namely $B(C_6F_4\text{-}4\text{-}CF_3)_3$.[21] In this manner, about ten substituted pyridine N-O-$B(C_6F_4\text{-}4\text{-}CF_3)_3$, among them 3-benzyl, cyano, nitro, phenyl, 2”-naphthyl, 2’- and 3’-pyridinylpyridines, as well as a 2-pheylalkynyl- and a 3-steroidalpyridine N-oxide, were converted to their 4-CF_3 derivatives by Me_3SiCF_3 and tetrabutylammonium difluorotriphenylsilicate (TBAT) (2 eq. each) at -40 °C for 10 h, but also requiring $PhI(O_2CCF_3)_2$ (2 eq. at rt for 10 h), to oxidize the intermediate 1,4 dihydropyridines (Scheme 11).



Scheme 11

Photochemical decomposition of trifluoroacetic anhydride [TFAA $(CF_3CO)_2O$] mediated by a Ru-(bipyridine)$_3Cl_2$ complex served as a CF_3 radical source in the presence of pyridine N-oxide. It was proposed that the latter was trifluoroacetylated on O *in situ*, and thus acted as a CF_3 radical source under mild conditions. This led to introduction of a CF_3 group at C-3 of N-methyl-2-pyridone or its 5-carbomethoxy analog on a gram scale. After the product was heated with $POCl_3$-PCl_3 (or $POBr_3$-PBr_3) at 120 °C, N-demethylation afforded the 2-chloro-3-trifluoromethylpyridine in modest yield[22] (Scheme 12).



Scheme 12

Thus, the combination of introducing a CF_3 group into a pyridine, followed by reduction to a Me group[7] could serve as a viable route for C-methylation of pyridines.[10]

2.2 REACTION OF A Me NUCLEOPHILE WITH AN ELECROPHILIC PYRIDINE

Pyridine can play a dual role, as nucleophile due to the unshared electron pair on N, or as electrophile, involving resonance structures of the C=C-C=N moiety, rendering the C-2 or C-4 carbon as electropositive. This can be further influenced by the nature of substituents present. One should also keep in mind that RLi or RMgX are not only nucleophiles; they can also abstract a hydrogen from a pyridine or in cases where a halogen is present can lead to halogen R exchange.

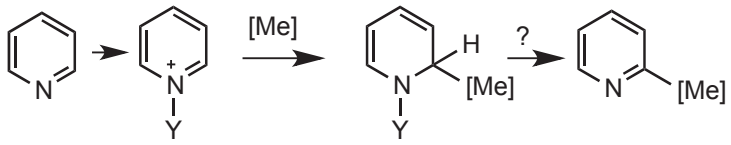
2.2.1 MeLi (Mg, Cu) nucleophiles

MeLi, MeMgBr and Me_2CuLi can add to pyridines at C-2 or C-4, forming either 1,2- or unstable

1,4-dihydropyridines, which often can be transformed to methylated pyridines by oxidation. The more electrophilic pyridinium ions or pyridine N-oxides are much better electrophiles than pyridines, and this suggests a multi-step process for pyridine methylation. After formation of a pyridinium entity from a pyridine, addition of a methyl nucleophile can take place readily, leading to a C-methylated dihydropyridinium species. If the latter is readily convertible to a methylated pyridine, this represents a viable pathway to pyridine methylation. However, since the C-2 hydrogen in pyridines is acidic, it can be abstracted by strong bases like MeLi or MeMgX and lead to side products. Methyl radicals likewise can add to pyridines or more readily to protonated pyridines (pyridinium ions) preferring attack at the 2-position.

In general, addition of a carbon nucleophile to a pyridinium species usually leads to a 1,2- or 1,4-dihydropyridine. A large number of pyridinium species are known in which the N-substituent Y can be alkyl, aryl, a C=O group, an O-substituent, an N-substituent, a Si group or BF_3. Many examples are shown in an excellent review by Charette.[23]

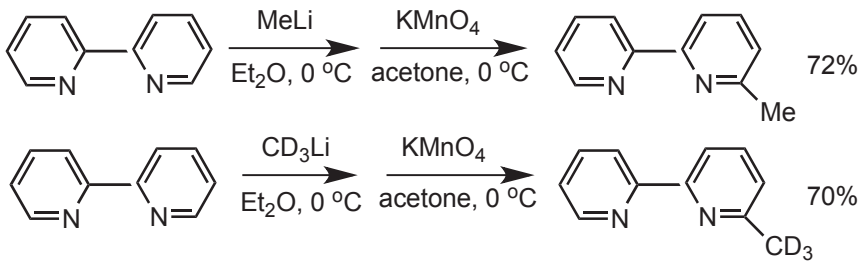
For ultimate formation of a C-methylated pyridine, after addition of a Me nucleophile [Me], it is obviously advantageous, in fact important, that the N-substituent Y in dihydropyridinium derivatives be a good leaving group so that facile elimination of HY from the dihydropyridine intermediate can take place to reconstitute the aromatic pyridine (Scheme 13).



Scheme 13

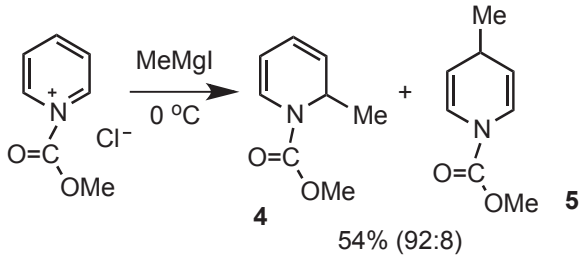
This makes N-alkyl or N-arylpyridinium compounds less suitable substrates than N-oxides or N-OMe derivatives. Sometimes, elimination of HY to form a methylated pyridine was observed to occur during nucleophile addition, either when an oxidizing agent is present or in cases where Y is O- (pyridine N-oxides) or OMe (N-methoxypyridinium ions) without requiring additional steps.

Addition of methyllithium or Grignard reagents to pyridines is temperature dependent and usually not very efficient. Yet, the important ligand 2,2'-bipyridine was converted to 6-Me-2,2'-bipyridine in 72% yield by addition of MeLi in ether at 0 °C, followed by oxidation of the dihydropyridine derivative by $KMnO_4$ in acetone.[24] The CD_3 analog of 6-Me-2,2'-bipyridine was similarly prepared in 70% yield using CD_3Li.[25] In the same manner, 4.4'-bipyridine was methylated at C-2 (Scheme 14).



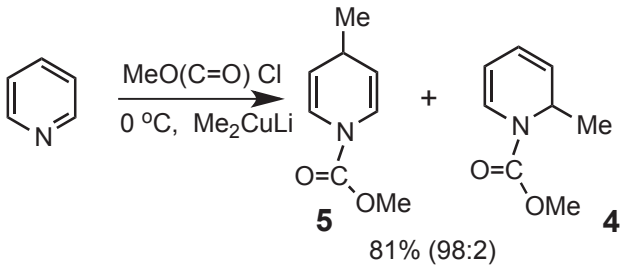
Scheme 14

Methyl Grignard reagents preferentially add to pyridinium salts in a 1,2-manner (addition to the C=N) leading to 2-methyl-1,2-dihydropyridines in modest yield. For instance, reaction of N-methoxycarbonylpyridinium chloride with MeMgI at 0 °C gave mainly the 2-Me-1,2-dihydro derivative in 54% yield (ratio of **4:5** = 92:8)[26] (Scheme 15).



Scheme 15

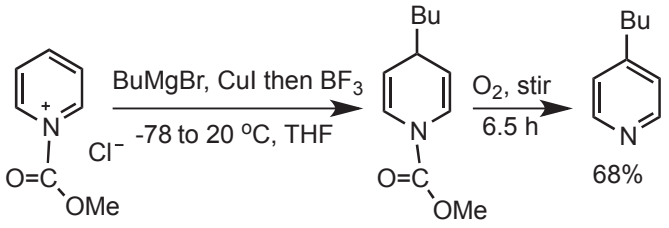
The softer Cu reagents preferentially attack at the 4-position (conjugated addition to C=C-C=N).[27] Thus, addition of 1.2 eq. of Me_2CuLi (or Mg), to 1 eq. of pyridine in ether at 0 °C, followed by 4 eq. of methyl chloroformate afforded in 81% yield 4-methyl-N-carbomethoxy-1,4-dihydropyridine **5** and 2-methyl-N-carbomethoxy-1,2-dihydropyridine **4** in a 98:2 ratio. It was shown that dimethyllithium cuprate does not react with pyridine, and reaction occurred only in the presence of methyl chloroformate, indicating that there is initially a reaction between the latter and pyridine. Instead of methyl chloroformate, diethyl phosphorochloridate can be employed (Scheme 16).



Scheme 16

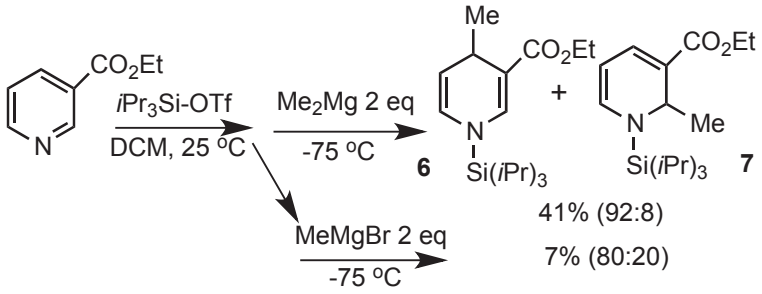
Reduction of pyridines to 1,2- and/or 1,4-dihydropyridines can be carried out by means of $NaBH_4$ or other hydrides and is known as the Fowler reaction.[28] The reduction works well in the presence of $ClCO_2Me$, leading to analogs of **4** and **5**.

Dihydropyridines represent useful substrates for C-methylpyridine synthesis only if they can be readily re-aromatized. An example where $KMnO_4$ was used to oxidize a dihydropyridine was shown in Scheme 14.[24,25] At least in one case, oxidaton of 4-*n*-butyl-N-carbalkoxydihydropyridine to a pyridine with simultaneous loss of the N-carbomethoxy group, was successfully achieved by stirring for a few hours under a stream of oxygen[29] (Scheme 17).



Scheme 17

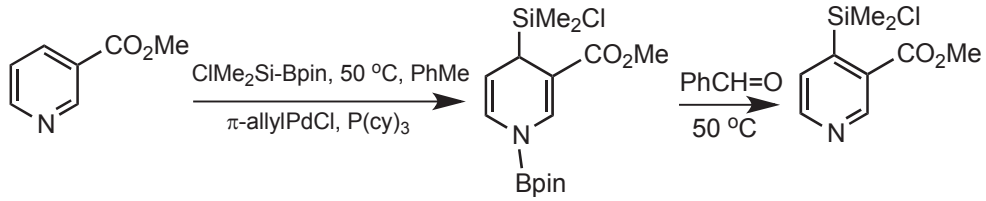
N-Trialkylsilylpyridinium salts also were employed in C-methylation, leading to dihydropyridines. In one case it was shown that dimethylmagnesium behaves differently than MeMgBr. For instance, Me_2Mg (2 eq.) and 3-carbethoxy-N-triisopropylsilylpyridinium salt in DCM at -75 °C afforded in 41% yield the 4-methyl-1,4-dihydropyridine **6**, together with a small amount of the 2-methyl regioisomer **7** in a 92:8 ratio,[30] as well as unreacted starting material. By contrast, MeMgBr under the same conditions led to a mixture of **6** and **7** in a ratio of 80:20 in only 7% yield (Scheme 18).



Scheme 18

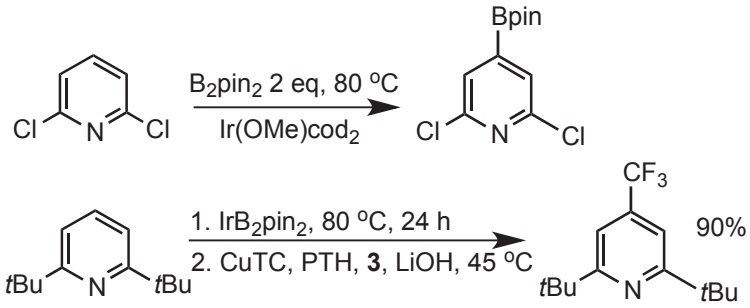
Silyl (pinacolato)boron (R_3Si-Bpin) adds in a 1,4-manner to 3-substituted pyridines like methyl nicotinate or to quinoline itself catalyzed by π-allyl-PdCl liganded to tricyclohexylphosphine, while addition to 4-substitted pyridines leads to 1,2-adducts.[31] Some 1,4-adducts were aromatized by warming with benzaldehyde at 50 °C. These silylpyridines could be substrates for methylation in which case the silyl

group can serve as a temporary protecting group that can be removed by means of fluoride ions (Scheme 19).



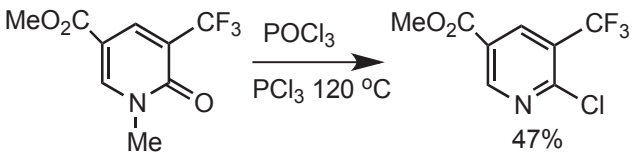
Scheme 19

Introduction of boron functions by means of bis(pinacolato)diboron (pinB-Bpin) into pyridines at C-3 and C-4, as well as into quinolines at the 3,6- or 3,7- positions, was reported under Ir catalysis.[32] When the Ir catalyzed borylation was followed by reaction with **3** (Togni reagent) and CuI or by methyl thiophene-2-carboxylate Cu(I) complex (0.1 mmol), 1,10-phenanthroline (0.2 mmol) and LiOH•H_2O, at 45 °C under Ar, in a sealed bomb, a high yield of the trifluoromethylated product was obtained (Scheme 20).



Scheme 20

N-Alkylation of pyridines affords N-alkylpyridinium salts, which are readily attacked by methyllithium, magnesium or copper reagents at C-2 or C-4 to form methylated dihydropyridines. However, de-alkylation of the latter is difficult. Hence, this method is used mainly if the methylated N-alkyldihydropyridinium species are desired. Nevertheless, an example was reported in which 5-carbomethoxy-3-trifluoromethyl-N-methyl-2-pyridone was converted to 5-carbomethoxy-3-trifluoromethyl-2-chloropyridine with simultaneous loss of the N-methyl group by heating with $POCl_3$-PCl_3[22] (Scheme 21).

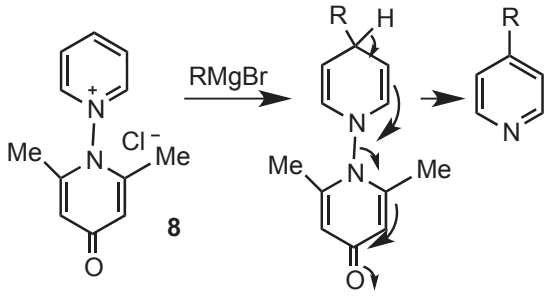


Scheme 21

Pyridine N-oxides and quinolone N-oxides were used extensively in alkylation/methylation. They are readily obtained by oxidation of pyridines or quinolines, respectively, with a variety of oxidizing agents such as H_2O_2-HOAc, *m*-CPBA, H_2SO_5, dimethyldioxirane, oxaziridines, and trimethylsilyl peroxide,[33] and can be reduced back to pyridines or quinolines, respectively, by means of Zn dust-NH_4Cl, Pd/C-NH_4CO_2H, $POCl_3$, TFAA in MeCN followed by NaI, or other reducing agents.[34] In addition, pyridine N-oxides possess an acidic alpha hydrogen and can undergo alpha lithiation with lithium diisopropylamide (LDA) or BuLi.

Since formation of pyridine N-oxides from pyridines amplifies their electrophilic character, it facilitates reaction with methyl nucleophiles, including methyl radicals. Therefore, N-oxides were used extensively to introduce methyl groups into pyridines, as well as into quinolines, and the N-oxide group can be considered a temporary protecting group used in C-methylation. Furthermore, pyridine N-oxides can be converted to 2-chloropyridines by warming with thionyl chloride or to 2-pyridones by means of trifluoroacetic anhydride (TFAA), thus providing an entry into C-Me substituted 2-chloropyridines or 2-pyridones.

Pyridines, as well as pyridinium ions, are preferentially attacked by MeMgX or MeLi at C-2. In order to favor an alkyl group attack at C-4, Katritzky and coworkers[35] devised a 2,6-dimethyl-4-oxo-l,4-dihydropyridylpyridinium derivative **8** possessing a good leaving group on N. This led to regiospecific formation of 4-alkylpyridine in good yield by reaction of **8** with alkyl Grignard reagents. Steric hindrance by the 2,6-dimethyl groups on the 4-oxo-l,4-dihydro-1-pyridyl N-substituent prevented attack by the alkyl group at C-2 of **8**. Apparently, this was not reported for introduction of a 4-methyl group (Scheme 22).

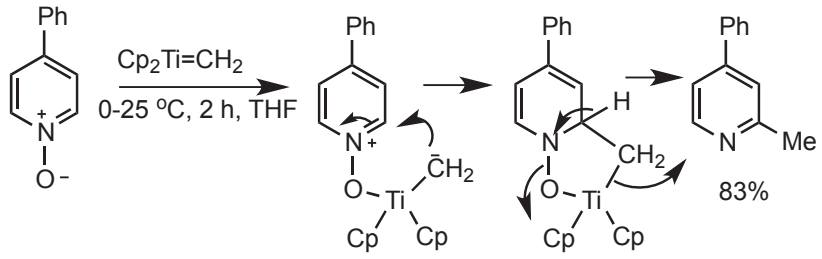


Scheme 22

Another good leaving group in dihydropyridines is the OMe substituent on nitrogen (vide infra under pathway **2.5**).

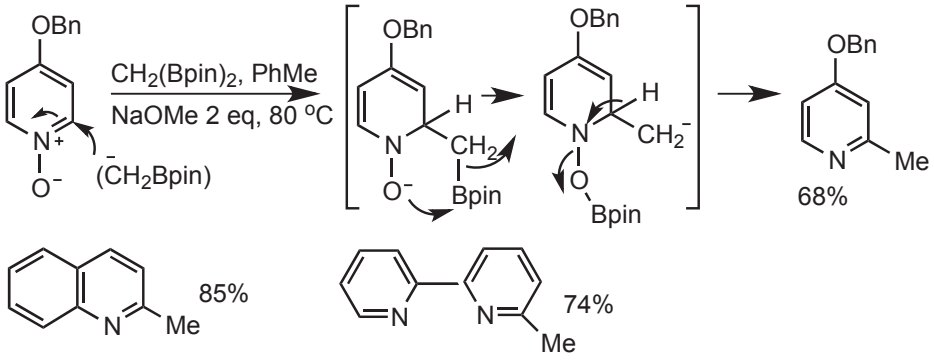
A few studies reported introduction of a methyl group into pyridine N-oxides that proceeded with concurrent deoxygenation, thus not requiring a separate aromatization step. An example is the interesting methylation of pyridine N-oxide with concurrent deoxygenation to 2-methylpyridine by means of the

Tebbe reagent, $Cp_2Ti{=}CH_2$, at room temperature, described by Nicolaou.[36] This likely involves coordination of the titanium with the oxygen of pyridine N-oxide and CH_2 transfer to the 2-position with deoxygenation (Scheme 23).



Scheme 23

Cho[37] and Kim reported methylation-deoxygenation of 4-phenyl-, 4-benzyloxy-, 2-phenyl-, 2-N-Boc-methylaminopyridine N-oxides to 2-methylpyridines in good yields. The reaction was carried out at 80 °C in the presence of a base but in the absence of transition metals, using bis[(pinacolato)boryl]-methane, $CH_2(B\text{-}pin)_2$, as methyl source. The suggested pathway involves attack of methoxide ion on boron of $CH_2(B\text{-}pin)_2$ followed by formation of the anion of CH_2 B-pin, which adds to C-2- of the N-oxide, ultimately followed by elimination of pinBO. Under these conditions 6-methyl-2,2-bypyridine was prepared in 74% yield, while quinoline N-oxide furnished 2-methylquinoline 85% (Scheme 24).



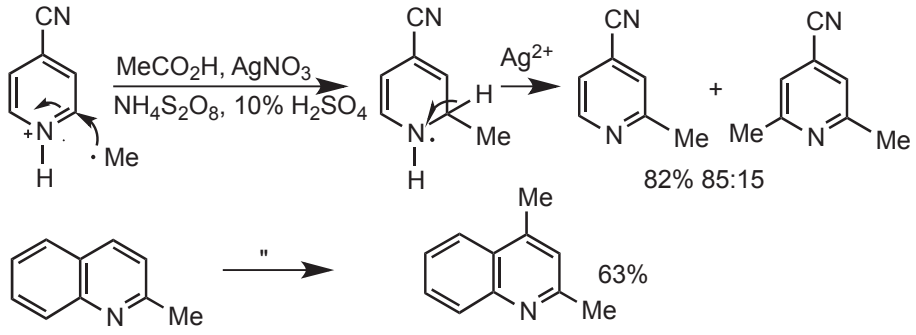
Scheme 24

2.2.2 Methyl radicals as nucleophiles

The use of methyl radicals, instead of metalated Me species, is an attractive route for introduction of methyl groups into electron deficient heteroarenes, among them pyridines and quinolines, and some examples were already mentioned above. A frequently used substrate for reaction with Me radicals is protonated pyridine. Pyridinium ions possess a significantly lower LUMO than pyridines,[38] and hence can react much more readily with Me nucleophiles such as Me radicals.

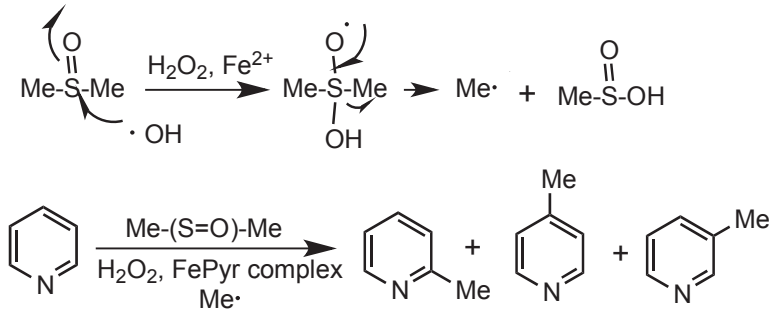
The best-known example in which alkyl radicals attack protonated pyridines and quinolines is the Minisci reaction,[39] which involves silver(I) mediated decarboxylation of carboxylic acids (R-CO_2H) to R radicals in the presence of persulfate oxidant; it was employed to introduce a variety of R groups (aryl, alkyl, and specifically Me) into electron deficient pyridines, as well as quinolines.

For instance, 4-cyanopyridine in the presence of 10% H_2SO_4, 5 eq. of $MeCO_2H$, 10 eq. of $AgNO_3$ and one eq. of $(NH_4)_2S_2O_8$ at 70 °C furnished the 2-Me- and the 2,6-dimethyl-4-cyanopyridine (85:15) in 82% yield and 41% conversion. Pyridine was converted almost quantitatively to a mixture of 2-Me-, 4-Me and 2,4-dimethylpyridine (2.3:2.5:51). The nature of the solvent was shown to affect the regioselectivity.[40] The reaction involves oxidation of Ag^+ by $S_2O_8^{2-}$ to Ag^{2+} and SO_4 radical anions. The latter could mediate decomposition of acetic acid to Me radicals and CO_2, with formation of sulfate ions. Addition of Me radicals to the C=N bond of the protonated pyridine would then be followed by reaction with Ag^{2+} and formation of H^+ and the 2-methylated pyridine. In this manner, 2-methylquinoline afforded in 63% isolated yield 2,4-dimethylquinoline[41] (Scheme 25).



Scheme 25

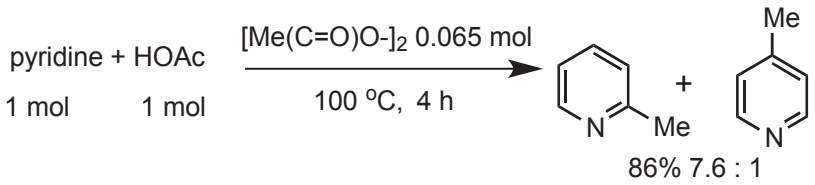
Alternatively, Minisci *et al.*[42] showed that methyl radicals can be accessed from DMSO and OH radicals, the latter resulting from reaction of H_2O_2 with Fe^{2+}. Minisci's group was one of the first to show that *t*-BuOOH or *t*Bu-O-O-tBu can be used in a free radical methylation, with the *t*Bu group acting as a Me source,[43] and that other peroxides as well as oxaziranes can be used in free radical methylation of pyridine or quinoline *via* methyl radicals, albeit in low yields (Scheme 26).



Scheme 26

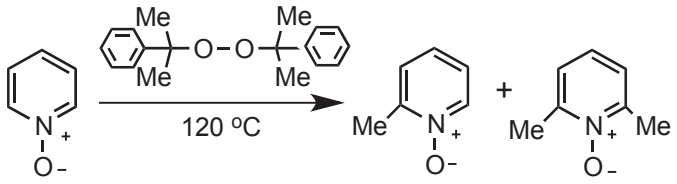
The methyl radical is less stable than other alkyl radicals and is also a more reactive nucleophile. Minisci and coworkers found that attack by alkyl radicals on protonated pyridines is not very selective, but prefers attack at C-2 over C-4 or C-3, with methyl radicals being even less selective. Thus, a mixture of 2-, 3- and 4-methylpyridine together with other products was reported to result from an iron-complex catalyzed free radical reaction of pyridine with DMSO-H_2O_2 as methyl source.[44]

An early example reported in 1954 in which acetic acid served as methyl radical source is the low conversion electrolysis of acetic acid (330 g) in pyridine (270 g) from which 10.1 g (3.5% yield) of a mixture of 2- and 4-methylpyridine in 2.8:1 ratio was isolated. By comparison the thermal decomposition of diacetyl peroxide to methyl radicals in pyridine-acetic acid furnished 2- and 4-methylpyridine in a ratio of 7.6:1 and in 86% yield (based on diacetyl peroxide)[45] (Scheme 27).



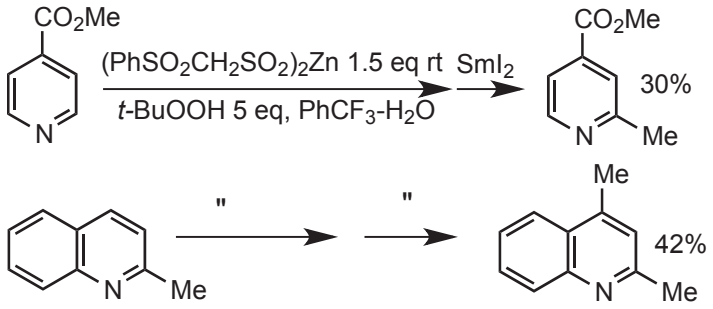
Scheme 27

Oxidative, metal free cross-coupling of ethers at C-2 of pyridine N-oxide or quinoline N-oxide takes place with *t*butyl hydroperoxide (TBHP) but no methylation example was reported.[46] On the other hand, employing dicumyl peroxide as methyl source at 120 °C led to oxidative methylation at C-2 of several quinoline N-oxides, while pyridine N-oxide afforded a mixture of 2-Me and 2,6 di-Me, in the absence of metal catalysts[47] (Scheme 28).



Scheme 28

After introduction of a Me group into a pyridine or quinoline, the product is often difficult to separate from the starting material. To alleviate this problem, Baran *et al.* proposed a two-step process, inspired by S-adenosylmethionine methyl transferase, namely introduction of a CH_2-SO_2Ph group into heteroarenes by a free radical reaction, followed by reduction of the $PhSO_2$ group. The CH_2-SO_2Ph containing product, being of much higher molecular weight was easily separated from the starting material. This was followed by reduction of the $PhSO_2$-CH_2 to a Me group, which can be accomplished by means of either SmI_2, Mg in MeOH, NaHg, or Ra Ni. Zinc bisphenylsulfonylmethyl sulfinate, $(PhSO_2CH_2\text{-}SO_2)_2Zn$, served as $PhSO_2$-CH_2 reagent. In this manner, 4-carbomethoxypyridine was methylated in a two-step procedure in modest yield[48] (Scheme 29).



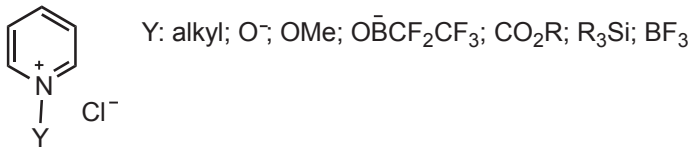
Scheme 29

Recently there has been a revival in the application of radical additions to heteroarenes. Advances in photochemically catalyzed formation of Me and CD_3 radicals made methyl radicals available for introduction into pyridines and quinolines from green substrates such as MeOH. This is discussed below under pathway **2.5**.

2.3 REACTION OF A Me ELECTROPHILE WITH A PREFORMED PYRIDINE NUCLEOPHILE

The unshared electron pair on nitrogen renders pyridines or quinolines weak nucleophiles that can react with a Me electrophile like MeI, Me_2SO_4 or MeOTf. Indeed, reaction of pyridine with MeI leads to N-methylpyridinium iodide by N-alkylation and heating of the latter at high temperature (ca. 300 °C),

known as the Ladenburg rearrangement,[49] represents one of the earliest formations of C-methylpyridines, albeit as a mixture of monomethyl pyridines and other byproducts in low yield. This method is hardly employed today, although it was considered as a possible pathway in certain cases involving Me radicals. But pyridines, as well as electrophilic pyridinium species, can be converted to metalated nucleophiles by proton abstraction using a strong base. Alternatively, halopyridines can be transformed by halogen-metal exchange into metalated nucleophiles. Such metalated derivatives are readily trapped by Me electrophiles leading to C-methylated pyridines. A large variety of N-substituted pyridinium species are known and they possess acidic C-H bonds. Some examples are indicated below, among them pyridine N-oxides, which can be useful intermediates for C-methylation (Scheme 30).

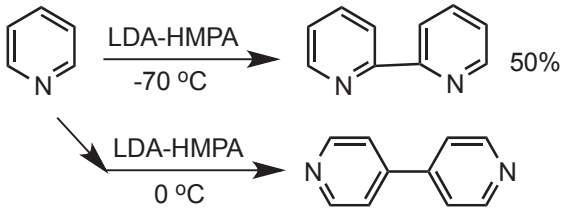


Scheme 30

A variety of bases were employed to abstract a hydrogen from pyridines, preferentially at C-2, providing metalated derivatives which were alkylated, although not often, with methyl electrophiles. The effectiveness of H-abstraction suffers from competition by addition of the base/nucleophile to the C=N. Hence the use of hindered bases is preferred. Among the common Li bases that were used, some being more selective than others, are *t*BuLi, LDA, lithium 2,2',6,6'-tetramethylpiperidide (LTMP), lithium 2-(dimethylamino)ethoxide ($LiOCH_2CH_2NMe_2$, LDMAE) known as Caubere's base,[50] and the superbase BuLi-KO*t*Bu, (usually in a ratio of 1:1 but also in other ratios) known as Schlosser's base.[1] These bases as well as BuLi, can be employed to abstract a hydrogen from pyridines, pyridine N-oxides or from corresponding quinoline derivatives.[51] Proton abstraction by base is highly dependent on reaction conditions, especially temperature, time and solvent, and sometimes conflicting reports appeared in the literature. A comprehensive review[52] by Mongin and Harrison-Marchand describes many examples in which "mixed aggregate" bimetallic reagents were used for proton abstraction also in heteroarenes, followed by trapping with an electrophile, but very rarely by a Me electrophile. These mixed metallic reagents are usually derived from Li, Na, K or Mg bases combined with either another alkali metal species (Li, Na, K) or with a compound containing another metal from group 2 to group 13 (Mg, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Al) as Lewis acidic centers, in different stoichiometric ratios. Additives such as HMPA, DABCO and TMEDA can change the selectivity. For instance, LDA in the presence of HMPA at -70 ^{o}C, instead of simple proton abstraction, converted pyridine *via* single electron transfer

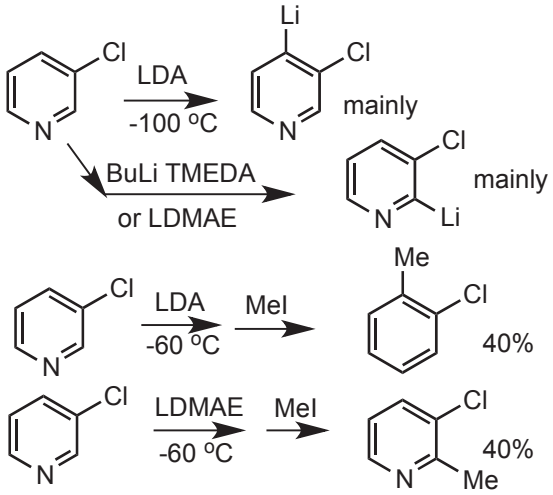
(SET) to 2,2'-bipyridine in 50% yield. Also, quinoline was transformed to 2,2'-biquinoline in 70% yield.[53]

Furthermore, when the reaction of pyridine with LDA and HMPA was carried out at 0 °C, 4,4'-bipyridine was isolated. It was suggested that HMPA stabilizes pyridine radical anion intermediates, promoting SET[54] (Scheme 31).



Scheme 31

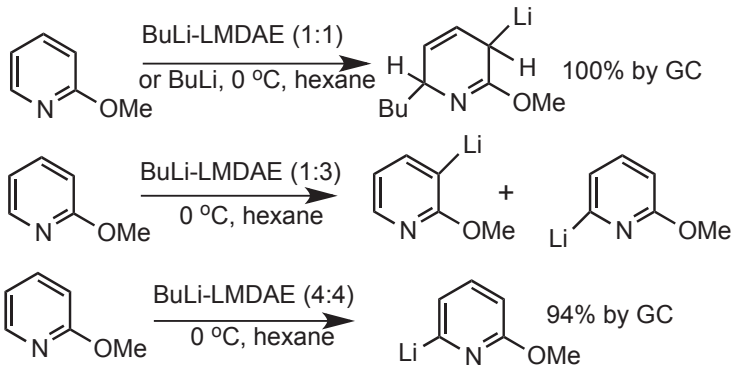
Base abstraction of a proton from pyridine or quinoline takes place preferentially at C-2. Obviously, the choice of base as well as the temperature are important. The presence of halogens (F, Cl, Br, CF_3) can be tolerated during H-subtraction from halopyridines at low temperature (-75 to -100 °C), but sometimes exchange lithiation or benzyne products were observed, especially when BuLi was employed.[55] Here again the choice of base and reaction conditions can lead to different results. Thus, 3-chloropyridine with LDA at -100 °C furnishes the 4-Li derivative while BuLi with TMEDA, or using lithium 2-(dimethylamino)ethoxide provides mainly the 2-lithiated species, the latter presumably due to Li chelation. 3-Chloropyridine treated with LDA at -60 °C, followed by MeI, gave 4-Me 3-Cl in 40% yield.[56] Careful studies indicated that small amounts of a regioisomer were also present (Scheme 32).



Scheme 32

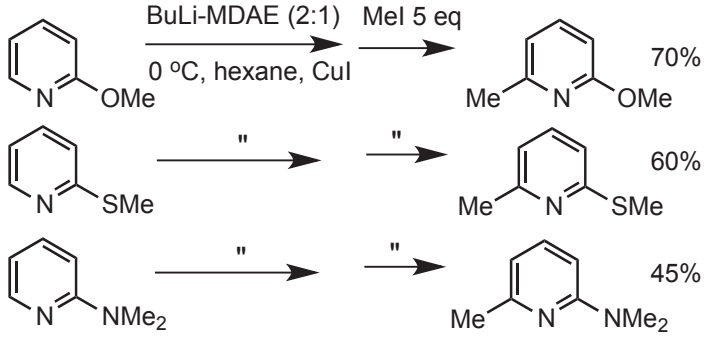
4-Chloropyridine is deprotonated at C-3 with LDA, but with LDMAE it gives mainly the 2-Li derivative.[57] Lithiation of 2-CF_3-pyridine normally occurred at the 3-position, but with LDMAE as base the 6-lithio derivative was produced.[58] The lithiated pyridines then may react selectively with various electrophiles, including in a few cases with Me species. The presence of CO_2H, C=O-N, or C-N substituents directs the lithio bases to their alpha position rather than alpha to the N, due to Li ion chelation.

Caubère *et al*.[59] examined the effect on proton abstraction from pyridines by changing the BuLi/LMDAE ratio followed by trapping of the Li species with different electrophiles. In the case of 2-methoxypyridine, BuLi-LDMAE (2:1) in hexane at 0 ºC, followed by reaction with 5 eq. of MeI in the presence of a small amount of CuI led to 70% of 6-methylated product (52% isolated). However also 25% of 6-butyl-2-methoxy-3-methylpyridine had formed by initial addition of BuLi at C-6. With Me_2SO_4 only 14% of this side product was isolated together with 70% of 2-methoxy-6-methylpyridine.[60] Changing reaction conditions and ratios of BuLi-LDMAE in the reaction with 2-methoxyypyridine led to either lithiation at C-3 or at C-6 as well as to 3,6-addition of BuLi.[59]



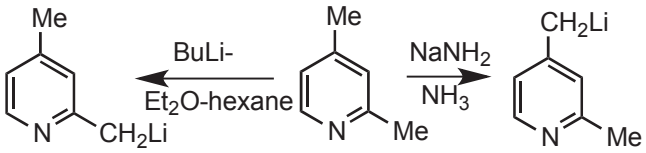
Scheme 33

Using the same conditions, 2-thiomethylpyridine afforded 60% of 6-methyl-2-thiomethylpyridine, while 2-dimethylaminopyridine gave the 6-methylated product in 45% yield (Scheme 34).



Scheme 34

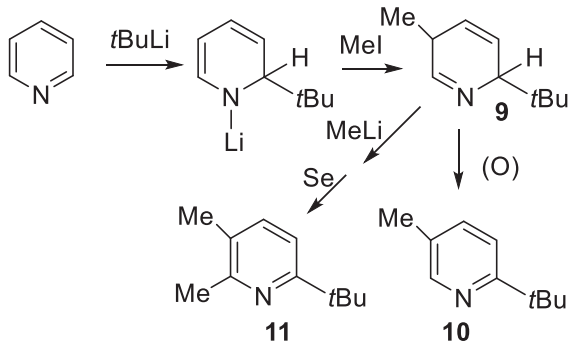
It is known that methyl substituents on pyridines or quinolines possess an acidic hydrogen that can be abstracted by strong base. In fact, it is possible to differentiate between two methyl groups on a pyridine or quinoline for further functionalization with an electrophile by choice of a proper base. For 2,4-dimethylpyridine it was shown that BuLi led preferentially to the 2-CH_2Li derivative while $NaNH_2$ in liquid ammonia or LDA furnished the 4-CH_2Li analog. 2,4-Dimethylquinoline behaved similarly[61] (Scheme 35).



Scheme 35

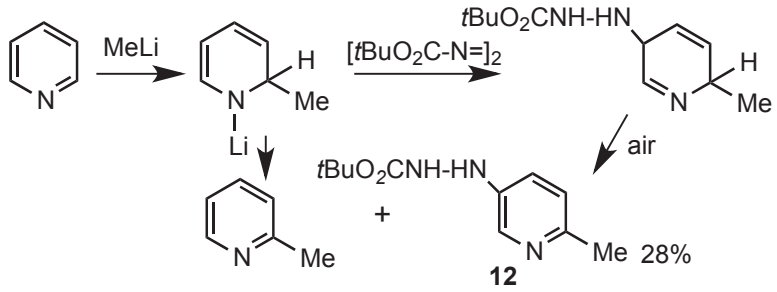
The sensitivity of methyl groups in a pyridine or quinoline to strong base is exemplified by formation of 2-ethylquinoline (30% isolated) on exposure of quinoline to BuLi-LDMAE (4 equiv.) at -78 ºC followed by MeI (10 eq.).[60]

Electrophilic methylation of pyridine was reported to take place by first adding an alkyl lithium to the C=N and trapping the resulting lithiated enamine derivative with MeI. In this manner 2-*t*-butyl-5-methylpyridine **10** or 2,3-dimethyl-6-*t*-butylpyridine **11** were obtained by a series of consecutive steps, starting with addition of *t*BuLi to the C=N of pyridine. This was followed by trapping the resulting lithio enamine with MeI. The 2,5-dihydropyridine **9** thus obtained was unstable and decomposed by aromatization to 2-*t*-butyl-5-methylpyridine **10**. Alternatively, **9** was trapped by addition of MeLi to the C=N and the product was aromatized by heating with Se powder to **11**[62] (Scheme 36).



Scheme 36

Formation of a 2-Me-5-hydrazinopyridine **12** in low yield together with 2-methylpyridine resulted from 1,2-addition of MeLi to pyridine at -20 °C followed by trapping of the lithiated intermediate with di-*t*-butyl azodicarboxylate at -70 °C and air oxidation[63] (Scheme 37).

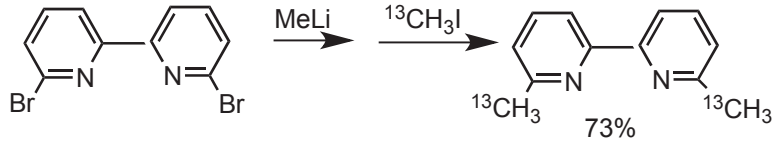


Scheme 37

While abstraction of H-2 from pyridine N-oxide with *i*PrMgCl at -78 °C was achieved and the metalated C-2 species was trapped with several carbon electrophiles, this was apparently not reported for methylation.[64]

Bromine-lithium as well as bromine-magnesium exchanges take place regioselectively. Thus, 3-bromopyridine is converted by BuLi at low temperature to 3-lithiopyridine or by *i*PrMgCl to the 3-magnesium derivative.

6,6'-Dilithio-2,2'-bipyridine, derived by Br-Li exchange from the 6,6'-dibromo derivative using MeLi, was converted to 6,6'-bis$^{13}CH_3$-2,2'-bipyridine (73%) by reaction with $^{13}CH_3I$[65] (Scheme 38).



Scheme 38

2.4 REACTION OF A Me ELECTROPHILE WITH AN *IN SITU* FORMED PYRIDINE NUCLEOPHILE OR UNDER CROSS-COUPLING *VIA* TRANSITION METAL CATALYSIS

Two attractive methods that were employed recently for introduction of alkyl groups into heteroarenes, specifically for methylation of pyridines, involve conversion of halopyridines either *via* metalation (mainly Mg, Li) followed by coupling with an electrophilic methyl, or *via* cross-coupling reactions under transition metal catalysis (i.e., Pd, Ni).

Some examples of the first method have already been alluded to above. Grignard reagents are very sensitive reagents that are usually employed at low temperatures, but in 2004 Knochel[66] introduced the isopropylmagnesium chloride lithium chloride complex (*i*PrMgCl•LiCl), known as Turbo Grignard, for *in situ* generated halogen-Mg exchange under mild conditions (25 down to -78 °C).

Complementary to the Turbo Grignard reagent for activation of magnesium reagents is the "Ate

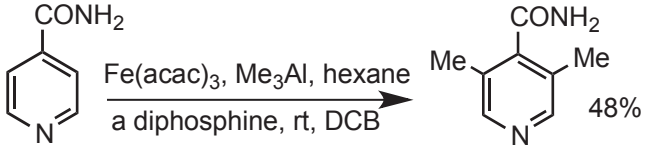
Complex",[52] which features a less polar metal-anion bond (compared to Li reagents), making it more selective at ambient rather than cryogenic temperatures, thus allowing a greener alkylation. Instead of using an alkali-metal halide salt, such as LiCl, as in the Turbo Grignard, an organo-alkali-metal "magnesiate" is formed, simply by varying the stoichiometric ratio of organo-magnesium to organo-lithium reagent in the mixing of the ether solutions of the chosen Grignard and alkyl-Li.[52] This results in metathesis into a special complex with anionic activation for the Mg.

In 2010 the Nobel prize in chemistry was awarded to Profs. Heck, Negishi[67] and Suzuki[68] for "Pd catalyzed cross-coupling as a tool to make C-C bonds", since then it has become one of the most important synthetic transformations developed in the twentieth century where nearly any two fragments can be coupled with the right catalyst system.

Recent advances in transition metal catalysis, especially Pd catalyzed coupling[69] have provided efficient examples of cross coupling of an aryl or alkyl electrophile with a pyridine but only recently has Pd catalyzed coupling of Me to nucleophilic pyridine species been reported. The latter are usually derived from a halopyridine. Pyridines are generally considered mild electrophiles but they can be halogenated and are most readily accessible as their 3-halo (Br, I, Cl) derivatives. Similarly, 2- or 4-pyridones are readily converted to 2- or 4-alkoxypyridines which likewise provide 5-halo or 3-halo derivatives respectively. These halogenated pyridines are readily converted to nucleophilic metalated species that can be used for introduction of alkyl groups, including Me, by cross coupling. Some of the most effective methods of C-methylation of N-heterocycles are Me electrophiles such as MeI, Me_2SO_4, MeOTf, $MeB(OR)_3$.

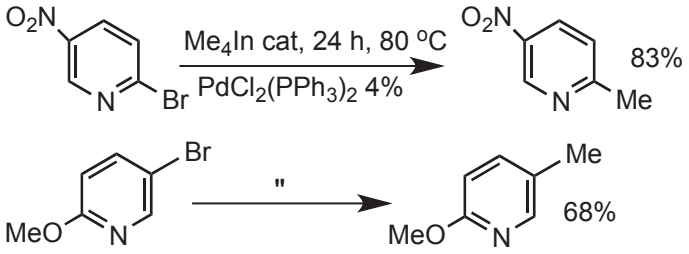
Pyridineboronic acids are not very stable and often undergo protodeboronation, an undesirable side reaction[70] leading to replacement of B by H. Hence, methylation of pyridine *via* Suzuki coupling, is more efficient employing $MeB(OR)_2$. Molander has shown the advantage of employing potassium methyl-trifluoroborate $MeBF_3K$ in Pd catalyzed cross-coupling of heteroarenes under mild conditions.[71] Unlike pyridine itself, pyridine N-oxide can be cross coupled at C-2 directly with an aryl bromide under Pd catalysis;[72] here the corresponding methylation has not been reported.

A N-containing neighboring group directed methylation of 4-carbamidopyridine was reported to give the 3,5-dimethyl derivative in 48% yield.[73] The Fe(III) $(acac)_3$ catalyzed coupling took place with Me_3Al in hexane as a Me source at rt in the presence of a diphosphine and 2,3-dichlorobutane (DCB) as an oxidant (Scheme 39).



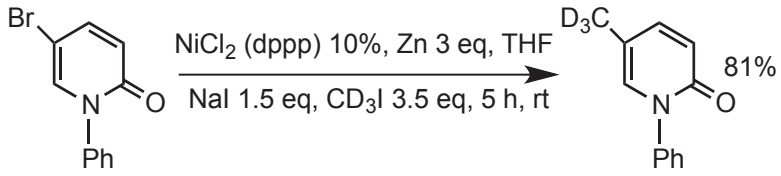
Scheme 39

The first example of a Pd catalyzed methylation of pyridines appears to be the methylation of a few 2-bromo- and 3-bromopyridines in 68–99% yield, when carried out with the aid of bis[μ-[2-(dimethylamino)ethanolato-N,O:O]] tetramethylindium. For instance 2-bromo-5-nitropyridine gave the 2-methyl analog in 83% yield and 5-bromo-2-methoxypyridine provided the 5-bromo derivative in 68% yield. The methylations used $PdCl_2(PPh_3)_2$ (4%) and required 24 h at 80 °C. An analogous tetramethylgallium catalyst also worked in some cases[74] (Scheme 40).



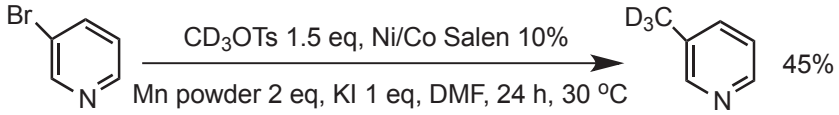
Scheme 40

Only more recently have other Pd catalyzed methylations of pyridines been reported. Liao *et al.*[75] described an effective Negishi procedure for the methylation of aryl halides with methyl-*d*$_3$ iodide (CD_3I, 3.5 eq.) including the synthesis of SD-560 from 2-hydroxy-5-bromopyridine in 70% overall yield. The reaction proceeded at room temperature in THF under catalysis of 10 mol%. 1,3-bis(diphenylphosphino)propane nickel(II) chloride ($NiCl_2$(dppp)) with the addition of zinc powder (4.0 eq.) and NaI (1.5 eq.) (Scheme 41).



Scheme 41

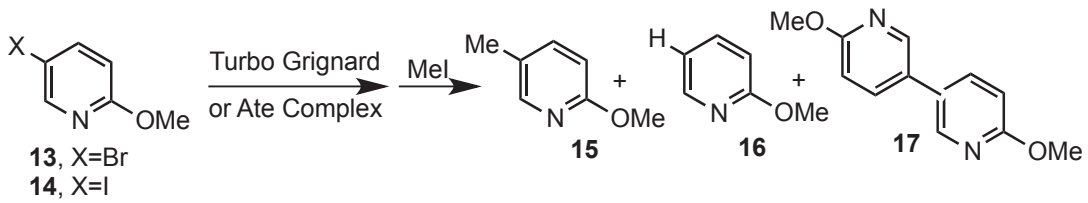
Very recently Komeyama *et al*. described a new approach for the trideuteriomethylation of aryl halides using trideuteriomethyl *p*-toluenesulfonate (CD_3OTs) under nickel and nucleophilic cobalt catalysis.[76] Thus, 3-deutereomethylpyridine resulted in 45% yield from reaction of 3-bromopyridine with CD_3OTs, a Ni/Co Salen catalyst, 2 eq. of Mn powder, and KI in DMF at 30 °C (Scheme 42).



Scheme 42

Unpublished efforts[77] towards a green route to SD-560, the methyl-deuterated version of the drug Pirfenidone (N-phenyl-2-methoxy-5-methylpyridine) explored methylation and deuteromethylation of 5-bromo-2-methoxypyridine **13** and 5-iodo-2-methoxypyridine **14** into 2-methoxy-5-methyl pyridine **15** *via* lithiation/magnesiation route or *via* Pd catalyzed Suzuki coupling. This example highlights problems associated with green methylation of pyridines. Lithiation of **13** and **14** resulted in a reactive lithium species, followed by cross-methylation with MeI, giving rise to **15** but also to des-methyl **16** and to other process-related impurities such as bipyridine **17**. In the case of **16**, separation from **15** proved to be almost impossible.

When Turbo Grignard was employed for halogen–magnesium exchange,[77] in **13** followed by addition of MeI (4 eq.) or methyl triflate (1.2 eq.) in 2-Me-THF at -10 °C to room temperature, HPLC monitoring initially indicated formation of magnesium intermediate in 98%, reflecting the high efficacy of the halogen/metal exchange. Nevertheless, **16** accumulated with time up to almost 50%, together with 35% of the dimer **17**, and ~15% of desired **15** (Scheme 43).

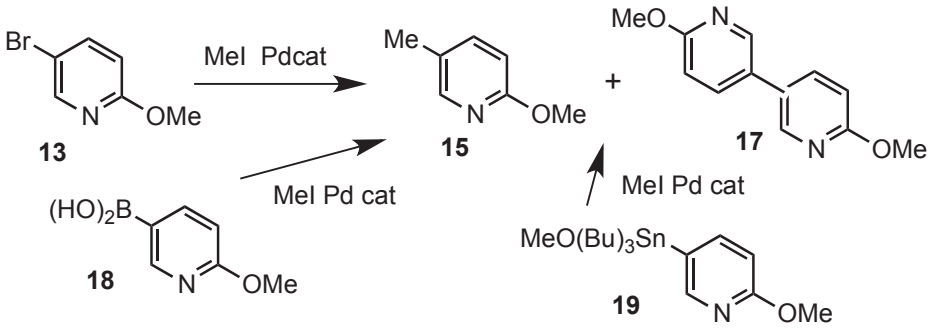


Scheme 43

Exposure of **13** or **14** to 3 eq. of "Ate Complexes" (BuLi and *i*PrMgCl or butylmagnesium chloride), followed by 4 eq. of MeI at -15 °C, the reaction was stalled at ca. 60% of **15** together with **16** but no **17**. At -15 °C to 0 °C and to room temperature ca. 80% conversion into **15** was observed, however the reaction required a large excess of MeI, while with less MeI and longer reaction time and low concentration of **13**, proto-dehalogenated **16** accumulated except at very high dilution (3 L volumes) of solvent but the results were not reproducible nor green.

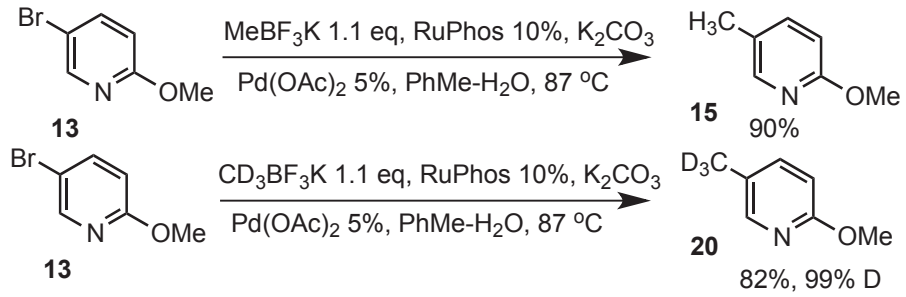
Several coupling attempts[77] toward a green synthesis of **15** by means of transition metal-catalyzed cross-methylation of **18** using different catalysts/ligand complexes, such as: $Pd(OAc)_2$, $PdCl_2(dppf)$,[78] $Cu(AcO)_2 \cdot H_2O/Ag_2O$,[79] tri-1-naphthylphosphine ($P(1\text{-}Nap)_3$)[80] with different methylation reagents

including $MeBF_3K$,[81] in various solvent systems under basic conditions failed to furnish **15** in high yield and purity. Stille coupling with MeI and **19**[82] as well as the use of MeZnI[83] in Negishi coupling still led to mixtures with poor yields of desire **15**. Reactions were monitored by TLC and HPLC against known markers of **16** and dimer **17** (Scheme 44).



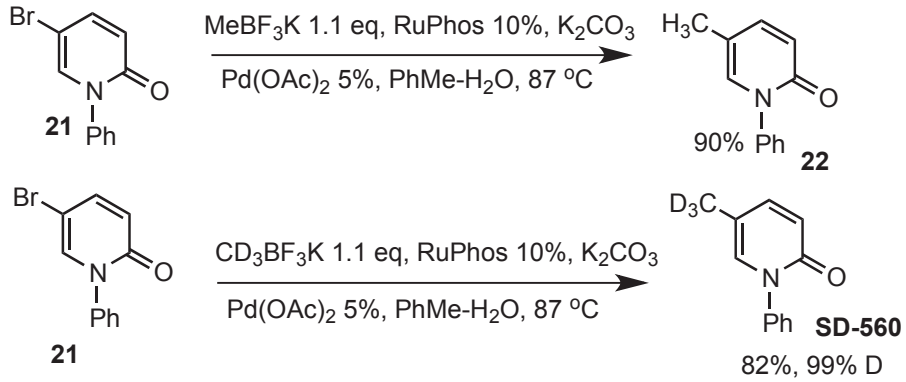
Scheme 44

All conditions of Scheme 43 gave mixtures of the H product, **16**, and the dimer **17**. However, Hassner, Falb *at el*.[5] described a successful Suzuki–Miyaura cross-coupling of **13** to **15** with either potassium methyltrifluoroborate or its deuteron analog CD_3BF_3K, or with methylboronic acid or $CD_3B(OH)_2$ under 5 mol% $Pd(OAc)_2$ catalysis with 5-10% of 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos)[84] as an essential ligand. The methylation of **13** to **15** proceeded in 90% yield for Me and in 82% yield for formation of the CD_3 analog **20** at 99% isotopic purity in toluene/water mixture with K_2CO_3 at 87 ºC, with less than 1% of **16** or **17** side products detected by HPLC (Scheme 45).



Scheme 45

Moreover these conditions led to efficient methylation and deutereomethylation of the N-phenyl-5-bromopyridone[5] (Scheme 46). Thus pirfenidone **22** was obtained pure (90%) from **21** and SD-560 resulted in high yield and 99% isotopic purity under the same conditions using CD_3BF_3K.

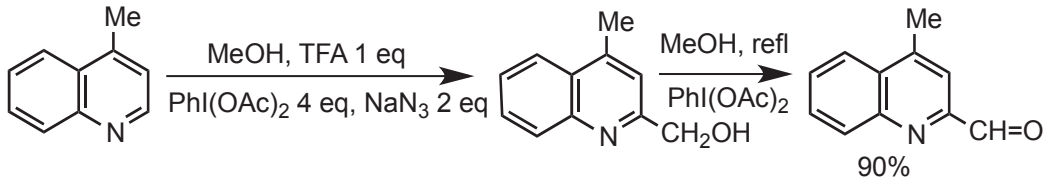


Scheme 46

2.5 METHYLATION USING METHANOL OR OTHER ALCOHOLS AS A Me RADICAL SOURCE, INCLUDING LIGHT ACTIVATED REDOX REACTIONS WITH MeOH

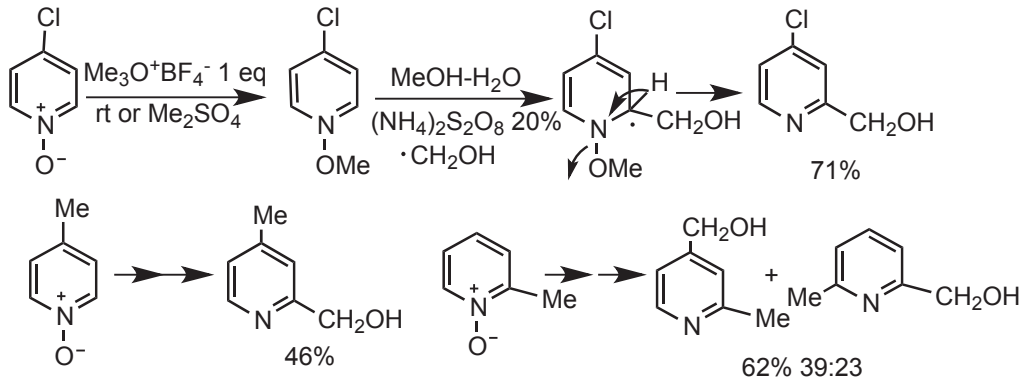
Recently, several research groups successfully used methanol as a green source of either CH_2OH or Me radicals for introduction of such groups into heteroarenes, often activated by light. Also, longer-chain alcohols were used as Me radical source, although this required higher temperature.

In 1993, Minisci *et al.* showed that MeOH can serve as a source of CH_2OH radicals that react with 4-methylquinoline to form the 2-hydroxymethyl or the 2-formyl derivative in high yield[85] (Scheme 47).



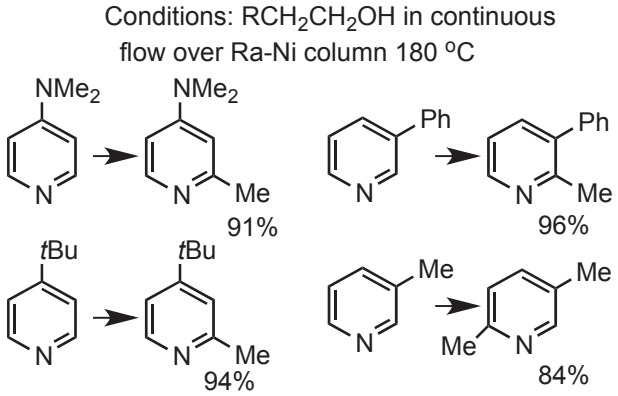
Scheme 47

2-Hydroxymethylpyridines were prepared,[86] in good yield starting with N-methoxypyridinium salts, MeOH and ammonium persulfate. It was shown that the advantage of using N-methoxypyridinium salts over pyridine N-oxides in reactions with hydroxymethyl radicals is the facile elimination of MeOH from 2-hydroxymethyl-1,2-dihydro-N-methoxydihydropyridinium intermediates, leading ultimately to much improved yields of 2-hydroxymethylpyridines. The N-methoxypyridinium substrates were obtained by treating pyridine N-oxides with $Me_3O^+ BF_4^-$ or Me_2SO_4 (Scheme 48).



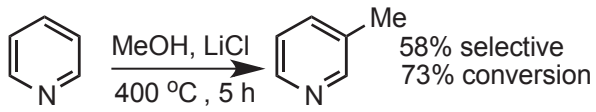
Scheme 48

Even longer-chain alcohols like propanol or decanol at high temperature were shown to be a source of Me radicals. An example is the high yield methylation of pyridine at C-2, as well as of alkyl, phenyl and dimethylamino substituted pyridines, in a flow system at over 180 °C through a packed column with Ra-Ni in the presence of 1-propanol.[87] The reaction presumably proceeds by high temperature decomposition of 1-propanol, or also of 1-decanol, on the surface of the nickel catalyst, involving either Me radicals or intermediate N-methylpyridinium species (Scheme 49).



Scheme 49

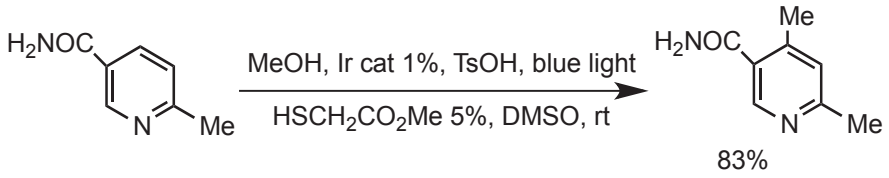
While in most cases pyridines are methylated preferentially at C-2, a recent patent claimed formation of 3-methylpyridine with 58% selectivity and 73% conversion by exposure of pyridine to supercritical MeOH in the presence of LiCl at 400 °C for 5 h.[88] (Scheme 50).



Scheme 50

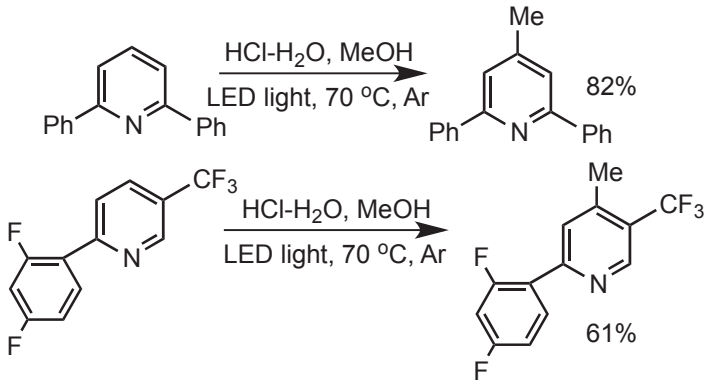
Recent studies reported the use of MeOH in photoredox reactions leading to C-methylation of pyridines and quinolines. These reactions were shown to involve formation of CH_2OH radicals and required either the presence of a transition metal catalyst or of an acid, the latter reminiscent of the presence of an acid in the Minisci methylation by Me radicals (shown in pathway **2.2**).

MacMillan *et al.* showed[89] the effectiveness of MeOH in a photoredox methylation of several pyridines and quinolones in high yield catalyzed by Ir and thiol catalysts at rt. For instance 3-carbomethoxy- or 3-carbamido-6-methylpyridine afforded the 4-methylated products in 82% yield and 2-methyl-5-hydroxypyridine was converted to its 2, 4-dimethyl derivative (91%) (Scheme 51). On the other hand 2-phenyl or 4-phenylpyridine gave mixtures of mono and dimethylated products.



Scheme 51

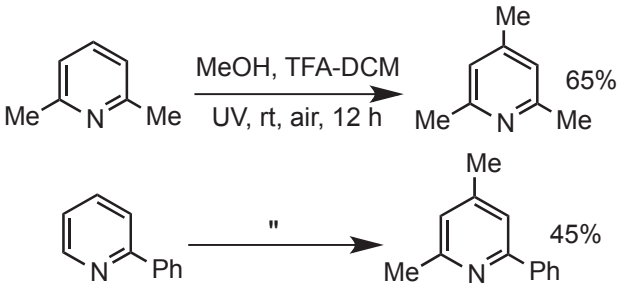
Barriault *et al.*[90] used MeOH effectively as a Me radical source in redox processes with UVA-LED light to introduce Me groups into several substituted pyridines and quinolines in good yield, which varied with reaction conditions. Due to the proximity of the light source to the reaction mixture, the temperatures reached 70 °C. Under these redox conditions, methylation occurred at C-4, among other positions; for 2-phenylpyridine and 2,6-diphenylpyridine, the yields were 61% and 82%, respectively (Scheme 52).



Scheme 52

In an extensive study Li *et al.*[91] demonstrated. that MeOH can be employed in a photo redox reaction even in the absence of metal catalysts and at rt for C-methylation of heteroarenes, including several

pyridines and quinolines. The reactions proceeded in good yield in methanol solvent in the presence of TFA and dichloromethane (DCM). The presence of DCM was found to be essential in radical formation, and apparently involves hemolytic C-Cl bond cleavage. Instead of DCM, $CHCl_3$ or acetone were also effective. Formation of CH_2OH radicals were proposed as well as possible mechanistic pathways. A Me group was introduced at C-4 of 2,6-dimethylpyridine in 65% yield, while 2-phenyl- as well as 4-phenylpyridine produced dimethyl derivatives in ca. 45% yield. Methylation of quinolines proceeds in higher yields, see below (Scheme 53).

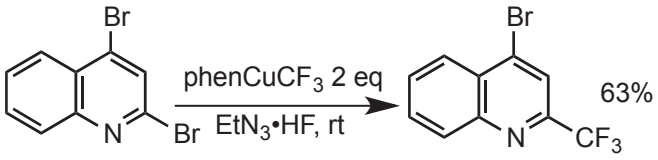


Scheme 53

3. C-METHYLATION OF QUINOLINES

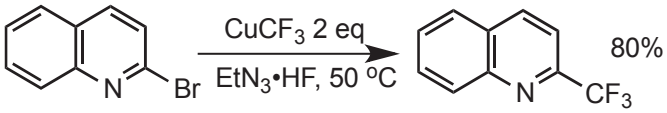
Most methylation pathways of pyridines are likewise applicable to quinolines or isoquinolines and *vice versa*. Yet, while 2-methylquinoline N-oxide was obtained by nucleophilic methyl transfer from sulfoxonium ylide, $NaCH_2(S{=}O)$-Me, to quinoline N-oxide,[92] pyridine N-oxide remained inert under these conditions. Methylation of pyridines usually occurs at C-2 or C-4, with a preference for the C-2 position, while in quinolines introduction of a Me group can also take place at C-8, the peri position near the nitrogen, in addition to the usual methylation at C-2 and C-4.

For 4-trifluoromethylpyridine, reduction of the CF_3 group to Me was recently shown to take place in 96% yield at 80 °C within 2 h in the presence of NaO*t*Bu and 2-propanol, mediated by a triazolyl-liganded Ru-Pd bimetallic catalyst;[7] hence, trifluoromethylation becomes a viable method for methylation of pyridines or quinolines. Similar to trifluoromethylation of bromopyridines, by Br to CF_3 exchange, employing phen-$CuCF_3$, some bromoquinolines underwent analogous reactions. For instance, 2,4-dibromoquinoline gave selectively 4-Br-2-trifluoromethylquinoline in 65% yield, together with a small amount of the 2,4-bis-trifluoromethylquinoline[21] (Scheme 54).



Scheme 54

In a similar manner, $CuCF_3$-mediated Br to CF_3 exchange converted 2-bromoquinoline into the 2-CF_3 derivative in 80% yield[20] (scheme 55).

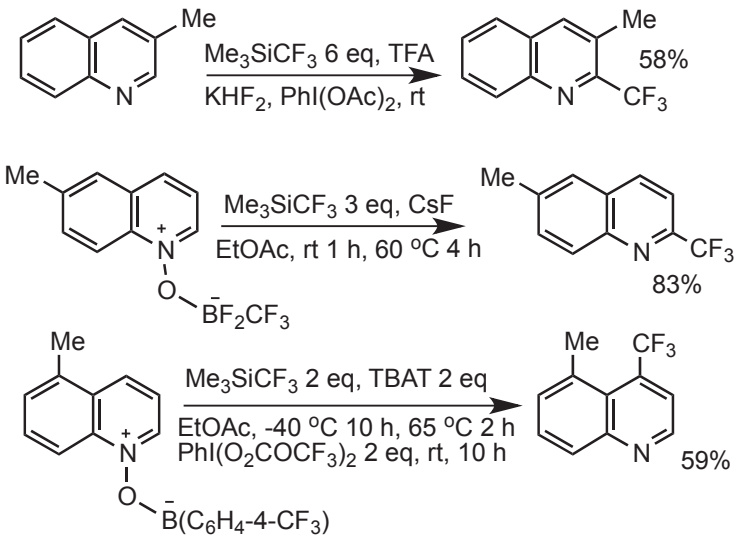


Scheme 55

Kuninobu, Kanai *et al.* recently employed trimethylsilyltrifluoromethane (Me_3SiCF_3) to introduce a CF_3 group regioselectively into quinolines. Thus 3-methylquinoline in the presence of 6 eq. of Me_3SiCF_3, TFA and KHF_2 (3 eq. each) and a trimethylene urea as a Lewis base in dioxane at rt with $PhI(OAc)_2$ as an oxidant provided in 58% yield the 2-CF_3 derivative[93] (Scheme 56). Under these conditions over twenty 6-substituted quinolines were directly converted to their 2-CF_3 derivatives in 32–60% yield with formyl, OAc, acetylene, olefin substituents unaffected by the oxidizing agent. Phenanthroline and quinine likewise led to their 2-trifluorinated compounds albeit in low yield.

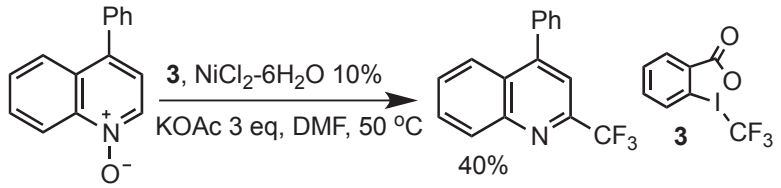
The same authors also showed that higher yields of 2-CF_3 substituted quinolines could be achieved by treating the stronger electrophiles, quinoline N-oxide-O-BF_2CF_3 complexes, obtained from quinoline N-oxides with CF_3BF_3K and BF_3•OEt_2, with Me_3SiCF_3 and CsF (3 equiv. each) for 1 h at rt and 4 h at 60 °C, without requiring an oxidizing agent (Scheme 56). Thus, 6-methoxyquinoline afforded the 2-CF_3 derivative in 93% yield, while 2-trifluoromethylated quinine was formed in 75% yield.[20]

Furthermore, these authors were able to introduce selectively CF_3 groups also at the 4-position of 3-substituted quinolines *via* quinoline N-oxides by attaching to O a much bulkier B group, namely $B(C_6F_4\text{-}4\text{-}CF_3)_3$.[21] For instance several 3-, 5-, 6-, or 7-substituted quinoline N-oxides were converted to their 4-CF_3 derivatives by means of Me_3SiCF_3 and tetrabutylammonium difluorotriphenylsilicate (TBAT) (2 eq. each) at -40 °C for 10 h, but also requiring $PhI(O_2CCF_3)_2$ (2 eq.) at rt for 10 h to oxidize the intermediate 1,4-dihydroquinolines (Scheme 56).



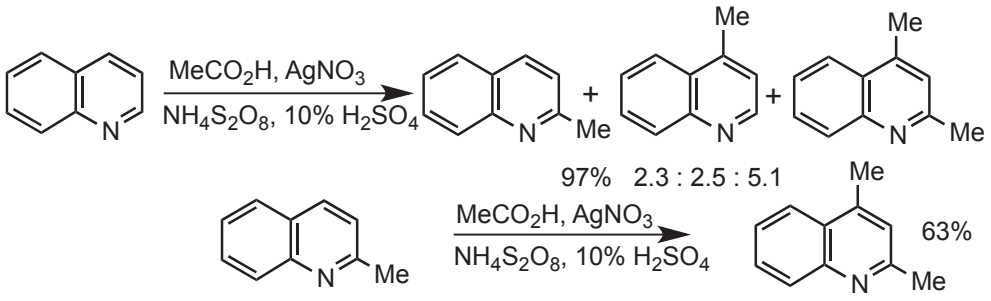
Scheme 56

Introduction of a CF_3 group into quinolone N-oxides was achieved with concurrent deoxygenation, mediated by periodide reagent **3**.[19] 4-Methyl-, 4-phenyl-, and 4-methoxyquinoline N-oxide were converted into respective 2-trifluoromethyl-4-substituted quinolines in 35–44% yield, and hydroquinine provided 2-trifluoromethylquinine in 54% yield (Scheme 57).



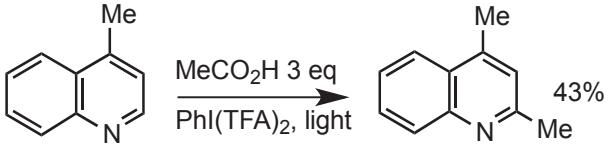
Scheme 57

Minisci and coworkers[41] prepared a few methylated quinolines *via* methyl radicals formed from $MeCO_2H$, Ag ions and $(NH_4)_2S_2O_8$. Quinoline itself led to a mixture of 2-Me-, 4-Me- and 2,4-dimethylquinoline in a ratio of 2.3:2.5:5.1 in 97% yield, while 2-methylquinoline afforded 2,4-dimethylquinoline in 63% yield. Acridine, a benzoquinoline, was methylated solely at C-9, albeit in only 11% yield (Scheme 58).



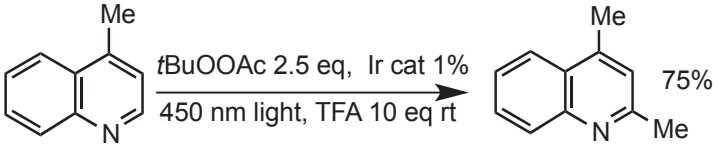
Scheme 58

A recent report described the application of $MeCO_2H$ and $PhI(TFA)_2$ in a light induced reaction to introduce Me at C-2 of 4-methylquinoline in 43% yield[94] (Scheme 59).



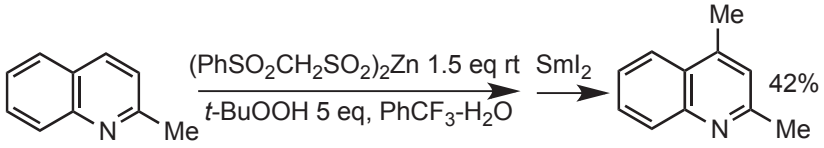
Scheme 59

*t*Butyl peroxides are a good source of methyl radicals and were used to introduce Me groups into heteroarenes. DiRocco *et al.*[95] methylated 4-methylquinoline by photochemical decomposition at 450 nm of *t*butyl peracetate (2.5 eq.) in the presence of 1% of an Ir(III) catalyst and TFA at room temperature. The best yield, of 75% for 2,4-dimethylquinoline, was obtained using HOAc, HOAC-water or dichloroethane (DCE) as a solvent. It was suggested that Me radicals resulted from decomposition of *t*BuO radical formed by redox reaction of the Ir catalyst with protonated *t*butyl peracetate. In this manner, the antitumor agent camptothecin was methylated at C-4 of the quinoline segment in 77% yield (Scheme 60).



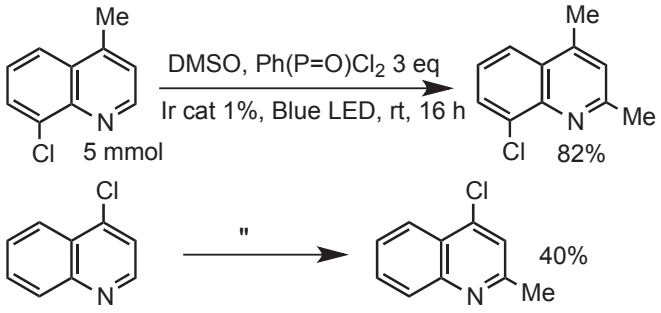
Scheme 60

To facilitate separation of a methylated heteroarene from starting material, Baran introduced the higher molecular weight $PhSO_2$-CH_2 group, which was then reduced to a Me with SmI_2. Zinc bisphenylsulfonylmethyl sulfinate ($Zn(PhSO_2CH_2$-$SO_2)_2$), in the presence of *t*-BuOOH, served as the $PhSO_2$-CH_2 reagent and was employed to introduce a 4-methyl substituent into 2-methylquinoline in modest yield[48] (Scheme 61).



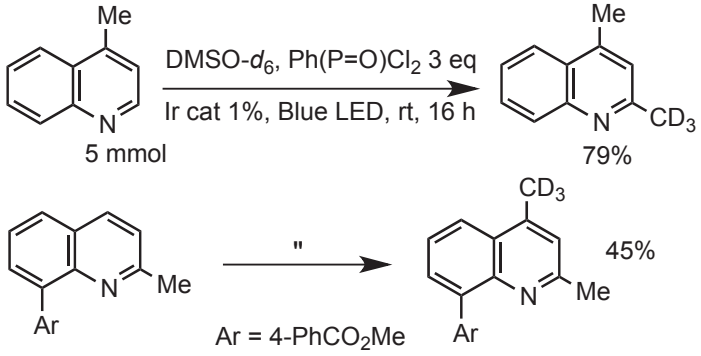
Scheme 61

Several substituted quinolines (and isoquinolines) were methylated at C-2 in high yield by means of DMSO, which was activated by phenylphosphoryl dichloride ($Ph(P=O)Cl_2$) and an Ir catalyst, as well as with blue LED light at room temperature. It was suggested that the reaction involves chlorodimethyl-sulfonium ions formed by interaction of DMSO with $Ph(P=O)Cl_2$ and subsequent SET, leading to Me radicals, which attack the 2-position of a quinolinium species in a manner reminiscent of Minisci methylation with DMSO. While quinoline itself was doubly methylated to 2,4-dimethylquinoline in 64% yield, 8-chloro-4-methylquinoline provided 8-chloro-2,4-dimethylquinoline in 82% yield, 4-chloroquinoline led to 4-chloro-2-methylquinoline in 40% yield, and 4-(4'-trifluoro)phenylquinoline gave the 2-methyl derivative in 85% yield[96] (Scheme 62).



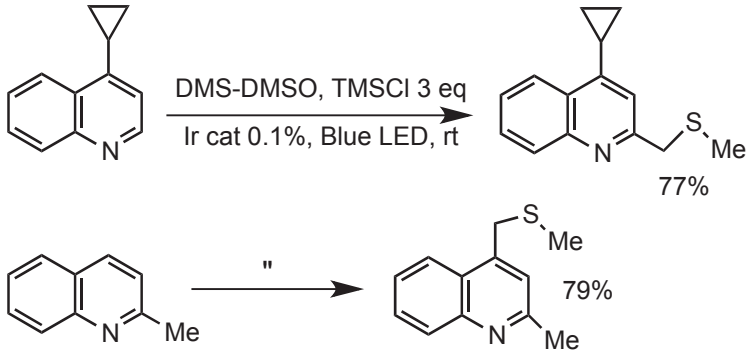
Scheme 62

Employing deuterated DMSO, a CD_3 group was introduced at C-2 of 4-methylquinoline (79% yield) or at C-4 of 2-methyl-8-(4'-carbethoxy)phenylquinoline (45% yield), as well as at C-2 of a quinoline featuring an 8-glucose derived carbamate (29% yield) (Scheme 63).



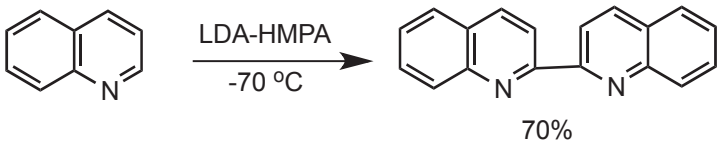
Scheme 63

Interestingly, the same authors found that simply switching from $Ph(P{=}O)Cl_2$ to trimethylsilyl chloride (TMSCl) and adding dimethyl sulfide (DMS) to the above-described system, still in the presence of the Ir catalyst and blue LED light at room temperature, it was possible *via* Pummerer rearrangement to introduce methylthiomethyl ($Me\text{-}S\text{-}CH_2$) radicals instead of Me radicals at C-2 or C-4 of several quinolines. Some examples are shown below. The $Me\text{-}S\text{-}CH_2$ substituent can of course be reduced to a Me group or oxidized to a sulfoxide or sulfone[96] (Scheme 64).



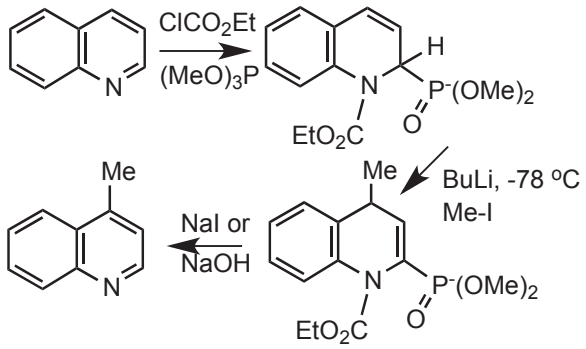
Scheme 64

Exposure of quinoline to LDA in the presence of HMPA produced 2,2'-biquinoline by SET[53] (Scheme 65).



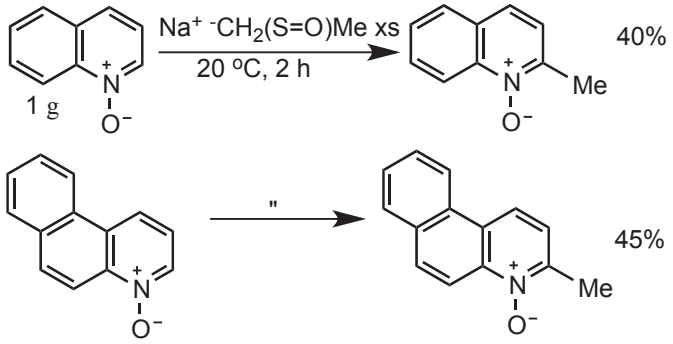
Scheme 65

In most cases methylation of quinolines takes place preferentially at C-2 or at both C-2 and C-4. Akiba *et al.*[29] obtained solely 4-methylquinoline, starting with quinoline, by a series of reactions in which the 2-position was first substituted by a phosphonate. Thus, formation of N-carbethoxyquinolinium chloride was followed by attack of trimethyl phosphite at C-2. The resulting phosphonate, upon treatment with BuLi at -78 °C and trapping of the conjugated carbanion with MeI at C-4, was converted to 4-methylquinoline in high yield. Treatment of the latter with NaI or NaOH produced 4-methylquinoline in modest yield. (Scheme 66).



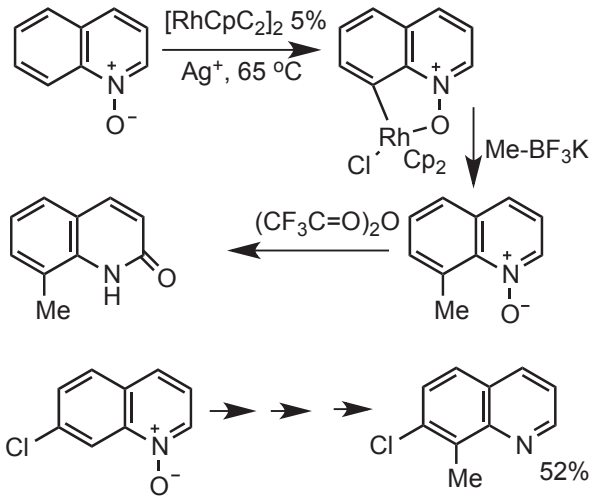
Scheme 66

As expected, quinolone N-oxides are better electrophiles than quinolines. In most cases quinoline N-oxides are methylated at C-2. Their exclusive methylation at C-2, using sulfoxonium ylide, prepared from NaH and DMSO at 70 °C, was reported, even though the charge density at C-2 is not the largest[92] (Scheme 67).



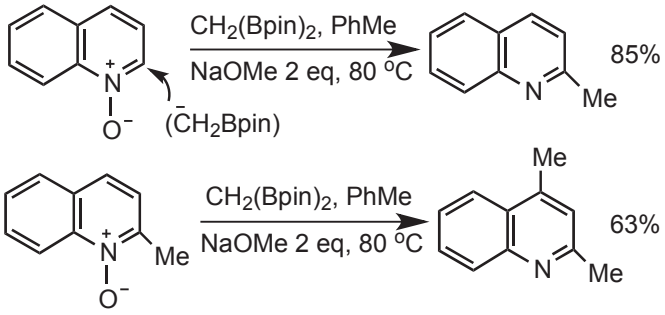
Scheme 67

On the other hand, various quinoline N-oxides underwent methylation exclusively at C-8 in high yield, mediated by $[RhCpCl_2]_2$ (5%) and Ag salts at 65 °C in dimethoxyethane (DME),[97] using $MeBF_3K$ as methyl source. Even 7-methylquinoline N-oxide yielded 52% of 7,8-dimethylquinoline N-oxide, rather than the 2-Me analog. The reaction involves coordination of Rh with the O of the N-oxide and insertion of Rh at C-8. After transmetalation with Me-BF_3K, the intermediate collapses to the 8-Me product and a Rh(I) species. The latter gets re-oxidized to Rh(III) by Ag^+. Rearrangement of 8-methylquinoline N-oxide with TFAA provided 8-methyl-2-quinolinone, while treatment with $POCl_3$ furnished 8-methyl-2-choroquinoline (Scheme 68).



Scheme 68

Methylation of several quinolone N-oxides with concurrent deoxygenation was carried out by means of bis(pinacolato)borylmethane (CH_2(B-pin)$_2$) as methyl source.[37] The reaction proceeded at 80 °C in the presence of base but in the absence of transition metals, and apparently involves an attack of a methoxide ion on boron of CH_2(B-pin)$_2$, followed by formation of the anion of CH_2B-pin, which adds to C-2- of the N-oxide, ultimately followed by elimination of pinBO. Some examples are formation of 2-methylquinoline from quinoline N-oxide (85% yield), 2,4-dimethylquinoline from 2-methylquinoline N-oxide (63% yield) and 2-methyl-9-methoxyquinine from 9-methoxyquinine N-oxide (85% yield) (Scheme 69).

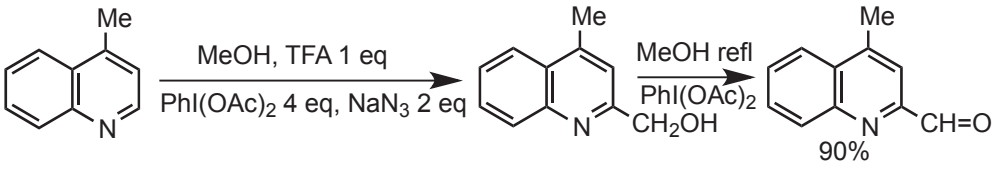


Scheme 69

1,4-Addition of a chlorodimethylsilylboronic ester to quinoline led to a 1,4-dihydroquinoline as the major product in 81% yield. Applying the deboronation-aromatization by means of benzaldehyde, as was employed for pyridines,[30] should lead to a 4-silylated quinoline that can be further employed in methylation.

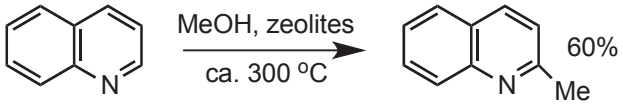
There are several reports in which methanol was used for introduction of Me or of CH_2OH groups into quinolines. Already in 1993, Minisci *et al.* showed[85] that MeOH can serve as a source of CH_2OH radicals

that react with 4-methylquinoline to form the 2-hydroxymethyl or 2-formyl derivative in high yield. In this case, the reaction of 4-methylquinoline in MeOH was refluxed in the presence of 1 eq. of TFA, 2 eq. of NaN_3 and 4 eq. of $PhI(OAc)_2$. Presumably, N_3 radicals were formed, which abstracted a hydrogen from MeOH to produce CH_2OH radicals that attacked the 2-position of quinolines (Scheme 70).



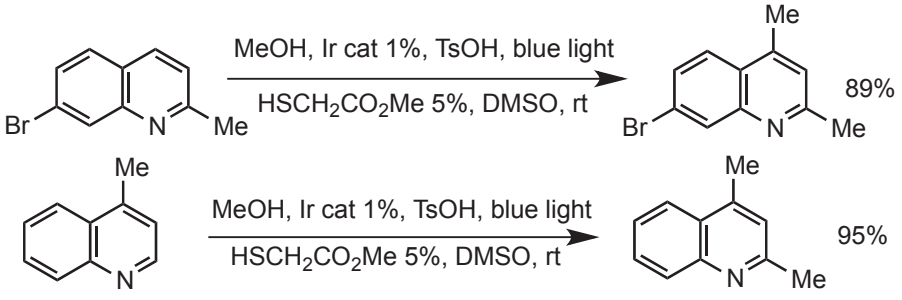
Scheme 70

According to a 1992 patent, methylation of quinoline at C-2 can be achieved in 50% yield by heating quinoline with MeOH at ca. 300 °C under pressure for 4 h with Raney-Co or Raney-Ni catalysts.[69] Similar results (60% yield) were reported by vapor phase methylation of quinoline with MeOH over lanthanide zeolites at 260–350 °C[98] (Scheme 71).



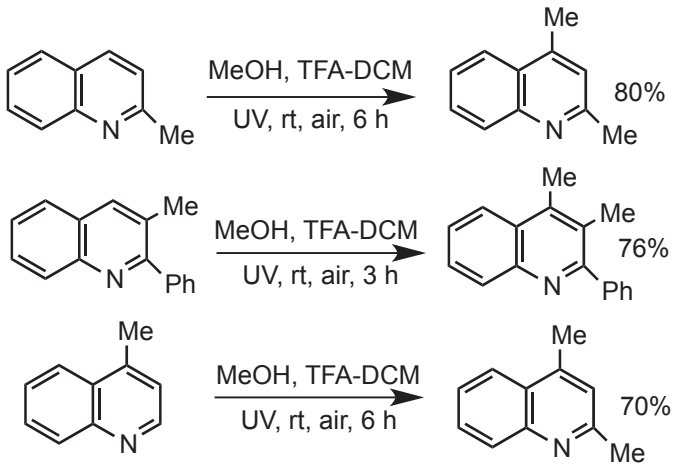
Scheme 71

High yield photoredox methylation of some quinolines catalyzed by an Ir catalyst and a thiol like methyl 2-mercaptoacetate was described by Jin and MacMillan[89] using MeOH as the Me source. While quinolone itself gave a mixture of 2-and 4-methylated products (43% and 22% yield respectively), 4-methylquinoline afforded the 2,4-dimethylpyridine in 95% yield and 6-bromo-2-methylquinoline led to the 4-methylated derivative in 89% yield (Scheme 72).



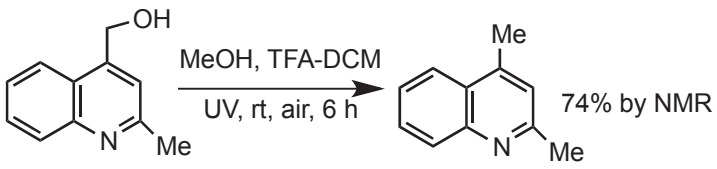
Scheme 72

As was the case with pyridines, Li *et al.*[91] described a photo-induced green methylation of quinolines that took place readily in MeOH in the presence of TFA-DCM at rt in air usually within 6 h. The yields were high and even water can be present. In this manner, 2-methyl- or 2-phenylquinoline, as well as several 2-arylquinolines were converted to their 4-methyl derivative in ca. 80% yield. 4-Methylquinoline furnished the 2-Me derivative (70%), while 4-deutereomethyl-2-methylquinoline, with some simultaneous D-incorporation at C-3 and at C-2-Me, resulted from 2-methylquinoline by using CD_3OD. CD_3OH led to 66% incorporation of a CD_2H group at C-4. only. Interestingly, it was possible to obtain 4-ethyl-2-phenylquinoline in 60% yield by the reaction of EtOH with 2-phenylquinoline. These authors also found that the beneficial effect of TFA may be due to the fact that it shifted the UV absorption of 2-methylquinoline from 270 nm to 300 nm and increased the absorption intensity as well (Scheme 73).



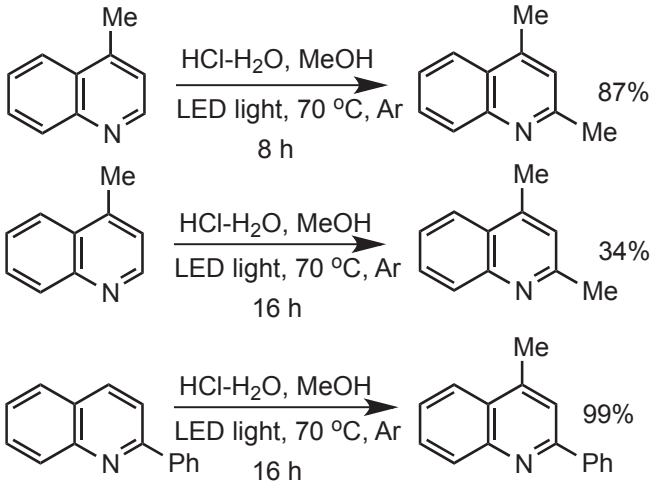
Scheme 73

Furthermore, they showed that 4-hydroxymethyl-2-methylquinoline was converted to 2,4-dimethylquinoline in 74% yield using MeOH, TFA under uv light in the presence of air at rt, opening a potential route for introduction of a Me group *via* hydroxymethylpyridines or quinolines (Scheme 74).



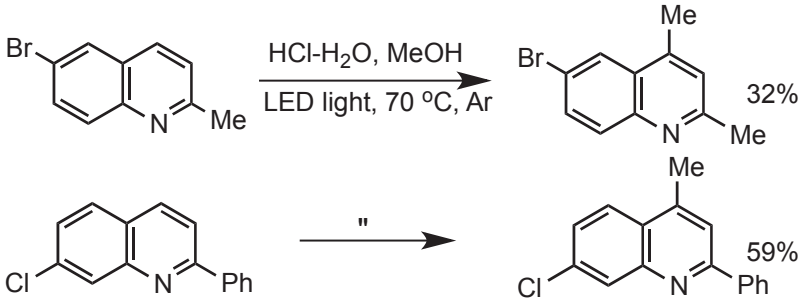
Scheme 74

Introduction of a methyl group at C-2 of 4-methylquinoline was achieved in 76–80% yield in the presence of 2M HCl in MeOH, or by means of a 1:1 mixture of MeOH:MeCN under UVA LED irradiation at 70 °C, with MeOH acting as a methyl source. Some examples are shown below[90] (Scheme 75).



Scheme 75

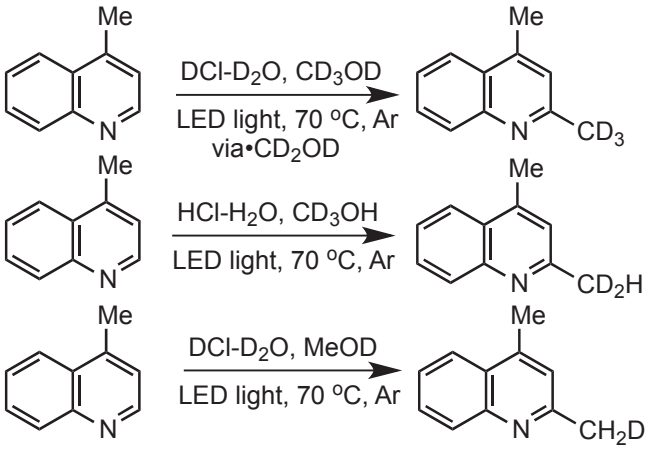
With methyl *t*butyl ether instead of MeOH as Me source, 2,4-dimethylquinoline was obtained from 4-methylquinoline in the presence of 2M HCl under UVA LED irradiation, albeit in only 34% yield. Although methylation of 2-methylquinoline by MeOH and LED was not successful, its 6-halogenated (F, Br, Cl) derivatives were converted to their 2,4-dimethylated products in modest yields. Likewise, 7-chloro-2-methylquinoline afforded the 4-methylated products in 59% yield (Scheme 76).



Scheme 76

The methylation apparently involves photo-induced formation of CH_2OH radicals. It was proposed that interaction of photoactivated quinolinium ions with MeOH led to CH_2OH radicals, which attack the quinolinium species at C-2 or C-4. The CH_2OH-substituted intermediates would lose water with formation of a 2-methylene derivate that on protonation yields the final product. Evidence of this was provided by using deuterated reagents. Thus, by means of CD_3OD and DCl in D_2O it was possible to introduce CD_3 at C-2 of 4-methylquinoline in 73% yield. When CD_3OH and HCl in H_2O were used, a CD_2H group was introduced at C-2, while using MeOD and DCl in D_2O afforded the 2-CDH_2 analog in 77% yield.[90] These extensive studies using deuterated reagents suggested that a CD_2OH radical is first

introduced at C-2, followed by elimination of water to a 2-methylene derivative, and then a H or D is derived from HCl in H_2O or from DCl in D_2O (Scheme 77).



Scheme 77

By employing *i*-PrOH instead of MeOH, these authors[90] also discovered that under UVA-LED conditions, quinolines can be reduced to 1,2,3,4-tetrahydroquinolines, presumably *via* ketyl radicals. This constitutes an approach to C-methylated 1,2,3,4-tetrahydroquinolines. By employing *i*PrOD and DCl in D_2O, they were able to prepare d_8-4-methyl-2,2,3,3,4,5,6,8-tetrahydroquinoline from 4-methylquinoline in 61% yield.

4. SUMMARY

There is a dearth of examples in the literature describing introduction of Me or CD_3 groups into pyridines and quinolines, compared to alkylation or arylation of these heterocycles, as well as in marked contrast to methylation of simple arenes, some examples suffer from lack of high yields, good regioselectivity, reproducibility and are not green. This review depicts examples from the earlier literature as well as newer green methods involving free radical species and redox reactions employing MeOH and recent Suzuki and Negishi couplings. In addition to reported routes, some potential routes for methylation of these heteroarenes are considered, including introduction of functional groups that can be converted readily to Me, such as CF_3 or boron derivatives.

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Prof. Alfred Hassner received his PhD. in chemistry with Prof. N.H. Cromwell at the University of Nebraska and was a postdoctoral fellow with Prof. L. F. Fieser at Harvard. He was professor of chemistry at the University of Colorado, Boulder, at State University of New York, Binghamton and at Bar Ilan University in Israel. He was visiting professor at several universities in Europe, the USA and at Kyushu Institute of Technology. Currently he is Emeritus professor at Bar Ilan University.
Prof. Hassner is the recipient of several honors like Lady Davis, von Humboldt, Fulbright, A. W. Killam and the Israel Chemical Society Prize for Excellence. His research has spanned over several areas of synthetic and stereochemistry, including dipolar cycloaddition of azides, oximes and nitrile oxides, small ring heterocycles, steroids and acylation catalysts. He first proposed the concept of regioselectivity and was editor of several monographs and author of "*Organic Syntheses Based on Name Reactions*".

Dr. Eliezer Falb received his PhD. in Medicinal and Synthetic Chemistry from Bar-Ilan University, Israel, under the direction of Prof. Abraham Nudelman and Prof. Alfred Hassner. Currently he is a director in Galmed Pharmaceuticals, Ltd. engaged with drug development for treatment of liver disease. Before joining "Galmed" he spent 18 years at Teva Pharmaceutical Industries Ltd. in several positions in its Innovative R&D. Dr. Falb started his industrial career as a Senior Chemist in an Israeli Bio-Tech/Start-Up where he was involved in the development of a new concept of Backbone Cyclic Peptides, as a tool for drug discovery.
In addition, Dr. Falb holds LL.B. from The Buchmann Faculty of Law, Tel-Aviv University and LL.M. in commercial law from The Radzyner Law School Interdisciplinary-Center Herzliya.