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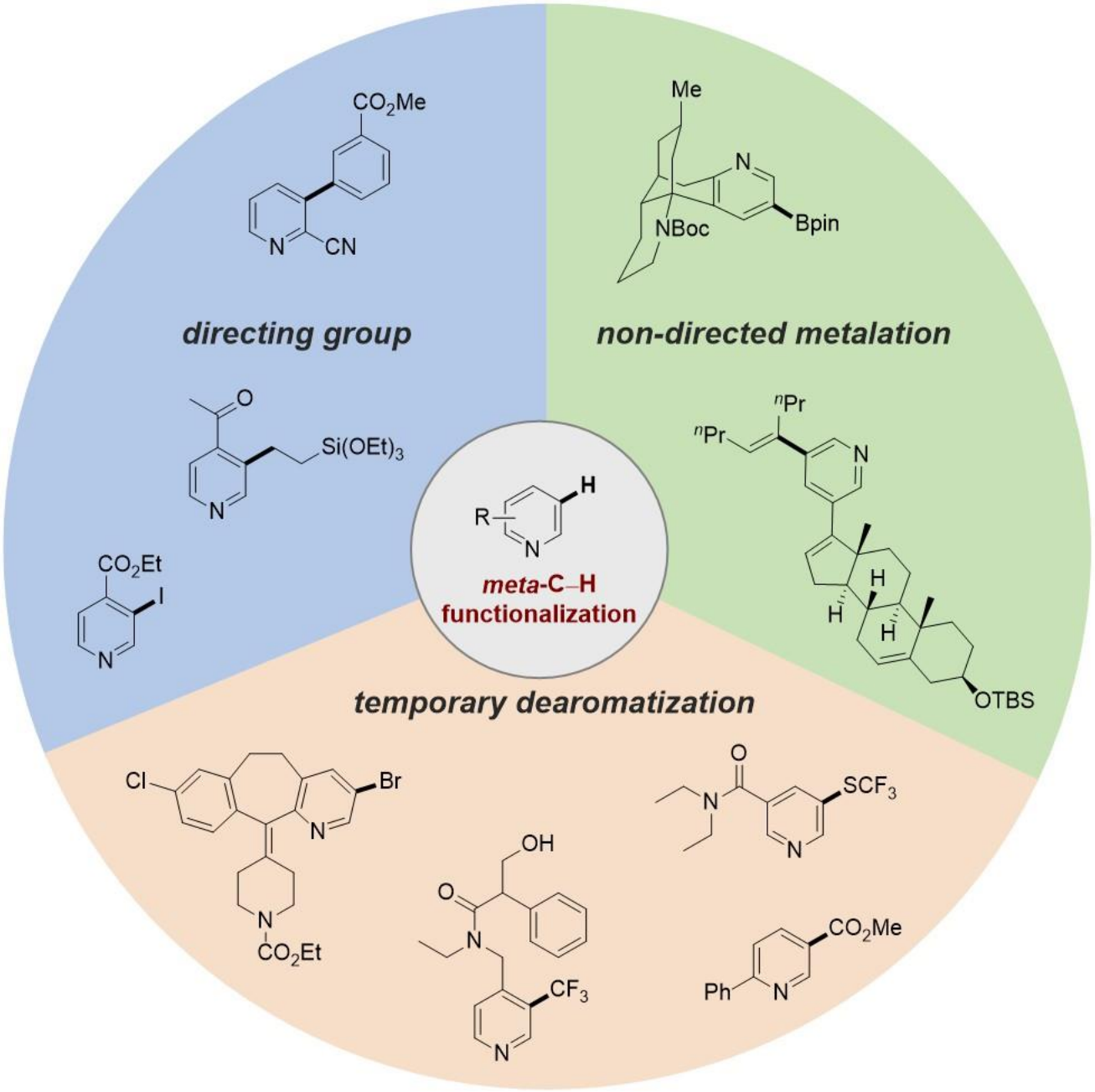
REVIEW

meta-Selective C−H Functionalization of Pyridines

Hui Cao, Qiang Cheng, and Armido Studer*



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REVIEW

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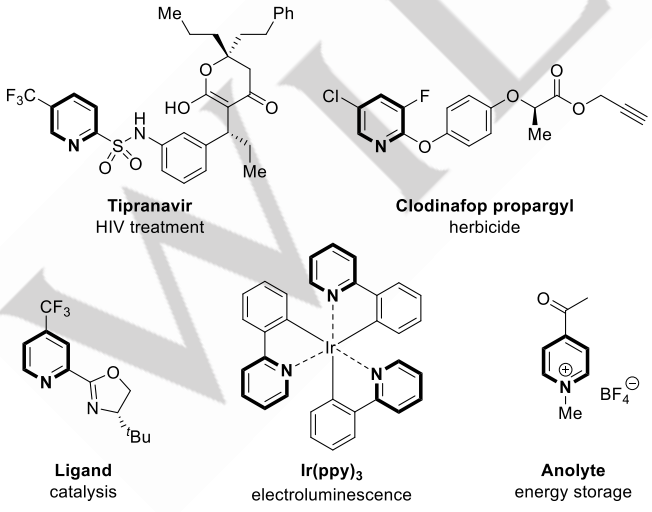
Abstract: The pyridine moiety is an important core structure for a variety of drugs, agrochemicals, catalysts, and functional materials. Direct functionalization of C–H bonds in pyridines is a straightforward approach to access valuable substituted pyridines. Compared to the direct *ortho*- and *para*-functionalization, *meta*-selective pyridine C–H functionalization is far more challenging due to the inherent electronic properties of the pyridine entity. This review summarizes currently available methods for pyridine *meta*-C–H functionalization using a directing group, non-directed metalation, and temporary dearomatization strategies. Recent advances in ligand control and temporary dearomatization are highlighted. We analyze the advantages as well as limitations of current techniques and hope to inspire further developments in this important area.

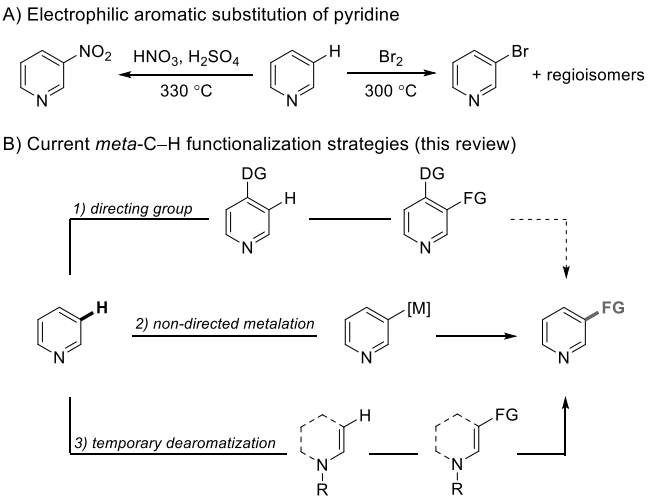
1. Introduction

Pyridine serves as a starting material for a wide variety of chemicals with useful applications in biological and materials sciences (Scheme 1).[1-4] Pyridine is the second most common nitrogen heterocycle in FDA approved pharmaceuticals, and it exists in 18% of the top-selling agrochemicals.[2] Pyridine also appears as a core structure in ligands and functional materials.[3,4] The adorning substituents on the pyridine ring contribute to the widespread application of pyridines by influencing their chemical, physical, and biological properties.[1,2] As a result, synthetic methods to access functionalized pyridines are of high importance for various fields.



Scheme 1. Pyridines appear as core structures in drugs, ligands, and materials.

Among the different methods for pyridine construction, the direct functionalization of "inert" C–H bonds in pyridines undoubtedly represents the most straightforward and step-economical approach, and, further, this strategy is advantageous for the late-stage functionalization of complex pyridine-containing compounds.[5] Pyridine is an electron-deficient heterocycle, due to the sp^2-hybridized nitrogen atom. Moreover, the nitrogen atom with a lone pair of electrons can be protonated or coordinated to a Lewis acid, rendering the heteroarene even more electron-deficient, in particular at the 2- and 4-positions. As a consequence, current protocols mainly address pyridine functionalization at the *ortho*- and *para*-positions, relying on its electronically biased reactivity.[6,7] Along these lines, established approaches include directed metalation,[8,9] Minisci-type radical reactions,[10] and nucleophilic addition to N-activated pyridines.[11,12] *meta*-Functionalization of pyridines, on the other hand, is far more challenging.[13] Electrophilic aromatic substitution (S_EAr) has been used for pyridine *meta*-halogenation and *meta*-nitration (Scheme 2A). However, the harsh reaction conditions required and low regioselectivity limit the application of these protocols.[14,15] Milder *meta*-selective functionalization reactions have been developed in recent decades by approaches involving preinstalled directing groups, non-directed metalation and temporary dearomatization (Scheme 2B). Some reported methods feature high *meta*-regioselectivity and efficiency, and accordingly have been used in drug development and natural product synthesis. This review summarizes current strategies for the *meta*-C–H functionalization of pyridines and highlights the recent advances in ligand control and temporary dearomatization. Advantages and limitations of different approaches are critically discussed. We note that some synthetic methods address the *meta*-C–H functionalization of quinolines and isoquinolines but could not be extended to pyridines.[16,17] These works are not covered in this review for the sake of brevity.



Scheme 2. Strategies for the *meta*-C–H functionalization of pyridines. DG = directing group. FG = functional group.

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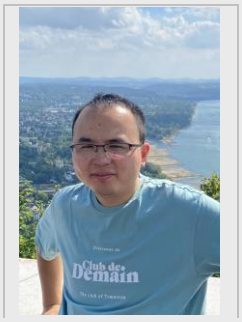
Biographical Sketch. **Hui Cao**

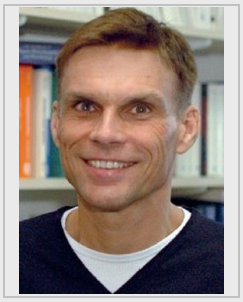
Hui Cao received his PhD in 2021 from National University of Singapore, working on photocatalyzed molecular modification, supervised by Prof. Jie Wu. He is now a postdoctoral researcher in the group of Prof. Armido Studer, pursuing the development of methodologies for pyridine functionalization.

Biographical Sketch. **Qiang Cheng**



Qiang Cheng received his PhD in 2018 from Shanghai Institute of Organic Chemistry, CAS under the direction of Prof. Shu-Li You. He then moved to Max-Planck-Institut für Kohlenforschung, working as a postdoctoral fellow with Prof. Tobias Ritter. In 2022, he joined the group of Prof. Armido Studer as a postdoctoral researcher, working on method development for pyridine functionalization. In 2023, he started his independent career at College of Chemistry and Molecular Sciences in Wuhan University.

Biographical Sketch. **Armido Studer**

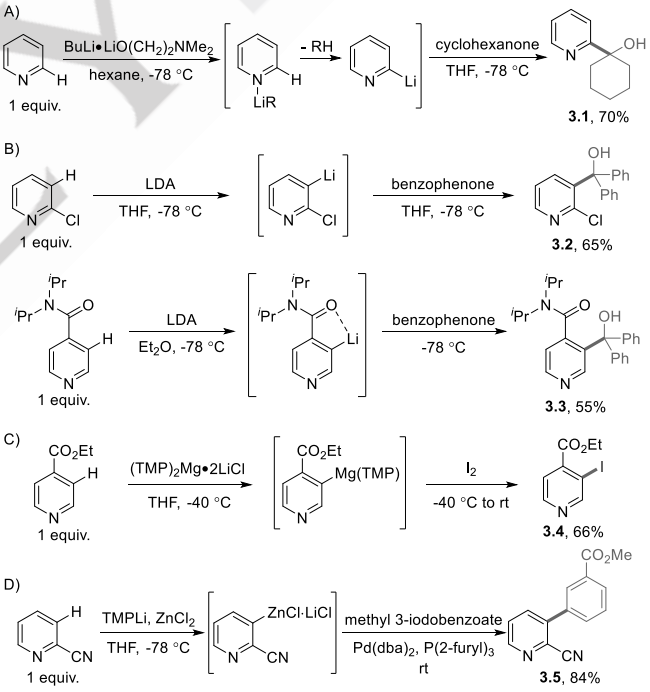


Armido Studer received his PhD in 1995 (ETH Zürich, Dieter Seebach). He continued as a Postdoc at the University of Pittsburgh (Dennis P. Curran). In 1996 he started his independent career at the ETH. In 2000, he was appointed as Associate Professor in Marburg and in 2004 as Full Professor in Münster. His current research interests focus on the development of new synthetic methods, living radical polymerizations, the preparation of functional polymers, and the development of methods for the chemical modification of surfaces.

2. *meta*-Functionalization Controlled by Directing Groups

The very low reactivity of pyridine in S_EAr reactions can be overcome by installation of a strong electron-donating group at the *ortho* position. For instance, the amino group can be easily introduced to the 2-position in pyridines by the Chichibabin amination.[18] This substituent changes the electronic property of the pyridine core, and "electronically directed" C5-selective bromination on such 2-amino pyridines was realized at room temperature with *N*-bromosuccinimide (NBS)[19] or a bromide salt under oxidative electrochemical conditions[20]. If required, the 2-amino group can be removed later by conversion to a diazonium salt, followed by reduction. An alternative method for hydrodeamination was developed by Katritzky using pyrilium salts.[21]

Like other aryl-metal reagents, pyridyl metal complexes engage in substitution or addition reactions with a variety of electrophiles to provide functionalized pyridines.[22] Strong bases such as *n*-butyl lithium (*n*BuLi) and lithium diisopropylamide (LDA) are generally used for the deprotonation of pyridine C–H bonds to generate the corresponding metalated pyridines. Lithiation of the parent pyridine selectively occurs at the *ortho*-position (**3.1**, Scheme 3A).[23] At first glance this regioselectivity is surprising because theoretical calculations revealed the *ortho* C–H proton of pyridine to be less acidic than the *meta* and *para* protons.[24] In these cases, *ortho*-selectivity results from the precomplexation of lithium base with pyridine, thereby increasing the *ortho*-C–H acidity and directing the metalation. To achieve selective *meta*-metalation, a directing group, such as methoxy, halogen or an aminocarbonyl group preinstalled at the *ortho* or *para* position of pyridine, is required (Scheme 3B-3D).[25,26] Exclusive *meta*-selectivity has been achieved using this directed metalation strategy (**3.2**-**3.5**). Knochel and co-workers have developed a milder base, $(TMP)_2Mg{\cdot}2LiCl$ (TMP = 2,2',6,6'-tetramethylpiperidyl), for pyridine metalation which allows the deprotonation to occur in the presence of ester, nitrile, or ketone functionalities (Scheme 3C).[27] In 2014, the Knochel group also showed that the unstable lithiated pyridines can be transmetalated *in situ* with $ZnCl_2$ to give the corresponding pyridylzinc reagents (Scheme 3D).[28] The pyridylzinc reagents have good thermal stability and can react with various electrophiles or engage in Negishi cross coupling reactions (**3.5**).



Scheme 3. Directed metalation of pyridine through deprotonation. TMP = 2,2',6,6'-tetramethylpiperidyl. dba = dibenzylideneacetone.

The directing-group-mediated metalation and functionalization of pyridine would ideally be performed with a catalytic amount of a metal reagent. Along this line, Grigg and Savic reported the ruthenium-catalyzed *meta*-alkylation of 4-acetylpyridine with various alkenes (Scheme 4A).[29] Yu and co-workers disclosed the palladium-catalyzed *meta*-arylation of 4-aminocarbonylpyridines with aryl bromides (Scheme 4B),[30] and Shi et. al. developed the

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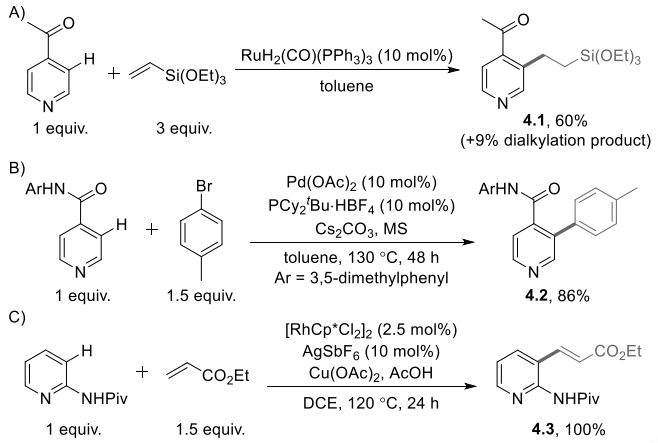
rhodium-catalyzed oxidative C3-olefination of *N*-(pyridin-2-yl)pivalamide with alkenes (Scheme 4C).[31] The acetyl, aminocarbonyl, and amidyl groups served as directing groups in these transformations. Such a strategy was also employed for the directed alkynylation, trifluoromethylation, amination, nitration, hydroxylation, etherification, and fluorination of pyridine *meta*-C–H bonds, and the scopes and mechanisms of these processes were reviewed by Larionov and co-workers.[13]



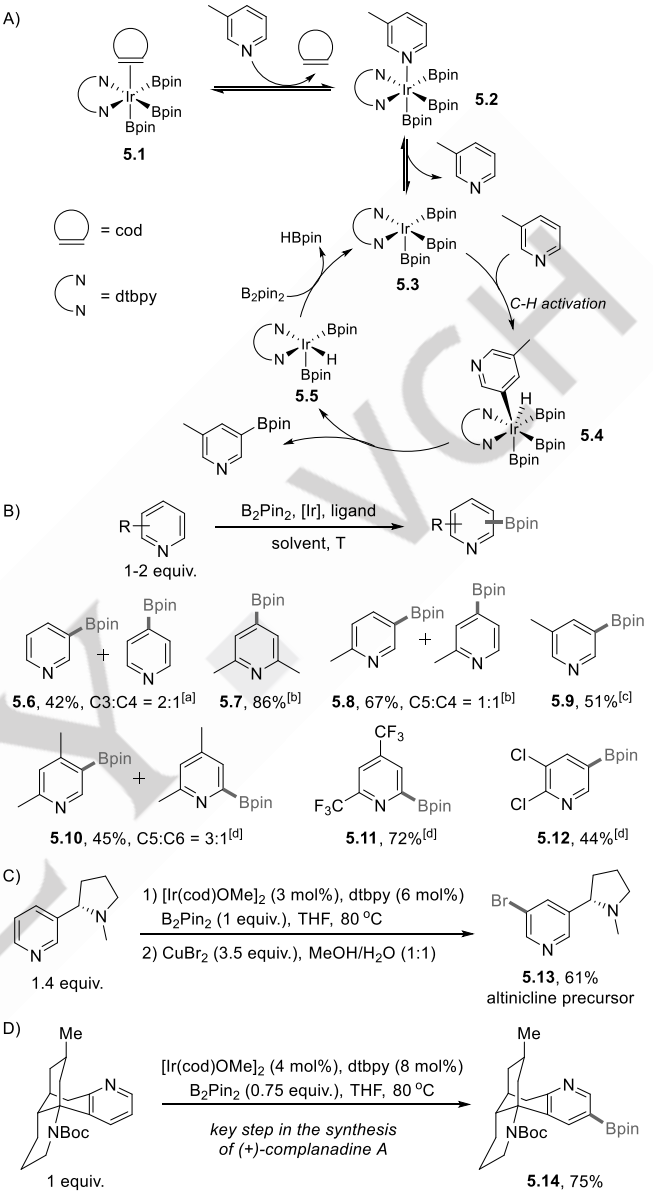
Scheme 4. Directed functionalization of pyridine through transition metal catalysis. MS = molecular sieve.

3. *meta*-Functionalization by Non-directed Metalation

Directed *meta*-functionalization of pyridine takes advantage of existing functional groups and offers expedient access to densely functionalized pyridines. However, the requirement of a preinstalled directing group severely limits the generality of these methods. The installation and removal of a directing group are often cumbersome, costly, and lowers the atom-efficiency. In the past decades addressing these critical points, non-directed strategies have been developed using transition-metal catalysis and ligand control. Herein, we categorize these methods by the different catalyst classes employed.

3.1. Iridium-catalyzed functionalizations

Pyridyl boronates are versatile building blocks that can be readily converted to a wide range of functionalized pyridines. Since Hartwig, Ishiyama, and Miyaura's pioneering study in 2002,[32] Ir-catalyzed C–H borylation of pyridine has become a valuable tool to access pyridinyl boronates.[33-35] A typical catalytic system consists of an Ir-based catalyst ($[Ir(cod)X]_2$ (cod = 1,5-cyclooctadiene, X = Cl or OMe) and the dtbpy (4,4'-di-*tert*-butyl-2,2'-dipyridyl) ligand with bis(pinacolato)diboron as the borylating reagent. In a proposed catalytic cycle (Scheme 5A),[34] the resting state of the Ir-catalyst contains pyridine substrate (**5.2**). Dissociation of the pyridine substrate furnishes the active bipyridine-coordinated Ir(III) trisboryl complex **5.3**, which undergoes rate-limiting oxidative addition with the *meta* C−H bond to form the Ir(V) complex **5.4**. Subsequent C−B reductive elimination gives the targeted pyridinyl boronate and the Ir(III) hydride **5.5**. Catalyst **5.3** can be regenerated through hydride-boryl metathesis from **5.5**.



Scheme 5. Ir-catalyzed C–H borylation of pyridines. [a]B_2pin_2, $[Ir(cod)Cl]_2$ (1.5 mol%), dtbpy (3 mol%), octane, 100 °C. [b]B_2pin_2, $[Ir(cod)OMe]_2$ (2.5 mol%), dtbpy (5 mol%), hexanes, rt. [c]B_2pin_2, $[Ir(cod)OMe]_2$ (3 mol%), dtbpy (6 mol%), THF, 80 °C. Isolated yield after ipso bromination with $CuBr_2$. [d]B_2pin_2, $[Ir(cod)OMe]_2$ (1.5 mol%), dtbpy (3 mol%), mtbe, rt or 80 °C. cod = 1,5-cyclooctadiene. dtbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl. mtbe = methyl *tert*-butyl ether.

The regioselectivity in Ir-catalyzed borylation is determined by an interplay of steric, electronic, and ligand effects.[33-35] The reaction of the parent pyridine gave two borylated products with 67% *meta*-selectivity (**5.6**, Scheme 5B).[32] The *ortho*-borylated product was not detected, due to slow C–H activation and product instability.[34] Selectivity in the borylation of differently methyl-substituted pyridines is controlled by steric and electronic effects (**5.7**-**5.10**).[33-36] Thus, 2,4-dimethylpyridine underwent borylation predominantly at the *meta*-position (**5.10**). However, the more

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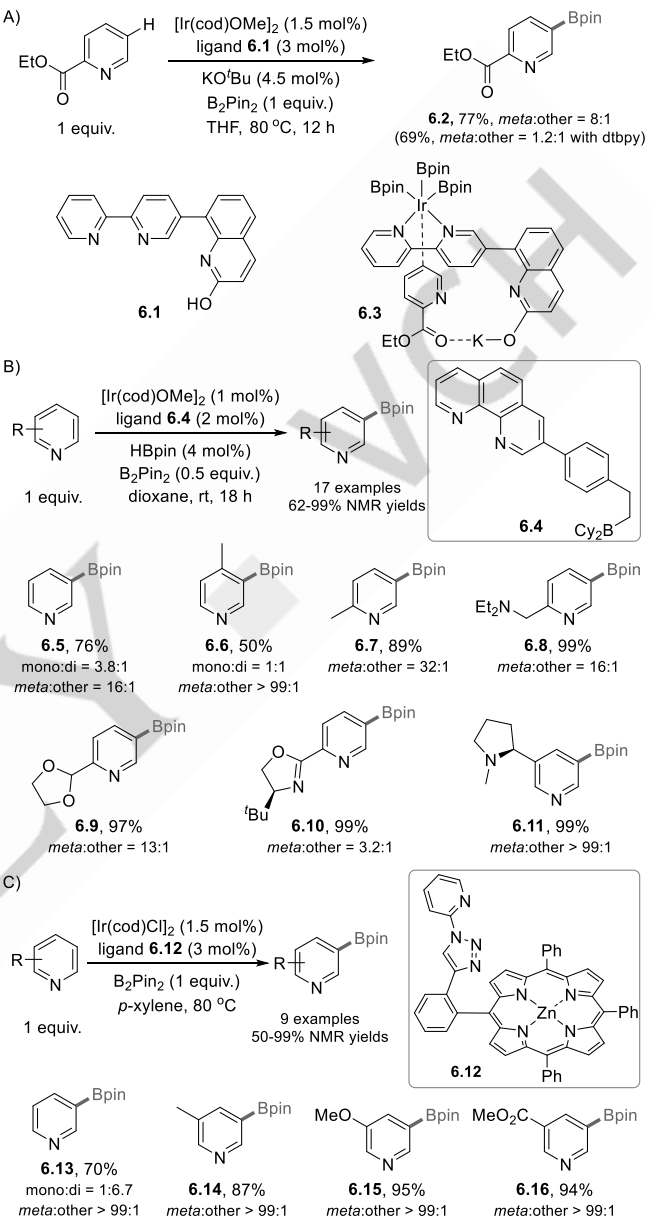
electron-deficient 2,4-bis(trifluoromethyl)pyridine underwent *ortho*-selective borylation (**5.11**).[33] For 3-substituted and 2,3-disubstituted pyridines, iridium-catalyzed borylation occurs with excellent *meta*-selectivity (e.g., **5.9** and **5.12**). This valuable reaction has meanwhile found applications in drug development and natural product synthesis. For example, Hartwig and co-workers applied the Ir-catalyzed *meta*-C–H borylation to the synthesis of *meta*-bromonicotine (**5.13**, Scheme 5C),[36] which served as a precursor to altinicline, an investigational drug for the treatment of Parkinson's disease. Moreover, the Ir-catalyzed *meta*-C–H borylation of pyridine was employed by Sarpong and co-workers as a key step for the total synthesis of (+)-complanadine A (**5.14**, Scheme 5D).[37]

In an effort to realize *meta*-selective C–H borylation of less sterically biased pyridines, Chattopadhyay and co-workers reported in 2017 an Ir-catalyzed *meta*-C–H borylation of ethyl 2-picolinate (Scheme 6A).[38] The use of the established dtbpy ligand furnished the borylation products with poor *meta*-selectivity (*meta* to others 1.2 to 1). In contrast, nearly 90% *meta*-selectivity was obtained with the designed ligand **6.1**. The potassium alkoxide formed *in situ* from ligand **6.1** through deprotonation with potassium *tert*-butoxide is capable of recognizing the oxygen atom of the ester carbonyl group *via* a noncovalent interaction (**6.3**). The L-shaped ligand thus directs Ir-catalyzed C–H activation to the site *para* to the ester group (**6.3**). This key noncovalent interaction was validated by a series of control experiments.

The Lewis basicity of the pyridine nitrogen can also be used for regioselectivity control through interaction with a ligand. In 2019, Nakao and co-workers developed a process that represents the first general method for *meta*-C–H borylation of pyridines, using a novel iridium-Lewis acid bifunctional catalyst (Scheme 6B).[39] The designed 1,10-phenanthroline ligand bearing a Lewis acidic alkylborane moiety (**6.4**) interacts with the sp^2-hybridized nitrogen atom of the pyridine moiety, which accelerates iridium catalysis and also controls regioselectivity. Pyridines with diverse substitution patterns were efficiently *meta*-borylated at room temperature (**6.5**-**6.11**). The parent pyridine and 4-picoline gave a mixture of mono- and di-borylation products with excellent overall *meta*-selectivity (**6.5** and **6.6**). 3-Substituted pyridines such as nicotine can be readily *meta*-C–H functionalized (**6.11**). A wide range of 2-substituted pyridines underwent highly C5-selective borylation in excellent yields (**6.7**-**6.10**), although the *meta*-selectivity decreased in a few cases (e.g., **6.10**). Notably, a Lewis basic amine functionality was tolerated without loss of site-selectivity (**6.8**). However, poor *meta*-selectivity (22-46% selectivity) was observed with C2-halogen-, methoxy-, or carbonyl pyridines, likely due to decreased Lewis basicity of the pyridine.

More recently, Gramage-Doria and co-workers disclosed a supramolecular approach for *meta*-selective C–H borylation of pyridines (Scheme 6C).[40] The rationally designed iridium catalyst contains a zinc(II)-porphyrin pocket that enables pyridine binding through Zn···N interaction (**6.12**). The interaction is as tight as those found in some enzymes, offering relatively strong association constant between the pyridine substrate and the catalyst. Good yields and exclusive *meta*-selectivity were noted for the parent pyridine (**6.13**) as well as for several 3-substituted pyridines (**6.14**-**6.16**). However, the method failed to promote the borylation of 2- and 4-substituted pyridines because these substrates do not meet the steric profile to enter the catalyst recognition pocket. A competition experiment using an equimolecular mixture of 2-methyl, 3-methyl, and 4-methyl pyridines delivered exclusively the 3-methyl-pyridine-derived boronic ester **6.14**, which resembles enzyme-catalyzed substrate-selective reactions.



Scheme 6. Ir-catalyzed *meta*-C–H borylation of pyridines through ligand control.

The scope of iridium-catalyzed *meta*-C–H functionalization of pyridines goes beyond borylation. In 2015, Hartwig and Cheng reported an Ir-based catalytic system for the general C–H silylation of arenes and heteroarenes (Scheme 7A).[41] With $Ir(cod)(OMe)]_2$ as catalyst, 2,4,7-trimethyl-1,10-phenanthroline (**7.1**) was identified as the ligand of choice. A sterically encumbered phenanthroline, 2,9-dimethyl-1,10-phenanthroline, was defined later as a more active ligand for such transformations.[42] The reactions were carried out with $HSiMe(OSiMe_3)_2$ as the silylating reagent and cyclohexene as the hydrogen acceptor. 3-Methylpyridine, an unprotected azaindole,

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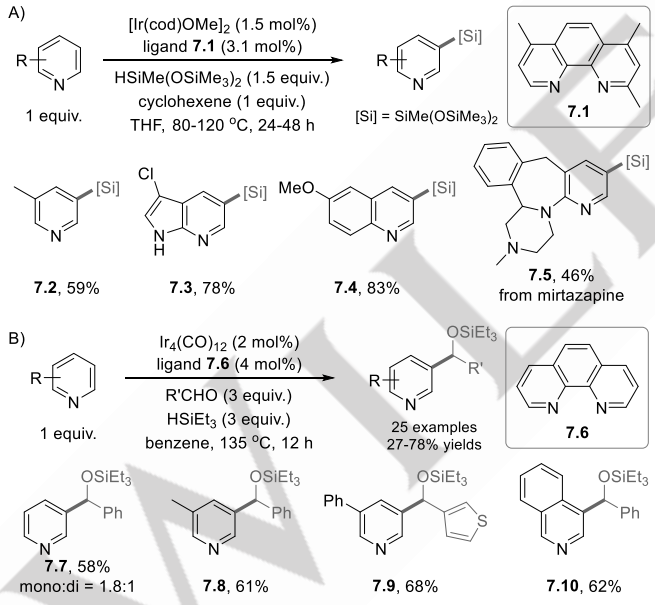
and 6-methoxyquinoline were silylated in good yields with exclusive *meta*-selectivity on the pyridine core (**7.2**-**7.4**). The use of the heterocycle as limiting reagent and good functional group tolerance render this method applicable to late-stage functionalization of drugs. As an example, the *meta*-silylation of the pyridine core of mirtazapine, an antidepressant drug, was achieved in 46% yield (**7.5**). However, concomitant silylation of the benzene ring was also observed in this transformation (14% yield). Like the aryl boronates discussed above, the silylation products can be further transformed through oxidation, halogenation or cross-coupling reactions.

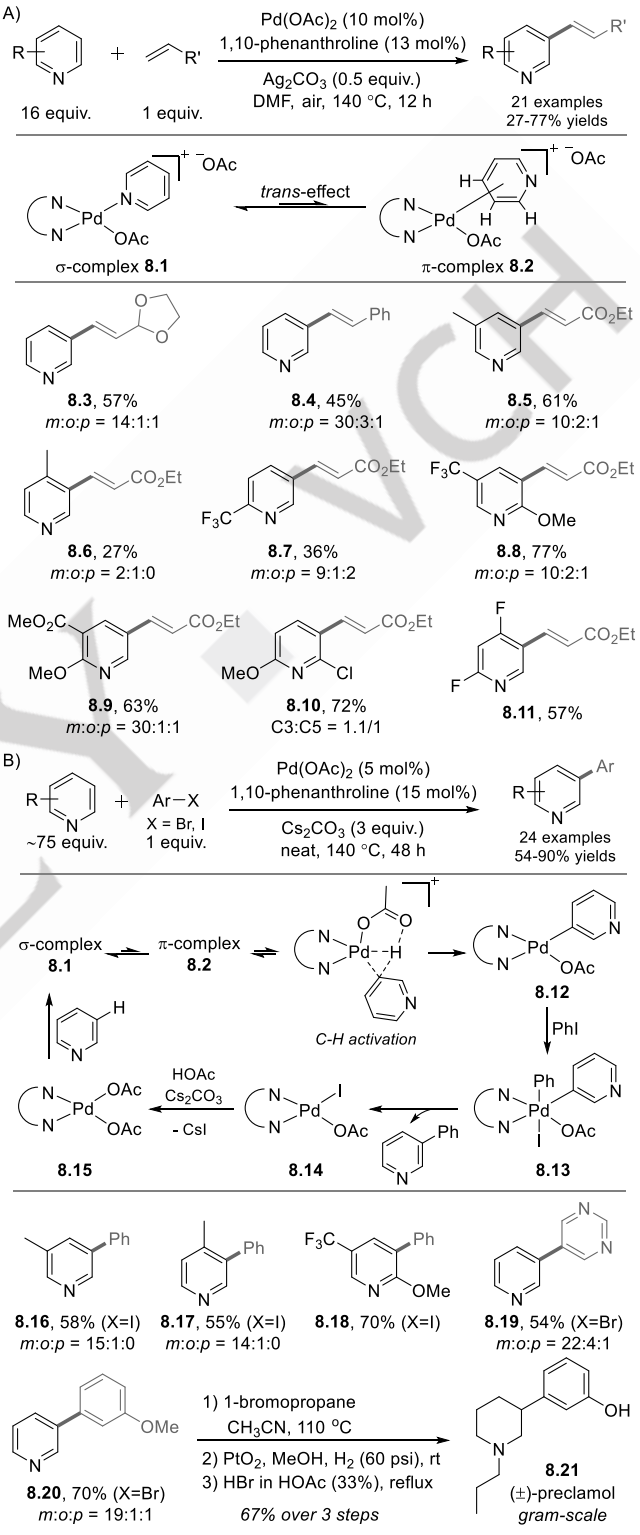
In 2011, Shi and Li described an iridium-catalyzed *meta*-selective alkylation of pyridines through addition of the intermediate pyridyl-Ir-complexes to aldehydes (Scheme 7B).[43] $Ir_4(CO)_{12}$ was identified as the catalyst of choice, while Mn, Re, Ru, and Rh complexes were not active. With 1,10-phenanthroline (phen, **7.6**) as ligand, the alkylation reaction was carried out in the presence of triethylsilane with various aromatic aldehydes. The parent pyridine, 3-substituted pyridines as well as quinolines and isoquinolines were selectively alkylated in the *meta*-position (**7.2**-**7.4**), but the reactions of 2-substituted pyridines gave very low yields (<5%). Like iridium-catalyzed C–H borylation, the regioselectivity in this process is largely determined by steric factors. Based on mechanistic studies, the authors proposed that the reaction occurs by oxidative addition of a silyl iridium complex to the pyridine *meta*-C–H bonds and subsequent insertion to the aldehyde C=O bond.



Scheme 7. Ir-catalyzed *meta*-C–H silylation and alkylation of pyridines.

3.2. Palladium-catalyzed functionalizations

In 2011, Yu, Ye, and Gao reported a palladium-catalyzed *meta*-selective oxidative alkenylation of pyridines (Scheme 8A).[44] Although strong coordination of the pyridine N atom with the Pd(II) center (**8.1**) can prevent the catalyst from interacting with pyridine *meta*-C–H bonds, the authors proposed that the presence of a small amount of the π-complex (**8.2**) could trigger the catalytic reaction. The use of a bidentate ligand (phen) enhances the rate of the ligand exchange on Pd due to the *trans*-effect,[45] which prevents catalyst deactivation and is beneficial for the turnover.



Scheme 8. Pd-catalyzed *meta*-C–H alkenylation and arylation of pyridines.

With air and silver carbonate as oxidants, the alkenylation reaction was carried out in DMF at 140 °C using an excess of the pyridine substrate (16 equiv.). The yield decreased from 87% to

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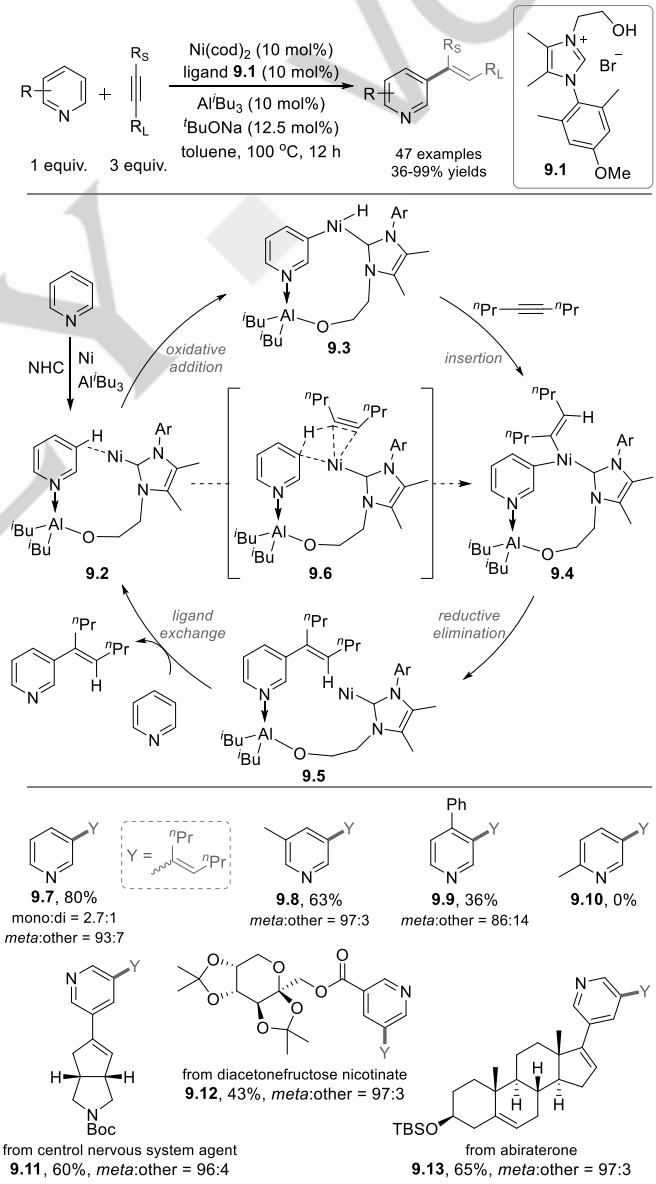
37% upon reducing the amount of pyridine from 16 to 4 equivalents. A possible explanation is the low concentration of the reactive π-complex (**8.2**) due to weak binding of Pd(II) with the pyridine π-ring. Terminal alkenes bearing ketal, aryl, ester, and amide moieties were suitable reactants, delivering the corresponding alkenylated products in moderate to good yields (**8.3**-**8.11**). The reaction is primarily *meta*-selective, although some concomitant *ortho*- and *para*-alkenylation was observed. The *meta*-alkenylation is applicable to both electron-rich and electron-poor pyridines with diverse substitution patterns, but *ortho*- and *para*-substituents on pyridine retarded the reaction to some extent (e.g., **8.6** and **8.7**). The authors postulated that the mechanism involves a palladium-mediated C–H bond cleavage rather than a Lewis acid-mediated Friedel–Crafts reaction on the basis of the primary kinetic isotope effect (κ_H/κ_D = 4.0).

Based on the $Pd(OAc)_2$/phen system, Yu and co-workers published another study on palladium-catalyzed *meta*-C–H arylation of pyridines using aryl halides as the electrophiles (Scheme 8B).[46] In the proposed mechanism, the Pd π-complex **8.2** triggers *meta*-C–H activation to form the aryl-Pd(II) species **8.12** through concerted metalation/deprotonation. Oxidative addition of iodobenzene to **8.12** to give **8.13** followed by reductive elimination furnishes the desired 3-phenylpyridine along with Pd(II) complex **8.14**. Ligand exchange (**8.15**) and coordination with pyridine regenerate the Pd σ-complex **8.1**. A large excess of pyridines is still required, as reducing the pyridine amount from 75 equiv. to 6 equiv. resulted in a significantly lower yield (from 92% to 18%). Under slightly modified conditions, electron-rich or electron-poor aryl bromides and aryl iodides were found to be viable coupling partners, and some heteroaryl bromides were also tolerated (e.g., **8.19**). However, aryl chlorides did not engage in this reaction. Compared to the Pd-catalyzed alkenylation (Scheme 8A), a higher *meta*-selectivity for pyridine arylation was observed (e.g., **8.5** vs. **8.16**, **8.6** vs. **8.17**). The value of this methodology was demonstrated by a short gram-scale synthesis of (±)-preclamol (**8.21**), a dopamine autoreceptor agonist. A similar study on Pd-catalyzed *meta*-arylation of pyridines using aryl tosylates as the coupling partners was reported by Tan and co-workers.[47] Yu and co-workers also showed that Pd-catalyzed *meta*-arylation of pyridines can be accomplished using simple arenes (e.g., benzene) as the arylating reagents in solvent quantities.[48]

3.3. Nickel-catalyzed functionalizations

In view of the low reactivity of palladium toward *meta*-C–H functionalization of pyridines (Scheme 8),[45-48] more efficient methods to transform pyridine *meta*-C–H bonds to C–C bonds are highly desirable, especially those suitable for functionalization of complex pyridines. A recent breakthrough in the field was made by Ye, Yu, and co-workers *via* ligand-ligated Ni–Al anchoring catalysis (Scheme 9).[49] Using the designed carbene ligand **9.1** bearing a free hydroxyl group, in combination with $Ni(cod)_2$ and a Lewis acid co-catalyst (Al^iBu_3), nearly exclusive *meta*-C–H alkenylation was achieved with the pyridine as the limiting reagent. The bifunctional carbene ligand **9.1** could ligate both Ni and Al, thus forming a long-distance bimetallic backbone (**9.2**). The Al Lewis acid reacts with the OH group to give an Al-alkoxide fragment that can coordinate to the pyridine substrate to control the site-selectivity (**9.2**). The proposed catalytic cycle includes *meta*-C–H oxidative addition (**9.3**), migratory insertion of alkyne (**9.4**), reductive elimination (**9.5**), and ligand exchange. An alternative pathway to generate intermediate **9.4** is C–H activation *via* direct ligand–ligand hydride transfer (**9.6**).

A wide range of sterically and electronically varied pyridines were alkenylated in 43%–99% yields with up to 98:2 *meta*-selectivity. Excellent *meta*-selectivity was achieved for the parent pyridine (**9.7**) and 3-substituted pyridines (e.g., **9.8**). The presence of a *para*-phenyl group led to lower reactivity and site-selectivity (**9.9**). The method showed poor tolerance towards *ortho*-substituents (e.g., **9.10**), likely due to hindered coordination of the Al-Lewis acid with the pyridine N-atom. Silyl ether, amine, ester, amide, and boronic ester, among other functional groups, were well-tolerated. Importantly, this methodology enabled smooth alkenylation of various complex pyridines at the *meta*-position of the pyridine core (e.g., **9.11**-**9.13**), demonstrating its potential in late-stage drug development.



Scheme 9. Ni/Lewis acid co-catalyzed *meta*-alkenylation of pyridines.

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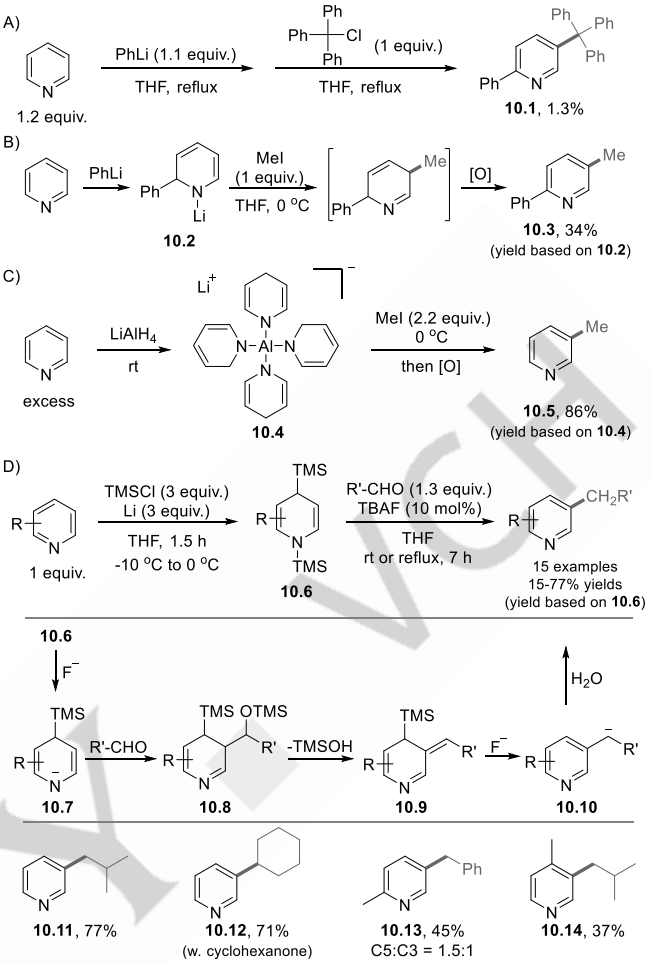
4. *meta*-Functionalization through Temporary Dearomatization

In addition to directed and non-directed metalation, *meta*-C–H functionalization of pyridines has also been achieved through temporary dearomatization (Scheme 2B). In such approaches, pyridines are first transformed to more electron-rich intermediates through a dearomatization process. These dearomatized intermediates bear enamine or dienamine units and are most nucleophilic at the β-nitrogen position. They can react with different electrophiles and can then be rearomatized to eventually form the targeted *meta*-functionalized pyridines. Importantly, the temporary dearomatization strategy reverses the electronic property of the parent pyridine and generally guarantees exclusive *meta*-selectivity. Compared to the installation and removal of directing groups, dearomatization and rearomatization of pyridines are easier to realize and can be conducted in one pot. However, challenges associated with such a strategy are incompatible reagents and low overall yields due to the additional dearomatization and rearomatization steps. In recent years, a significant increase in reaction scope and efficiency has been achieved following temporary dearomatization strategies, which substantially broaden the applications of *meta*-C–H functionalization of pyridines. These reports are organized in the following sections by the choice of the initial dearomatization method.

4.1. Dearomatization with stoichiometric metal reagents

In 1959, Huisgen and Grashey reported that the reaction between trityl chloride and the adduct from pyridine and phenyllithium gives small amounts of 2-phenyl-5-trityl pyridine (**10.1**) as the only constitutional isomer (Scheme 10A).[50] Later, the structure of the σ-complex resulting from the nucleophilic addition of phenyllithium to pyridine was confirmed as the *ortho*-adduct by Giam and Stout (**10.2**).[51] These dearomatized cyclic dienamines are sensitive towards moisture, oxygen or heat, and accordingly efficiently rearomatize to pyridines upon treatment with oxygen.[51] Despite their instability, Giam and Stout found that these dienamine intermediates can react with electrophiles (e.g., iodomethane) selectively at the C5-position and then rearomatize (Scheme 10B), thus representing an interesting method to prepare 2,5-disubstuted pyridines.[52] Both alkyl and aryl lithium reagents were used for the initial dearomatization step. Alkyl, aryl, bromo, carboxyl, formyl, and hydrazino groups were introduced to the C5-position of pyridines using an alkyl halide, an aryl iodide, Br_2, CO_2, $Fe(CO)_5$ or azodicarboxylate as the electrophile.[52-55] Nonetheless, these methods deliver 2,5-disubstituted pyridines; 3-monosubstituted pyridines are not accessible through this approach. To address this problem, Giam and Abbott conducted reductive dearomatization by mixing lithium aluminum hydride with excess pyridine (Scheme 10C).[56] The *in situ* formed lithium tetrakis(*N*-dihydropyridyl) aluminate (**10.4**)[57] was then allowed to react with an alkyl halide or bromine to provide, after oxidation, 3-monosubstituted pyridines in good yields. As an example, the 3-methylated pyridine **10.5** was obtained in 86% yield.



Scheme 10. *meta*-Functionalization of pyridines through temporary dearomatization with stoichiometric metal reagents.

Tsuge and co-workers employed a reductive disilylation protocol for temporary dearomatization and achieved *meta*-selective alkylation of pyridines through such intermediates (Scheme 10D).[58,59] Pyridines were first transformed to the corresponding 1,4-disilyl-1,4-dihydropyridines (**10.6**) in 27-37% yields using trimethylsilyl chloride (3 equiv.) and lithium powder (3 equiv.). Under an inert atmosphere, these air-sensitive intermediates then reacted with aldehydes or ketones in the presence of tetrabutylammonium fluoride to afford *meta*-alkylated pyridines. In the proposed mechanism, N-desilylation by fluoride generates an aza-enolate **10.7**, which reacts with the aldehyde to form the corresponding adduct. Silylation with TMSCl gives **10.8**, which upon elimination of silanol affords **10.9**. Renewed fluoride-induced desilylation, followed by protonation, finally gave the *meta*-alkylated pyridine. Aliphatic aldehydes, aromatic aldehydes, and ketones were found to be eligible electrophiles. Exclusive *meta*-selectivity was observed for the parent pyridine as well as for 2-, 3- and 4-picoline (**10.11**-**10.14**).

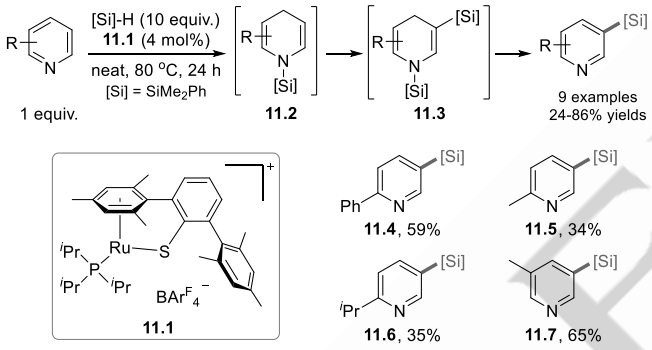
4.2. Dearomatization through catalyzed reduction

Conventional pyridine reductive dearomatization methods rely on the use of stoichiometric metal reagents[50-59] or on noble metals under high pressure of hydrogen gas[60-62] and frequently suffer from low yield, a lack of chemo- and regioselectivity, harsh

10.1002/anie.202302941

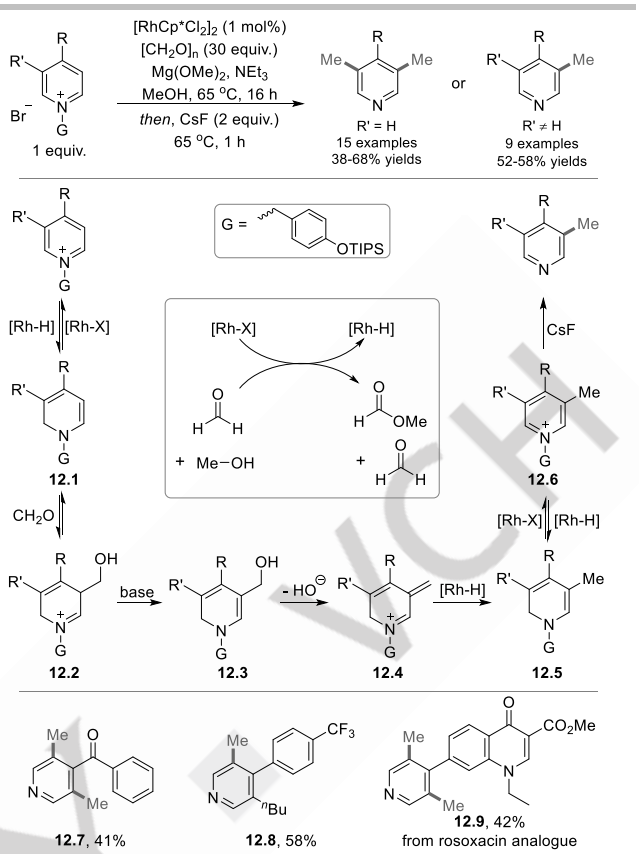
reaction condition, and poor functional group tolerance. In the past decades, several catalytic strategies for the mild dearomatization of pyridines have been developed,[63,64] and some of these techniques have found applications for *meta*-C–H functionalization of pyridines.

In 2015, Oestreich and Wübbolt successfully applied ruthenium-catalyzed reversible pyridine hydrosilylation for the *meta*-silylation of pyridines (Scheme 11).[65] The authors proposed a three-step sequence comprising initial 1,4-hydrosilylation, dehydrogenative silylation of the *N*-silylated enamine **11.2**, and subsequent retro-hydrosilylation of **11.3**, with all 3 steps promoted by the same cationic ruthenium catalyst **11.1**. The structures of the intermediates **11.2** and **11.3** were confirmed by ^{1}H NMR spectroscopy and individual syntheses. The reactions were run by using an excess of the silane (10 equiv.) under neat conditions. Among the tested silanes, dimethylphenylsilane was identified as the only effective silylation reagent for this cascade. Under the optimal reaction conditions, 2-aryl, 2-alkyl, and 3-methyl pyridines were selectively silylated at the C5-position in moderate to good yields (**11.4**-**11.7**), while the parent pyridine, 3-phenyl pyridine, and 4-substituted pyridines gave a complex reaction mixture with the targeted *meta*-silylation products formed in low yields.



Scheme 11. Ru-catalyzed *meta*-silylation of pyridines through temporary dearomatization.

Applying hydrogen borrowing chemistry,[66-68] Donohoe and co-workers developed a Rh-catalyzed process to introduce the pharmaceutically relevant methyl group[69] to the *meta*-position of pyridines (Scheme 12).[70] The feedstock chemicals methanol and formaldehyde were used as reducing and methylation reagents. Quaternarization of the pyridine starting material with a benzyl bromide is necessary to activate the pyridine moiety towards metal hydride reduction. The reaction is proposed to occur by reductive dearomatization of the activated pyridinium salt by hydride, followed by a nucleophilic addition of the dienamine (**12.1**) to formaldehyde under basic conditions. The formed hydroxymethylated enamine **12.3** can then eliminate water to give a π-extended iminium species **12.4**, which can accept a hydride at the exocyclic position. Rearomatization and subsequent one-pot cleavage of the activating group by CsF finally give the *meta*-methylated pyridine. For 4-monosubstituted pyridines, an iterative process leads to doubly *meta*-methylated products (e.g., **12.7**). Unfortunately, this methodology is not suitable for methylation of pyridines that lack a *para*-substituent. Such pyridines gave complex mixtures likely due to over reduction by the metal hydride.

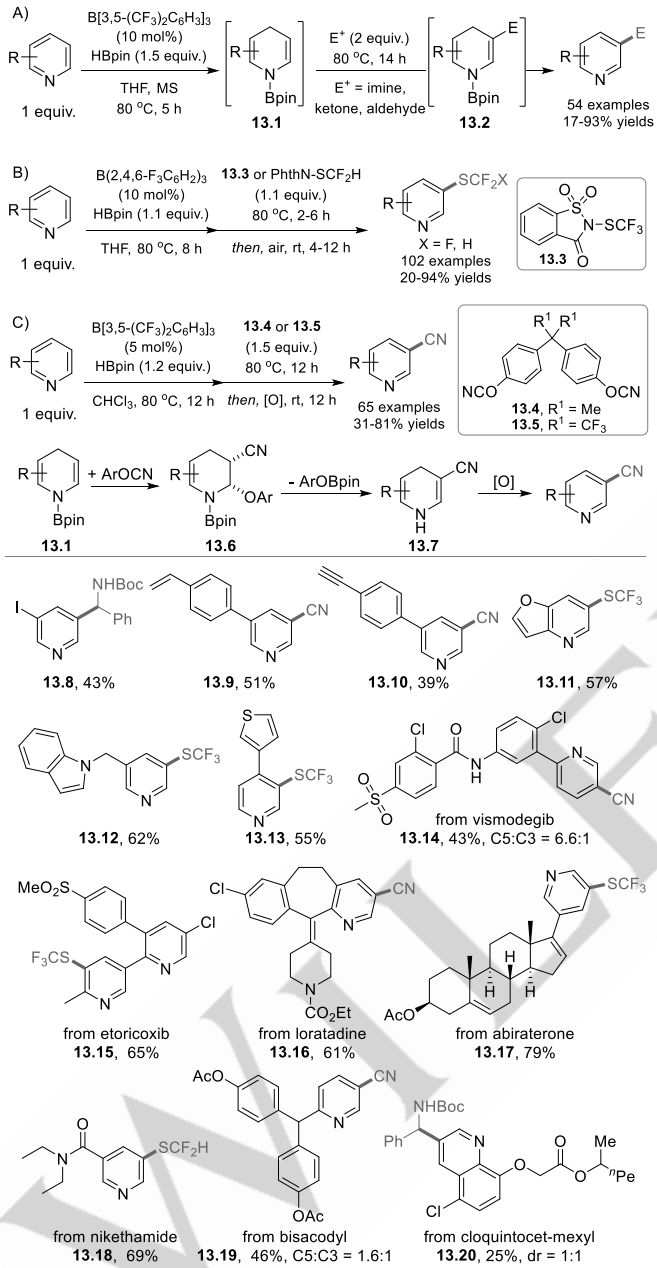


Scheme 12. Rh-catalyzed *meta*-methylation of pyridines through temporary dearomatization.

Recently, Wang and co-workers employed borane-catalyzed pyridine hydroboration[63] for temporary dearomatization and developed highly efficient one-pot methods for the *meta*-functionalization of pyridines (Scheme 13).[71-73] Pharmaceutically important trifluoromethylthiyl (SCF_3),[74] difluoromethylthiyl (SCF_2H),[75] cyano,[76] as well as alkyl groups were selectively installed at the *meta*-position of pyridines using different electrophiles. Interestingly, mechanistic investigations revealed the multiple roles the borane catalyst plays in these processes. For instance, in the *meta*-alkylation reaction (Scheme 13A), the borane complex $B[3,5\text{-}(CF_3)_2C_6H_3]_3$ first catalyzes the 1,4-hydroboration of pyridine with HBpin, and then facilitates the alkylation of the intermediate *N*-borylated 1,4-dihydropyridine (**13.1**) by activating the electrophile. Rearomatization of the alkylation product **13.2** is also promoted by the borane catalyst with the electrophile (e.g., imine) acting as a sacrificial hydride acceptor. Unlike the alkylation reaction, an external oxidant (air) is used for the oxidative rearomatization in the trifluoromethylthiolation reaction (Scheme 13B), whereas formal elimination of ArOBpin from the adduct **13.6** and subsequent treatment with external oxidant give the cyanation product (Scheme 13C). Despite different reaction pathways, all these *meta*-functionalization methods are compatible with sterically and electronically different pyridines. Potentially reactive functional groups, such as iodo (**13.8**), terminal alkene (**13.9**), terminal alkyne (**13.10**), and electron-rich arenes (**13.11**-**13.13**) are well tolerated. Importantly, these processes occur with pyridine as the limiting reagent, rendering them applicable to late-stage modification of various drugs (e.g., **13.14**-**13.20**). A similar *meta*-

10.1002/anie.202302941

trifluoromethylation of quinolines was reported by Kuninobu and co-workers using a borane-catalyzed pyridine hydrosilylation for the initial dearomatization.[77] Togni reagent I was employed as the electrophilic trifluoromethylation reagent in this case, and one example with a pyridine as the substrate was also reported (3-phenyl pyridine), albeit a low yield was achieved (37%).



Scheme 13. Borane-catalyzed *meta*-functionalization of pyridines through temporary dearomatization. MS = molecular sieve. Phth = phthalimide. pin = pinacolato.

4.3. Dearomatization to Zincke imine intermediates

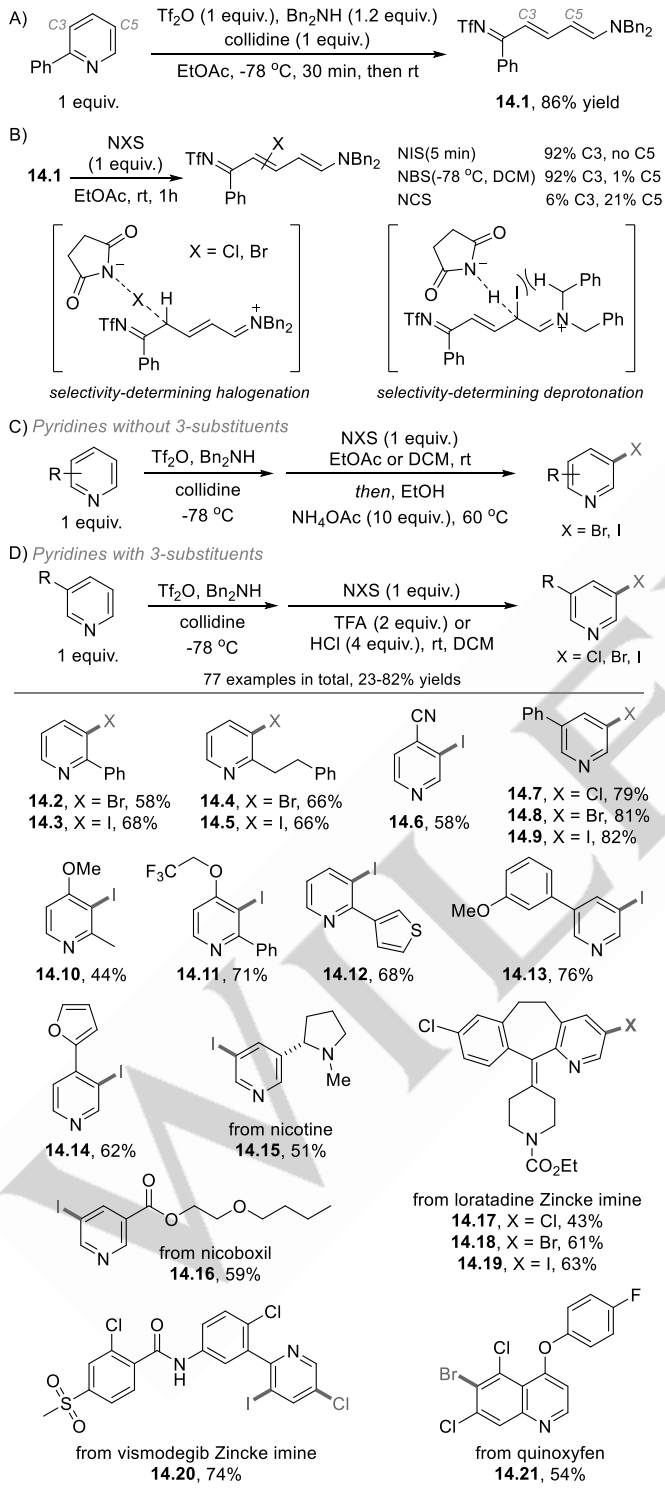
Reductive dearomatization of pyridines generates 1,2- or 1,4-dihydropyridines that are unstable towards air and prone to oxidation (Schemes 10-13). To avoid non-productive oxidative aromatization, the reaction partners for dihydropyridines must be limited to electrophiles with a low reduction potential,[73] and this requirement constrains applicable *meta*-functionalization reactions. Therefore, dearomatization methods that allow generation of dearomatized pyridine intermediates with enhanced redox stability are highly demanded. Two recent breakthroughs along these lines are discussed herein.[78]

meta-Halogenation of pyridines could serve as a platform for various subsequent bond-forming reactions. In addition, the halopyridines themselves are of high importance as the halo substituents can facilitate intermolecular interactions with biological targets such as proteins.[79] Despite more than a century of synthetic endeavors, methods to access *meta*-halopyridines have been largely limited to S_EAr reactions, which are not efficient, as discussed in the introduction. In 2022, McNally, Paton, and co-workers reported *meta*-halogenation of pyridines by a ring-opening, halogenation, and ring-closing sequence (Scheme 14).[80] A modified Zincke reaction[81] with Tf_2O (triflic anhydride) and Bn_2NH (dibenzylamine) effectively converts pyridines to acyclic imine intermediates that are stable towards air and column chromatography (Scheme 14A). Treating the Zincke imine intermediate **14.1** derived from 2-phenyl pyridine with *N*-halosuccinimides gave iodinated or brominated imine products in excellent yields with >20:1 C3-selectivity, while the yields and selectivity for chlorination were poor (Scheme 14B). Adding EtOH and NH_4OAc to the halogenated imine products, followed by heating at 60 °C, eventually furnished the C3-halogenated pyridines after cyclizing rearomatization. This protocol was conducted as a one-pot process (Scheme 14C) and is applicable to the C3-selective bromination and iodination of pyridines that lack any 3-substituents (e.g., **14.2**-**14.6**). Despite the steric hindrance, even 2,4-disubstituted pyridines underwent C3-selective iodination (**14.10** and **14.11**). A different one-pot protocol was applied for 3-substituted pyridines (Scheme 14D). After formation of the Zincke imine intermediates, the addition of acid and *N*-halosuccinimides directly afforded the corresponding C5-halogenated pyridines (e.g., **14.7**-**14.9**). These two protocols cover a broad range of pyridines with excellent C3- or C5-selectivity (77 examples, 23 to 82% yields). Notably, the pyridine core was selectively halogenated in the presence of other electron-rich arenes and heteroarenes (e.g., **14.12**-**14.14**), which would not be possible in conventional S_EAr reactions. In the case of low-yielding Zincke imine formation, a two-pot process by using isolated Zincke imine intermediates for the halogenation gave higher overall yields (e.g., **14.17**-**14.20**). The utility of this methodology was demonstrated by the late-stage functionalization of 17 complex drugs and drug-like compounds (e.g., **14.15**-**14.21**). Notably, sequential *meta*-halogenation reactions allow the introduction of two orthogonal synthetic handles for further transformations (e.g., **14.20**). Surprisingly, the halogenation of quinolines occurred on the benzene core (e.g., **14.21**).

The mechanism and regioselectivity of Zincke imine halogenation were analyzed with computational methods. Electrophilic halogenation, followed by deprotonation, was found to be the most energetically favorable pathway. The calculated energy profiles suggested kinetically controlled regioselectivity in the irreversible overall reactions. The regioselectivity of chlorination and bromination is governed by the C-halogen bond-formation step (Scheme 14B). Bromination proceeds through a late transition state and strongly favors addition at the C3 position ($\Delta\Delta G^{\ddagger}$ = 2.6 kcal mol^{-1}), while chlorination proceeds through an

10.1002/anie.202302941

early transition state with little regioisomeric preference ($\Delta\Delta G^{‡}$ = 0.4 kcal mol^{-1}). In the case of iodination, deprotonation is the rate- and selectivity-determining step, due to reversible formation of the C–I bond. The excellent C3-selectivity ($\Delta\Delta G^{‡}$ = 3.4 kcal mol^{-1}) results from unfavorable $A^{1,3}$ strain between the enamine carbon substituent and the iodide that would develop during C5-deprotonation (Scheme 14B).



Scheme 14. *meta*-Functionalization of pyridines through dearomatization to Zincke imine intermediates.

4.4. Dearomatization through Huisgen 1,4-dipolar cycloaddition

Alongside McNally and co-workers' report, our group independently developed a versatile and highly practical *meta*-C–H functionalization of pyridines by a redox-neutral dearomatization-rearomatization sequence (Scheme 15).[82] Compared to reductive dearomatization strategies (Schemes 10-13), the redox-neutral activation strategy renders the dearomatized intermediates enough redox stability for the installation of pharmaceutically privileged trifluoromethyl[83] and halo[79] substituents through radical or ionic pathways. In the designed sequence, Huisgen 1,4-dipolar cycloaddition[84,85] with commercial dimethyl acetylenedicarboxylate (DMAD) and methyl pyruvate (MP) converted a variety of pyridines to electron-rich oxazino-pyridines with an excellent average yield of 89% (Scheme 15A). Importantly, the formed oxazino pyridines are bench-stable and could engage in regioselective radical or ionic functionalizations using different radical precursors or electrophilic reagents. For the radical transformation, the reaction was conducted with commercial perfluoroalkyl iodides and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under blue light irradiation in acetonitrile. Halogenations were readily achieved with the corresponding *N*-halosuccinimides in dichloromethane under mild conditions. Acid-promoted rearomatization finally provides the targeted *meta*-functionalized pyridines (Scheme 15B).

A series of pyridines with varied steric and electronic properties gave the targeted functionalized pyridines with exclusive *meta*-selectivity (75 examples, 21 to 98% yields). Previously, poor regioselectivity has been noted in radical trifluoromethylation of unbiased pyridines owing to polarity-mismatch.[86] In this study, the electrophilic trifluoromethyl radical electronically matches with the nucleophilic oxazino-pyridine, which accounts for the excellent regioselectivity obtained. For substrates with two *meta*-C–H positions available (e.g., **15.1** and **15.2**), only mono-functionalized products were formed. Interestingly, the chlorination and the bromination/iodination of 2-aryl pyridines provided different isomers (e.g., **15.5**-**15.7**, **15.11** and **15.12**), in each case with complete control over regioselectivity. We assume that the chlorination is irreversible due to the stronger C–Cl bond, resulting in the kinetic isomer (C3-product). However, for bromination and iodination, initial halogenation is reversible, and deprotonation becomes the regioselectivity-determining step with the thermodynamic product (C5-product) being formed exclusively. The trifluoromethylation and halogenation reactions occurred selectively on the pyridine ring in the presence of electron-rich arenes (e.g., **15.2**-**15.3** and **15.21**), which shows that the activation mode outcompetes innate S_EAr-type reactivity. For substrates bearing multiple pyridine cores, the regioselectivity of the initial Huisgen 1,4-dipolar cycloaddition is controlled by the nucleophilicity and the steric shielding of the pyridine N-atom, thus producing mono-functionalization products selectively (e.g., **15.22**). The developed *meta*-functionalizations of pyridines are practical for the late-stage functionalization of a range of drugs that contain pyridine moieties (e.g., **15.11**-**15.25**), and the methodology can be readily carried out as one-pot processes without isolation of the intermediate oxazino-pyridines (e.g., **15.15** and **15.25**). Along with trifluoromethylation and halogenation, various functionalities, including pentafluoroethyl, nitro, sulfanyl, and selenyl groups, could be selectively introduced (**15.13**-**15.20**). Moreover, this method can be readily extended to other N-

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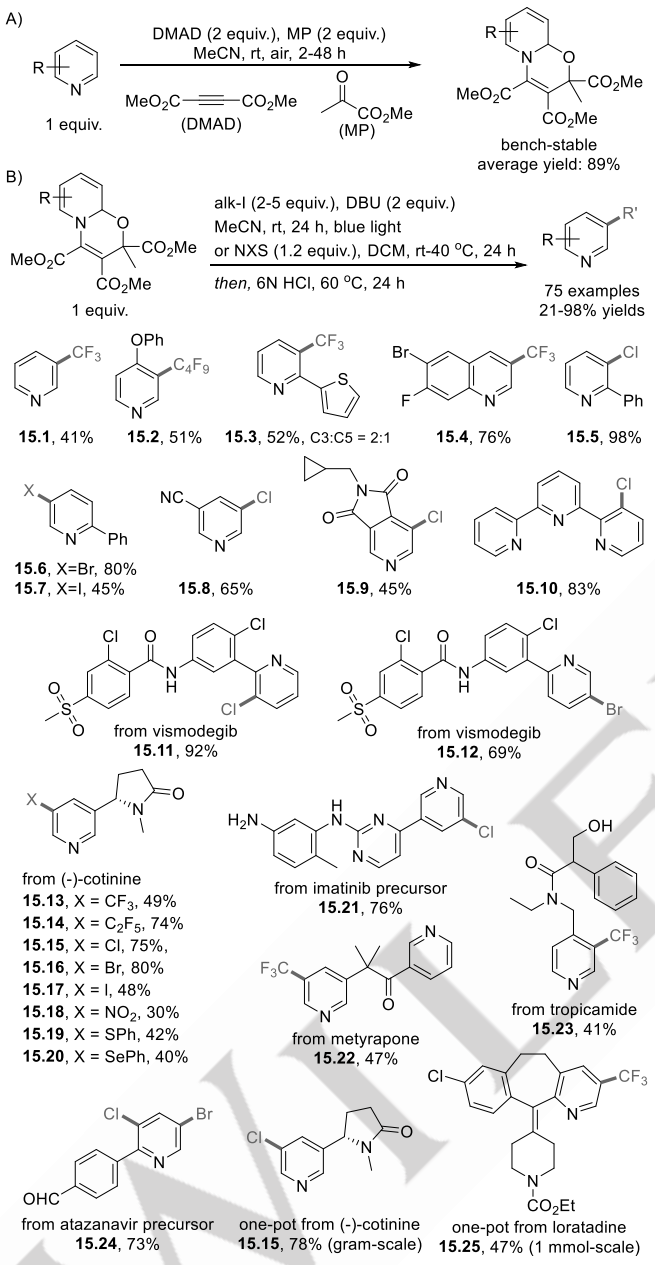
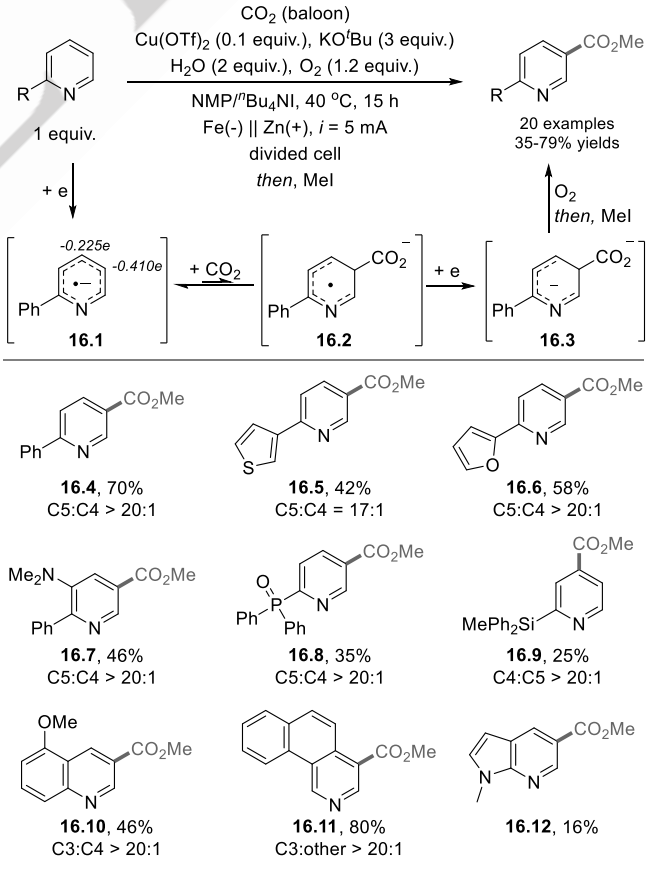
heterocycles such as quinolines, isoquinolines, and thiazoles (e.g., **15.4**). Highly selective sequential *meta-meta'*-difunctionalization was also realized without isolation of the mono-functionalized intermediates.



Scheme 15. *meta*-Functionalization of pyridines through Huisgen 1,4-dipolar cycloaddition.

4.5. Dearomatization through electrochemical reduction

Electrochemistry creates electrons and holes that can be used for controlled reductions and oxidations.[87,88] Very recently, Yu, Lin, and co-workers explored pyridine electroreduction and developed an elegant C5-selective C–H carboxylation of pyridines for the synthesis of nicotinic acid derivatives (Scheme 16).[89,90] With Fe and Zn as cathode and sacrificial anode, the electrochemical reaction proceeded in an $^{n}Bu_4NI$/NMP solution saturated with CO_2 under a constant current of 5 mA. The presence of $Cu(OTf)_2$, $KO^{t}Bu$, and small amounts of H_2O and O_2 as additives was beneficial to the reaction yield. Excellent C5-selectivity was observed for 2-aryl pyridines. In the proposed mechanism, 2-phenyl pyridine first undergoes single-electron reduction at the cathode to form a radical anion **16.1**. According to calculations, the C5 position of **16.1** has the highest electron density, which accounts for the site-selective nucleophilic addition to CO_2. The formed adduct **16.2** is further reduced at the cathode to afford a dianionic species **16.3**. Subsequent oxidative rearomatization with O_2 finally affords the C5-carboxylation product. Under the optimal reaction conditions, a wide range of 2-aryl pyridines were selectively carboxylated at the C5-position in good yields (e.g., **16.4**-**16.6**). 2-Phosphinoyl pyridines also underwent regioselective C5-carboxylation (**16.8**). However, a 2-silyl pyridine afforded exclusively the C4-carboxylated product **16.9**, which was attributed to increased electron density at the C4 position. Pyridine derivatives with other substituents, such as the parent pyridine, 2-acetyl pyridine, 3-cyano pyridine, and 4-phenyl pyridine, gave only traces or no carboxylation products. These results suggest that the 2-aryl and 2-phosphinoyl groups might stabilize the productive radical and anionic intermediates (**16.1**-**16.3**). This methodology was extended to *meta*-C–H carboxylation of other N-heterocycles such as quinolines and azaindoles (**16.10**-**16.12**). The authors also developed an electrochemical method for the C4-selective C–H carboxylation of pyridines *via* hydrogen atom transfer enabled by paired-electrolysis.



Scheme 16. Electrochemical *meta*-carboxylation of pyridines through temporary dearomatization.

5. Summary and Outlook

Compared to the functionalization of *ortho*- and *para*-C–H bonds in pyridines, *meta*-selective functionalization is far less explored, due to the biased electronic profile of the pyridine moiety. Elegant methods have been developed for pyridine *meta*-functionalization using directing-groups. However, installation and removal of a directing group increase costs and consequently decrease overall reaction efficiency. To avoid the need of a directing group, great efforts have been devoted to the development of non-directed pyridine *meta*-C–H functionalization. Transition-metal catalysis, especially iridium-catalyzed borylation, has proven to be highly valuable to install functionalities at the pyridine *meta*-position. In recent years, several advances have been made through ligand control and exploring non-covalent interactions using Ir-, Pd-, and Ni-catalysis. These approaches have significantly broadened the scope of transition-metal catalyzed pyridine *meta*-functionalization. Another emerging and highly valuable strategy relies on temporary dearomatization of pyridines. Several methods have been developed along this line. Taken together, they enabled installation of a wide variety of synthetically and pharmaceutically important functionalities at the *meta*-position of pyridines under mild conditions. This approach was also successfully applied to late-stage modification of C–H bonds in pyridine-containing drugs.

Despite these significant advances, there still exist many challenges in this research area. Transition-metal catalysis is limited by the scope of introduced functions/groups, and transformations using earth-abundant metal or heterogeneous catalysts are underdeveloped. A general problem of the temporary dearomatization approach is the low atom-economy and consequently large amount of waste generated in the dearomatization-rearomatization sequence. Hence, the recycling of dearomatization reagents deserves attention. Moreover, general methods to introduce fluoro, hydroxyl, and aminyl substituents directly at the pyridine *meta*-position remain to be discovered. Considering the newly developed enabling techniques for *meta*-C–H functionalization of pyridines, we anticipate more advances in this emergent and active research area.

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Keywords: pyridine • *meta*-selective • C–H functionalization • late-stage functionalization • dearomatization

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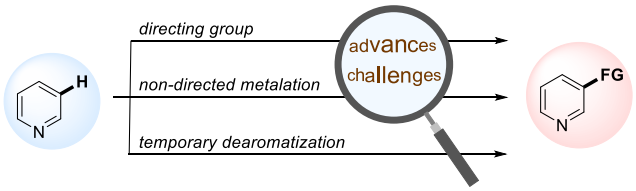

Functionalized pyridines have broad applications in chemical science. However, direct functionalization of pyridine C–H bonds at the *meta*-position is difficult. Significant advances have been achieved in recent years through directing group, non-directed metalation or temporary dearomatization strategies. Herein, we describe the advances and challenges in the development of *meta*-selective functionalization of pyridines.