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Recent advances in the synthesis of C2-functionalized pyridines and quinolines using *N*-oxide chemistry

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Abstract. While remarkable progress has recently been made for the direct C-H-functionalization of azines, its application is still limited by a lack of accessible functional groups (primarily carbon-based) and poor regioselectivity. In contrast, C2-functionalized pyridines and quinolines can be easily synthesized by treating readily available *N*-oxides with various reagents under appropriate activation conditions. This review seeks to comprehensively document the available synthetic methods for introducing functional groups at the C2 position of pyridines and quinolines. In this work, we highlight recent developments in the C2-functionalization of pyridine and quinoline *N*-oxides and address both the mechanisms and regioselectivity of the reactions. We also describe the pathways and reactive species involved in these processes and highlight a number of medically relevant nitrogen heteroaromatics.

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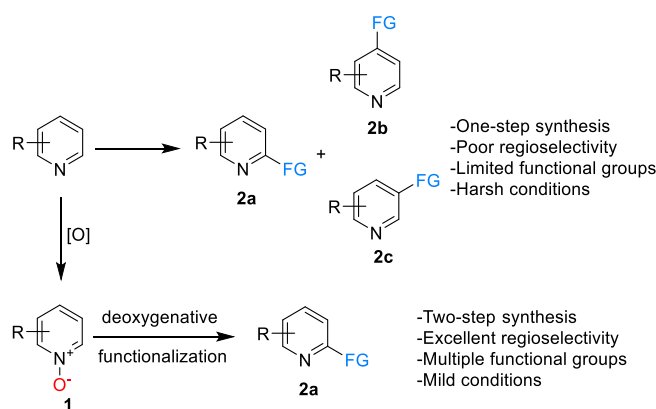
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Keywords: Nitrogen heterocycles; Synthetic methods; Nitrogen oxides; C-H activation; Fused-ring systems

1 Introduction

Pyridines and quinolines are among the most prevalent heterocyclic structural units in medicinal chemistry and materials science, with numerous bioactive C2-functionalized pyridines and quinolines already identified (Figure 1). Directly functionalizing pyridines is a central challenge in modern synthetic organic chemistry due to the poor selectivity and reactivity associated with the low energy π -system. Despite rapid developments over the past ten years, the direct functionalization of pyridines remains difficult due to the limited number of accessible functional groups (primarily carbon-based) and poor regioselectivity (Scheme 1).^[1] In general, these reactions display C2 selectivity, although C4- and C3-functionalized products (**2b** and **2c**, respectively) have been obtained.^[2] Moreover, harsh activation conditions are required for increasing pyridine

reactivity, such as the use of strong acids for Minisci reactions. One effective approach for addressing these problems involves the use of pyridine *N*-oxides **1**, which are easily accessible and more reactive than pyridines (Scheme 1). The oxygen-directed functionalization of these compounds results in excellent regioselectivity. In addition, numerous activating reagents have been developed that allow the synthesis of C2-functionalized pyridines and quinolines under mild conditions.



Scheme 1. Functionalization of pyridines.

Dong Wang is currently an associate professor at Jinggangshan University. He obtained a B. Eng. degree and a M. Eng. degree from Beijing Institute of Technology. He received his Ph.D. in Chemistry from Louisiana State University (USA, 2011) under the guidance of professor William E. Crowe. After his Ph.D., he successively worked in two pharmaceutical companies. He then worked as an associate professor at Tianjin University of Science and Technology until 2020. His research is focused primarily upon the development of new strategies and methodologies for the synthesis of nitrogen heterocycles (website: https://www.x-mol.com/groups/wang_dong).



Dr Laurent Désaubry is a CNRS research director at the University of Strasbourg in France (website: <http://desaubry.u-strasbg.fr/>) and adjunct professor at Tianjin University of Science and Technology (TUST) in China. After a Ph.D. degree in medicinal chemistry at the University of Strasbourg and a 4 year postdoctoral internship at SUNY at Stony Brook, he joined CNRS and was promoted CNRS research



director (corresponds to full professor) in 2014. He became also adjunct professor at TUST in 2015. His research covers medicinal chemistry and the development of new synthetic methodologies.

Gaoyu Li graduated from Puyang No.1 senior high school in 2014 and won the second prize of Henan Chemistry Competition when he was a junior high school student. He received his bachelor's degree from Henan University of Chinese Medicine in 2018. He participated in the Innovative Learning Projects for College Students and served as the team leader, and he won the second prize of The 1st National Pharmaceutical College

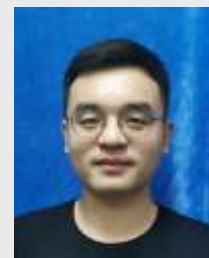


Pharmacy Students Innovation and Entrepreneurship and Experimental Teaching Reform Competition. In 2018, he joined Dr. Dong Wang's group, and has been researching in heterocyclic chemistry.

Mindong Huang graduated from Ningyang No.4 high school in 2014. He received his bachelor's degree from Yantai University in 2018 and won the Excellent Graduation Thesis Award. Since 2018, he has been studying in Tianjin University of science and technology and joined Dr. Dong Wang's group, researching in heterocyclic chemistry.



Shixin Zheng graduated from Licheng No. 2 high school in 2015 and won the first prize in the National Middle School Student Web Page Production Contest. He obtained his bachelor's degree from Shandong First Medical University in 2019 and won the first prize in the Shandong Provincial Medical and Biological Skills Competition. In 2019, he joined Dr. Dong Wang's group and has been researching in heterocyclic chemistry.



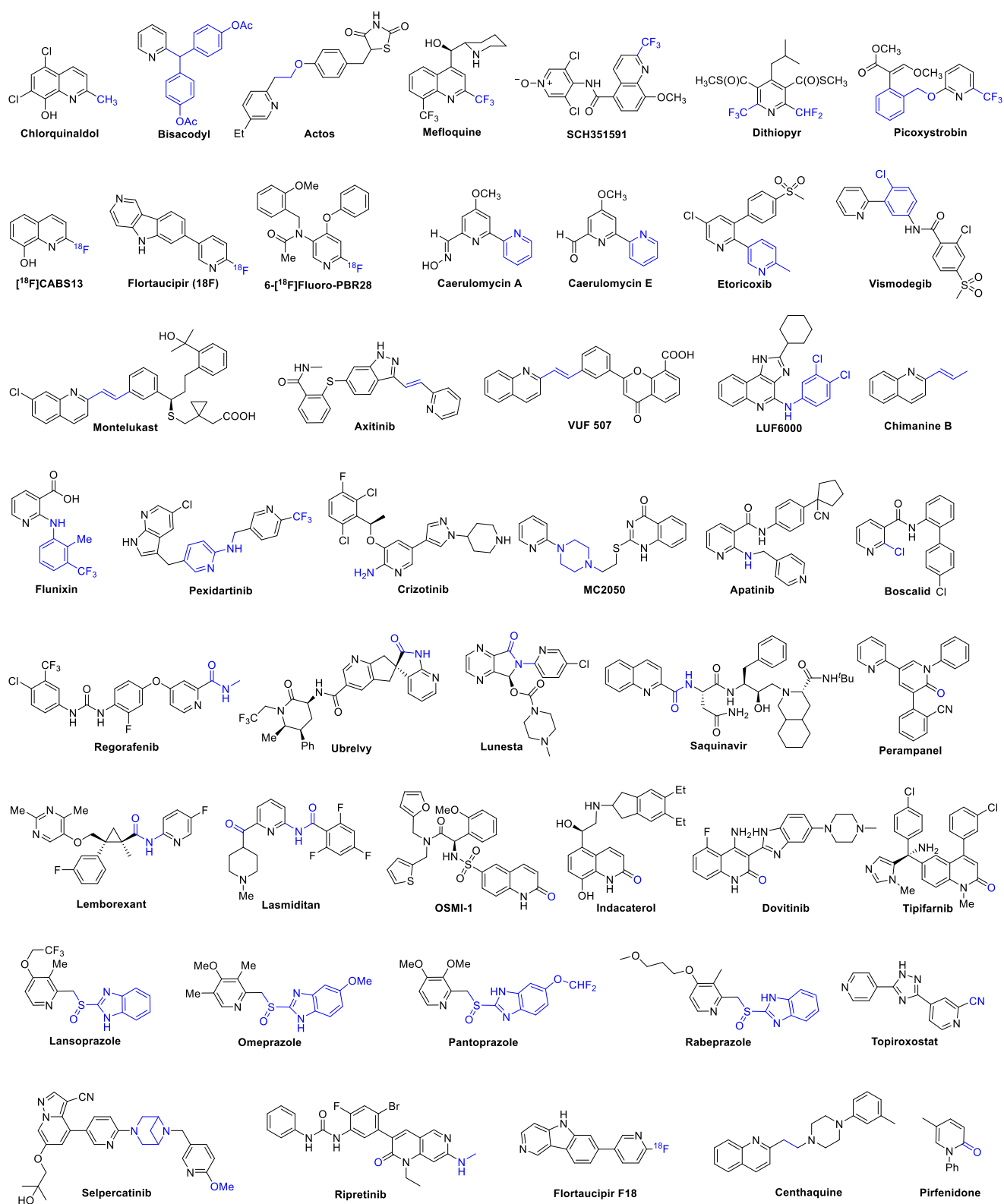


Figure 1. Representative, bioactive C2-functionalized pyridines and quinolines.

There are excellent reviews related to the use of activated pyridines and quinolines in heterocycle synthesis. For example, a 2012 review by Charette and coworkers detailed the synthesis of pyridine and dihydropyridine derivatives by selective addition to *N*-activated pyridines (including *N*-oxides),^[3] and Wang and Zhang published an update on the

chemistry of heteroaromatic *N*-oxides in 2015.^[4] Nevertheless, a comprehensive review on the application of *N*-oxide chemistry to the synthesis of fused pyridine derivatives and functionalization at the C2-benzylic position of pyridine *N*-oxides is lacking. In addition, there have been notable advancements in the synthesis of simple C2-functionalized

pyridines/quinolines from pyridine/quinoline *N*-oxides. Accordingly, an updated and comprehensive review of this field is essential.

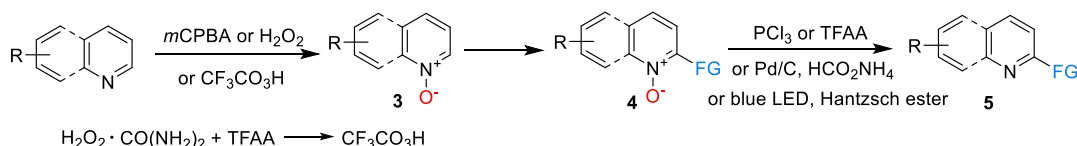
This work describes recent advances in the C2-H-functionalization of pyridine/quinoline *N*-oxides as follows: (1) simple C2-H-functionalization, (2) annulation of C3-substituted azine *N*-oxides, and (3) functionalization at the C2-benzylic position of pyridine/quinoline *N*-oxides. The significant progress made by Fagnou, He, Larionov, Londregan, Singh, Tomkinson, Wang, Wu, Zhao, and many others are detailed. As reviews related to simple C2-H-functionalization are available, only the seminal work published in the past five years and earlier representative achievements are described in this review. The major achievements for the remaining two topics are exhaustively discussed.

Along with the two general reviews concerning *N*-oxide chemistry mentioned above, several types of reactions have been reviewed. Reactions related to Grignard additions were reviewed by Almqvist and colleagues in 2011.^[5] Transition-metal-catalyzed functionalization of *N*-oxides was reviewed by Yan and coworkers in 2014.^[6] The photochemistry of *N*-

oxides was reviewed by Poole in 2017.^[7] Loska reviewed pyridine *N*-oxide cycloadditions in 2015^[8] and 2017^[9]. Quinoline *N*-oxide alkenylations were reviewed by Kouznetsov and coworkers in 2020.^[10]

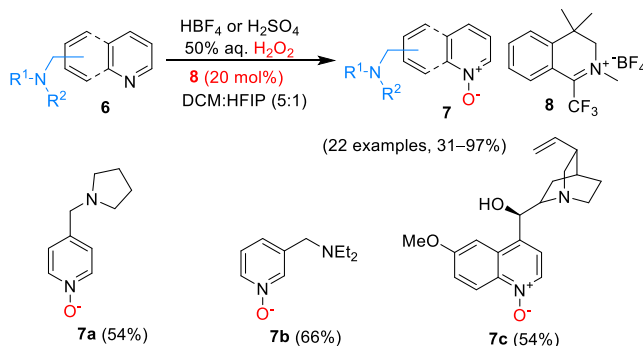
1.1 Synthesis and Reduction

There are a number of commercially available and inexpensive azine *N*-oxides. Pyridine or quinoline *N*-oxides **3** can be easily prepared by oxidation of the corresponding nitrogen heterocycles with known reagents (Scheme 2).^[11] The standard laboratory oxidant for small scale reactions is *m*CPBA, but column purification is required to remove the 3-chlorobenzoic acid byproduct. Hydrogen peroxide is remarkably effective and more commonly used in industry as no purification is needed. Unfortunately, recovering the product from the aqueous phase is difficult due to the good solubility of *N*-oxides in water. Peroxytrifluoroacetic acid, usually generated *in situ* by the reaction of urea hydrogen peroxide with TFAA, is practical for electron-deficient nitrogen heteroaromatics. In addition, some pyridine/quinoline *N*-oxides can be prepared by ring-closing reactions.^[4, 12]



Scheme 2. Common methods for oxidizing pyridines/quinolines and reducing *N*-oxides.

Non-deoxygenative *N*-oxide functionalization requires the reduction of product **4** (Scheme 2). Although several reductants are applicable, such as TFAA^[13] and Pd/C,^[14] the most commonly employed and effective reagent is PCl₃.^[15] Recently, two studies also investigated the visible-light-photocatalyzed deoxygenation of heterocyclic *N*-oxides.^[16]



Scheme 3. Selective heteroaryl *N*-oxidation.

The selective oxidation of *N*-heteroarenes in the presence of amines was first achieved in 2018. The

N-oxides were selectively formed in the presence of more reactive secondary and tertiary amines using an *in situ* protonation strategy and an iminium salt organocatalyst **8** (Scheme 3).^[17] Hilinski's team initially investigated the reaction using traditional peracid oxidants under acidic conditions, but only the undesired tertiary amine oxide was formed. The group then employed trifluoromethyl iminium salt **8**, which they previously developed for use in catalytic oxaziridinium-mediated oxidation. Encouragingly, they obtained the desired product **7** in good yield. This method was also successfully applied to the one-step synthesis of quinine *N*-oxide **7c**.

1.2 Mechanisms of *N*-oxide Chemistry

N-oxide chemistry has evolved with modern organic chemistry, resulting in the discovery of novel heterocyclic *N*-oxide reactions. There are primarily four mechanisms governing the C2-functionalization of pyridine/quinoline *N*-oxides (Scheme 4). Reissert discovered the first path in 1905.^[18] The coordination of an activating agent to the *N*-oxide enhances the electrophilicity of the C2 position in **9**, allowing nucleophilic attack and subsequent deprotonation/aromatization to give the C2-substituted product **11** (Scheme 4A). Numerous

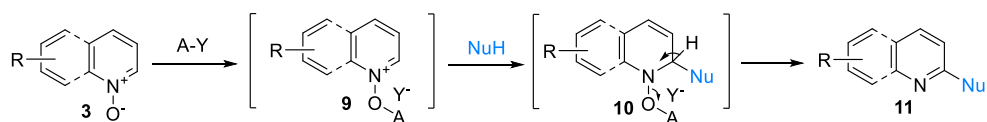
Reissert-type reactions have been explored since 1905 and the synthesis remains popular to this day. The next reaction path for the C2-functionalization of *N*-oxides was identified by Hamana and coworkers in 1983.^[19] Pyridine/quinoline *N*-oxides are natural 1,3-dipoles, making them viable substrates for dipolar cycloaddition to a wide variety of unsaturated carbon-carbon or carbon-heteroatom bonds (Scheme 4B). However, the low reactivity of these *N*-oxides, likely due to the stability of the aromatic system, renders them capable of reacting only with strong, electron-deficient dipolarophiles or highly reactive ones, such as benzyne. The cycloaddition product **12** is generally unstable owing to the disruption of aromaticity, and restoration of the conjugated system drives cleavage of the N–O bond to afford **13**.

In 2005, Fagnou and coworkers reported a novel direct arylation of pyridine *N*-oxides catalyzed by Pd(OAc)₂,^[14] which has attracted considerable attention. The aryl-palladium intermediate **14** forms via coordination of the palladium atom to the *N*-oxide and subsequent electrophilic attack at the C2 carbon atom (Scheme 4C). Transfer of the functional group

onto **14** produces **15**, which is converted to **4** via reductive elimination.^[20]

Minisci reactions, in which radicals add to pyridines under oxidizing and strongly acidic (usually TFA) conditions, are an effective method for the direct functionalization of pyridines.^[21] Although this approach has undergone extensive development, it is primarily limited to the use of carbon-based radicals, such as alkyl, acyl, and aryl radicals.^[21b, 21c] Wu's group recently reported the synthesis of 2-acetoxyated quinolines under oxidizing conditions via Cu-catalyzed radical addition to quinoline *N*-oxide.^[22] This displayed a fourth reaction path, Minisci-type reactions, for the C2-functionalization of *N*-oxides (Scheme 4D). Notably, metal catalysis is not essential for the reactions, and several methods can be used for quenching the radical cation species **16** to afford product **4** or **5**. This novel reaction class is superior to standard Minisci reactions as a variety of radicals can be employed, likely due to the lower activation energy of the *N*-oxide reagents. In addition, the reaction is amenable to a wider substrate scope since it is performed under neutral conditions.

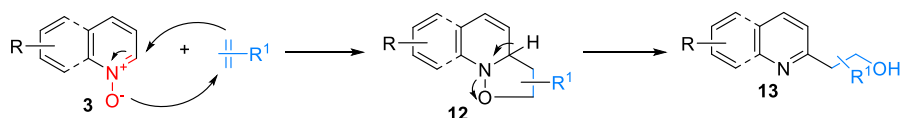
A. Nucleophilic addition to electrophile-activated *N*-oxides: Reissert-type (1905)



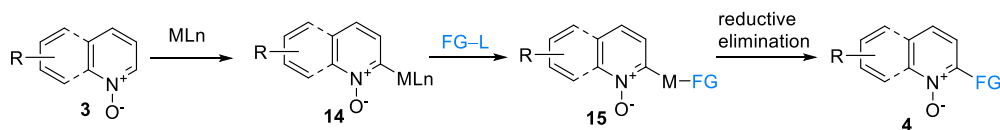
A-Y = Ts₂O, Ms₂O, TsCl, MsCl, Ac₂O, RCOCl, BzBr, PyBroP, I₂, PhI(OAc)₂, etc.

Nu = halide, amine, alcohol, thiol, sulfonamide, pyridone, silyl ketene acetal, malonate, etc.

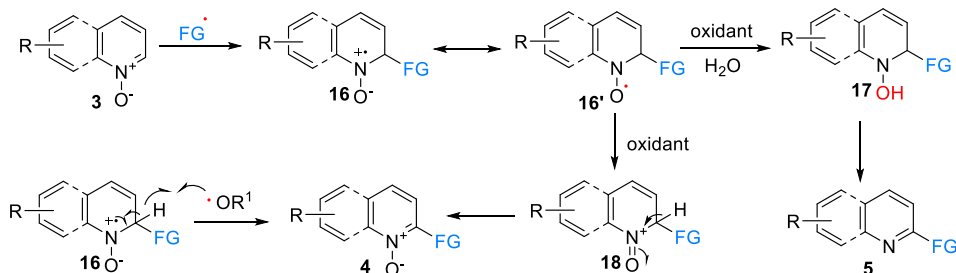
B. 1,3-Dipolar cycloaddition to *N*-oxides: [3+2] mechanism (1983)



C. Metal-catalyzed arylation or alkenylation of *N*-oxides (2005)



D. Minisci-type radical addition to *N*-oxides: SET mechanism (2013)



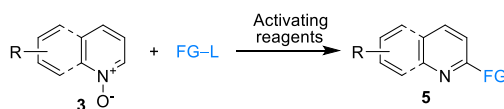
Scheme 4. Primary reaction mechanisms for pyridine/quinoline *N*-oxide reactions.

2 Simple C2-H-Functionalization

Various functional groups have been introduced at the C2 position of pyridines/quinolines in high efficiency under mild conditions. The reactants and

activating reagents used for deoxygenative functionalization are summarized in Table 1.

Table 1. Deoxygenative C2-functionalization of pyridines/quinolines.



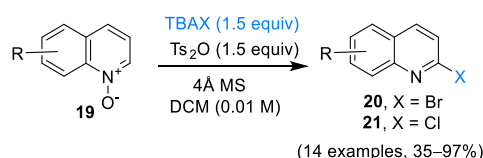
Entry	-FG	Substrate(s) ^a	Activation	FG-L	Ref
1	-F	P/Q NOs	TFAA	R ₃ N then TBAF	27
2	-Cl, -Br	Q NOs	Ts ₂ O	TBAX	23
		P NOs	POX ₃ + DMF (COX) ₂		24 25
3	-Cl	Q NOs	Ph ₃ P + CCl ₃ CN		26
4	-NH ₂	P/Q NOs	Ts ₂ O	^t BuNH ₂ then TFA	28
		P NOs	TsCl	Saccharin then HCl	29
5	-NR ¹ R ²	P/Q NOs	PyBroP	R ¹ R ² NH	30
		Q NOs	HP(O)(O ⁱ Pr) ₂	R ¹ R ² R ³ N	31
		Q NOs	HP(O)(OEt) ₂	R ¹ R ² NH	32
		P/Q NOs	TFAA	DABCO then NuH	33
		Q NOs	Tf ₂ O	R ¹ R ² NH	34
6	-NHR	Q NOs	CuCl ^b	PhCO ₂ N R ¹ R ²	41
		Q NOs	AgBF ₄ ^b	RNCS	35
7	-NHAr	P/Q NOs	—	RCON ₃	36
8	-NHC(O)R	P/Q NOs	CH ₃ CN + ArN ₂ BF ₄		37
		Q NOs	(COCl) ₂	RC(O)NH ₂	43
		Q NOs	BAIL-1 ^c or TsOH NH ₂ NHCO ₂ Me + Selectfluor	RCN	45-46 47
9	-NR ¹ C(O)R	P/Q NOs	Tf ₂ O	RC(O)NHR ¹	44
10	-NHC(O)NR ₂	P NOs	MeSO ₃ H	R ₂ NCN	49
11	-NRC(O)NHR ¹	Q NOs	CuSO ₄ ·5H ₂ O ^b	RN=C=NR ¹	51
12	-NHSO ₂ Ar	Q NOs	PhI(OAc) ₂ + Ph ₃ P	ArSO ₂ NH ₂	54
		Q NOs	Ni(OAc) ₂	FN(SO ₂ Ar) ₂	55
13	-NRSO ₂ Ar	P NOs	PyBroP	ArSO ₂ NHR	53
		P/Q NOs	PyBroP	NaOAc + H ₂ O	56
		Q NOs	MsCl	H ₂ O	57
14	-OH	Q NOs	DIAD + PdCl ₂	H ₂ O	58
		P/Q NOs	PyBroP	ROH	59-61
		Q NOs	CuBr ₂	RSO ₂ Na + K ₂ S ₂ O ₈	64
15	-OR	Q NOs	FeCl ₃	RSO ₂ Na + TBHP	65
		P/Q NOs	HP(O)(O ⁱ Pr) ₂	RSO ₂ Cl or ArSO ₂ Na	68
		P/Q NOs	NaI + TBHP I ₂ + H ₂ O ₂	RSO ₂ NHNH ₂	69-70
		P/Q NOs	I ₂ (+ TBHP) TsCl	RSO ₂ Na	71-72 74
		Q NOs	Zn + ultrasound	RSO ₂ Cl	73
16	-SO ₂ R	Q NOs	FeNO ₃ + microwave K ₂ S ₂ O ₈	ArSO ₂ Na	67 75
		Q NOs	CuOTf	ArN ₂ BF ₄ + DABSO	66
		Q NOs	Na ₂ S ₂ O ₅	ArN ₂ BF ₄	77
18	-CH ₂ CO ₂ Me	P NOs	PyBroP	CH=C(OTBS)OMe	87
19	-CH ₂ CH(OH)CO ₂ R	Q NOs	—	CH ₂ =CHCO ₂ R	89
20	-CH ₂ R	P/Q NOs	RCH(Bpin) ₂ + MeONa		93
21	-CHRR ¹	P/Q NOs	RR ¹ C(Bpin) ₂ + MeONa		94
22	-Alkyl	P/Q NOs	Alkyl-PPh ₃ X + ^t BuOK		95

23	-CH=CHEWG	Q NOs	Pd(OAc) ₂	CH ₂ =CHEWG	97
24	-CH=CHAr	Q NOs	I ₂	CH ₂ =CHAr	98
25	-CH=CHR	Q NOs	AcOH or TsOH	CH ₂ =CHR	99-100
26	-Ar	P NOs	Cu(acac) ₂	ArB(OR) ₂	104
		Q NOs	ArSO ₂ NHNH ₂ + electrochemistry		111
27	-R (R = alkyl, alkenyl, aryl)	P/Q NOs	CuCl	RMgX•MgCl ₂	106
28	-R (R = alkenyl, aryl)	Q NOs		RB(OH) ₂	110
29	-CF ₃	Q NOs	CF ₃ SiMe ₃ + ^t BuOK		112
		P/Q NOs	NiCl ₂	Togni's reagent	113
30	-COR	P/Q NOs	AgNO ₃	RC≡CH + K ₂ S ₂ O ₈	115
		P NOs	Mes-Acr ⁺ ClO ₄ ⁻	RC≡CR ¹	91
31	-CH(EWG) ₂	P NOs	PyBroP	CH ₂ (EWG) ₂	53
		Q NOs	HP(O)(OEt) ₂	CH ₂ (EWG) ₂	32
32	-SCF ₃	P/Q NOs	2,4-(NO ₂) ₂ PhSO ₂ Cl	AgSCF ₃	118
			Ts ₂ O		119
33	-SR	P NOs	PyBroP	RSH	53
34	-P(O)(OR) ₂	P/Q NOs	HP(O)(OR) ₂		122
35	-N ₃	P/Q NOs	DPPA		120
			P NOs	ClCONMe ₂	125
36	-CN	P/Q NOs	microwave	TMSCN	128
		Q NOs	PhI(OAc) ₂	127	

[a] P NOs: pyridine *N*-oxides; Q NOs: quinoline *N*-oxides. [b] These are promoters of the reaction. [c] BAIL-1 is 1-(1-propylsulfonic)-3-methylimidazolium chloride.

2.1 Halogenation

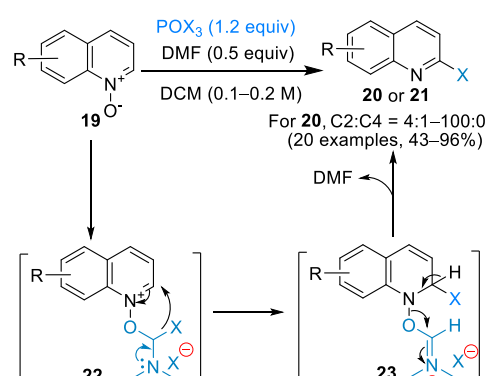
A regioselective C2-bromination/chlorination of quinoline *N*-oxides under mild conditions was presented by Baran and coworkers in 2013 (Scheme 5).^[23] This method employs tosic anhydride as the activating agent and tetra-*n*-butylammonium halide as the nucleophilic halide source. Although the regioselectivity is excellent, the highly dilute conditions (0.01 M) render this method impractical.



Scheme 5. C2-bromination/chlorination of quinoline *N*-oxides.

To eliminate the use of activating agents in conventional Reissert-type reactions, our group successfully employed the Vilsmeier reagent as both the activator and nucleophilic halide source, resulting in a highly practical method for the regioselective halogenation of fused heterocyclic *N*-oxides, including quinolines, isoquinolines, and diazine *N*-oxides (Scheme 6).^[24] In contrast to conventional methods that require large volumes of POX₃ (usually as solvent), only a stoichiometric quantity is needed. Initial coordination of the *in situ*-generated Vilsmeier reagent to *N*-oxide **19** afforded the activated quinoline complex **22**, which is converted to a quaternary ammonium salt **23** via intramolecular

nucleophilic attack by the halide. Subsequent rearomatization affords the desired 2-halogenoarenes **20** or **21** and DMF, which proceeds into the next catalytic cycle. The regioselectivity of this reaction was found to be excellent for chlorides and moderate for bromides.

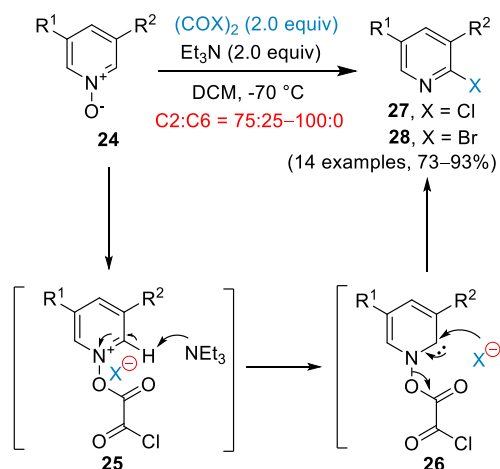


Scheme 6. C2-halogenation of quinoline *N*-oxides under mild conditions.

This strategy was used by two other groups. In 2015, Amgen scientists reported a highly efficient and regioselective halogenation of unsymmetrical pyridine *N*-oxides (**24**) under mild conditions (Scheme 7).^[25] The C2/C6 regioselectivity is excellent, with the halide being incorporated at the electron-deficient side of most substrates. Compound **24** is first activated by oxalyl chloride. The C2 proton of the resulting pyridinium chloride **25** is extracted by triethylamine to generate a highly reactive carbene intermediate **26**, which reacts with a halide anion to afford products **27** or **28**. This transformation could

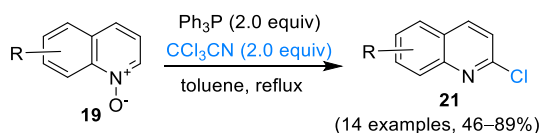
also be performed at room temperature with similar regioselectivity but slightly lower yields.

Priority: -OAr > -Br > -SAr, -F > -Cl > -Br > -CO₂R



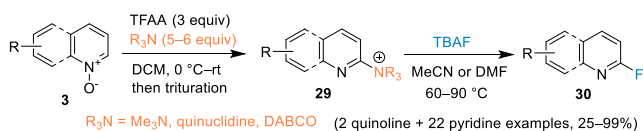
Scheme 7. Regioselective C2-halogenation of pyridine *N*-oxides.

Guo and coworkers reported a regioselective chlorination of quinoline and isoquinoline *N*-oxides using $\text{PPh}_3/\text{CCl}_3\text{CN}$ in refluxing toluene (Scheme 8).^[26] Despite using several common brominating agents, no bromination products were obtained.



Scheme 8. C2-chlorination of quinoline *N*-oxides using $\text{PPh}_3/\text{CCl}_3\text{CN}$.

Due to the low reactivity of the fluoride anion, the direct fluorination of aromatics and heteroaromatics remains problematic. Avid Radiopharmaceuticals developed a facile synthesis of 2-fluoropyridines via 2-pyridyltrialkylammonium salts **29** generated from *N*-oxides **3** (Scheme 9).^[27] This method benefits from the simplified preparation and separation of **29**, which was limited in previous methods.



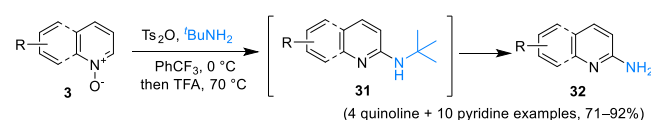
Scheme 9. Facile synthesis of 2-fluoropyridines and 2-fluoroquinolines.

2.2 Amination

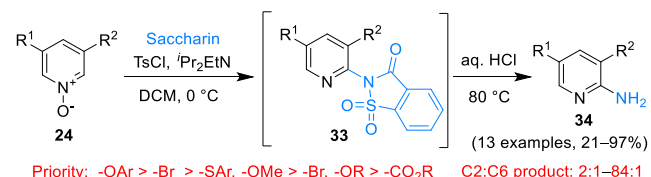
Both deoxygenative and non-deoxygenative aminations of pyridine/quinoline *N*-oxides have been reported. Activating reagents or electron-deficient dipolarophiles are typically required for deoxygenative aminations, whereas transition-metal catalysts are commonly used for non-deoxygenative aminations.

2.2.1 Organic Reagent/Base-Promoted Deoxygenative Amination

In contrast with C2-halogenation, C2-amination of pyridines or quinolines is challenging due to the competitive reaction between the amine and activating agent. Merck scientists successfully solved this problem using an attenuated ammonia surrogate, ${}^t\text{BuNH}_2$, which retained the capacity to be deprotected (Scheme 10).^[28] However, the specificity of this amine substrate is too limited to find broad applicability.



Scheme 10. One-pot amination of pyridine/quinoline *N*-oxides.



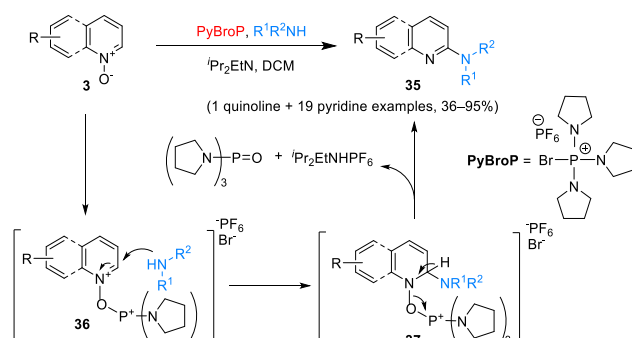
Priority: -OAr > -Br > -SAr, -OMe > -Br, -OR > -CO₂R C2:C6 product: 2:1–84:1

Scheme 11. C2-amination of 3,5-disubstituted pyridine *N*-oxides.

Similarly, inexpensive and commercially available saccharin was employed by Amgen scientists for the regioselective amination of unsymmetrical 3,5-disubstituted pyridine *N*-oxides (**24**, Scheme 11).^[29] *In situ* deprotection under acidic conditions allows for a one-pot process.

Phosphorous-based activating reagents are particularly attractive because the formation of the P=O bond provides a strong thermodynamic driving force for the reaction. In 2010, Londregan and colleagues at Pfizer identified PyBroP, a commercially available phosphonium salt, as an excellent activating reagent for the amination of both pyridine and quinoline *N*-oxides with a variety of amines (Scheme 12).^[30] The reaction likely proceeds via the activated pyridine complex **36**. Nucleophilic attack of the amine at the C2 position of **36** yields **37**. Base-mediated rearomatization affords the desired 2-aminopyridine **35** and phosphoryltripyrrolidine, the only significant organic byproduct of the reaction. It

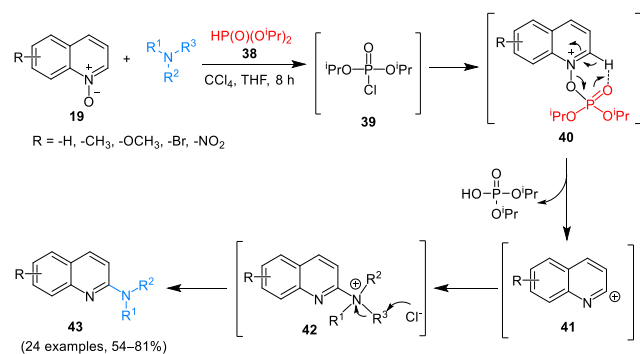
should be noted that PyBroP is a universal activating reagent for the functionalization of *N*-oxides and has been widely used for reactions with various nucleophiles, including amines, phenols, sulfonamides, sulfoximines, malonates, pyridones, thiols, and silyl ketene acetals.



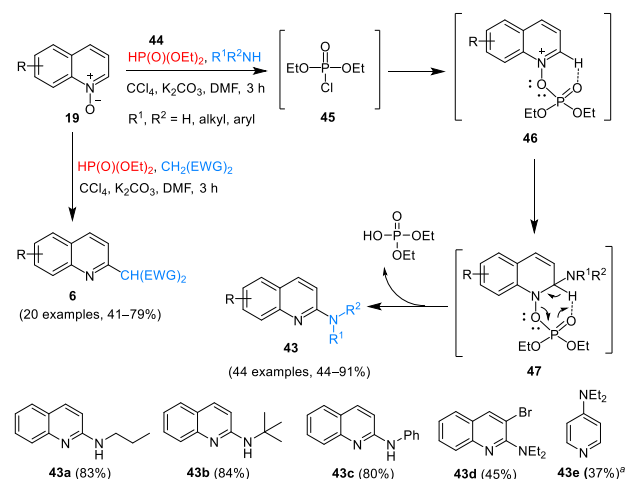
Scheme 12. General method for the mild C2-amination of pyridine and quinoline *N*-oxides.

Another notable phosphorous-based activating agent was developed by Zhao's group and used for the synthesis of a series of 2-(dialkylamino)quinolines through the direct reaction of quinoline *N*-oxides with trialkylamines in the presence of diisopropyl *H*-phosphonate **38** and CCl_4 (Scheme 13).^[31] This activating reagent is more efficient than PyBroP for the synthesis of (dialkylamino)quinolines, but cannot be used with pyridine *N*-oxides or primary amines.

This group extended the substrate scope to include ammonia, a variety of primary and secondary amines, and reactive methylene compounds. The use of such a wide range of nucleophiles was enabled by activation with diethyl *H*-phosphonate **44** and K_2CO_3 in CCl_4 and DMF (Scheme 14).^[32] The method has proved less effective for pyridine *N*-oxides and large excesses of amines are required. Notably, the C4-aminated product (**43e**) predominates when pyridine *N*-oxide substrates are employed.

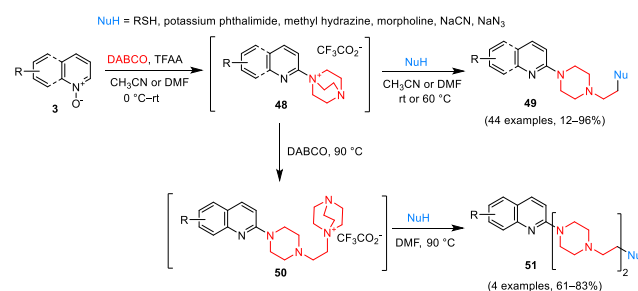


Scheme 13. Dialkylamination of quinoline *N*-oxides with tertiary amines.



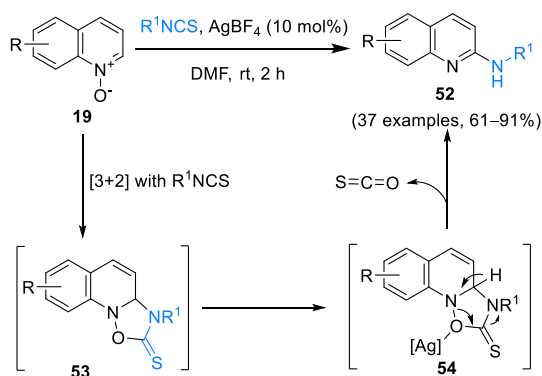
Scheme 14. Amination and alkylation of quinoline *N*-oxides with secondary amines. ^a 10 equiv of amine were used.

Introduction of piperazine to the C2 position of pyridines/quinolines is desirable as several bioactive pyridine/quinoline derivatives contain this functionality. Using a similar strategy to that of Avid Radiopharmaceuticals,^[27] Karchava's team developed a simple, one-pot synthesis of piperazine-functionalized **49** and **51**. Under the activation of TFAA, initial reaction of *N*-oxides **3** with DABCO followed by *in situ* treatment of the resultant 2-pyridyltrialkylammonium salts **48** or **50** with nucleophiles provides the desired ring-opening products (Scheme 15).^[33] The amination of quinoline *N*-oxides with various amines was also realized under the activation of trifluoromethanesulfonic anhydride (Tf_2O).^[34]

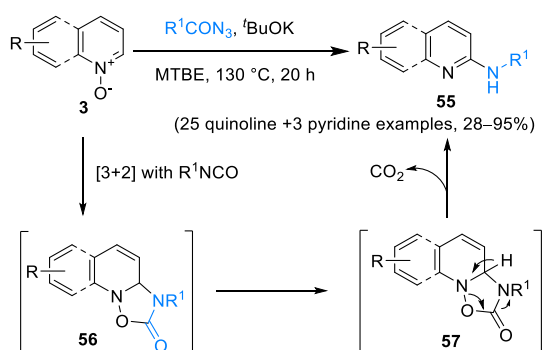


Scheme 15. One-pot synthesis of substituted *N*-(2-pyridyl)-*N'*-ethylpiperazines.

He's group recently reported a non-Reissert-type synthesis of 2-aminoquinolines **52** via AgBF_4 -catalyzed 1,3-dipolar cycloaddition with isothiocyanates (Scheme 16).^[35] This reaction is unfortunately not amenable to pyridine *N*-oxides.

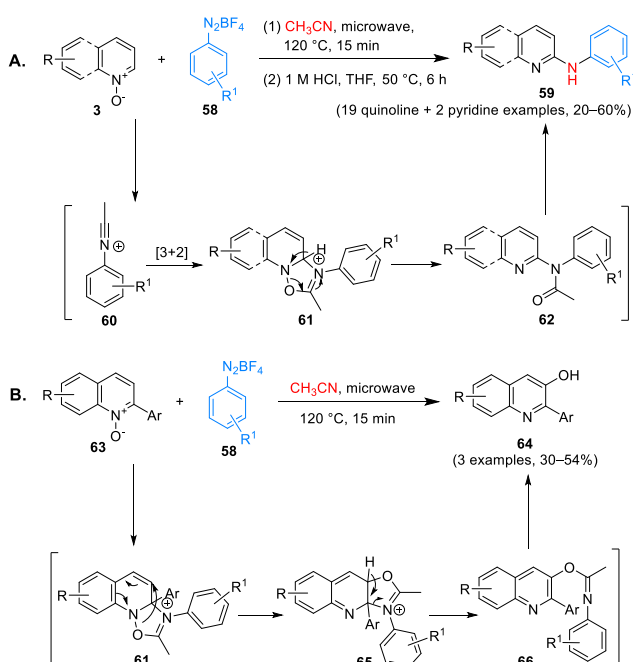


Scheme 16. AgBF₄-catalyzed deoxygenative C2-amination.



Scheme 17. Deoxygenative C2-amination with acyl azide.

In 2020, Kim's group described a similar transformation with isocyanate via a Curtius rearrangement from the starting acyl azide (Scheme 17).^[36] Despite the harsh reaction conditions, this reaction is applicable to pyridine *N*-oxides, as well as more complex molecules, such as quinidine and fasudil, with products obtained in moderate yields.



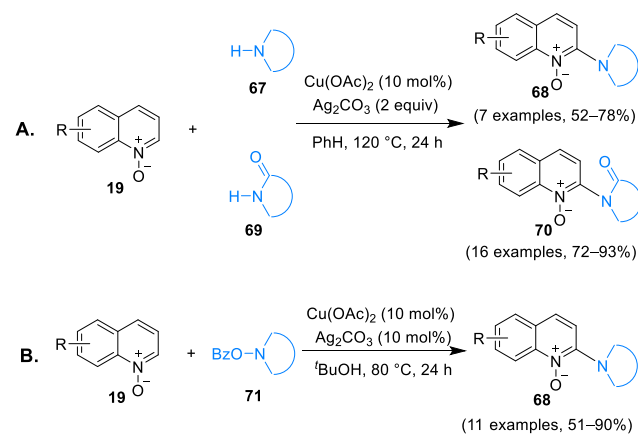
Scheme 18. Three-component reaction of *N*-oxides, aryldiazonium salts, and acetonitrile.

Sharma's group disclosed a microwave-assisted synthesis of 2-anilinoquinolines **59** via three-component reaction (Scheme 18A).^[37] Aryldiazonium tetrafluoroborate **58** reacted with acetonitrile under microwave heating to produce **60**, which then underwent [3+2] cycloaddition with **3** to provide **61**. Interestingly, 2-arylquinoline *N*-oxides **63** afforded 3-hydroxy-2-arylquinolines **64** under the identical reaction conditions (Scheme 18B). The reaction may proceed through intermediate **61**, which on 1,3-oxygen transfer followed by rearomatization gave **66**.

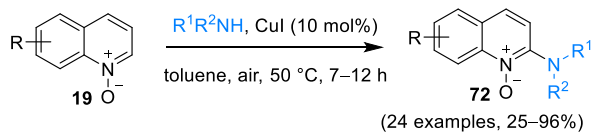
2.2.2 Metal-Catalyzed Amination

In 2013, Li's team conducted Cu(II)-catalyzed reactions for the amination and amidation of quinoline *N*-oxides in refluxing benzene (Scheme 19A).^[38] Ag₂CO₃ was used to oxidize the generated CuOAc into the active catalyst. Utilizing *O*-benzoyl hydroxylamines as the nitrogen source, the same catalyst system was also successfully applied to the synthesis of **68** at lower temperatures (Scheme 19B).^[39] Cu(I)-catalyzed amination under milder conditions was also developed, which included atmospheric oxidation of the Cu(I) catalyst to the active Cu(III) complex (Scheme 20).^[40]

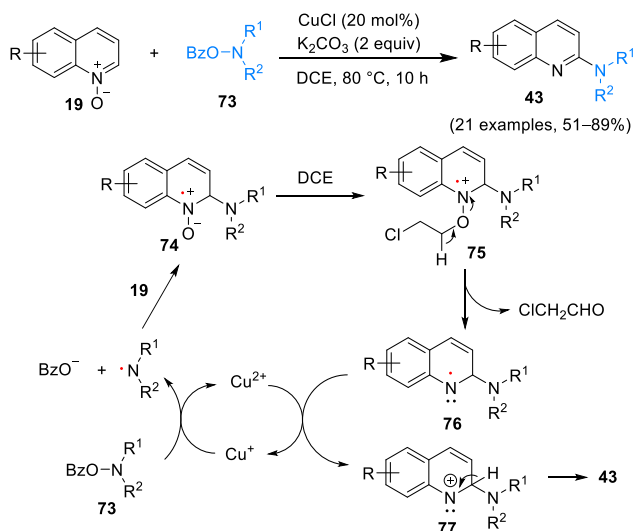
Deoxygenative amination through metal catalysis is also reported (Scheme 21).^[41] Notably, DCE serves as both the solvent and reductant in this transformation. *O*-benzoyl hydroxylamine **73** was reduced by Cu⁺ to generate an aminyl radical, which reacted with **19** to produce intermediate **74**. Subsequently, **74** underwent the reaction with DCE to give **75**, which released ClCH₂CHO to form radical **76**. Finally, **76** was oxidized by Cu²⁺ and further rearomatized to afford **43**. Patel's group reported another Cu(I)-catalyzed deoxygenative amination of quinoline *N*-oxides with *N*-(2-(arylthio)aryl)cyanamides through an autoreduction process.^[42]



Scheme 19. Cu-catalyzed amination/amidation of quinoline *N*-oxides with cyclamines/lactams or *O*-benzoyl hydroxylamines.



Scheme 20. Cu-catalyzed amination with secondary amines.

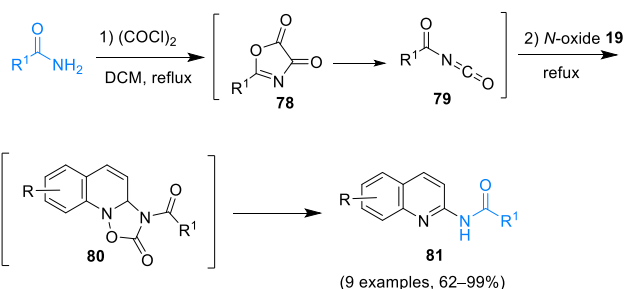


Scheme 21. Cu-catalyzed deoxygenative amination with *O*-benzoyl hydroxylamines. Note: this reaction mechanism is suggested based on our understanding and, thus, slightly differs from the original paper.

2.3 Amidation

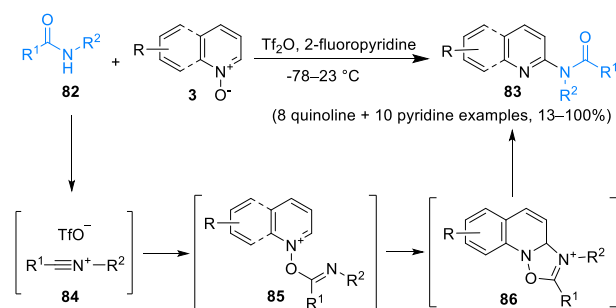
2.3.1 *N*-acylated 2-Aminopyridines and 2-Aminoquinolines

Isocyanate was first shown to be a suitable reagent for the C2-amidation of quinoline/isoquinoline *N*-oxides by Couturier and coworkers in 2006 (Scheme 22).^[43] In this reaction, isocyanate **79**, generated via an *in situ* reaction between the primary amide and oxalyl chloride, undergoes 1,3-dipolar cycloaddition with quinoline *N*-oxide **19**, followed by decarboxylative aromatization of the adduct to give **81**. Unfortunately, the strongly acidic conditions and long reaction times (typically > 20 h) greatly limit the application of this reaction.



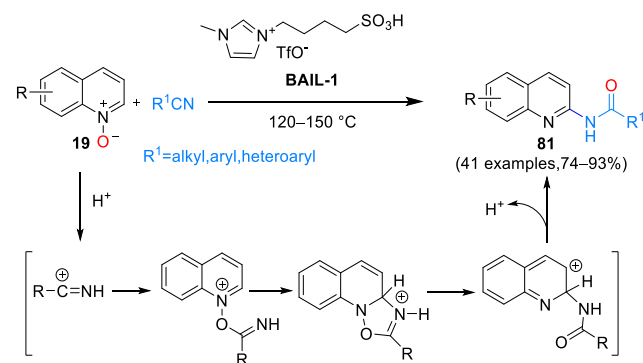
Scheme 22. C2-amidation of quinoline *N*-oxides with primary amides.

The Tf₂O-promoted amidation of pyridine, quinoline, and isoquinoline *N*-oxides with secondary amides in the presence of 2-fluoropyridine as the base was developed by Medley and Movassaghi in 2009 (Scheme 23).^[44] Interestingly, mechanistic studies suggested the formation of a nitrilium ion **84**.



Scheme 23. C2-amidation of pyridine/quinoline *N*-oxides with secondary amides.

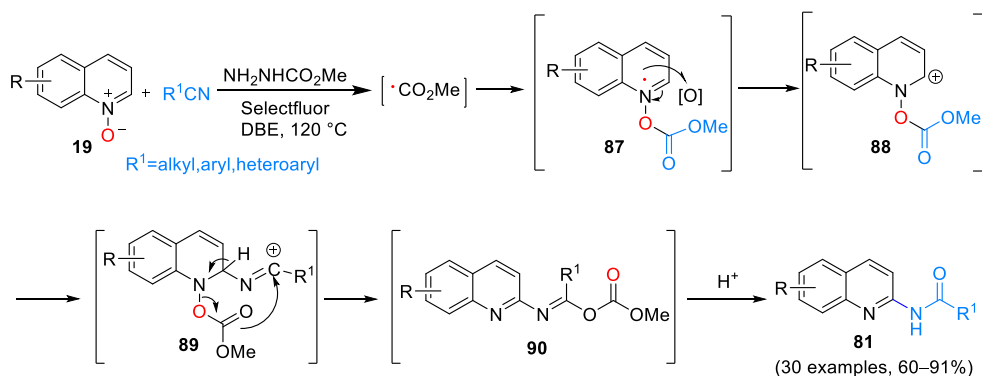
He's group developed a facile and eco-friendly approach for the production of various *N*-acylated 2-aminoquinolines from quinoline *N*-oxides and nitriles in acidic ionic liquid (Scheme 24).^[45] Beneficially, the ionic liquid could be recycled for several reactions. A similar amidation of quinoline *N*-oxides can be achieved by heating at high temperatures in TsOH rather than acidic ionic liquid.^[46]



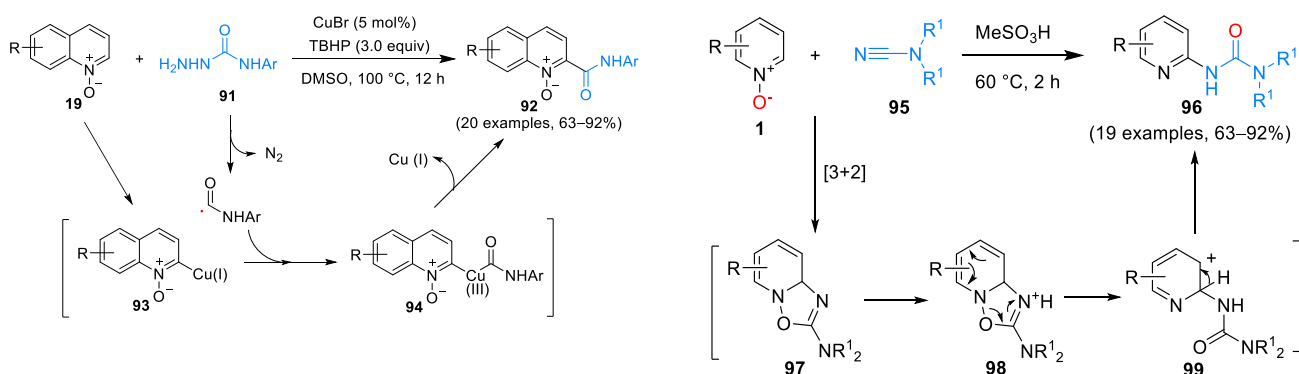
Scheme 24. Ionic-liquid-promoted amidation of quinoline *N*-oxides with nitriles.

Notably, He's group reported another efficient protocol operating through a radical activation pathway, with nitriles used as the amide source and methyl carbazate as both the radical activating reagent and oxygen source (Scheme 25).^[47] First, methyl carbazate was oxidized by Selectfluor to generate a carbon-centered ester radical with the release of molecular nitrogen, HF, and tetrafluoroborate. The ester radical reacted with **19** to

produce a radical intermediate, **87**, which was further oxidized to give a quinolinium intermediate, **88**. Subsequent transformations would afford **81**. Although the previous three methods are facile and efficient, the high-temperature conditions render them impractical for complex molecules.

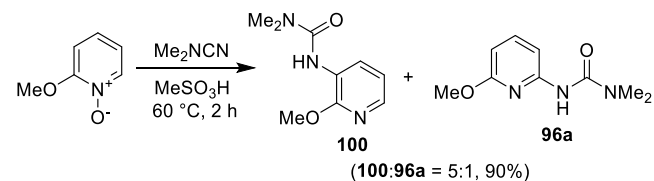


Scheme 25. Amidation of quinoline *N*-oxides with nitriles via radical activation. Note: this reaction mechanism is suggested based on our understanding and, thus, slightly differs from the original paper.



Scheme 26. Cu-catalyzed amidation of quinoline *N*-oxides.

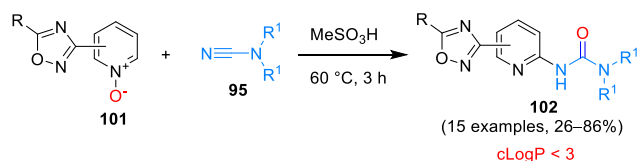
Cu(I)-catalyzed non-deoxygenative amidation of quinoline *N*-oxides was efficiently achieved with hydrazinecarboxamides **91** and TBHP (Scheme 26).^[48]



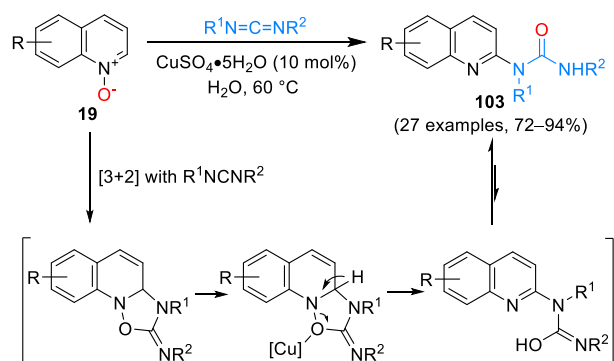
Scheme 27. Amidation of pyridine *N*-oxides with dialkylcyanamides.

Kukushkin and coworkers reported the synthesis of useful pyridine-2-yl substituted urea, **96**, via a 1,3-dipolar cycloaddition pathway utilizing pyridine *N*-oxides **1** and dialkylcyanamides **95** under acidic and solvent-free conditions (Scheme 27).^[49] Notably, the C5-functionalized product, **100**, predominated when the reaction was performed with 2-methoxypyridine *N*-oxide. This method was later applied to the synthesis of pharmaceutically privileged oxadiazole-

substituted urea, **102** (Scheme 28).^[50] All the synthesized targets had cLogP values of <3, which complies with the “lead-like” criteria.



Scheme 28. Synthesis of oxadiazole-substituted *N*-pyridinylurea.

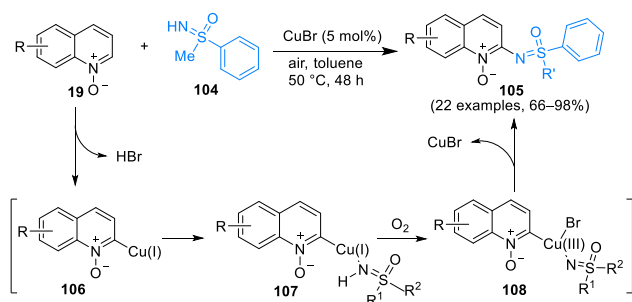


Scheme 29. Amidation of quinoline *N*-oxides with carbodiimides.

In 2019, He’s team disclosed the Cu-catalyzed synthesis of quinolin-2-yl substituted ureas in water (Scheme 29).^[51] which was initiated by a [3+2] cycloaddition between quinoline *N*-oxides and carbodiimides. The reaction is exceptionally green because it involves 100% atom economy, water as solvent, and easy operation.

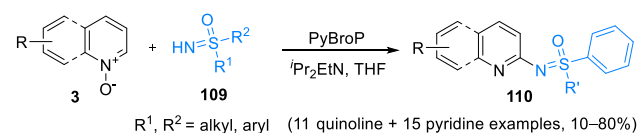
2.3.2 Sulfoximation and Sulfonamidation

In 2016, Bolm’s group developed a non-deoxygenative sulfoximation of quinoline *N*-oxides with NH-sulfoximines (Scheme 30).^[52] The process is catalyzed by CuBr in air and proceeds by dual C-H/N-H activation. However, this reaction is not applicable to pyridine *N*-oxides.



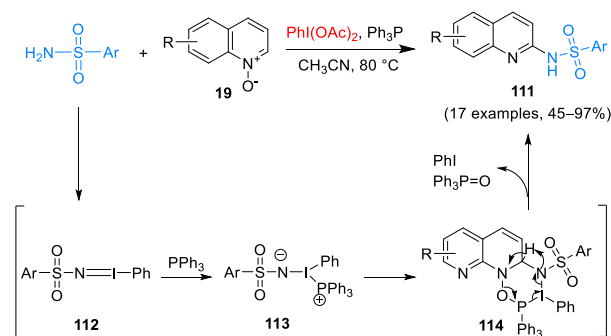
Scheme 30. Cu-catalyzed sulfoximation of quinoline *N*-oxides.

The deoxygenative sulfoximation of both pyridine and quinoline *N*-oxides was achieved by Singh’s team under PyBroP activation conditions (Scheme 31).^[53] The reaction conditions were also suitable for use with enantiopure substrates and furnished products without any racemization. In addition, the method was successfully applied to the sulfoximation of azine-based functional molecules, such as 2,2’-bipyridine, 1,10-phenanthroline, and quinine.



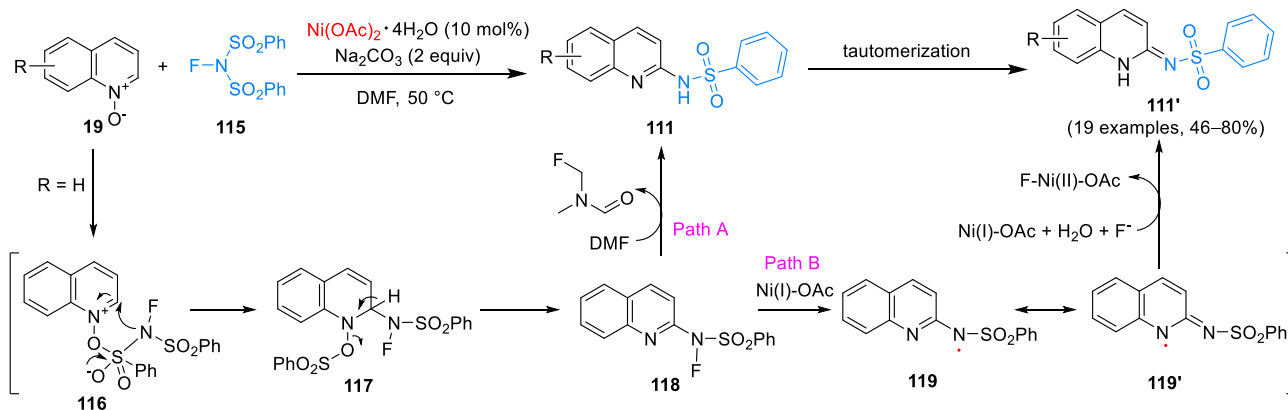
Scheme 31. Sulfoximation of heteroaromatic *N*-oxides under PyBroP activation conditions.

The nucleophilic addition of sulfonamides had not been achieved until recently because of the poor nucleophilicity of these compounds. Bao’s group developed a new method to synthesize quinoline sulfonamides **111** from quinoline *N*-oxides, sulfonamides, PhI(OAc)₂, and PPh₃ (Scheme 32).^[54] The method is applicable to a variety of quinoline *N*-oxides and sulfonamides. Sulfonamides react with PhI(OAc)₂ to produce sulfonyl imino iodo arene **112** and acetic acid. Notably, the 1,3-dipolar [3+3]-cycloaddition of quinoline *N*-oxides with **112** may have occurred via the generation of a six-membered intermediate, **114**.



Scheme 32. Hyperiodine-mediated sulfonamidation of quinoline *N*-oxides.

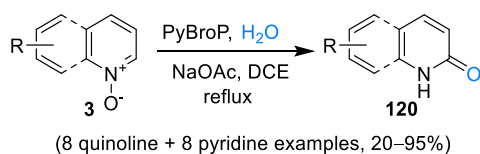
Ni-catalyzed sulfonamidation using *N*-fluorobenzenesulfonimide (NFSI, **95**) as the amidating reagent was an efficient method described by Wu’s group in 2019 (Scheme 33).^[55] Two tentative reaction mechanisms were proposed based on control experiments. Interestingly, the 1,2-dihydro-2-iminoquinoline products, **111’**, are tautomers of 2-sulfonylaminoquinolines **111**.



Scheme 33. Ni-catalyzed sulfonamidation of quinoline *N*-oxides.

2.4. Hydroxylation

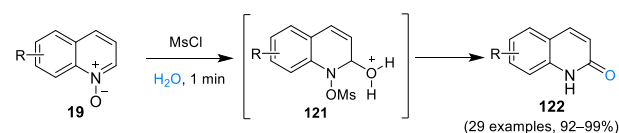
Traditional methods for synthesizing 2-pyridones and 2-quinolinones **120** involve refluxing *N*-oxides in acetic anhydride and hydrolyzing the resulting acetylated products. Our group developed a mild and efficient alternative, employing sodium acetate, water, and PyBroP as the activating agent (Scheme 34).^[56] Notably, this method has a wide substrate scope, including both electron-rich and electron-poor quinolines, pyridines, and isoquinolines.



Scheme 34. Hydroxylation of pyridine/quinoline *N*-oxides with water and PyBroP.

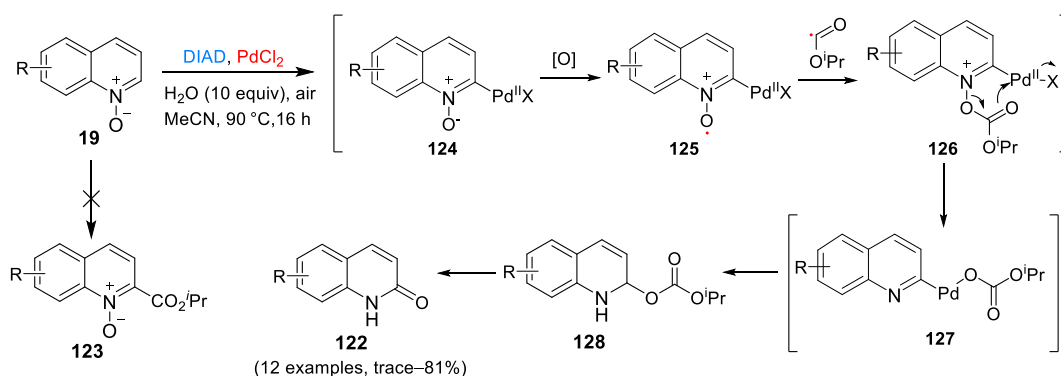
He's group later described an efficient, rapid, and environmentally benign route to 2-quinolinones **122** that relies on the activation of quinoline *N*-oxides by MsCl in water. The desired products crystallized *in situ* and were isolated via simple filtration to afford analytically pure compounds without the need for further purification (Scheme 35).^[57] Nevertheless, this

method is ineffective for pyridine and quinoxaline *N*-oxides.



Scheme 35. Aqueous synthesis of 2-quinolinones.

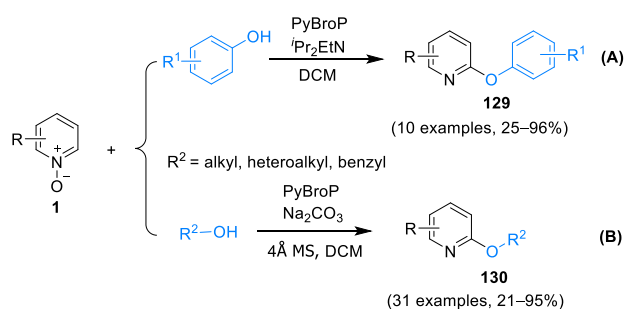
Wu and coworkers serendipitously identified a unique pathway involving azodicarboxylates. Based on several carbonylative transformations with diethyl azodicarboxylate catalyzed by palladium, they assumed that the carbonylation product **123** (Scheme 36) should be formed. However, 2-quinolinones **122** were produced, with DIAD acting as both the activating agent and the oxidant in the Pd(II)-catalyzed transformation of quinoline *N*-oxides.^[58] Intermediate **124** was oxidized by either air or DIAD to generate radical cation **125**, which reacted with the carboxylic radical generated *in situ* from the decomposition of DIAD. Importantly, the reaction proceeded under mild conditions and without the need for a dry or inert environment.



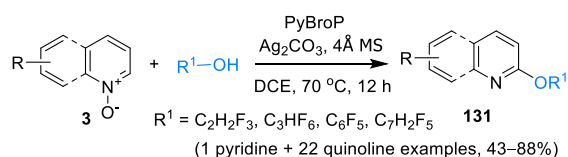
Scheme 36. PdCl₂-catalyzed synthesis of 2-quinolinones. Note: this reaction mechanism is suggested based on our understanding and, thus, slightly differs from the original paper.

2.5 Alkoxylation and Aryloxylation

In 2011, Londregan and colleagues reported a mild, one-pot synthesis of 2-aryloxy pyridines **129** from pyridine *N*-oxides and phenols (Scheme 37A).^[59] The conditions were identical to their previous amination method,^[30] with PyBroP used as the activating agent. The group later reported the synthesis of 2-alkoxy pyridines **130** by reaction of non-aromatic alcohols with *N*-oxides (Scheme 37B).^[60] Minimal product was obtained using the conditions employed for the synthesis of 2-aryloxy pyridine. However, changing the base from DIPEA to sodium carbonate resulted in a dramatic improvement in the yield, likely due to an increase in the lifetimes of both PyBroP and the activated intermediate **36** (Scheme 12). A similar strategy using silver carbonate allowed for the introduction of fluoroalkoxy groups onto quinolines, isoquinolines, and pyridines (Scheme 38).^[61] Two byproducts, viz. 2-bromoquinoline and 2-quinolinone, were detected when DIPEA was used as the base. Yield was improved dramatically upon switching the base to sodium carbonate. The best yield was obtained when silver carbonate was used as the base, which suppressed the formation of 2-bromoquinoline by forming a precipitate with the bromide ion derived from PyBroP. The 2-quinolinone byproduct was suppressed by using molecular sieves. This is a promising strategy as the addition of fluorinated groups can improve the lipophilicity, bioavailability, and metabolic stability of organic molecules, which is highly significant for preclinical drug development.

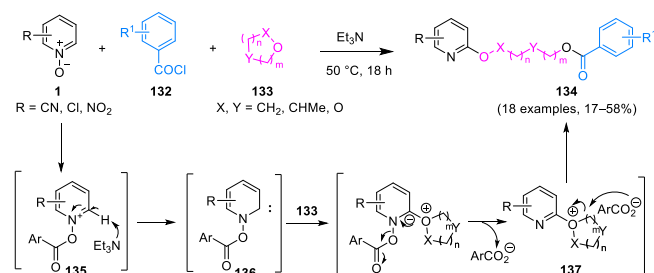


Scheme 37. C2-aryloxylation and alkoxylation of pyridine *N*-oxides.



Scheme 38. Preparation of fluoroalkoxy *N*-heterocycles from heterocyclic *N*-oxides.

Tomkinson's team developed a three-component reaction involving electron-deficient pyridine *N*-oxides, acyl chlorides, and cyclic ethers in the presence of triethylamine to afford 2-alkoxy pyridines **134** in low to medium yields (Scheme 39).^[62] This system employs the cyclic ether as both the reactant and solvent and is proposed to occur via formation of carbene intermediate **136**.

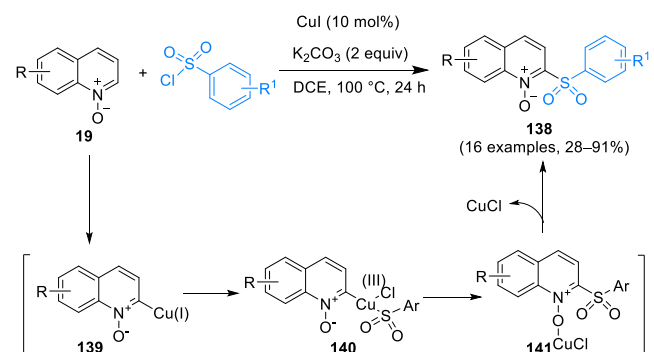


Scheme 39. Alkoxylation of pyridine *N*-oxides with cyclic ethers and acyl chlorides.

2.6 Sulfonylation

2.6.1 Metal-Catalyzed Sulfonylation

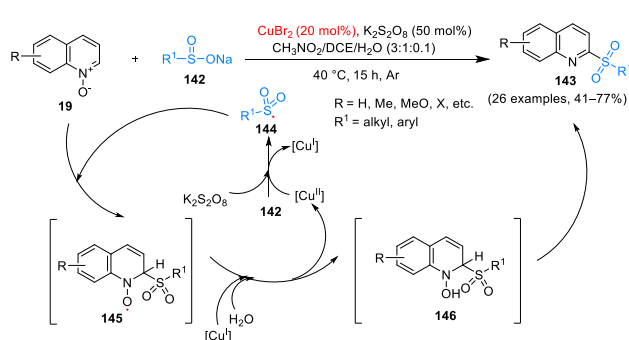
In 2013, Wu's group showed that CuI could catalyze the non-deoxygenative sulfonylation of quinoline *N*-oxides using aryl sulfonyl chlorides (Scheme 40).^[63] Both electron-rich and electron-poor phenyl sulfonyl chlorides are compatible with this process. However, the reaction is not amenable to pyridine/pyrazine/pyrimidine *N*-oxides.



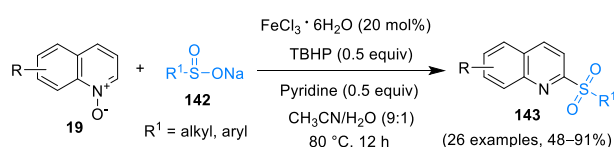
Scheme 40. Non-deoxygenative sulfonylation of quinoline *N*-oxides.

Unlike the above-mentioned Cu(I)-catalyzed non-deoxygenative sulfonylation, deoxygenative sulfonylation occurs in the presence of Cu(II)-catalysts or oxidizing reagents. Pan's group

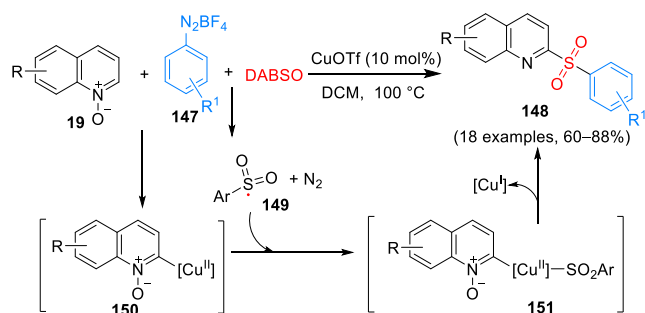
introduced a unique, regioselective, Cu-catalyzed deoxygenative sulfonylation of quinoline *N*-oxides using sodium sulfonates **142** in the presence of the radical initiator $K_2S_2O_8$ (Scheme 41).^[64] Electron-rich aromatic sulfonates generally performed better than electron-poor reagents. Mechanistic studies suggest that the reaction proceeds through a Minisci-type radical coupling step involving a sulfonyl radical, **144**, formed via the Cu(II)- or $K_2S_2O_8$ -mediated oxidation of sodium sulfinate, **142**. Quinoline displayed expectedly poorer reactivity, being unable to react under the standard conditions in control experiments. $FeCl_3$ and TBHP were also successfully employed for the deoxygenative sulfonylation of quinoline *N*-oxides (Scheme 42).^[65] Wang's group enabled the same transformation by generating a sulfonyl radical, **149**, through the reaction of DABSO [DABCO•(SO₂)₂] and aryldiazonium tetrafluoroborate using Cu(I) salt as a catalyst (Scheme 43).^[66]



Scheme 41. Cu-catalyzed deoxygenative sulfonylation of quinoline *N*-oxides.

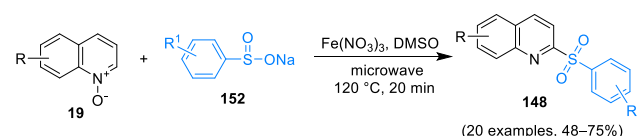


Scheme 42. Iron-catalyzed deoxygenative sulfonylation of quinoline *N*-oxides.



Scheme 43. Cu-catalyzed, three-component sulfonylation of quinoline *N*-oxides.

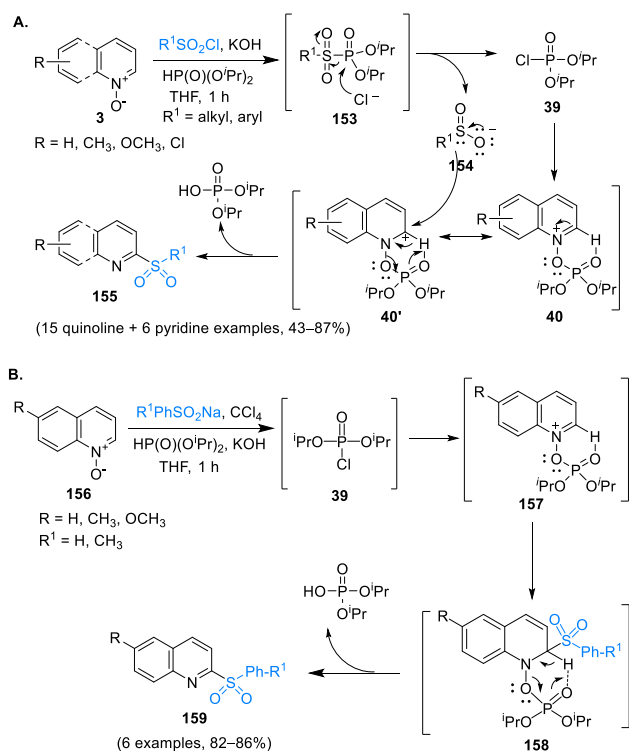
Iron (III)-catalyzed, oxidant-free reactions at higher temperatures are possible for deoxygenative sulfonylation (Scheme 44).^[67] These reactions include a broad range of substrates and proceed with good regioselectivity and functional group tolerance. In general, sodium arylsulfonates bearing electron-donating substituents showed superior reaction efficiency to those substituted with electron-withdrawing groups. Unfortunately, aliphatic sodium sulfonates were found to be unsuitable under the current conditions. Although the reaction mechanism is not fully understood, mechanistic studies suggest a non-radical pathway.



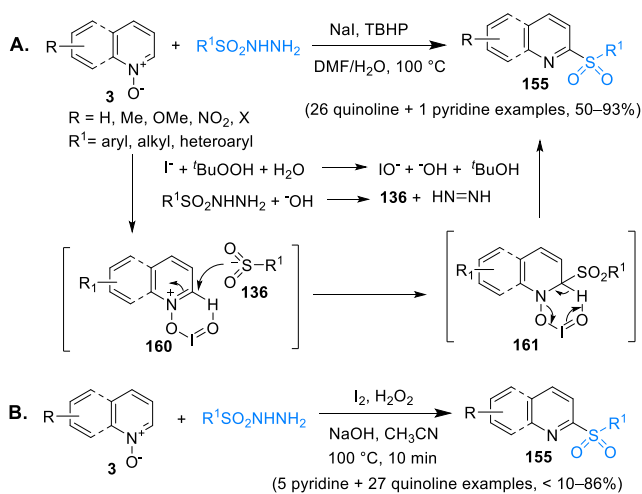
Scheme 44. Iron-catalyzed, regioselective arylsulfonylation of quinoline *N*-oxides.

2.6.2 Organic Reagent/Base-Promoted Deoxygenative Sulfonylation

Zhao's group developed a procedure superior to high-temperature, metal-catalyzed sulfonylation for building a large variety of both 2-(aryl/alkyl sulfonyl)pyridines and 2-(aryl/alkyl sulfonyl)quinolines. Their method employed the direct C-H functionalization of pyridine/quinoline *N*-oxides with sulfonyl chlorides or sodium sulfonates by activation with *H*-phosphonates at ambient temperatures (Scheme 45).^[68] Remarkably, the *H*-phosphonates play a dual role in the reaction, generating both the functioning activating agent, diisopropyl chlorophosphate (**39**), and the sulfonyl anion, **154**.



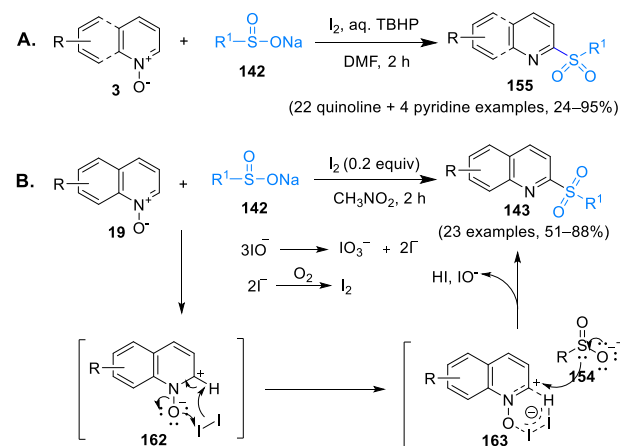
Scheme 45. Sulfonylation of quinoline/pyridine *N*-oxides by activation with *H*-phosphonates.



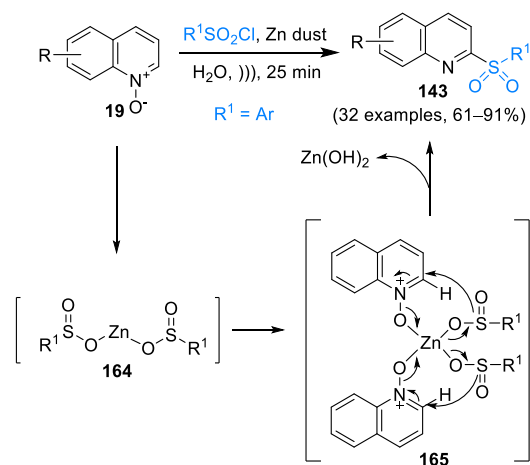
Scheme 46. Sulfonylation of *N*-oxides with sulfonyl hydrazides and hypiodites.

Another efficient metal-free sulfonylation was accomplished using *N*-oxides and sulfonyl hydrazides through activation by hypiodite, generated *in situ* from NaI and TBHP (Scheme 46A).^[69] Unfortunately, the reaction is not effective for most pyridine *N*-oxides. One alternative to this method uses iodine and H₂O₂ to induce the rapid sulfonylation of *N*-oxides (Scheme 46B).^[70] A gram-scale reaction was conducted through this route and resulted in only a slight loss of product. A similar transformation, but without *in situ* generation of a sulfonyl anion, was

achieved through a direct reaction with sodium sulfinates in the presence of I₂ and TBHP at room temperature (Scheme 47A).^[71] Interestingly, Zhao's group found that this reaction could even be performed without TBHP. Moreover, I₂ is an effective activating agent and can be regenerated by air oxidation of the iodide ion produced in the reaction (Scheme 47B).^[72]



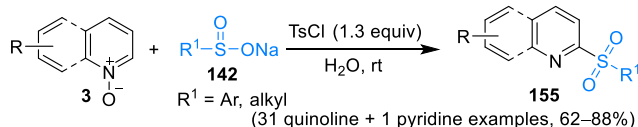
Scheme 47. Iodine/(TBHP)-promoted sulfonylation of *N*-oxides with sodium sulfinates.



Scheme 48. Ultrasound-accelerated sulfonylation of quinoline *N*-oxides in water.

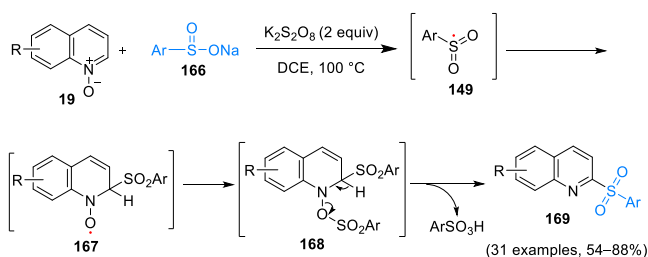
In 2017, an efficient, ultrasound-accelerated one-pot synthesis of 2-sulfonylquinolines in water was developed by He's group (Scheme 48).^[73] Ultrasound irradiation aided in the zinc-dust-mediated reduction of the sulfonyl chloride to a zinc bisulfinate compound, **164**. Quinoline *N*-oxide **19** coordinates with **164** to generate the reactive intermediate, **165**, which undergoes intramolecular nucleophilic addition to form the sulfonated product, **143**, with subsequent release of zinc hydroxide. Compared with conventional heating conditions, the ultrasound-assisted techniques improved efficiency and minimized side reactions. The group later reported a

TsCl-promoted aqueous sulfonylation that proceeds via the traditional Reissert-type mechanism (Scheme 49).^[74] Beneficially, this reaction is suitable for both alkyl and aryl sulfinates.



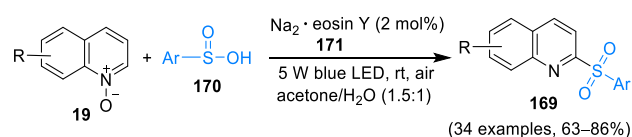
Scheme 49. TsCl-promoted sulfonylation of quinoline/pyridine *N*-oxides.

He's team also developed a Minisci-type reaction for the sulfonylation of quinoline *N*-oxides with sodium sulfinates (Scheme 50).^[75] Sodium sulfinates **166** play a dual role of the sulfonylation source and the activating reagent. Mechanistic studies suggest that the *in situ* generation of sulfonyl radicals **149** is a key factor in obtaining the deoxygenative sulfonylated products. In contrast, the similar reaction developed by Pan's team allowed for lower temperature conditions but necessitated the use of CuBr₂ as a catalyst (Scheme 41).^[64]

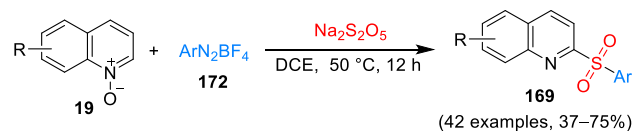


Scheme 50. Metal-free deoxygenative sulfonylation of quinoline *N*-oxides.

Sulfonyl radicals **149** have been generated and employed in two additional methods. Visible-light-induced deoxygenative C2-sulfonylation of quinoline *N*-oxides with sulfinic acids was described using an organic dye, **171**, as the catalyst (Scheme 51).^[76] The generation of **149** using this method is eco-friendly and mild, employing ambient air as the sole oxidant. Xia's group developed a three-component sulfonylation using quinoline *N*-oxides, sodium metabisulfite, and aryldiazonium tetrafluoroborates **172** to provide C2-sulfonylated products **169** in moderate to good yields (Scheme 52).^[77] The aryldiazonium tetrafluoroborates decompose to generate an aryl radical, which subsequently attacks Na₂S₂O₅ to give sulfonyl radical **131**.

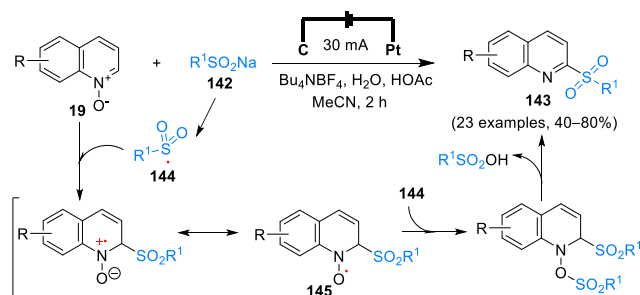


Scheme 51. Visible-light-induced sulfonylation of quinoline *N*-oxides.



Scheme 52. Three-component sulfonylation of quinoline *N*-oxides.

Electrochemistry is an emerging, environmentally benign strategy for modern organic synthesis as no oxidant or reductant is required. One application of this technology is exemplified by Lei's sulfonylation of quinoline *N*-oxides using sodium sulfinates via a Minisci-type mechanism (Scheme 53).^[78] Sodium sulfinates **142** act as both the sulfonylation source and the activating agent.

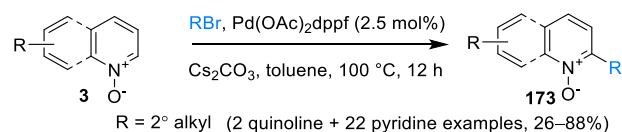


Scheme 53. Electrochemical deoxygenative C2 sulfonylation of quinoline *N*-oxides.

2.7 Alkylation

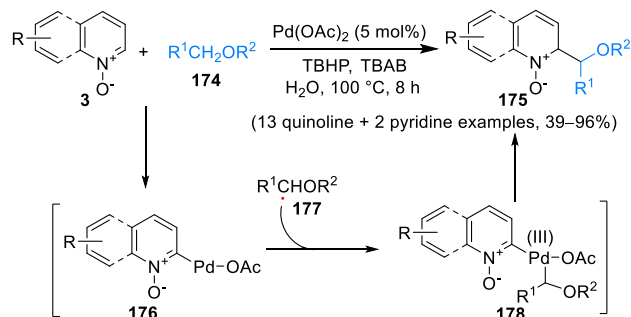
2.7.1 Metal-Catalyzed Non-Deoxygenative Alkylation

In 2013, Fu's group reported a Pd-catalyzed alkylation of pyridine/quinoline *N*-oxides using secondary, and even tertiary, alkyl bromides (Scheme 54).^[79] The reaction is convenient but requires two *N*-oxide equivalents.

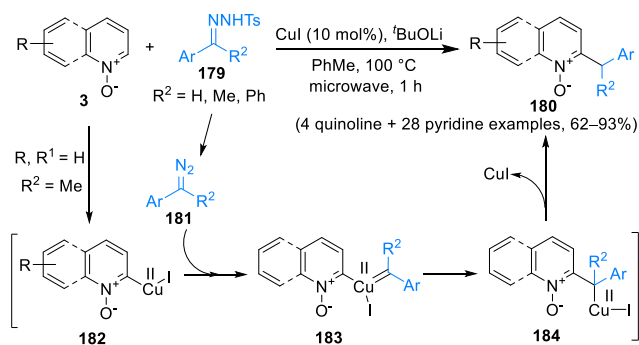


Scheme 54. Pd-catalyzed alkylation of quinoline/pyridine *N*-oxides with alkyl bromides.

Another Pd-catalyzed system was developed by Wu's group utilizing ethers or thioethers as both the reactant and solvent and TBHP as an oxidant (Scheme 55).^[80] Interestingly, Pd(III) species **178** are formed via reaction of **176** with radical **177**, which is generated *in situ* through TBHP-initiated hydrogen-atom abstraction.



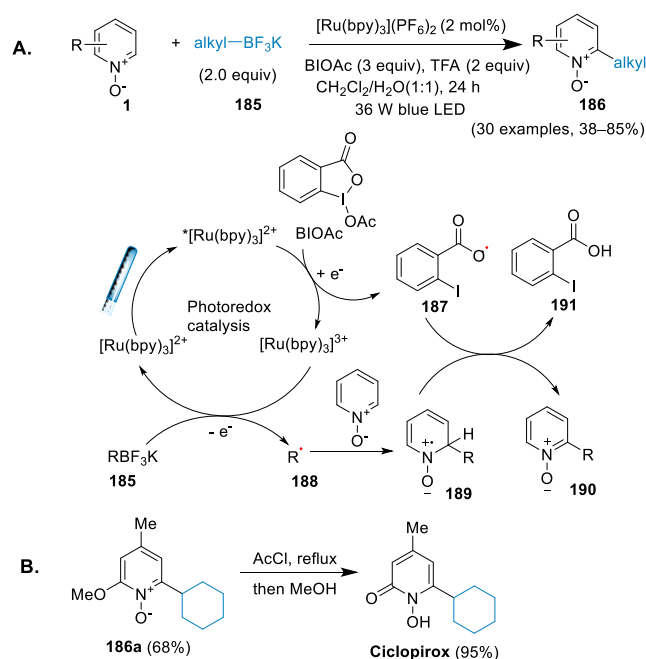
Scheme 55. Pd-catalyzed C2-alkylation of quinoline/pyridine *N*-oxides with ethers.



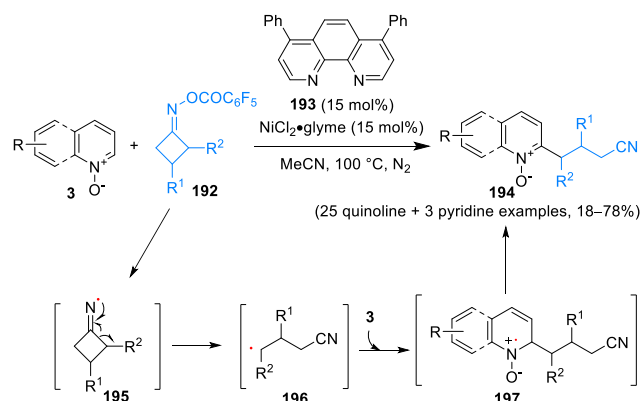
Scheme 56. Cu-catalyzed C2-alkylation of quinoline/pyridine *N*-oxides with *N*-tosylhydrazones.

N-tosylhydrazone is an efficient alkylating reagent for Cu-catalyzed reactions under basic conditions and high temperatures (Scheme 56).^[81] Diazo compound **181** is generated *in situ* from *N*-tosylhydrazone **179** in the presence of *t*BuOLi. Notably, copper-carbene species **183** are produced by the reaction of **181** and metalated intermediate **182**. Migratory insertion of C2-carbon to the carbenic carbon produces **184**, which upon protonation affords **180** and regenerates the CuI catalyst.

A photoredox-catalyzed direct C2-alkylation of pyridine *N*-oxides using alkyltrifluoroborate and hypervalent iodine(III) oxidant (BIOAc) under acidic conditions was developed by Xu's group in 2017 (Scheme 57A).^[82] The mild reaction proceeds by a Minisci-type mechanism and was successfully applied to the synthesis of the antifungal ciclopirox (Scheme 57B).



Scheme 57. Visible-light-induced C2-alkylation of pyridine *N*-oxides.



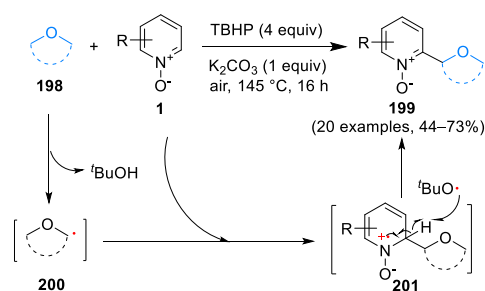
Scheme 58. Ni-catalyzed C2-alkylation of quinoline/pyridine *N*-oxides with cyclobutanone oximes.

A nickel-catalyzed direct C2–H cyanoalkylation of heteroaromatic *N*-oxides with cyclobutanone oximes was reported by Guo and coworkers (Scheme 58).^[83] Mechanistic studies suggest the formation of a radical intermediate, **196**, and single-electron transfer from the Ni complex.

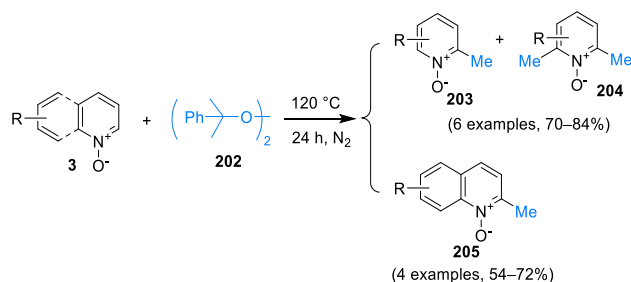
2.7.2 Organic Reagent/Base-Promoted Alkylation

In 2015, Wang and coworkers developed a novel and efficient radical addition of ethers to pyridine *N*-oxides in the presence of TBHP (Scheme 59).^[84] A similar approach was reported with quinoline *N*-oxides.^[85] Peroxide **202** was employed as a methyl radical precursor for the alkylation of both pyridine and quinoline *N*-oxides, resulting in the formation of both monomethylated and dimethylated products

(**203** and **204**, respectively) from pyridine substrates (Scheme 60).^[86]

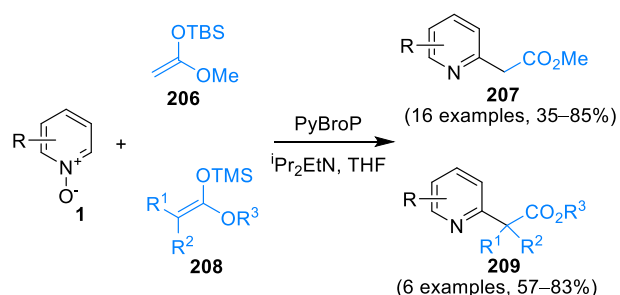


Scheme 59. Alkylation of pyridine *N*-oxides with ethers.

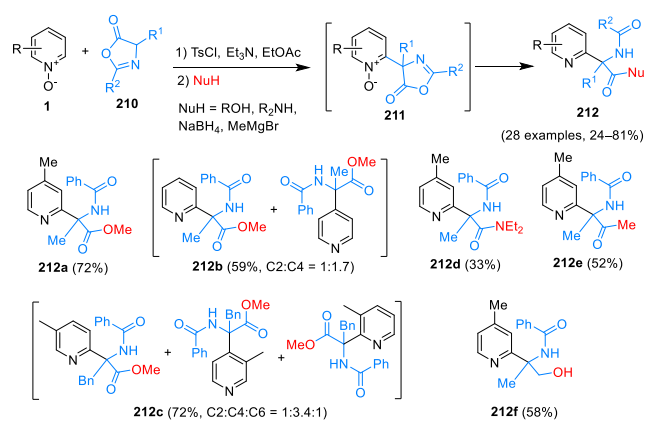


Scheme 60. Methylation of pyridine/quinoline *N*-oxides with peroxide.

Pyridine *N*-oxides can also be alkylated by the traditional Reissert-type mechanism. One such example is the synthesis of α -(2-azaheteroaryl) acetates **207** or **209** from the reaction between **1** and silyl ketene acetals **206** or **208**, respectively, activated by PyBroP (Scheme 61).^[87] It should be noted that the hexafluorophosphate counteranion of PyBroP is an important reaction component as it initiates the silicon–oxygen cleavage necessary for ketene acetal addition.



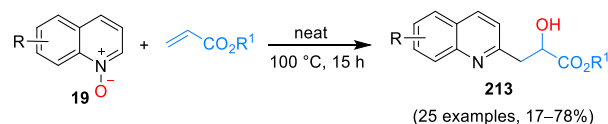
Scheme 61. Alkylation of pyridine *N*-oxides with silyl ketene acetals.



Scheme 62. C2-alkylation of pyridine *N*-oxides with azlactones.

Another example of a Reissert-type alkylation is the one-pot, three-component synthesis of α -pyridyl, α -substituted amino acid derivatives **212**. Readily available azlactones **210** were chosen as appropriate nucleophiles for the activated pyridine *N*-oxides because their pK_a values were similar to those of the carbon acids or phenols studied by Londregan. The reaction proceeds via TsCl-activated direct alkylation of pyridine *N*-oxides with **210** and subsequent ring opening with diverse nucleophiles (Scheme 62).^[88] Notably, the regioselectivity favors the C4 isomers for pyridine and 3-methylpyridine *N*-oxides.

Alkenes have also been used for pyridine *N*-oxide alkylations. Sharma and coworkers reported the first example with the synthesis of quinoline-substituted α -hydroxy carboxylic derivatives **213** from the reaction of quinoline *N*-oxides with electron-deficient olefins under catalyst- and solvent-free conditions at elevated temperatures (Scheme 63).^[89] The reaction proceeds through 1,3-dipolar cycloaddition, followed by cleavage of the N–O bond. Competition experiments with electronically distinct quinoline *N*-oxides suggested that electron-rich *N*-oxides are favored.

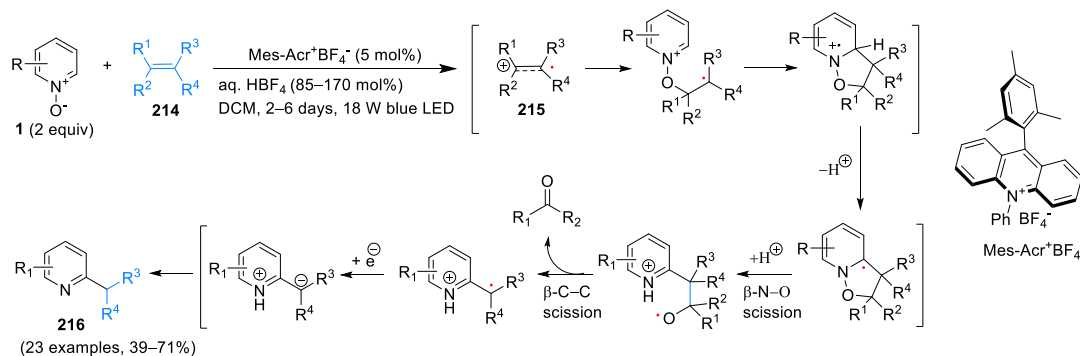


Scheme 63. Alkylation of quinoline *N*-oxides with alkenes.

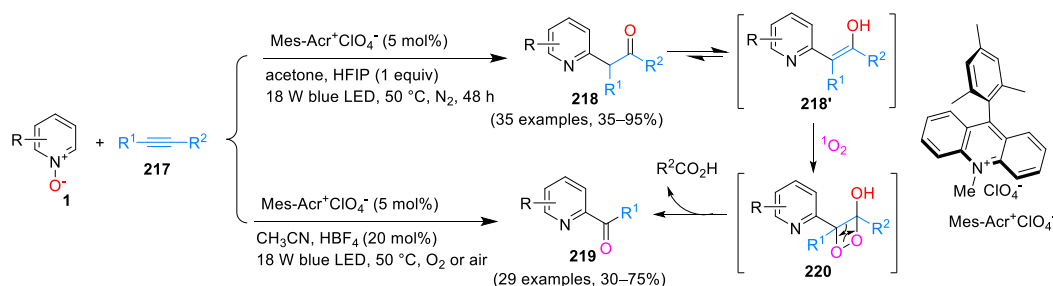
The photocatalyzed alkylation of pyridine *N*-oxides with neutral alkenes was later reported by Murakami and coworkers (Scheme 64).^[90] The coupling step was initiated by the radical cation intermediate, **215**, generated by photoirradiation of an alkene in the presence of a photocatalyst. This strategy was successfully applied to reactions between various *N*-oxides and alkenes, yielding pyridines with benzyl and secondary alkyl groups at the *ortho* position. Interestingly, when a similar visible-light-catalyzed

system was applied to alkynes and pyridine *N*-oxides, either the alkylated product **218** or the acylated product **219** was obtained in moderate to excellent yields, depending on whether the reaction was performed under an inert atmosphere (Scheme 65).^[91] The reaction under nitrogen proceeds via mechanism similar to the one for the reaction with alkenes. In an

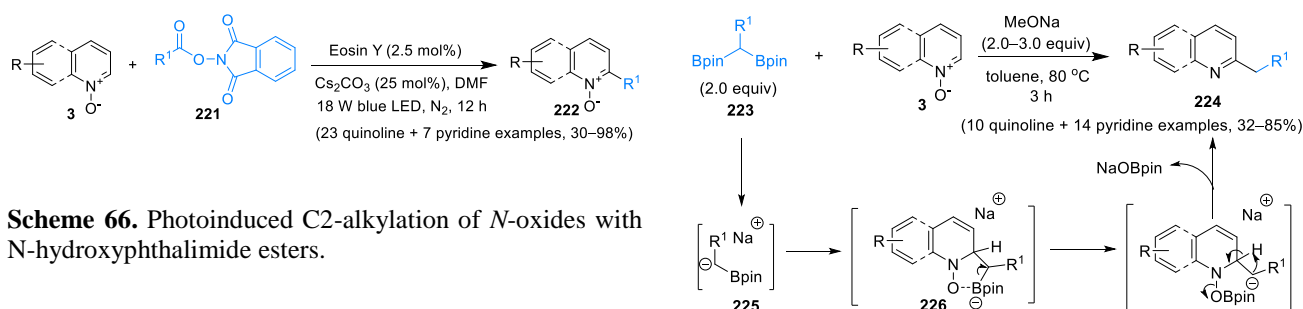
atmosphere of O₂ or air, singlet oxygen is produced via energy transfer between the light-excited photocatalyst and ³O₂. Then, the enol form, **218'**, of the alkylation product reacts with ¹O₂ to yield **220**, which collapses to afford **219** and the carboxylic acid byproduct.



Scheme 64. Reductive C2-alkylation of pyridine *N*-oxides with alkenes.



Scheme 65. Photoinduced C2-alkylation/acylation of pyridine *N*-oxides with alkynes.

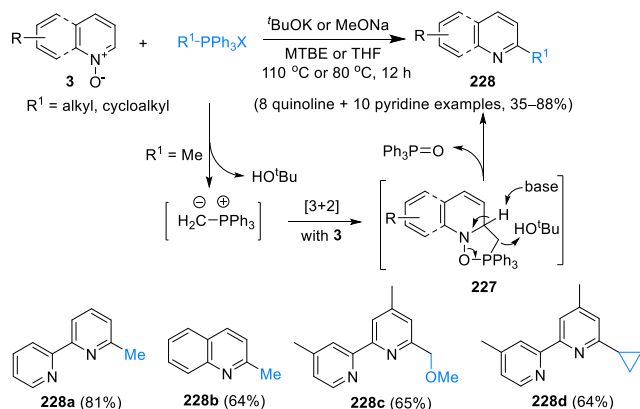


More recently, Zhou's team presented a visible-light-induced alkylation of heterocyclic *N*-oxides with *N*-hydroxyphthalimide esters **221** using organic dye Eosin Y as the photocatalyst (Scheme 66).^[92] Remarkably, this transformation is amenable to a wide range of primary, secondary, and tertiary alkyl groups and is applicable to several complex heterocyclic *N*-oxides.

Scheme 67. Alkylation of pyridine/quinoline *N*-oxides with diborylalkanes.

In 2016, an unprecedented, base-promoted deborylative primary alkylation of *N*-oxides with 1,1-diborylalkanes was reported by Cho's group (Scheme 67).^[93] The yield was higher for quinoline and pyridine substrates than for isoquinoline and quinoxaline substrates. The α -boryl carbanion intermediate, **225**, is initially generated by the reaction of a 1,1-diborylalkane with MeONa. Later,

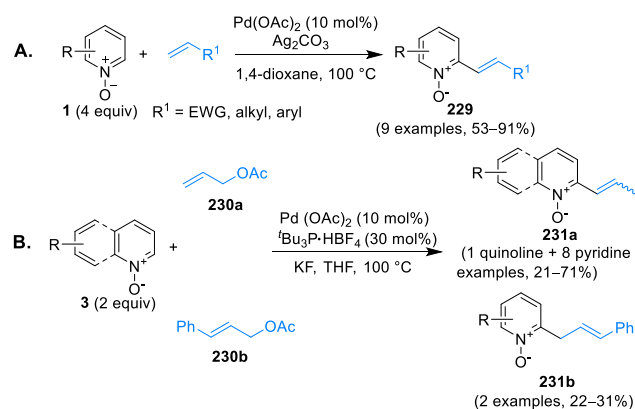
the same group disclosed a secondary alkylation protocol through a similar approach at higher temperatures.^[94] Kim and coworkers employed Wittig reagents for the alkylation of *N*-oxides (Scheme 68).^[95] Although the reaction requires a strong base and high temperatures, it proceeds well with both excellent positional-selectivity and functional-group compatibility. Phosphonium ylide was generated, which subsequently underwent intermolecular [3+2] annulation to afford intermediate **227**. Finally, aromatization by an external base afforded the alkylated product, **228**, along with triphenylphosphine oxide.



Scheme 68. Alkylation of pyridine/quinoline *N*-oxides with Wittig reagents.

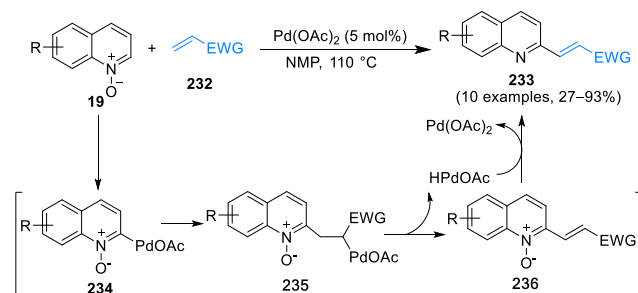
2.8 Alkenylation

In 2008, Chang's group developed a Pd(OAc)₂-catalyzed non-deoxygenative method for the alkenylation of pyridine *N*-oxides using silver carbonate as the oxidant (Scheme 69A).^[15a] While this method is efficient, its requirement for a large excess of *N*-oxides renders it impractical. The arylation of pyridine *N*-oxides with unactivated arenes like benzene is also realized under similar conditions, while a large excess of arenes (40 equiv) is required. Another Pd-catalyzed alkenylation is Poli's reaction with allyl acetate, which proceeds via an allylation/isomerization cascade to generate products **231** in low to moderate yields (Scheme 69B).^[96] When cinnamyl acetate **230b** is used, the same catalytic system promotes C2-cinnamylation of pyridine *N*-oxides without subsequent isomerization.

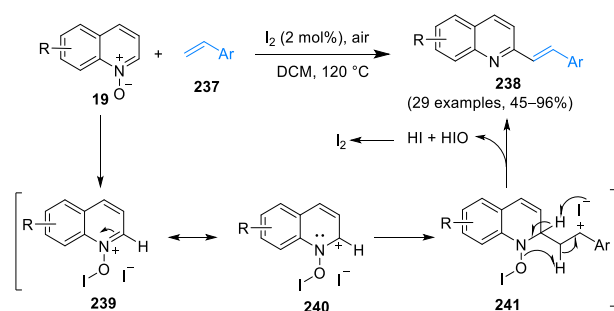


Scheme 69. Pd-catalyzed non-deoxygenative alkenylation of *N*-oxides.

Considering *N*-oxides as prototypical oxidants, Wu and coworkers developed a Pd-catalyzed deoxygenative alkenylation of quinoline *N*-oxides that eliminates the use of external oxidants and ligands (Scheme 70).^[97] Using this approach, quinoline *N*-oxide, and derivatives bearing electron-donating methyl groups at positions 3, 4, and 6, were smoothly alkenylated with acrylate at the C2 position in high yields. In contrast, electron-withdrawing substituents reduced the reactivity, and no desired product was obtained using 4-nitroquinoline-*N*-oxide as the substrate. Notably, the catalyst plays a direct role in deoxygenative functionalization, the final step of which involves the oxidation of palladium hydride by *N*-oxide intermediate **236**.



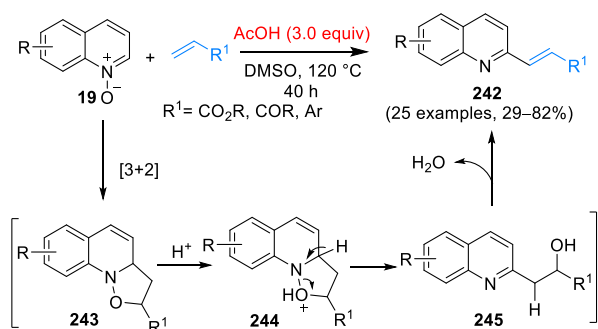
Scheme 70. Pd(OAc)₂-catalyzed alkenylation of quinoline *N*-oxides.



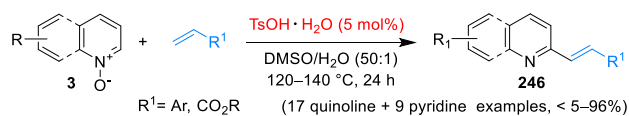
Scheme 71. I₂-catalyzed alkenylation of quinoline *N*-oxides.

In 2017, the same group reported an I₂-catalyzed alkenylation of azaheterocycle *N*-oxides, including quinoline, isoquinoline, and quinoxaline *N*-oxides (Scheme 71).^[98] Interestingly, the HI and HIO generated in the last step react to regenerate iodine for the next catalytic cycle.

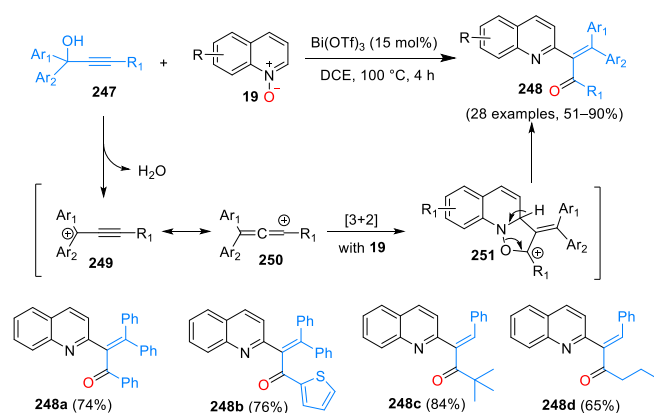
The alkenylation of *N*-oxides can also be achieved under acidic conditions. In 2016, Wang and coworkers reported the synthesis of 2-alkenylquinoline **242** by AcOH-promoted reductive olefination of quinoline *N*-oxide (Scheme 72).^[99] The protocol relies on a thermally promoted [3+2] cycloaddition between an *N*-oxide and an alkene to generate an isoxazolidine **243**. The Brønsted acid then promotes N-O cleavage and dehydration to afford the target compound, **242**. Catalytic TsOH·H₂O has also been employed for this transformation (Scheme 73).^[100]



Scheme 72. AcOH-promoted C2-alkenylation of quinoline *N*-oxides.



Scheme 73. Acid-catalyzed C2-alkenylation of pyridine, quinoline, and isoquinoline *N*-oxides.

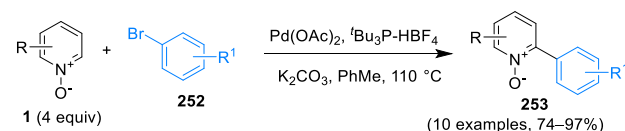


Scheme 74. Lewis-acid-catalyzed alkenylation of quinoline *N*-oxides.

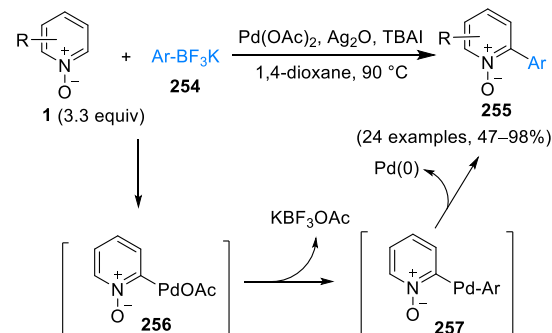
In 2017, Liang's group reported an efficient, Lewis-acid-catalyzed synthesis of medically valuable 2-(quinolin-2-yl)prop-2-en-1-ones **248** via dehydrogenative coupling of propargylic alkynols **247** with quinoline *N*-oxides (Scheme 74).^[101] Importantly, the reaction was efficiently scalable to gram quantities.

2.9 Arylation

Pd(OAc)₂/tBu₃P was identified as an effective system for the coupling of *N*-oxides and phenyl bromides by Fagnou in 2005 (Scheme 75).^[14] Although the reaction is efficient, four equivalents of *N*-oxides are required. Improved methods have been developed, including the coupling of *N*-oxides with unactivated arenes^[15a] and aryl or alkenyl tosylates and mesylates.^[102] Wei developed another Pd-catalyzed system for the arylation of pyridine *N*-oxides using potassium aryl- and heteroaryltrifluoroborates **254** (Scheme 76).^[103] Importantly, this method provides the desired biaryl products in moderate to high yields with good functional group tolerance and high regioselectivity. The mechanism involves *ortho*-C-H activation, transmetalation, and reductive elimination.



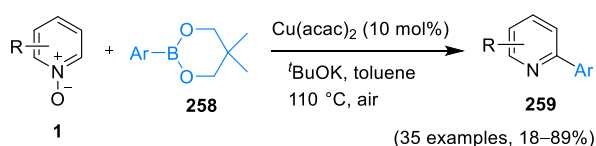
Scheme 75. Pd-catalyzed arylation of pyridine *N*-oxides with phenyl bromides.



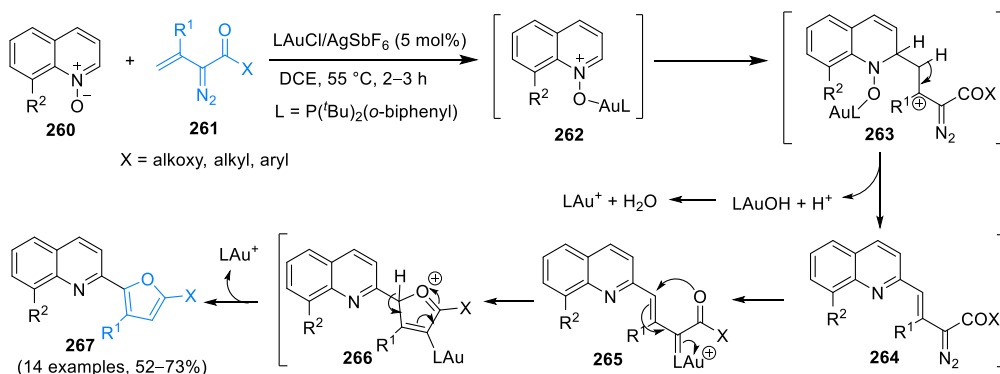
Scheme 76. Pd-catalyzed arylation of pyridine *N*-oxides with trifluoroborates.

Additional metal-catalyzed direct arylations of *N*-oxides have been described. Cu-catalyzed deoxygenative C2-arylation of pyridine *N*-oxides with arylboronic esters **258** was reported in 2014 (Scheme 77).^[104] In contrast to the above examples, which use a large excess of *N*-oxides, this reaction requires an excess of the coupling partner **258** (2 equiv). The mechanism may involve arylation of the pyridine *N*-oxides with arylboronic esters followed by deoxygenation of the resultant arylated pyridine

N-oxides with an organoboron reagent to produce the 2-aryl pyridines **259**.

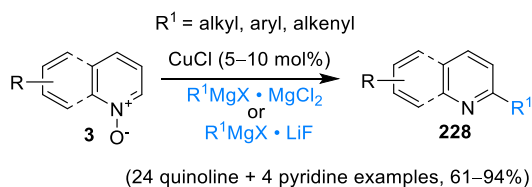


Scheme 77. Cu-catalyzed arylation of pyridine *N*-oxides with boronic esters.



Scheme 78. Au-catalyzed α -furanylations of quinolone *N*-oxides with alkenyldiazo carbonyl species.

Arylation using Grignard reagents is another powerful tool for the construction of 2-arylpyridines. It had been reported that Grignard reagents react with heterocyclic *N*-oxides to afford a mixture of non-deoxygenative addition and ring-opening products, which can be converted to **228** following treatment with dehydrating reagents.^[5] In 2014, Larionov's group described the direct synthesis of various 2-alkyl-, aryl-, and alkenyl-substituted pyridines and quinolines using Grignard reagents and *N*-oxides (Scheme 79).^[106] This approach utilizes both copper catalysis and activation by lithium fluoride or magnesium chloride. The utility of this method for the late-stage modification of complex *N*-heterocycles is exemplified by the facile syntheses of novel structural analogs of several antimalarial, antimicrobial, and fungicidal agents.

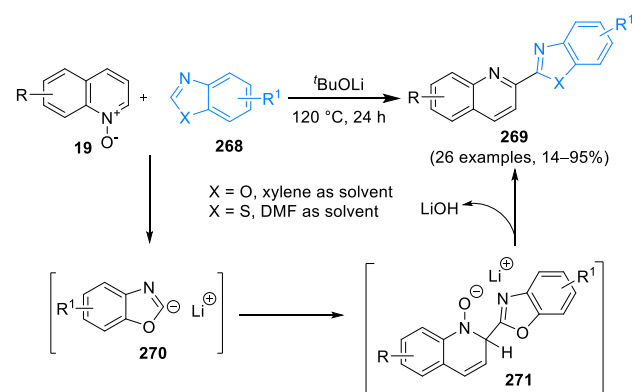


Scheme 79. Alkyl-, aryl-, and alkenylation of *N*-oxides by Cu-catalyzed Grignard addition.

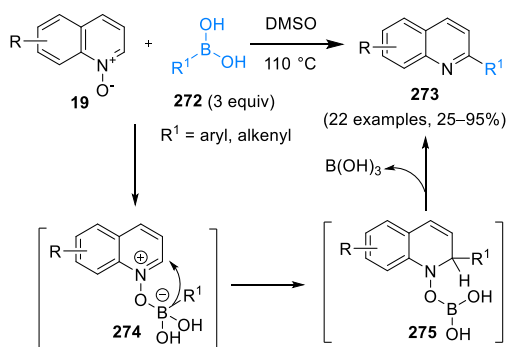
Visible-light-promoted non-deoxygenative arylation of pyridine and quinoline *N*-oxides has been

Liu reported an Au-catalyzed reaction between 8-alkylquinoline *N*-oxides **260** and vinyldiazo carbonyl compounds **261** to yield 2-furanyl-quinoline products **267** (Scheme 78).^[105] The nucleophilic attack of **261** on the Au(I)-bound oxide complex **262** generates **263**, which undergoes dehydration to form species **264**. Gold complexes then activate diazo decomposition of species **264** to yield gold carbenes **265**, which undergo an oxa-Nazarov cyclization to form furanylium cation **266** and ultimately **267**. This mechanism is highly speculative, and additional work is required for its confirmation.

realized with diaryliodonium tetrafluoroborate using Eosin Y as a photocatalyst.^[107] Transition-metal-free arylation of *N*-oxides has also been achieved via a Reissert-type mechanism. In 2015, Wu's group described a base-promoted cross-dehydrogenative coupling between quinoline *N*-oxides and 1,3-azoles **268** under air (Scheme 80).^[108] The mechanism involves the formation of intermediates **270** and **271** and the release of LiOH.



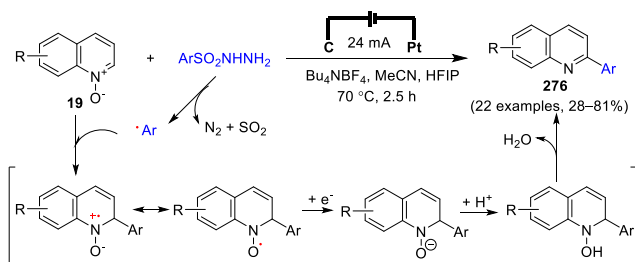
Scheme 80. Cross-dehydrogenative coupling of quinoline *N*-oxides with 1,3-azoles.



Scheme 81. Metal-free cross-coupling of quinoline *N*-oxides with boronic acids.

While the arylation of pyridine *N*-oxides with arylboronic acids requires AgNO_3 for catalysis,^[109] Antonchick and coworkers achieved both the arylation and alkenylation of quinoline *N*-oxides by directly reacting quinoline *N*-oxides with boronic acids **272** in hot DMSO (Scheme 81).^[110] Coordination of boronic acid **272** to the *N*-oxide brings the reactants into close proximity. Similar to a Petasis reaction, aryl migration of the boronic acid proceeds via nucleophilic attack at the C2 position to yield **275**. Concerted rearomatization and elimination of boric acid results in the deoxygenative formation of functionalized quinoline **273**.

The arylation of quinoline *N*-oxides has also been achieved electrochemically. One application of this technology is exemplified by Lei's arylation of quinoline *N*-oxides with aryl sulfonyl hydrazide through a Minisci-type mechanism (Scheme 82).^[111] The aryl radical is produced from sulfonyl hydrazide through the loss of three protons and electrons and the subsequent release of N_2 and SO_2 .

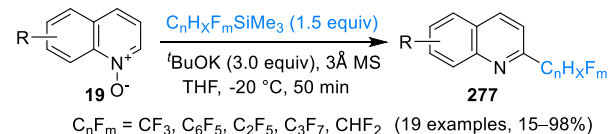


Scheme 82. Electrochemical deoxygenative C2-arylation of quinoline *N*-oxides.

2.10 Trifluoromethylation

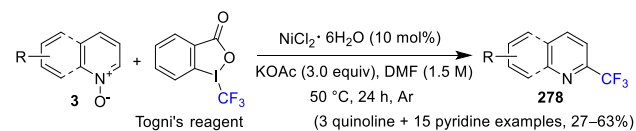
Despite the importance of fluoroalkyl-substituted heterocycles in medicinal and agricultural chemistry, the trifluoromethylation of *N*-oxides was not achieved until 2014. Larionov's group investigated reactions between heterocyclic *N*-oxides and perfluoroalkylsilanes affording 2-perfluoroalkyl/aryl-substituted heterocycles **277** in good to excellent yields (Scheme 83).^[112] This reaction was also exploited for the syntheses of new analogs of the

antimicrobial drug chlorquinaldol. Although this method is efficient for quinoline and isoquinoline *N*-oxides, low yields were obtained for pyridine *N*-oxide substrates.



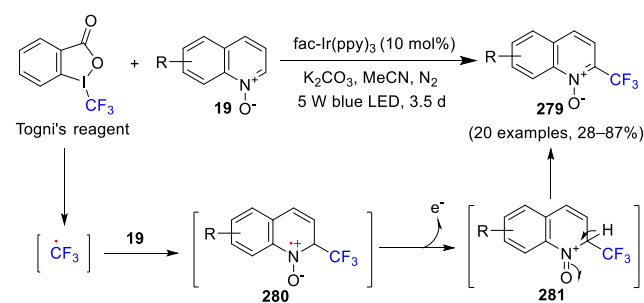
Scheme 83. Perfluoroalkylation of heterocyclic *N*-oxides.

Wu's team recently described a Ni-catalyzed trifluoromethylation of pyridine *N*-oxides in low to medium yields using Togni's reagent (Scheme 84).^[113] Beneficially, the reaction is easily scaled to gram quantities and has been applied to the late-stage trifluoromethylation of hydroquinine. While the mechanism is not fully understood, a radical pathway was proposed based on control experiments.



Scheme 84. Ni-catalyzed trifluoromethylation of *N*-oxides.

Interestingly, utilizing the same trifluoromethylation source, Gao and coworkers developed a visible-light-promoted non-deoxygenative trifluoromethylation of quinoline *N*-oxides in moderate to good yields (Scheme 85).^[114] This reaction proceeds via a Minisci-type radical addition.

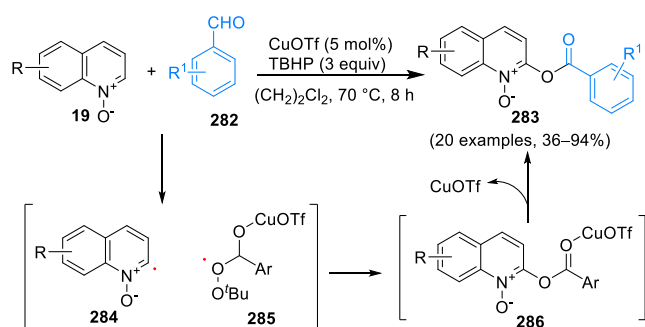


Scheme 85. Visible-light-promoted trifluoromethylation of quinoline *N*-oxides.

2.11 Miscellaneous

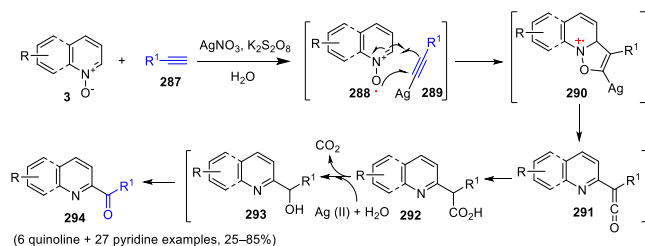
In 2013, Wu's team reported a CuOTf -catalyzed non-deoxygenative acetoxylation of quinoline *N*-oxides using aldehydes (Scheme 86).^[22] In contrast to traditional esterifications, this reaction uses TBHP as an oxidant and copper (I) salt as a catalyst to

synthesize the target product directly under mild and environmentally friendly conditions.

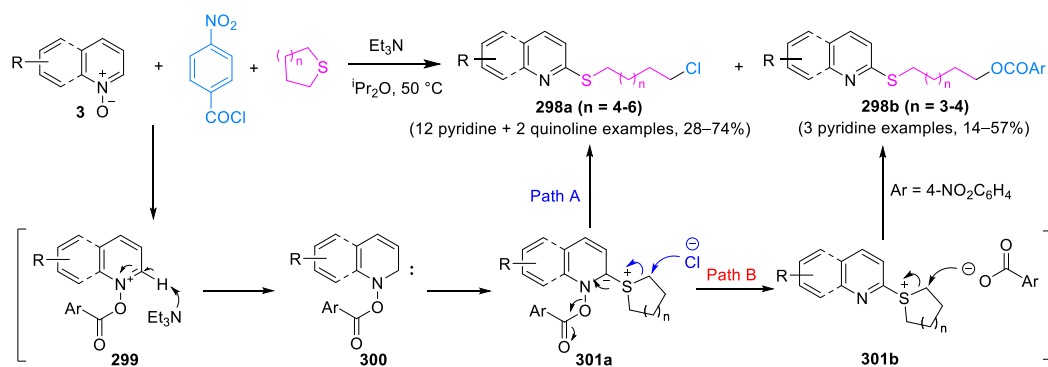


Scheme 86. Acetoxylation of quinoline *N*-oxides using aldehydes.

Few methods are available for the acylation of *N*-oxides. In 2018, Singh and coworkers reported a practical method for the Ag-catalyzed acylation of *N*-oxide using alkynes and $K_2S_2O_8$ as the oxidant (Scheme 87).^[115] Mechanistic studies indicated that the reaction proceeds through a Minisci-type radical addition and Wolff rearrangement of ketene **291** to produce **292**.

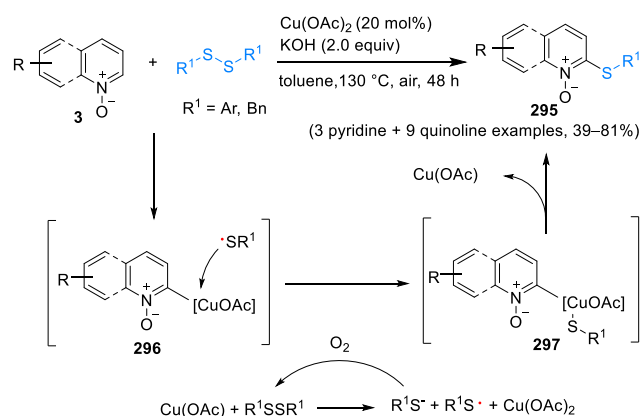


Scheme 87. Acylation of pyridine/quinoline *N*-oxides with alkynes.



Scheme 89. Three-component thiolation of pyridine/quinoline *N*-oxides.

Two groups achieved the trifluoromethylthiolation of *N*-oxides using distinct activating reagents



Scheme 88. Thiolation of pyridine/quinoline *N*-oxides with disulfides.

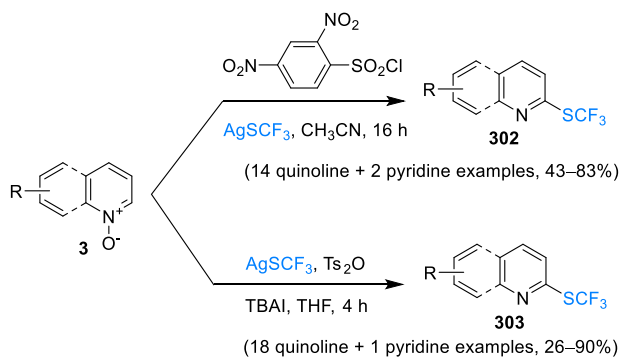
In 2018, Zhao, Wu, and coworkers reported a Cu-catalyzed non-deoxygenative thiolation of *N*-oxides with disulfides (Scheme 88).^[116] During the reaction, *N*-oxide undergoes a facile C-H cleavage to produce the aryl Cu(II) intermediate, **296**. The subsequent reaction with a thiyl radical forms the Cu(III) complex, **297**, which undergoes reductive elimination to yield the desired product, **295**, along with Cu(I) species. The active $Cu(OAc)_2$ catalyst is regenerated by the action of disulfides and air.

Tomkinson's team described a regioselective, three-component coupling reaction between pyridine *N*-oxide, acyl chloride, and thioether in the presence of triethylamine to give 2-thiolated pyridine **298a** and **298b** via carbene **300** (Scheme 89).^[117] The reaction follows path A to give **298a** for less strained sulfide, whereas more strained sulfide expedites the elimination of 4-nitrobenzoate, followed by recombination through ring opening to give **298b**.

(Scheme 90). Kuninobu and coworkers identified 2,4-dinitrobenzenesulfonyl chloride as the best activating

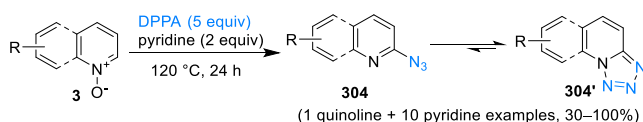
(Scheme 90). Kuninobu and coworkers identified 2,4-dinitrobenzenesulfonyl chloride as the best activating

agent following extensive studies with various sulfonyl chlorides.^[118] This method was applied to the synthesis of a quinidine derivative. Qing's group found that the combination of Ts₂O and TBAI activates the reaction of quinoline and isoquinoline *N*-oxides with AgSCF₃.^[119] This reaction was shown to proceed via the traditional Reissert-type mechanism, with TBAI activating AgSCF₃ to generate the nucleophilic SCF₃ anion.



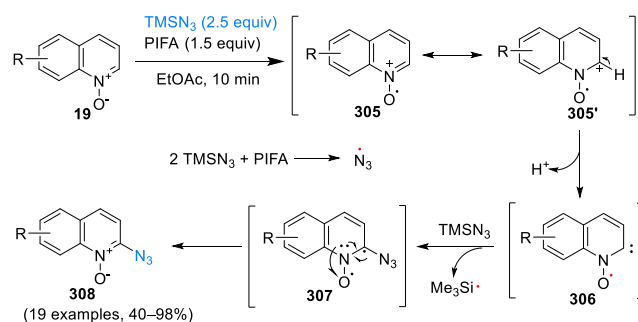
Scheme 90. Trifluoromethylthiolation of azine *N*-oxides.

A neat, high-temperature azidation of azine *N*-oxides with DPPA was accomplished by Keith in 2006 (Scheme 91).^[120] This method is more efficient than azidations using sulfonyl azide generated *in situ* by TMSN₃ and TsCl.

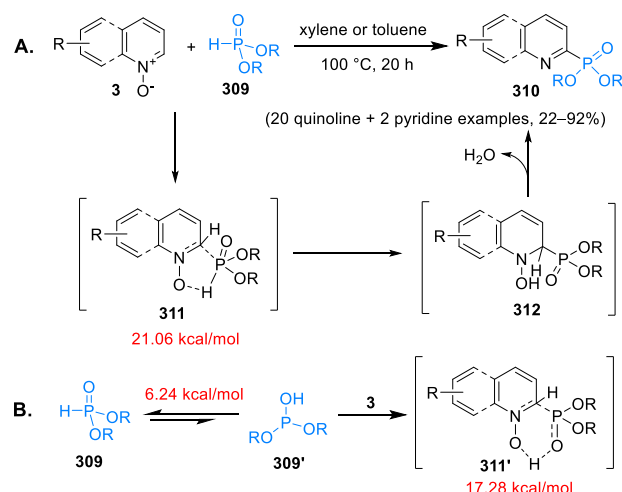


Scheme 91. Azidation of azine *N*-oxides with DPPA.

In 2015, Li and coworkers reported a non-deoxygenative azidation of quinoline *N*-oxides with TMSN₃ that occurred within 10 min at room temperature (Scheme 92).^[121] The quinoline *N*-oxide **19** would undergo single electron oxidation by an azide radical to generate the radical cation, **305** or **305'**. The reaction appears to involve a novel, carbene-stabilized N-O radical intermediate, **306**, which undergoes single-electron transfer to TMSN₃ to give the C2-azidation product, **308**.



Scheme 92. Azidation of quinoline *N*-oxides.

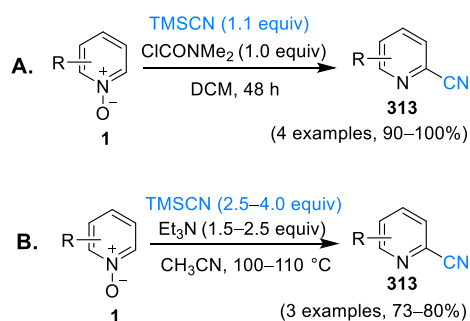


Scheme 93. Phosphonation of heteroaryl *N*-oxides with *H*-phosphonates.

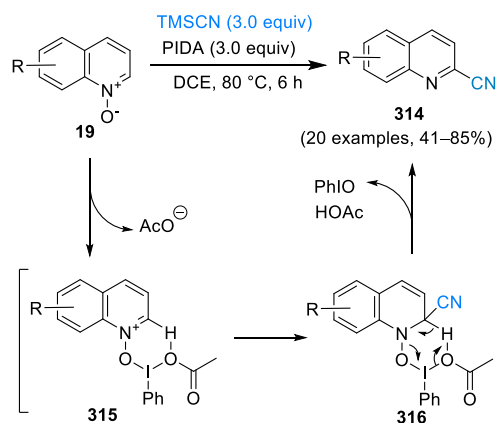
In 2014, Wu's group reported the phosphonation of *N*-oxides at elevated temperatures by direct reaction with *H*-phosphonates **309**, which play a dual role of the activating agent and the nucleophilic source (Scheme 93A).^[122] The reaction mechanism was rationalized by DFT studies calculated at the B3LYP/6-31G (d, p) level of theory (Scheme 93B).^[123] The *H*-phosphonates exist as mixtures of two tautomers **309** and **309'**, both of which can react to form **312** via intermediates **311** and **311'**, respectively. The second stage is the dehydration process, for which three possible reaction pathways are proposed: **309**-assisted dehydration, **309'**-assisted dehydration, and direct dehydration. The direct dehydration pathway is ruled out due to the very unfavorable activation barrier (35.40 kcal/mol). Although the **309'**-assisted pathway is more energy-favorable, **309'** lies 6.24 kcal/mol above **309** in the energy profile, leading to a similar energy barrier. Therefore, both the reaction pathways can proceed under the experimental conditions.

One of the earliest studies to introduce functional groups at the C2 position of pyridines involved cyanation of pyridine *N*-oxides via Reissert reaction.^[124] In 1983, Fife reported a popular cyanation method utilizing TMSCN as the cyanide

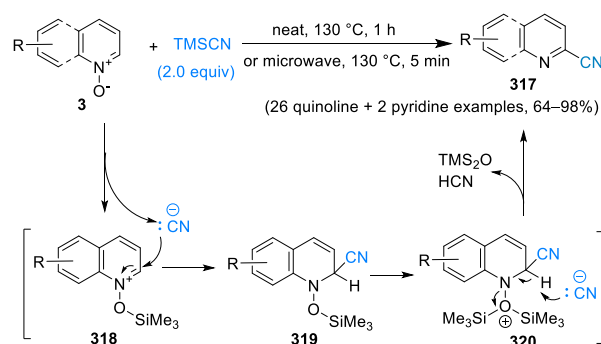
source with the activation of dimethylcarbamy chloride (Scheme 94A).^[125] It has also been reported that pyridine *N*-oxides can react directly with TMSCN at high temperatures without using any activating reagent (Scheme 94B).^[126] Triethylamine is required to neutralize the HCN formed. This reaction was revisited in 2019 by two research groups. Sun and coworkers found that the reaction with quinoline *N*-oxides can be activated by the eco-friendly and inexpensive hypervalent reagent PhI(OAc)₂ (PIDA, Scheme 95).^[127] The reaction proceeds quickly, but is not efficient enough for pyridine *N*-oxides. Das's group successfully prepared 2-cyanated pyridines and quinolines **317** under neat conditions at high temperatures either by conventional heating or microwave treatment (Scheme 96).^[128]



Scheme 94. Cyanation of pyridine *N*-oxides, as reported in 1983.



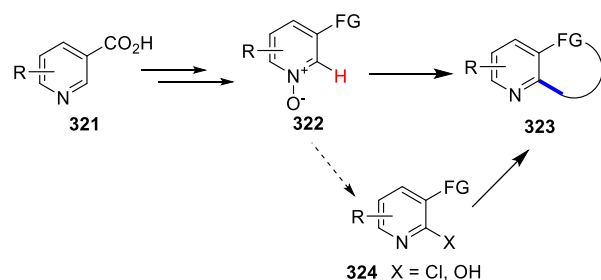
Scheme 95. Cyanation of quinoline *N*-oxides, as reported in 2019.



Scheme 96. Cyanation of *N*-oxides under neat conditions.

3 Annulation of C3-Substituted Pyridine/Quinoline *N*-oxides

Fused pyridine derivatives are extremely important due to their abundance in various biologically active natural products and synthetic pharmaceuticals (Figure 2). While some of these structures are underexplored, likely due to synthetic intractability, they have emerged as promising targets because their isosteric phenyl analogs have been designated privileged structures in drug development.^[129] Traditional synthetic approaches to **323** largely rely on nucleophilic aromatic substitution reactions (S_NAr) with 2-halogen- or hydroxyl-substituted pyridine derivatives **324**, which are themselves difficult to access (Scheme 97). Although **324** can be prepared from *N*-oxides **322** by the hydroxylation or chlorination methods described above, regioselectivity issues render this transformation impractical.



Scheme 97. Annulation via functionalization of C3-substituted pyridine *N*-oxides.

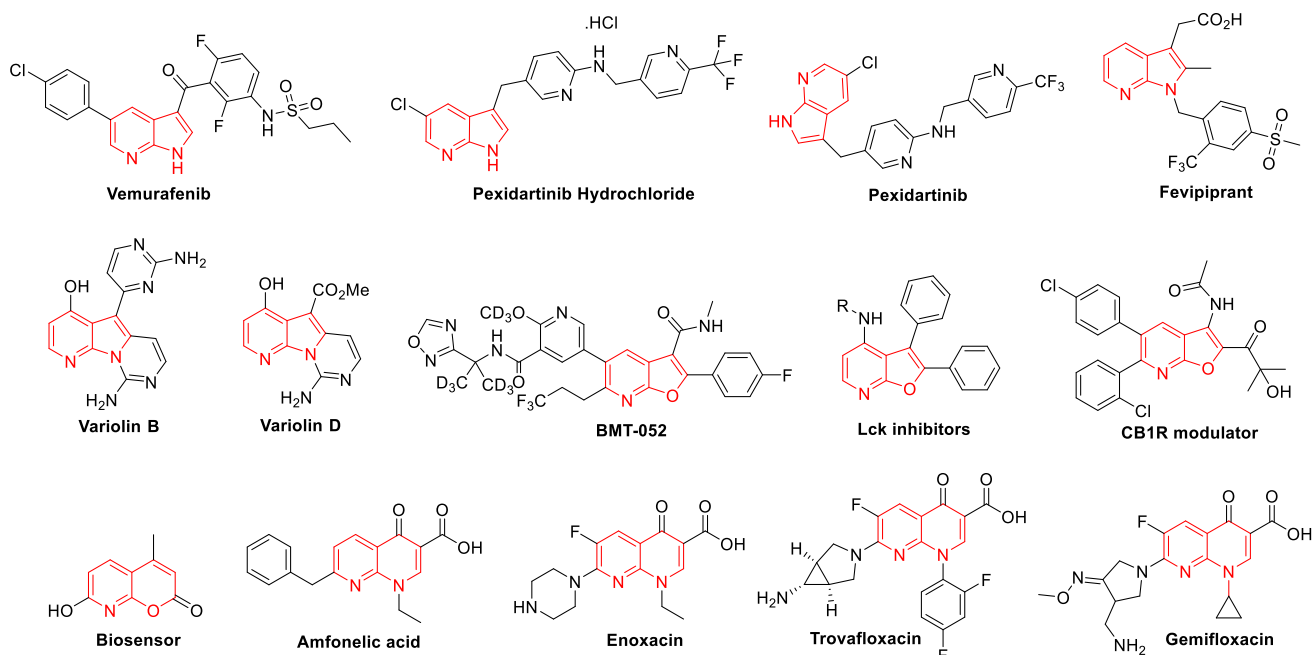
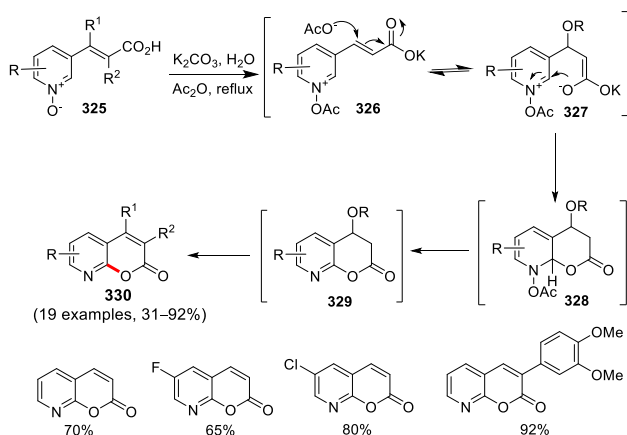


Figure 2. Representative, bioactive fused pyridine derivatives.

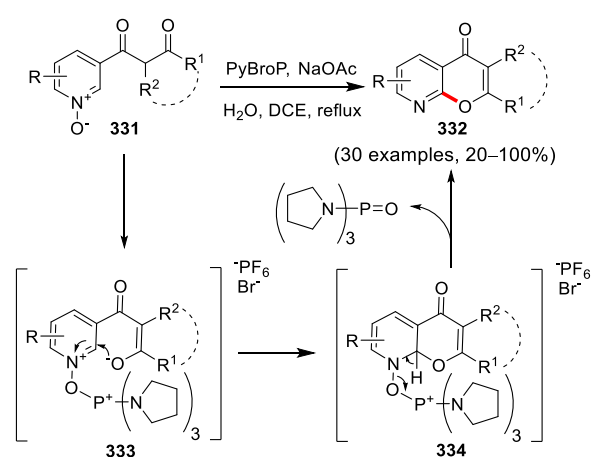
Departing from traditional methods, our group envisioned new synthetic strategies to access fused pyridine derivatives (Scheme 97). The naturally abundant, commercially available nicotinic acid derivatives **321** were selected as the starting material and converted to **322** by conventional methods. Direct functionalization of the C2-H bond in **322** allowed access to **323**.

Although azacoumarins **330** are promising targets, their synthesis had been confined to electron-rich pyridines.^[130] In 2017, our group presented a facile and general synthesis of 8-azacoumarins from *trans*-acrylic acid-functionalized pyridine *N*-oxides **325** (Scheme 98).^[131] Multiple transformations were involved in the key lactonization reaction, including conjugate addition, S_NAr , and elimination. Importantly, the double bond geometry is converted from *trans* to *cis* without the need for irradiation. In addition, this method is amenable to both electron-rich and electron-poor pyridine/quinoline *N*-oxides.



Scheme 98. Synthesis of 8-azacoumarins.

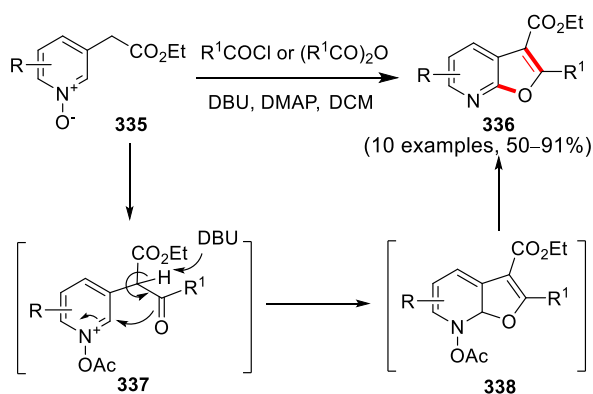
Building on this work, we developed a practical synthetic method for 8-azachromones **332** from readily available nicotines in only three steps. The key intramolecular *O*-heteroarylation reaction was achieved by PyBroP- or Ac_2O -activated nucleophilic addition of enolates to the C2 position of *N*-oxides **331** (Scheme 99).^[132]



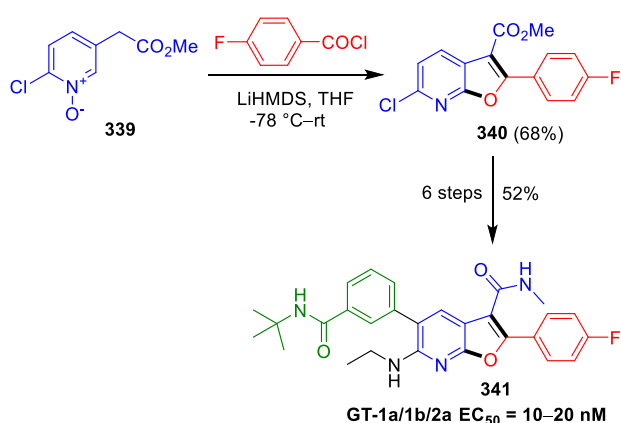
Scheme 99. Synthesis of 8-azachromones.

Emery's team reported a method for the metal-free synthesis of furo[2,3-*b*]pyridines **336** (also known as 7-azabenzofuran) at ambient temperatures (Scheme 100).^[133] 3-Ethylcarboxylate pyridine *N*-oxides **335**

react with acyl chloride or anhydride to form ethyl acetoacetate derivatives **337**, which undergo carbonyl deprotonation and cyclization to generate **338**. Finally, deprotonation and rearomatization provide the target products, **336**. Our group applied this method to the efficient synthesis of the potent HCV NS5B polymerase inhibitor, **341** (Scheme 101),^[134] providing six times greater total yield than that obtained through the original synthesis developed by BMS scientists,^[135] who used Pd-catalyzed cyclization to construct the 7-azabenzofuran core.

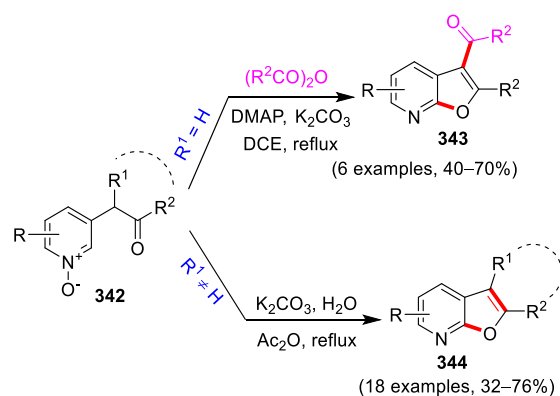


Scheme 100. Synthesis of 3-ethylcarboxylate-furo[2,3-b]pyridine.

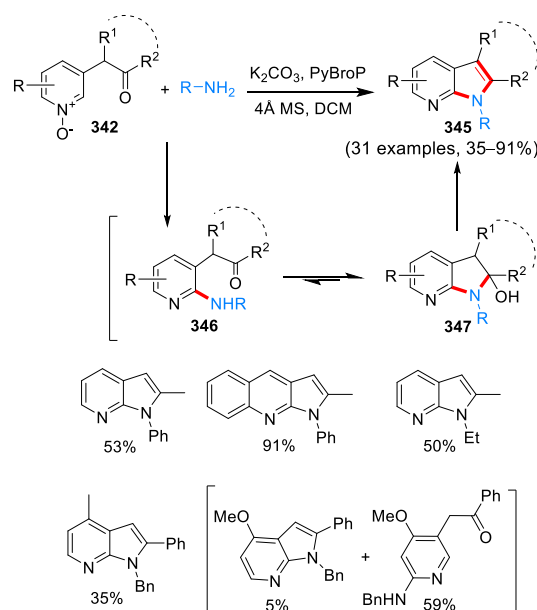


Scheme 101. Synthesis of a potent HCV NS5B polymerase inhibitor.

Emery's method is confined to the synthesis of 3-carboxylate-substituted 7-azabenzofurans. Our group has greatly extended the accessible targets utilizing **342** as substrates under two different conditions (Scheme 102).^[136]

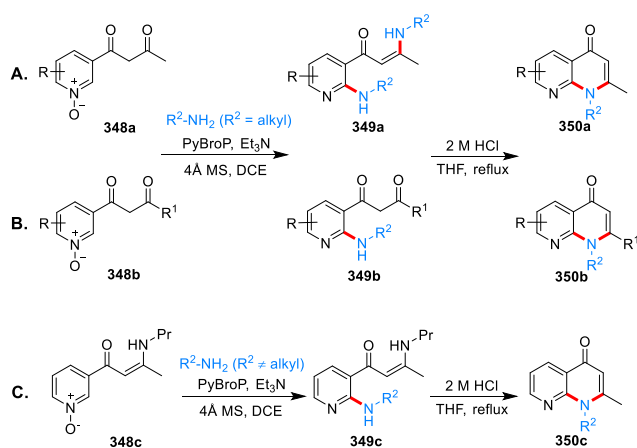


Scheme 102. Synthesis of 2,3-substituted furo[2,3-b]pyridine.



Scheme 103. Synthesis of 7-azaindoles.

In contrast to the conventional Pd-catalyzed synthesis of 7-azaindoles, we described a one-pot, transition-metal-free synthesis of 7-azaindoles involving amination of pyridine *N*-oxides **342** to yield **346** and intramolecular enamine formation (Scheme 103).^[137] Although the conditions are mild and allow for a wide substrate scope, the yield is generally moderate due to regioselectivity between C2- and C6-functionalization.



Scheme 104. Synthesis of 1,8-naphthyridones.

The highly regioselective amination (C2 vs. C6) of azine *N*-oxides was successfully applied to the synthesis of **349**, which were converted to 1,8-naphthyridones **350** smoothly under acidic conditions in nearly quantitative yield (Scheme 104).^[138] Interestingly, enamines **349a** were formed from **348a** (Scheme 104A), whereas **349b** were formed on substrates with non-methyl R^1 groups (Scheme 104B), likely due to steric hindrance precluding enamine formation. Enamine **348c** was found to be appropriate substrate with non-aliphatic amines, including ammonia and aromatic amines.

4 Functionalization at C2-Benzylic Position of Pyridine/Quinoline *N*-Oxides

Unlike the non-specific benzylic C-H activation of pyridines and benzenes, the C-H bond of an alkyl group α to nitrogen heteroaromatics can be specifically activated for functionalization (Figure 3). This activation is achieved by the well-established Boekelheide reaction, which is frequently used in heterocyclic chemistry for the formation of acylated products **354** by introducing oxygen onto alkyl groups α to nitrogen heteroaromatics (Scheme 105).^[139] The mechanism involves a [3,3]-sigmatropic rearrangement of **353**. An improved procedure was reported in 1995 by replacing Ac_2O with TFAA, which allows the reaction to occur at room temperature and, after saponification, generally provides the hydroxylated compounds **357** in good to excellent yields (Scheme 106).^[140]

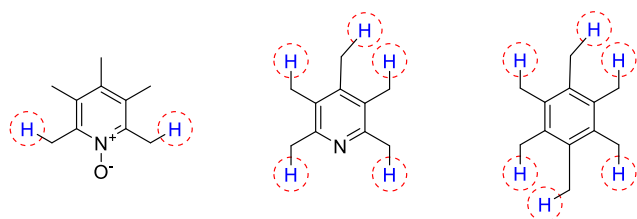
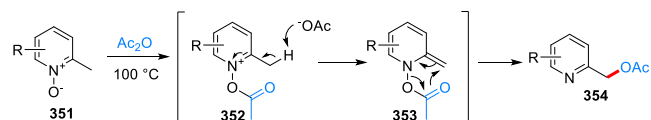
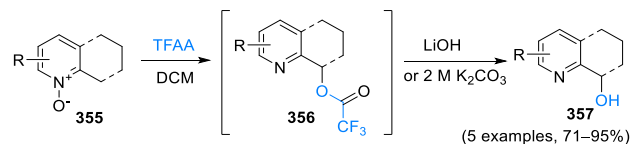


Figure 3. Activated C-H bonds in pyridine *N*-oxides and other aromatics.

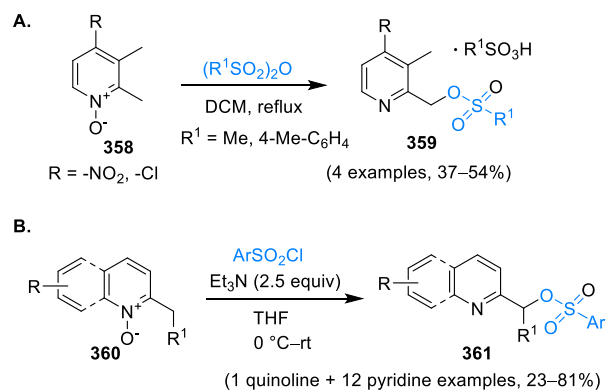


Scheme 105. Boekelheide reaction of 2-picolone *N*-oxides.



Scheme 106. TFAA-mediated Boekelheide reaction.

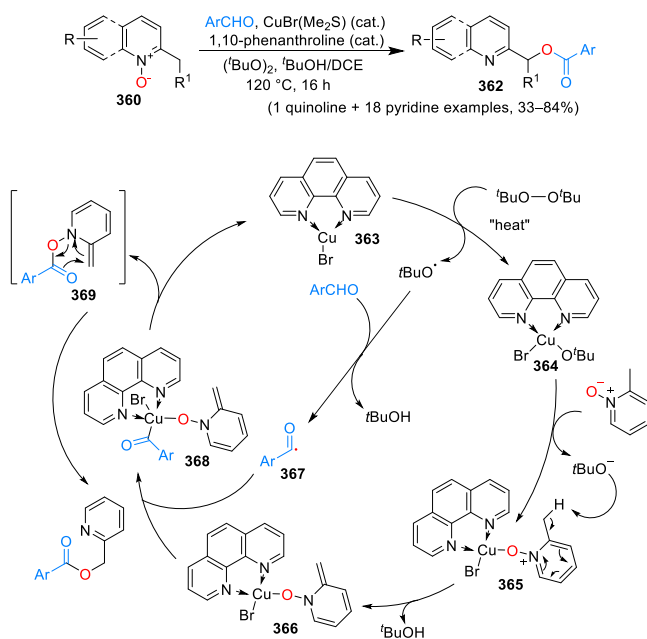
Although this reaction was developed in the 1950s, only recently have non-hydroxy functional groups been introduced at the C2-benzylic position. In 2006, Rádľ and coworkers reported the sulfonyloxylation of 2-methylpyridine *N*-oxide **358** by sulfonic anhydride, providing **359** as a salt in moderate yields via a mechanism similar to the Boekelheide reaction (Scheme 107A).^[141] Soulé's group later developed a mild, base-promoted reaction using benzene-sulfonyl chlorides (Scheme 107B).^[142]



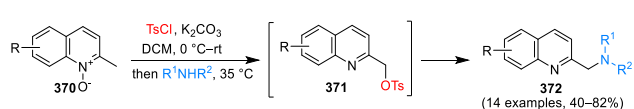
Scheme 107. Sulfonyloxylation at the α position of *N*-heterocycles.

This group also developed a scalable acyloxylation of 2-alkylpyridine *N*-oxides **360** with aromatic aldehydes via a Cu-catalyzed tandem reaction involving oxidative esterification followed by O-atom transfer of the resultant Boekelheide intermediates **369** (Scheme 108).^[143] Notably, this method enables the desymmetrization of 2,6-dialkylpyridines for the efficient synthesis of pincer ligands.

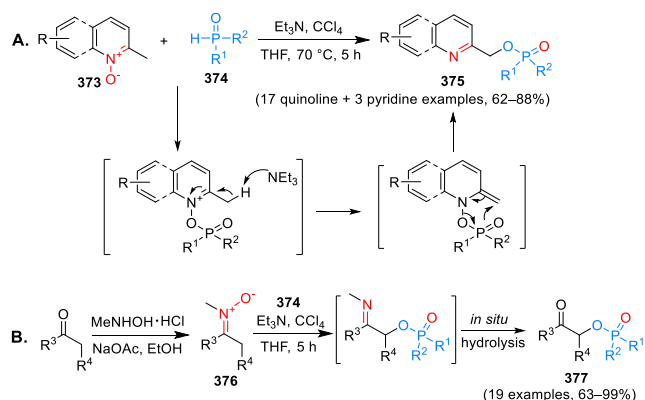
The benzylic amination of quinoline *N*-oxides was accomplished by a one-pot protocol using the sulfonated Boekelheide intermediate, **371** (Scheme 109).^[144] Unfortunately, 2-picolone *N*-oxides were not amenable to the reaction conditions.



Scheme 108. Acyloxylation of 2-alkylpyridine *N*-oxides with aldehydes.



Scheme 109. Amination of 2-methylquinoline *N*-oxides with amines.

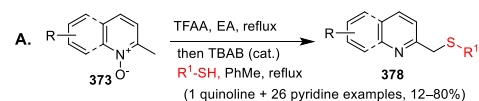


Scheme 110. Phosphorylation of 2-alkylpyridine *N*-oxides with phosphates.

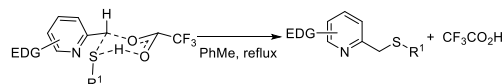
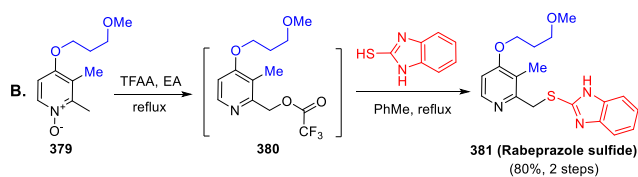
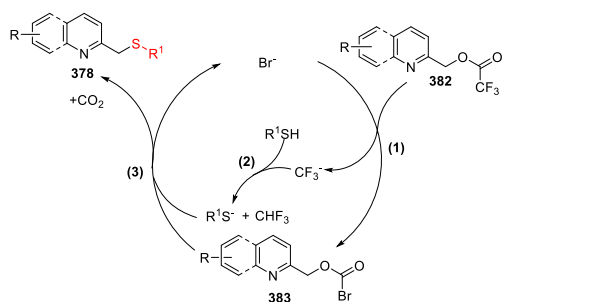
In 2017, Zhao's group reported the synthesis of *N*-heteroarylmethyl phosphates **375** by a novel, heteroatom [3,3]-sigmatropic rearrangement (Scheme 110A).^[145] This method was also successfully applied to reactions of nitrones **376** and dialkyl *H*-phosphonates **374** (Scheme 110B).

The direct thiolation at the α position of 2-picoline *N*-oxides to produce pyridine-2-ylmethyl thioethers **378** is critical, as these compounds are widely used as

the most advanced commercial intermediates for several important drugs, such as omeprazole, pantoprazole, lansoprazole, and rabeprazole. Our group developed a metal- and base-free, one-pot protocol involving a TFAA-mediated Boekelheide rearrangement of pyridine *N*-oxides and TBAB-catalyzed direct conversion of the trifluoroacetates to thioethers (Scheme 111A).^[146] Notably, this reaction is regioselective for the C2 methyl group and has been successfully applied to the synthesis of omeprazole sulfide and rabeprazole sulfide in good yields without the need for TBAB catalysis (Scheme 111B). Two plausible reaction pathways for the second step have been proposed. For highly electron-rich 2-picoline *N*-oxides, the reaction proceeds via direct S_N2 through a six-membered ring transition state (Pathway 2, Scheme 111). For other *N*-oxides, the trifluoromethyl group of **382** is replaced with a bromine atom to obtain the more reactive bromoformate intermediate **383** and CF_3^- , which abstracts a proton from R^1SH to produce R^1S^- and trifluoromethane. Nucleophilic addition of R^1S^- to **383** affords **378** and carbon dioxide and regenerates the bromide to complete the catalytic cycle.

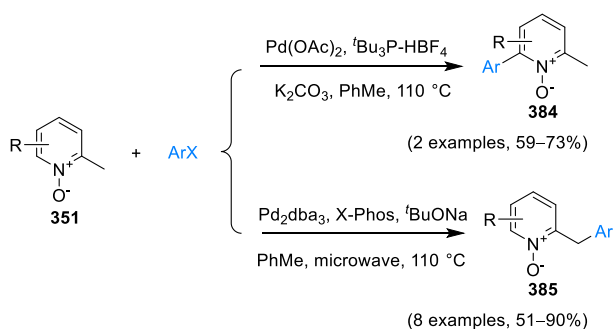


Pathway 1 (for other types of *N*-oxides)

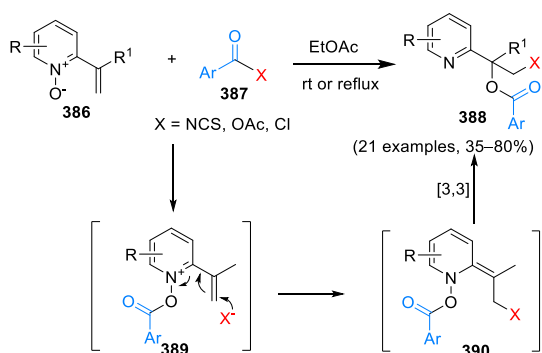


Scheme 111. Thiolation of 2-picoline *N*-oxides.

Benzylic C-H activation was also used in Fagnou's Pd-catalyzed direct arylation of 2-alkylpyridine *N*-oxides **351** (Scheme 112).^[147] The reaction conditions can be tuned to allow for site-selective arylation.



Scheme 112. Site-selective sp^2 and benzylic sp^3 arylation of 2-alkylpyridine N -oxides.

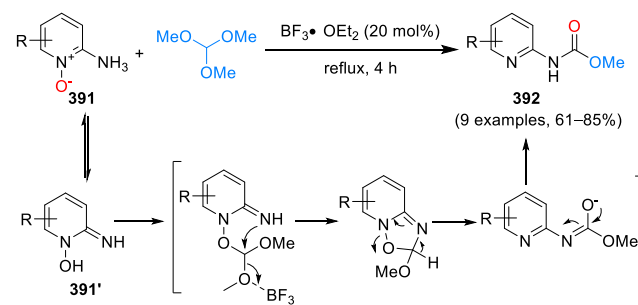


Scheme 113. Difunctionalization of alkenylpyridine N -oxides.

The functionalization of 2-alkenylpyridine N -oxides has also been achieved. Liang and coworkers reported an efficient difunctionalization of **386** to afford **388** through the tandem addition/Boekelheide rearrangement of intermediate **390** (Scheme 113).^[148] This method benefits from a 100% atom economy,

constructing several bonds simultaneously under mild reaction conditions.

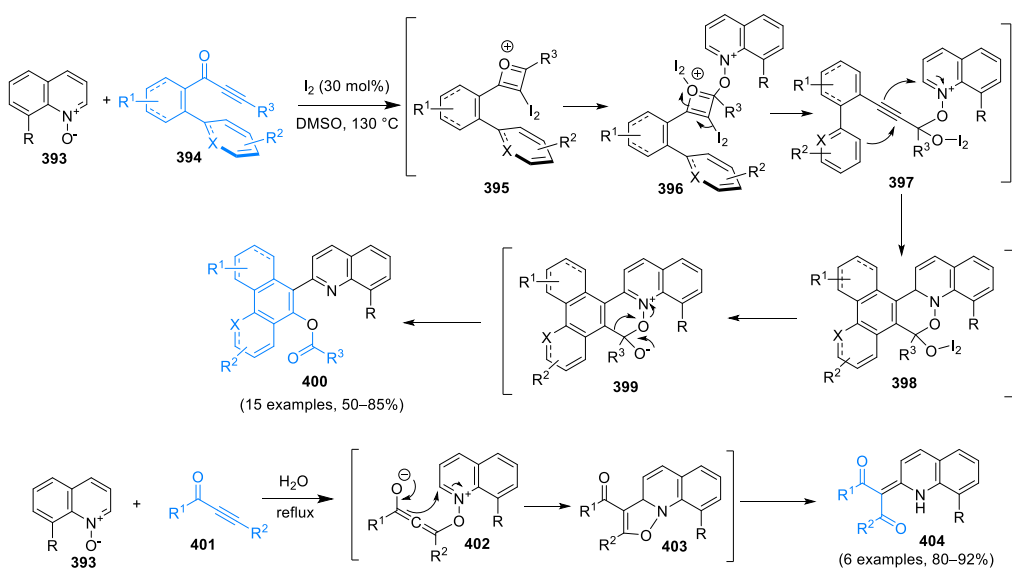
Some examples of C2-benzylic heteroatom-functionalization have been reported. Makhova's group recently described the BF_3 -catalyzed preparation of hetaryl carbamates **392** by condensation of 2-aminohetarene N -oxide **391** with trimethyl orthoformate followed by intramolecular N -oxide oxygen transfer (Scheme 114).^[149]



Scheme 114. Functionalization of aminopyridine N -oxides.

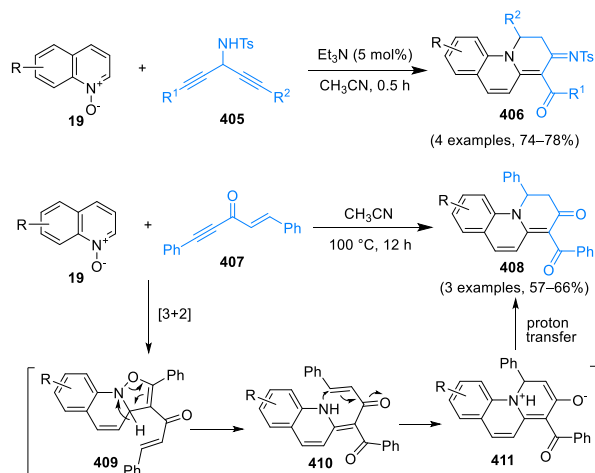
5 Applications to the Synthesis of Complex Azaheterocycles

Various applications of N -oxide chemistry in the synthesis of complex molecules have been reported previously. In 2016, Ji's group developed an efficient cycloaddition reaction between quinoline N -oxides and ynones **394** or **401**, resulting in remarkably complex quinoline derivatives **400** or **404**, respectively, in moderate to excellent yields (Scheme 115).^[150] Preliminary studies suggest these compounds have potential as metal ion probes, with a high binding constant measured for Hg^{2+} in acetonitrile.

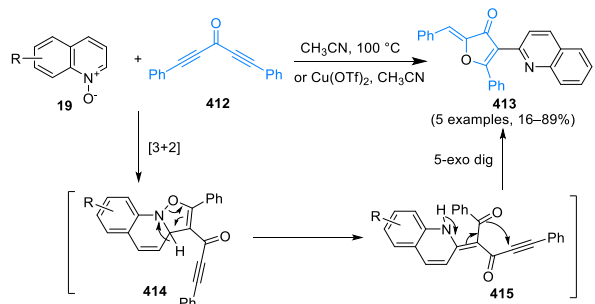


Scheme 115. Synthesis of complex quinoline derivatives.

Wang's group investigated reactions between 1,4-diyne **405** or 1-en-4-yn-3-ones **407** and (iso)quinoline *N*-oxides **19** that result in the formation of complex molecules **406** or **408** respectively, via cascade C=O/C=C/C–N bond formation (Scheme 116).^[151] These novel fluorophores were found to display green-blue fluorescence.



Scheme 116. Synthesis of 2,3-dihydro-1H-pyrido[1,2-a]quinolines.

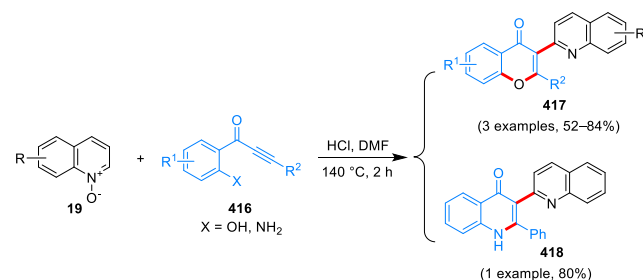


Scheme 117. Synthesis of 4-quinolinyl-3(2H)-furanones.

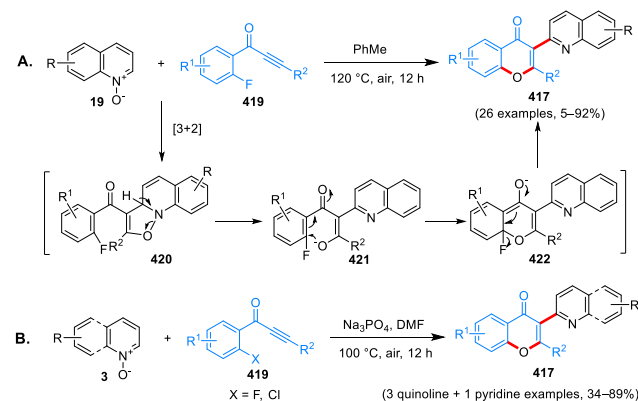
Interestingly, the synthesis of **413** through the reaction of (iso)quinoline *N*-oxides with 1,4-diyne-3-ones **412** can proceed with or without copper catalysis (Scheme 117).^[152] However, the copper catalyst promotes the final cyclization in **415** by activation of the carbon–carbon triple bond, providing better yields under milder conditions.

The Wang group also reported the synthesis of both 3-(2-quinolyl) chromones **417** and azachromones **418** from 2-hydroxyl- or amino-substituted ynone **416** and quinoline *N*-oxides via a similar mechanism under acidic conditions (Scheme 118).^[153] Their study primarily focused on reactions with quinoline and isoquinoline *N*-oxides and is not applicable to pyridine *N*-oxides. Cheng and coworkers were able to eliminate the need for acid by using the more reactive 2-fluoro ynone **419** (Scheme

119A).^[154] This method was also applied to pyridine, quinoline and isoquinoline *N*-oxides under basic conditions (Scheme 119B).



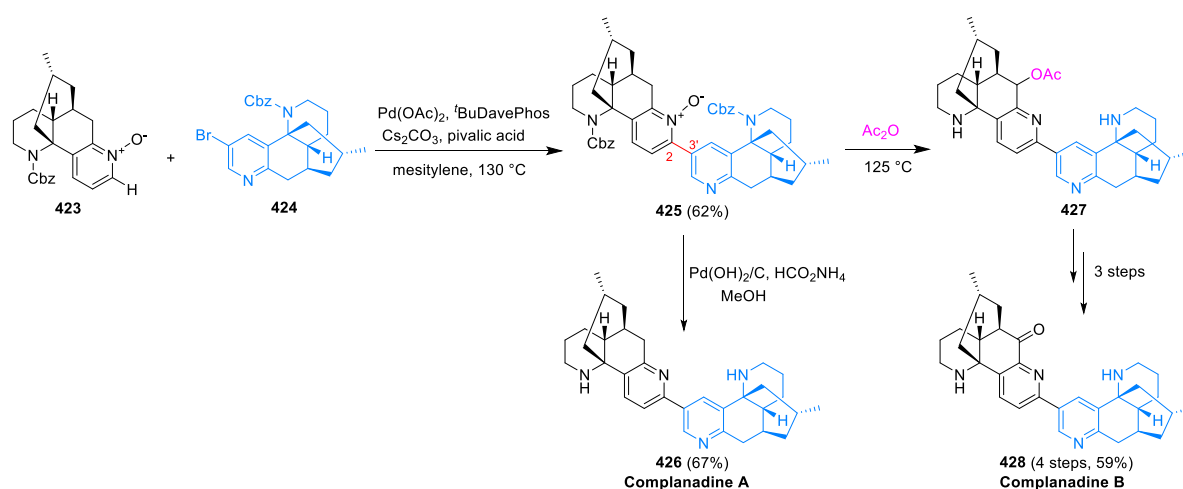
Scheme 118. Synthesis of 3-(2-quinolyl)chromones/azachromones.



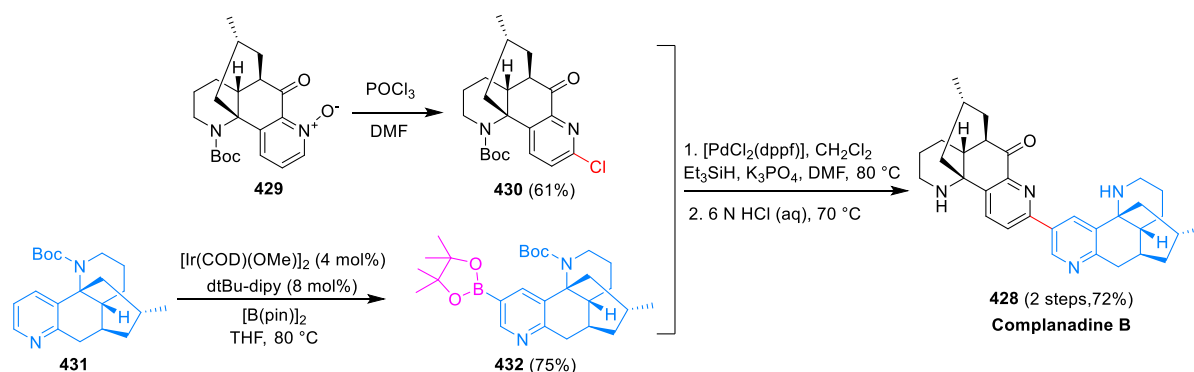
Scheme 119. Synthesis of 3-(2-quinolyl)chromones under additive-free conditions.

C2-functionalization methods have been applied to the synthesis of several natural products. For example, the 2,3'-bipyridyl framework of complanadines A and B was elegantly constructed by direct C2 arylation^[14, 147] of pyridine *N*-oxide **423** with 3-bromopyridine derivative **424** (Scheme 120).^[155] Interestingly, both **423** and **424** were assembled from the same *N*-protected lycodine. Reduction of **425** afforded complanadine A (**426**) and benzylic acetylation afforded **427**, which was converted to complanadine B (**428**) in three steps.

In comparison, Sarpong and coworkers constructed complanadine B via the Suzuki cross-coupling of pinacolboronic ester **432** with **430**, which was prepared by the chlorination of pyridine *N*-oxide **429** (Scheme 121).^[156] Unlike the direct coupling between *N*-oxide and aryl bromide (Scheme 120), in this protocol, **430** and **432** must be prepared in one step from **429** and **431**,^[157] respectively, thereby adding two additional steps to the overall process.



Scheme 120. Tsukano's total synthesis of complanadines A and B.



Scheme 121. Sarpong's total synthesis of complanadine B.

6 Conclusions and Perspectives

In summary, heterocyclic *N*-oxide reactions remain one of the most powerful tools for the C2-functionalization of nitrogen heteroaromatics. Although the chemistry of *N*-oxides has been explored for more than a century, the majority of reaction paths have only recently been discovered, with much of this progress made in the past five years. Advancements in modern organic chemistry technologies, such as photoredox catalysis with visible light and electrochemistry, have enabled access to previously challenging reactions, although further improvements are still necessary. There is a definitive need in green chemistry for the development of reactions involving catalytic quantities of activating reagents that produce water as the sole byproduct. Additional improvements should focus on functionalization at other positions, particularly at the rarely functionalized C3 position. One such attempt is exemplified by the *meta*-selective alkyne oxyarylation with pyridine *N*-oxides.^[158] Functionalization at C8 position of quinoline *N*-oxides is another promising area.^[159] Finally, there is great anticipation for the wide

application of *N*-oxide chemistry to the synthesis of complex nitrogen-containing heterocycles.

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References

- [1] K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302-9332.
- [2] a) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95-99; b) J. Kan, S. Huang, J. Lin, M. Zhang, W. Su, *Angew. Chem., Int. Ed.* **2015**, *54*, 2199-2203; c) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194-13196; d) J. Wen, R.-Y. Zhang, S.-Y. Chen, J. Zhang, X.-Q. Yu, *J. Org.*

- Chem.* **2012**, *77*, 766-771; e) F. O'Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122-12134.
- [3] J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642-2713.
- [4] Y. Wang, L. Zhang, *Synthesis* **2015**, *47*, 289-305.
- [5] H. Andersson, R. Olsson, F. Almqvist, *Org. Biomol. Chem.* **2011**, *9*, 337-346.
- [6] G. Yan, A. J. Borah, M. Yang, *Adv. Synth. Catal.* **2014**, *356*, 2375-2394.
- [7] J. S. Poole, *Top. Heterocycl. Chem.* **2017**, *53*, 1-41.
- [8] R. Loska, *Targets Heterocycl. Syst.* **2015**, *19*, 101-127.
- [9] R. Loska, *Top. Heterocycl. Chem.* **2017**, *53*, 85-110.
- [10] V. V. Kouznetsov, L. Y. Vargas Mendez, C. E. Puerto Galvis, M. C. Ortiz Villamizar, *New J. Chem.* **2020**, *44*, 12-19.
- [11] a) C. Coperet, H. Adolfsson, T.-A. V. Khuong, A. K. Yudin, K. B. Sharpless, *J. Org. Chem.* **1998**, *63*, 1740-1741; b) C. Coperet, H. Adolfsson, J. P. Chiang, A. K. Yudin, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 761-764; c) R. Baernardi, B. Novo, G. Resnati, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2517-2521.
- [12] A. R. Katritzky, J. N. Lam, *Heterocycles* **1992**, *33*, 1011-1049.
- [13] H. Andersson, T. Sainte-Luce Banchelin, S. Das, R. Olsson, F. Almqvist, *Chem. Commun.* **2010**, *46*, 3384-3386.
- [14] L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020-18021.
- [15] a) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256; b) D. Wenkert, R. B. Woodward, *J. Org. Chem.* **1983**, *48*, 283-289; c) K. S. Kanyiva, Y. Nakao, T. Hiyama, *Angew. Chem., Int. Ed.* **2007**, *46*, 8872-8874.
- [16] a) M. O. Konev, L. Cardinale, A. Jacobi von Wangelin, *Org. Lett.* **2020**, *22*, 1316-1320; b) K. D. Kim, J. H. Lee, *Org. Lett.* **2018**, *20*, 7712-7716.
- [17] R. M. B. Dyer, P. L. Hahn, M. K. Hilinski, *Org. Lett.* **2018**, *20*, 2011-2014.
- [18] A. Reissert, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 3415-3435.
- [19] Y. Ishiguro, M. Yoshida, K. Funakoshi, S. Saeki, M. Hamana, I. Ueda, S. Kawano, *Heterocycles* **1983**, *20*, 193-196.
- [20] Y. Tan, F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 3683-3686.
- [21] a) F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489-519; b) R. S. J. Proctor, R. J. Phipps, *Angew. Chem., Int. Ed.* **2019**, *58*, 13666-13699; c) A. C. Sun, R. C. McAtee, E. J. McClain, C. R. J. Stephenson, *Synthesis* **2019**, *51*, 1063-1072.
- [22] X. Chen, C. Zhu, X. Cui, Y. Wu, *Chem. Commun.* **2013**, *49*, 6900-6902.
- [23] S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate, P. S. Baran, *Org. Lett.* **2013**, *15*, 792-795.
- [24] a) D. Wang, H. Jia, W. Wang, Z. Wang, *Tetrahedron Lett.* **2014**, *55*, 7130-7132; b) D. Wang, Y. Wang, J. Zhao, L. Li, L. Miao, D. Wang, H. Sun, P. Yu, *Tetrahedron* **2016**, *72*, 5762-5768.
- [25] Y. Chen, J. Huang, T.-L. Hwang, M. J. Chen, J. S. Tedrow, R. P. Farrell, M. M. Bio, S. Cui, *Org. Lett.* **2015**, *17*, 2948-2951.
- [26] K. Qiao, L. Wan, X. Sun, K. Zhang, N. Zhu, X. Li, K. Guo, *Eur. J. Org. Chem.* **2016**, *2016*, 1606-1611.
- [27] H. Xiong, A. T. Hoye, K.-H. Fan, X. Li, J. Clemens, C. L. Horchler, N. C. Lim, G. Attardo, *Org. Lett.* **2015**, *17*, 3726-3729.
- [28] J. Yin, B. Xiang, M. A. Huffman, C. E. Raab, I. W. Davies, *J. Org. Chem.* **2007**, *72*, 4554-4557.
- [29] R. P. Farrell, M. V. Silva Elipse, M. D. Bartberger, J. S. Tedrow, F. Vounatsos, *Org. Lett.* **2013**, *15*, 168-171.
- [30] A. T. Londregan, S. Jennings, L. Wei, *Org. Lett.* **2010**, *12*, 5254-5257.
- [31] X. Chen, X. Li, Z. Qu, D. Ke, L. Qu, L. Duan, W. Mai, J. Yuan, J. Chen, Y. Zhao, *Adv. Synth. Catal.* **2014**, *356*, 1979-1985.
- [32] W.-Z. Bi, K. Sun, C. Qu, X.-L. Chen, L.-B. Qu, S.-H. Zhu, X. Li, H.-T. Wu, L.-K. Duan, Y.-F. Zhao, *Org. Chem. Front.* **2017**, *4*, 1595-1600.
- [33] D. I. Bugaenko, M. A. Yurovskaya, A. V. Karchava, *J. Org. Chem.* **2017**, *82*, 2136-2149.
- [34] Y. Nanaji, S. Kirar, S. V. Pawar, A. K. Yadav, *RSC Advances* **2020**, *10*, 7628-7634.
- [35] L.-Y. Xie, S. Peng, L.-L. Jiang, X. Peng, W. Xia, X. Yu, X.-X. Wang, Z. Cao, W.-M. He, *Org. Chem. Front.* **2019**, *6*, 167-171.
- [36] D. Kim, P. Ghosh, N. Y. Kwon, S. H. Han, S. Han, N. K. Mishra, S. Kim, I. S. Kim, *J. Org. Chem.* **2020**, *85*, 2476-2485.
- [37] A. K. Dhiman, D. Chandra, R. Kumar, U. Sharma, *J. Org. Chem.* **2019**, *84*, 6962-6969.
- [38] G. Li, C. Jia, K. Sun, *Org. Lett.* **2013**, *15*, 5198-5201.
- [39] G. Li, C. Jia, K. Sun, Y. Lv, F. Zhao, K. Zhou, H. Wu, *Org. Biomol. Chem.* **2015**, *13*, 3207-3210.
- [40] C. Zhu, M. Yi, D. Wei, X. Chen, Y. Wu, X. Cui, *Org. Lett.* **2014**, *16*, 1840-1843.
- [41] Z. Wang, M.-Y. Han, P. Li, L. Wang, *Eur. J. Org. Chem.* **2018**, *2018*, 5954-5960.
- [42] A. Behera, P. Sau, A. K. Sahoo, B. K. Patel, *J. Org. Chem.* **2018**, *83*, 11218-11231.

- [43] M. Couturier, L. Caron, S. Tumidajski, K. Jones, T. D. White, *Org. Lett.* **2006**, *8*, 1929-1932.
- [44] J. W. Medley, M. Movassaghi, *J. Org. Chem.* **2009**, *74*, 1341-1344.
- [45] L.-Y. Xie, S. Peng, L.-H. Lu, J. Hu, W.-H. Bao, F. Zeng, Z. Tang, X. Xu, W.-M. He, *ACS Sustainable Chem. Eng.* **2018**, *6*, 7989-7994.
- [46] X. Chen, M. Peng, H. Huang, Y. Zheng, X. Tao, C. He, Y. Xiao, *Org. Biomol. Chem.* **2018**, *16*, 6202-6205.
- [47] L.-Y. Xie, S. Peng, F. Liu, J.-Y. Yi, M. Wang, Z. Tang, X. Xu, W.-M. He, *Adv. Synth. Catal.* **2018**, *360*, 4259-4264.
- [48] G.-H. Li, D.-Q. Dong, Y. Yang, X.-Y. Yu, Z.-L. Wang, *Adv. Synth. Catal.* **2019**, *361*, 832-835.
- [49] V. A. Rassadin, D. P. Zimin, G. Z. Raskil'dina, A. Y. Ivanov, V. P. Boyarskiy, S. S. Zlotskii, V. Y. Kukushkin, *Green Chem.* **2016**, *18*, 6630-6636.
- [50] K. Geyl, S. Baykov, M. Tarasenko, L. E. Zelenkov, V. Matveevskaya, V. P. Boyarskiy, *Tetrahedron Lett.* **2019**, *60*, 151108.
- [51] L.-Y. Xie, S. Peng, F. Liu, Y.-F. Liu, M. Sun, Z.-L. Tang, S. Jiang, Z. Cao, W.-M. He, *ACS Sustainable Chem. Eng.* **2019**, *7*, 7193-7199.
- [52] H. Yu, C. A. Dannenberg, Z. Li, C. Bolm, *Chem. - Asian J.* **2016**, *11*, 54-57.
- [53] S. K. Aithagani, M. Kumar, M. Yadav, R. A. Vishwakarma, P. P. Singh, *J. Org. Chem.* **2016**, *81*, 5886-5894.
- [54] X. Yu, S. Yang, Y. Zhang, M. Guo, Y. Yamamoto, M. Bao, *Org. Lett.* **2017**, *19*, 6088-6091.
- [55] S. Han, X. Gao, Q. Wu, J. Li, D. Zou, Y. Wu, Y. Wu, *Org. Chem. Front.* **2019**, *6*, 830-834.
- [56] D. Wang, J. Zhao, Y. Wang, J. Hu, L. Li, L. Miao, H. Feng, L. Desaubry, P. Yu, *Asian J. Org. Chem.* **2016**, *5*, 1442-1446.
- [57] L.-Y. Xie, Y. Duan, L.-H. Lu, Y.-J. Li, S. Peng, C. Wu, K.-J. Liu, Z. Wang, W.-M. He, *ACS Sustainable Chem. Eng.* **2017**, *5*, 10407-10412.
- [58] J.-B. Peng, B. Chen, X. Qi, J. Ying, X.-F. Wu, *Org. Biomol. Chem.* **2018**, *16*, 1632-1635.
- [59] A. T. Londregan, S. Jennings, L. Wei, *Org. Lett.* **2011**, *13*, 1840-1843.
- [60] Y. Lian, S. B. Coffey, Q. Li, A. T. Londregan, *Org. Lett.* **2016**, *18*, 1362-1365.
- [61] D. Zhang, K. Qiao, J. Hua, Z. Liu, H. Qi, Z. Yang, N. Zhu, Z. Fang, K. Guo, *Org. Chem. Front.* **2018**, *5*, 2340-2344.
- [62] D. H. Jones, S. T. Kay, J. A. McLellan, A. R. Kennedy, N. C. O. Tomkinson, *Org. Lett.* **2017**, *19*, 3512-3515.
- [63] Z. Wu, H. Song, X. Cui, C. Pi, W. Du, Y. Wu, *Org. Lett.* **2013**, *15*, 1270-1273.
- [64] B. Du, P. Qian, Y. Wang, H. Mei, J. Han, Y. Pan, *Org. Lett.* **2016**, *18*, 4144-4147.
- [65] P. Li, Y. Jiang, H. Li, W. Dong, Z. Peng, D. An, *Synth. Commun.* **2018**, *48*, 1909-1918.
- [66] G.-H. Li, D.-Q. Dong, Q. Deng, S.-Q. Yan, Z.-L. Wang, *Synthesis* **2019**, *51*, 3313-3319.
- [67] W. Mai, M. Lv, X. Zhang, K. Lu, *J. Chem. Res.* **2017**, *41*, 705-708.
- [68] K. Sun, X.-L. Chen, X. Li, L.-B. Qu, W.-Z. Bi, X. Chen, H.-L. Ma, S.-T. Zhang, B.-W. Han, Y.-F. Zhao, C.-J. Li, *Chem. Commun.* **2015**, *51*, 12111-12114.
- [69] Y. Su, X. Zhou, C. He, W. Zhang, X. Ling, X. Xiao, *J. Org. Chem.* **2016**, *81*, 4981-4987.
- [70] R. Wang, Z. Zeng, C. Chen, N. Yi, J. Jiang, Z. Cao, W. Deng, J. Xiang, *Org. Biomol. Chem.* **2016**, *14*, 5317-5321.
- [71] L. Sumunnee, C. Buathongjan, C. Pimpasri, S. Yotphan, *Eur. J. Org. Chem.* **2017**, *2017*, 1025-1032.
- [72] W.-K. Fu, K. Sun, C. Qu, X.-L. Chen, L.-B. Qu, W.-Z. Bi, Y.-F. Zhao, *Asian J. Org. Chem.* **2017**, *6*, 492-495.
- [73] L.-Y. Xie, Y.-J. Li, J. Qu, Y. Duan, J. Hu, K.-J. Liu, Z. Cao, W.-M. He, *Green Chem.* **2017**, *19*, 5642-5646.
- [74] S. Peng, Y.-X. Song, J.-Y. He, S.-S. Tang, J.-X. Tan, Z. Cao, Y.-W. Lin, W.-M. He, *Chin. Chem. Lett.* **2019**, *30*, 2287-2290.
- [75] L.-Y. Xie, S. Peng, F. Liu, G.-R. Chen, W. Xia, X. Yu, W.-F. Li, Z. Cao, W.-M. He, *Org. Chem. Front.* **2018**, *5*, 2604-2609.
- [76] L.-Y. Xie, T.-G. Fang, J.-X. Tan, B. Zhang, Z. Cao, L.-H. Yang, W.-M. He, *Green Chem.* **2019**, *21*, 3858-3863.
- [77] G. You, D. Xi, J. Sun, L. Hao, C. Xia, *Org. Biomol. Chem.* **2019**, *17*, 9479-9488.
- [78] M. Jiang, Y. Yuan, T. Wang, Y. Xiong, J. Li, H. Guo, A. Lei, *Chem. Commun.* **2019**, *55*, 13852-13855.
- [79] B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616-619.
- [80] Z. Wu, C. Pi, X. Cui, J. Bai, Y. Wu, *Adv. Synth. Catal.* **2013**, *355*, 1971-1976.
- [81] A. K. Jha, N. Jain, *Chem. Commun.* **2016**, *52*, 1831-1834.
- [82] W.-M. Zhang, J.-J. Dai, J. Xu, H.-J. Xu, *J. Org. Chem.* **2017**, *82*, 2059-2066.
- [83] Y.-R. Gu, X.-H. Duan, L. Yang, L.-N. Guo, *Org. Lett.* **2017**, *19*, 5908-5911.
- [84] W. Sun, Z. Xie, J. Liu, L. Wang, *Org. Biomol. Chem.* **2015**, *13*, 4596-4604.

- [85] D. Dong, G. Li, D. Chen, Y. Sun, Q. Han, Z. Wang, X. Xu, X. Yu, *Chinese J. Org. Chem.* **2020**, *40*, 1766-1771.
- [86] G. Li, S. Yang, B. Lv, Q. Han, X. Ma, K. Sun, Z. Wang, F. Zhao, Y. Lv, H. Wu, *Org. Biomol. Chem.* **2015**, *13*, 11184-11188.
- [87] A. T. Londregan, K. Burford, E. L. Conn, K. D. Hesp, *Org. Lett.* **2014**, *16*, 3336-3339.
- [88] T. C. Johnson, S. P. Marsden, *Org. Lett.* **2016**, *18*, 5364-5367.
- [89] R. Kumar, I. Kumar, R. Sharma, U. Sharma, *Org. Biomol. Chem.* **2016**, *14*, 2613-2617.
- [90] W. Zhou, T. Miura, M. Murakami, *Angew. Chem. Int. Ed.* **2018**, *57*, 5139-5142.
- [91] J.-h. Xu, W.-b. Wu, J. Wu, *Org. Lett.* **2019**, *21*, 5321-5325.
- [92] P.-T. Qin, J. Sun, F. Wang, J.-Y. Wang, H. Wang, M. Zhou, *Adv. Synth. Catal.* **2020**, doi: 10.1002/adsc.202000517, in press.
- [93] W. Jo, J. Kim, S. Choi, S. H. Cho, *Angew. Chem. Int. Ed.* **2016**, *55*, 9690-9694.
- [94] C. Hwang, W. Jo, S. H. Cho, *Chem. Commun.* **2017**, *53*, 7573-7576.
- [95] S. Han, P. Chakrasali, J. Park, H. Oh, S. Kim, K. Kim, A. K. Pandey, S. H. Han, S. B. Han, I. S. Kim, *Angew. Chem. Int. Ed.* **2018**, *57*, 12737-12740.
- [96] F. Roudesly, L. F. Veiros, J. Oble, G. Poli, *Org. Lett.* **2018**, *20*, 2346-2350.
- [97] J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888-13889.
- [98] Z. Zhang, C. Pi, H. Tong, X. Cui, Y. Wu, *Org. Lett.* **2017**, *19*, 440-443.
- [99] H. Xia, Y. Liu, P. Zhao, S. Gou, J. Wang, *Org. Lett.* **2016**, *18*, 1796-1799.
- [100] G. E. M. Crisenza, E. M. Dauncey, J. F. Bower, *Org. Biomol. Chem.* **2016**, *14*, 5820-5825.
- [101] Y.-P. Han, X.-S. Li, X.-Y. Zhu, M. Li, L. Zhou, X.-R. Song, Y.-M. Liang, *J. Org. Chem.* **2017**, *82*, 1697-1704.
- [102] L. Ackermann, S. Fenner, *Chem. Commun.* **2011**, *47*, 430-432.
- [103] M. Li, X. Li, H. Chang, W. Gao, W. Wei, *Org. Biomol. Chem.* **2016**, *14*, 2421-2426.
- [104] Y. Shen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *Chem. Commun.* **2014**, *50*, 4292-4295.
- [105] V. V. Pagar, R.-S. Liu, *Org. Biomol. Chem.* **2015**, *13*, 6166-6169.
- [106] O. V. Larionov, D. Stephens, A. Mfuh, G. Chavez, *Org. Lett.* **2014**, *16*, 864-867.
- [107] D. Li, C. Liang, Z. Jiang, J. Zhang, W.-T. Zhuo, F.-Y. Zou, W.-P. Wang, G.-L. Gao, J. Song, *J. Org. Chem.* **2020**, *85*, 2733-2742.
- [108] X. Chen, X. Cui, F. Yang, Y. Wu, *Org. Lett.* **2015**, *17*, 1445-1448.
- [109] W. Mai, J. Yuan, Z. Li, G. Sun, L. Qu, *Synlett* **2012**, *23*, 145-149.
- [110] L. Bering, A. P. Antonchick, *Org. Lett.* **2015**, *17*, 3134-3137.
- [111] Y. Yuan, M. Jiang, T. Wang, Y. Xiong, J. Li, H. Guo, A. Lei, *Chem. Commun.* **2019**, *55*, 11091-11094.
- [112] D. E. Stephens, G. Chavez, M. Valdes, M. Dovalina, H. D. Arman, O. V. Larionov, *Org. Biomol. Chem.* **2014**, *12*, 6190-6199.
- [113] X. Gao, Y. Geng, S. Han, A. Liang, J. Li, D. Zou, Y. Wu, Y. Wu, *Tetrahedron Lett.* **2018**, *59*, 1551-1554.
- [114] C. Liang, W.-T. Zhuo, Y.-N. Niu, G.-L. Gao, *Synthesis* **2020**, *52*, 219-226.
- [115] S. Sharma, M. Kumar, R. A. Vishwakarma, M. K. Verma, P. P. Singh, *J. Org. Chem.* **2018**, *83*, 12420-12431.
- [116] M. Lai, K. Zhai, C. Cheng, Z. Wu, M. Zhao, *Org. Chem. Front.* **2018**, *5*, 2986-2991.
- [117] P. Frei, D. H. Jones, S. T. Kay, J. A. McLellan, B. F. Johnston, A. R. Kennedy, N. C. O. Tomkinson, *J. Org. Chem.* **2018**, *83*, 1510-1517.
- [118] R. Muta, T. Torigoe, Y. Kuninobu, *Org. Lett.* **2019**, *21*, 4289-4292.
- [119] S.-B. Zhang, X.-H. Xu, F.-L. Qing, *J. Fluorine Chem.* **2019**, *227*, 109367.
- [120] J. M. Keith, *J. Org. Chem.* **2006**, *71*, 9540-9543.
- [121] P. Li, J. Zhao, C. Xia, F. Li, *Org. Chem. Front.* **2015**, *2*, 1313-1317.
- [122] H. Wang, X. Cui, Y. Pei, Q. Zhang, J. Bai, D. Wei, Y. Wu, *Chem. Commun.* **2014**, *50*, 14409-14411.
- [123] W. Zhang, X. Zhao, Y. Qiao, X. Guo, Y. Wang, D. Wei, M. Tang, J. Niu, *Comput. Theor. Chem.* **2015**, *1071*, 33-38.
- [124] W. E. Feely, E. M. Beavers, *J. Am. Chem. Soc.* **1959**, *81*, 4004-4007.
- [125] W. K. Fife, *J. Org. Chem.* **1983**, *48*, 1375-1377.
- [126] H. Vorbrueggen, K. Krolikiewicz, *Synthesis* **1983**, 316-319.
- [127] F. Xu, Y. Li, X. Huang, X. Fang, Z. Li, H. Jiang, J. Qiao, W. Chu, Z. Sun, *Adv. Synth. Catal.* **2019**, *361*, 520-525.
- [128] B. K. Sarmah, M. Konwar, D. Bhattacharyya, P. Adhikari, A. Das, *Adv. Synth. Catal.* **2019**, *361*, 5616-5625.
- [129] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930.

- [130] a) H. Takano, T. Narumi, W. Nomura, H. Tamamura, *J. Org. Chem.* **2017**, *82*, 2739-2744; b) H. Takano, T. Narumi, W. Nomura, T. Furuta, H. Tamamura, *Org. Lett.* **2015**, *17*, 5372-5375; c) T. Narumi, H. Takano, N. Ohashi, A. Suzuki, T. Furuta, H. Tamamura, *Org. Lett.* **2014**, *16*, 1184-1187.
- [131] D. Wang, Y. Wang, J. Zhao, M. Shen, J. Hu, Z. Liu, L. Li, F. Xue, P. Yu, *Org. Lett.* **2017**, *19*, 984-987.
- [132] D. Wang, H. Feng, L. Li, Z. Liu, Z. Yan, P. Yu, *J. Org. Chem.* **2017**, *82*, 11275-11287.
- [133] F. Fumagalli, F. da Silva Emery, *J. Org. Chem.* **2016**, *81*, 10339-10347.
- [134] C. Fu, G. Li, M. Shen, L. Zhang, P. Yu, D. Wang, *Asian J. Org. Chem.* **2020**, *9*, 749-752.
- [135] K. J. Eastman, K. Parcella, K.-S. Yeung, K. A. Grant-Young, J. Zhu, T. Wang, Z. Zhang, Z. Yin, B. R. Beno, S. Sheriff, K. Kish, J. Tredup, A. G. Jardel, V. Halan, K. Ghosh, D. Parker, K. Mosure, H. Fang, Y.-K. Wang, J. Lemm, X. Zhuo, U. Hanumegowda, K. Rigat, M. Donoso, M. Tuttle, T. Zvyaga, Z. Haarhoff, N. A. Meanwell, M. G. Soars, S. B. Roberts, J. F. Kadow, *MedChemComm* **2017**, *8*, 796-806.
- [136] D. Wang, M. Shen, Y. Wang, J. Hu, J. Zhao, P. Yu, *Asian J. Org. Chem.* **2018**, *7*, 879-882.
- [137] D. Wang, J. Hu, J. Zhao, M. Shen, Y. Wang, P. Yu, *Tetrahedron* **2018**, *74*, 4100-4110.
- [138] L. Zhao, L. Hao, Y. Fu, Y. Cheng, G. Pan, L. Désaubry, P. Yu, D. Wang, *Adv. Synth. Catal.* **2020**, *362*, 3841-3845.
- [139] a) V. Boekelheide, W. J. Linn, *J. Am. Chem. Soc.* **1954**, *76*, 1286-1291; b) T. Cohen, G. L. Deets, *J. Am. Chem. Soc.* **1972**, *94*, 932-938.
- [140] C. Fontenas, E. Bejan, H. A. Haddou, G. G. A. Galavoine, *Synth. Commun.* **1995**, *25*, 629-633.
- [141] S. Radl, O. Klecan, J. Havlicek, *J. Heterocycl. Chem.* **2006**, *43*, 1447-1453.
- [142] C.-S. Wang, P. H. Dixneuf, J.-F. Soulé, *Org. Biomol. Chem.* **2018**, *16*, 4954-4957.
- [143] C.-S. Wang, T. Roisnel, P. H. Dixneuf, J.-F. Soulé, *Org. Lett.* **2017**, *19*, 6720-6723.
- [144] M. Liman, Y. E. Türkmen, *Tetrahedron Lett.* **2018**, *59*, 1723-1727.
- [145] Y. Yang, C. Qu, X. Chen, K. Sun, L. Qu, W. Bi, H. Hu, R. Li, C. Jing, D. Wei, S. Wei, Y. Sun, H. Liu, Y. Zhao, *Org. Lett.* **2017**, *19*, 5864-5867.
- [146] D. Wang, Z. Liu, Z. Wang, X. Ma, P. Yu, *Green Chem.* **2019**, *21*, 157-163.
- [147] L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266-3267.
- [148] X. Xun, M. Zhao, J. Xue, T. Hu, M. Zhang, G. Li, L. Hong, *Org. Lett.* **2019**, *21*, 8266-8269.
- [149] D. M. Bystrov, E. S. Zhilin, L. L. Fershtat, A. A. Romanova, I. V. Ananyev, N. N. Makhova, *Adv. Synth. Catal.* **2018**, *360*, 3157-3163.
- [150] Z.-S. Chen, F. Yang, H. Ling, M. Li, J.-M. Gao, K. Ji, *Org. Lett.* **2016**, *18*, 5828-5831.
- [151] B. Zhang, L. Huang, S. Yin, X. Li, T. Xu, B. Zhuang, T. Wang, Z. Zhang, A. S. K. Hashmi, *Org. Lett.* **2017**, *19*, 4327-4330.
- [152] X. Li, T. Wang, Z. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 696-701.
- [153] S. Zhang, C. Wu, Z. Zhang, T. Wang, *Org. Lett.* **2019**, *21*, 9995-9998.
- [154] J. Liu, D. Ba, Y. Chen, S. Wen, G. Cheng, *Chem. Commun.* **2020**, *56*, 4078-4081.
- [155] L. Zhao, C. Tsukano, E. Kwon, Y. Takemoto, M. Hirama, *Angew. Chem., Int. Ed.* **2013**, *52*, 1722-1725.
- [156] J. N. Newton, D. F. Fischer, R. Sarpong, *Angew. Chem., Int. Ed.* **2013**, *52*, 1726-1730.
- [157] D. F. Fischer, R. Sarpong, *J. Am. Chem. Soc.* **2010**, *132*, 5926-5927.
- [158] X. Chen, S. A. Ruider, R. W. Hartmann, L. Gonzalez, N. Maulide, *Angew. Chem., Int. Ed.* **2016**, *55*, 15424-15428.
- [159] For some selective examples, see: a) H. Hwang, J. Kim, J. Jeong, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 10770-10776; b) B. Wang, C. Li, H. Liu, *Adv. Synth. Catal.* **2017**, *359*, 3029-3034; c) C. You, C. Pi, Y. Wu, X. Cui, *Adv. Synth. Catal.* **2018**, *360*, 4068-4072; d) C. You, T. Yuan, Y. Huang, C. Pi, Y. Wu, X. Cui, *Org. Biomol. Chem.* **2018**, *16*, 4728-4733; e) R. Sharma, R. Kumar, U. Sharma, *J. Org. Chem.* **2019**, *84*, 2786-2797.

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