Université de Montréal

Transition metal-free desulfinative cross-coupling of 2-pyridyl sulfonates with organolithium reagents:

Mild access to 2-substituted pyridines

par
Da Li

Département de chimie, Université de Montréal
Faculté des arts et sciences

Mémoire présentée
en vue de l'obtention du grade de
Maître ès sciences
en chimie

Mars 2021

Université de Montréal
Département de chimie, Faculté des Arts et des Sciences

Ce mémoire intitulé

Transition metal-free desulfinative cross-coupling of 2-pyridyl sulfonates with organolithium reagents:
Mild access to 2-substituted pyridines

Présenté par
Da Li

A été évalué(e) par un jury composé des personnes suivantes

Shawn Collins
Président-rapporteur

Stephen Hanessian
Directeur de recherche

William D. Lubell
Membre du jury

Résumé

Le motif biaryl contenant la pyridine représente une structure omniprésente dans la chimie organique et médicinale. Ainsi, le développement de méthodes fiables de synthèse est continuellement désiré. Traditionnellement, les cycles azotés biarylés sont efficacement synthétisés par des réactions de couplage croisé catalytique. Cependant, la pyridine peut être difficilement fonctionnalisée en position C-2 compte tenu de sa déficience en électrons. Cette propriété limite son utilisation en tant que partenaire nucléophile dans les réactions de couplage croisé. Par exemple, dans le couplage de Suzuki-Miyaura, l'acide 2-pyridyle boronique est connu pour son instabilité. À l'inverse, les organométalliques du 2-pyridyle sont peu réactifs pour faire des réactions de substitution aromatique électrophile. La synthèse des pyridines 2-substituées est par conséquent un défi qui reste difficile à relever.

La première partie de ce mémoire est consacrée au développement récent des méthodes pour résoudre les problèmes de couplage avec des nucléophiles 2-pyridyles. En particulier, les approches classiques comme le couplage modifié de Suzuki-Miyaura, l'activation de liaison C-H des composés pyridinium N-activés, et l'arylation directe du cycle pyridine sont présentées. De plus, les approches alternatives qui utilisent la partie pyridine comme partenaire électrophile dans la réaction couplage avec les réactifs organométalliques sont également discutées.

Dans la deuxième partie de ce mémoire, une méthode de couplage croisée entre des esters de sulfonate de 2-pyridyles et des organolithiens est rapportée. Une variété de pyridines 2-substituées a été synthétisées avec succès en faisant réagir des sulfonates de pyridine avec des organolithiens (aryl, alkane, heteroaryle lithium) à basse température. La méthode permet également de s'affranchir de l'utilisation d'un quelconque métal de transition. Des études

mécanistiques montrent que le processus impliquant les composés lithiés s'apparente à une réaction de substitution nucléophile aromatique. Cependant, le mécanisme diffère lorsque la réaction met en jeu des réactifs de Grignard, où un processus de couplage entre deux ligands d'un intermédiaire σ-sulfurane peut être impliqué.

Mots-clés : Arylation direct, ester de 2-pyridine sulfonate, synthèse du motif biarylé, pyridine 2-substitué, lithiation, sans métaux de transition.

Abstract

Biaryl compounds containing the pyridine moiety represent a ubiquitous structure in both organic and medicinal chemistry. Therefore, finding new and reliable approaches for their synthesis is still of interest. Traditionally, azine containing biaryls are efficiently synthesized via transition-metal catalyzed cross-coupling reactions. However, due to its π-deficient nature, pyridine cannot be easily functionalized at the C-2 position to serve as nucleophile partner. For examples, in the Suzuki-Miyaura cross-coupling reaction, 2-pyridyl boronates are well known for their instability. 2-Pyridyl organometallics undergo electrophilic aromatic substitution poorly. Thus, the synthesis of 2-substituted pyridines remains a challenging task.

The first part of the thesis focuses on the recent methods to address the coupling issues of 2-pyridyl nucleophiles in cross-coupling reactions. Of note, the classical methods including Suzuki-Miyaura cross-coupling reactions, C-H activation of N-activated pyridinium species, and direct coupling reaction of pyridine are presented. Alternative approaches using the pyridine moiety as an electrophilic entity in the coupling with organometallic reagents are also discussed.

In the second part of the thesis, a transition metal-free desulfinative cross-coupling reaction of 2-pyridyl sulfonates with organolithium reagents is reported. A variety of 2-substituted pyridines were successfully synthesized in good yields, by treatment of neopentyl 2-pyridyl sulfonates and phenyl 2-pyridyl sulfonate with aryl, alkyl, and heteroaryl-lithium reagents at low temperature. Mechanistic studies showed that the coupling reaction with lithium reagents undergoes an S_NAr pathway. However, a ligand coupling process of a σ-sulfurane intermediate may be involved in the reaction with Grignard reagents to form the biaryl.

Keywords: Direct arylation, 2-pyridyl sulfonate esters, biaryl synthesis, 2-substituted pyridine, lithiation, transition metal-free reactions.

Table of contents

List of tables

List of figures

List of acronyms and abbreviations

Ac	acetyl
Alk	alkyl
Ar	aryl
br	broad (NMR)
Bu	butyl
Calcd.	calculated
Cat.	catalyst
°C	degree Celsius
δ	chemical shift
Cy	cyclohexyl
d	deuterated
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dt	doublet of triplets
dtt	doublet of triplet of triplets
D	Debye
DCM	dichloromethane
DMF	*N, N*-dimethylformamide
dba	dibenzylideneacetone
dppf	diphenylphosphinoferrocene
equiv.	equivalent
Eq.	equation
ESI	electrospray ionization
g	gramme
J	coupling constant (NMR)
Het	hetero
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy

h	hour
Hz	Hertz
i-Pr	isopropyl
M	molar (mol/L)
m	multiplet (NMR)
min	minute
MS	mass spectroscopy
Me	methyl
MHz	Megahertz
NADP	nicotinamide adenine dinucleotide phosphate
NHC	*N*-heterocyclic carbene
NO.	number
NMR	nuclear magnetic resonance
*n*Bu	*n*-butyl
pH	potential of hydrogen
Ph	phenyl
phen	phenanthroline
pin	pinacol
Piv	pivaloyl
ppm	parts per million
q	quadruplet (NMR)
quint	quintuplet (NMR)
R	organic substituent/alkyl, aryl
rt	room temperature
s	singlet (NMR)
sept	septuplet (NMR)
SMC	Suzuki-Miyaura cross-coupling
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophile aromatic subsitution
t	triplet (NMR)

TBAF	tetra-*n*-butylammonium fluoride
TFAA	trifluoroacetic anhydride
TM	transition metal
Temp.	temperature
TLC	thin layer chromatography
THF	tetrahydrofuran
TMS	tetramethylsilane
*t*Bu	*tert*-butyl
UV	utraviolet

献给李树宝和史占晶

Remerciements

Je veux d'abord remercier sincèrement à mon directeur de recherche, le professeur Stephen Hanessian pour m'avoir accepté dans votre groupe de recherche et de m'avoir permis de travailler sur des projets intéressants et adéquates à mon niveau. Durant ces deux ans et demi d'études, vous avez toujours été disponible pour me guider et m'aider à réfléchir sur mon projet, sans votre aide et votre judicieux conseils, il m'aurait été impossible de réussir. Merci pour tout ce que vous faites pour moi, je n'oublierai jamais.

Ensuite, j'aimerais remercier Michèle pour votre soutien indispensable tout au long de mon étude. C'est grâce à votre présence essentielle que je peux travailler sans soucis dans le lab et avancer solidement dans mon étude. Merci aussi pour tout ce que vous faites pour le groupe, on est une grande famille!

Un grand merci à Adrien pour ton accompagnement quotidien pendant toute mon étude de maîtrise. Merci de m'avoir enseigné pas à pas toutes les techniques essentielles de laboratoires et d'avoir répondu avec patience à toutes mes questions ignorantes et incessantes.

Je tiens aussi à remercier Sofiane, Edouard et JB pour la maintenance et le fonctionnement du lab, sans vous, laboratoire n'aurait jamais roulé. Merci aussi pour tous vos conseils qui m'ont été donnés, ça m'a été très utile pour régler tout type de problème.

Je tiens également à remercier Akash, Barbara, Greg, Jithu, Raja, Raphaël, Scarlett et Vito pour les longues et intéressantes discussions de chimie qu'on a eues ensemble et pour l'aide que vous m'avez apportée tout au long de mon étude.

Je remercie aussi Aida pour tout le soutien administratif que vous m'avez accordé durant ces années d'études.

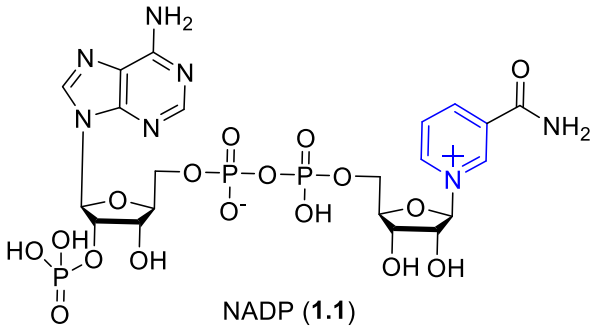
Finalement, je remercie mes parents pour m'avoir poussé et permis d'aller plus loin dans mes études. Merci pour votre soutien et vos encouragements.

Chapter 1. Introduction

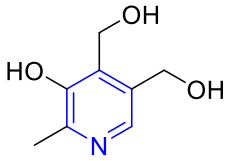
1.1 Overview of 2-substituted pyridines

Pyridines belong to the most prominent and most important class of nitrogen-containing heterocycles. Due to their ubiquity, pyridine derivatives have found numerous applications in diverse fields (Figure 1). For example, derivatives such as nicotinamide adenine dinucleotide phosphate (NADP) (**1.1**) plays a key role in both biological and chemical systems involved in various oxidation-reduction process in living organisms.[1] Niacin (**1.2**) and pyridoxine (**1.3**) are important vitamins in the human body.[2] Other than prominent roles in biologically relevant processes, the pyridine core is also well known in the pharmaceutical field. In fact, according to the MDL Drug Data Registry, pyridine is a component of over 7000 existing drugs,[3] such as Etoricoxib (**1.4**) and topoisomerase inhibitor **1.5**. The pyridine core ranks second among the most used heterocycles in medicinal compounds.[4] In addition, countless pyridines have been also found in agrochemicals such as pyridinenitrile (**1.6**) and chlorantraniliprole (**1.7**) exhibiting fungicidal and pesticidal respectively.[4,5] Finally, pyridine derivatives like bipyridines (**1.8**) and terpyridines (**1.9**) are extensively used in coordination chemistry to complex various metal ions.[6]

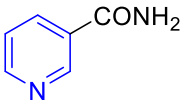
Natural products



NADP (**1.1**)
Coenzyme

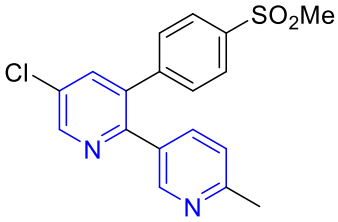


Pyridoxine (**1.3**)
Vitamin B6

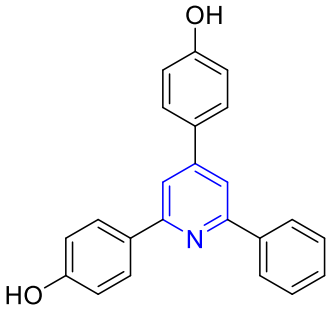


Niacin (**1.2**)
Vitamin B3

Drugs

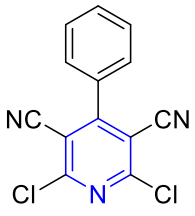


Etoricoxib (**1.4**)
Anti-inflammatory

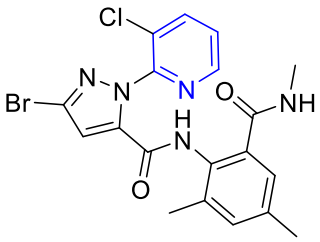


Topoisomerase inhibitor **1.5**
Anti-cancer

Agrochemicals

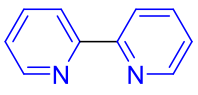


Pyridinenetrile (**1.6**)
Fungicide

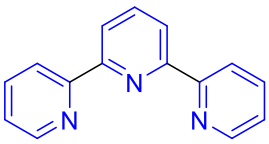


Chlorantraniliprole (**1.7**)
Pesticide

Chemistry



2,2'-bipyridine (**1.8**)
Ligand



2,2',2''-terpyridine (**1.9**)
Ligand

Figure 1. Diverse utilisations of pyridine derivatives.

Despite the great importance of pyridine derivatives, the electron-deficiency of pyridines makes their functionalization a challenging task, especially at the 2-position.[7] In fact, over the past three decades, a large number of articles have been published for the development of 2-pyridyl organometallic reagents that can be used in cross-coupling reactions.[8–15] However, all of the methods show one or more important drawbacks, including poor stability of the 2-pyridyl building block,[9,11–15] use of toxic metals[8] and low reaction efficiency with halide coupling partners.[10,11,13–16] Even in the prominent Suzuki-Miyaura cross-coupling reaction (SMC), 2-pyridyl boronates may be unstable and can undergo a facile protodeboronation process after the formation of the boron-ate-complex (Figure 2).[17] An electron withdrawing substituent, such as chloro or trifluoromethyl group, on the 6 position of the pyridine ring may minimize the protodeboronation of 2-pyridyl boronates but require more steps to install.[18]

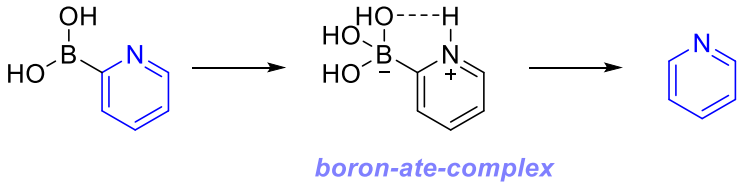


Figure 2. Possible protodeboronation mechanism for 2-pyridyl boronic acid.[17]

For example, according to the survey of the Pfizer internal electronic laboratory notebook for SMC couplings, only 28 reactions out of a total of 358 led to a product yield of at least 20% when 2-pyridyl boronates were employed as nucleophilic partners (Figure 3).[18]

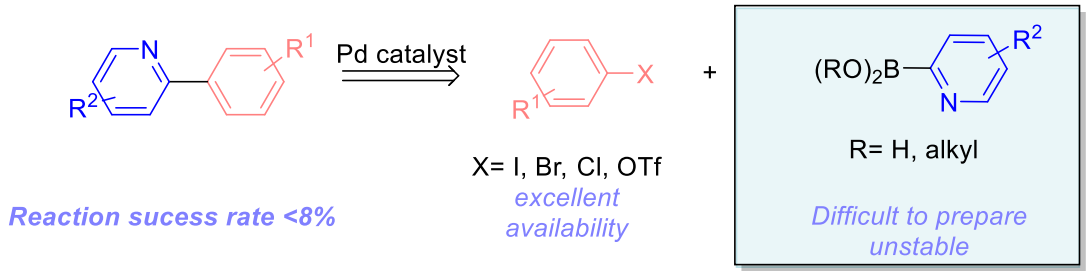


Figure 3. Problem of the Suzuki-Miyaura cross-coupling reaction with pyridine boronates.

Aside from traditional cross-coupling reactions, oxidative cross-coupling of two 2-pyridyl nucleophiles via double C-H activation have encountered the same problem, as electron-deficient (hetero)arenes are unreactive in electrophilic aromatic substitution (S_EAr) chemistry with metalated partners (Figure 4).[19]

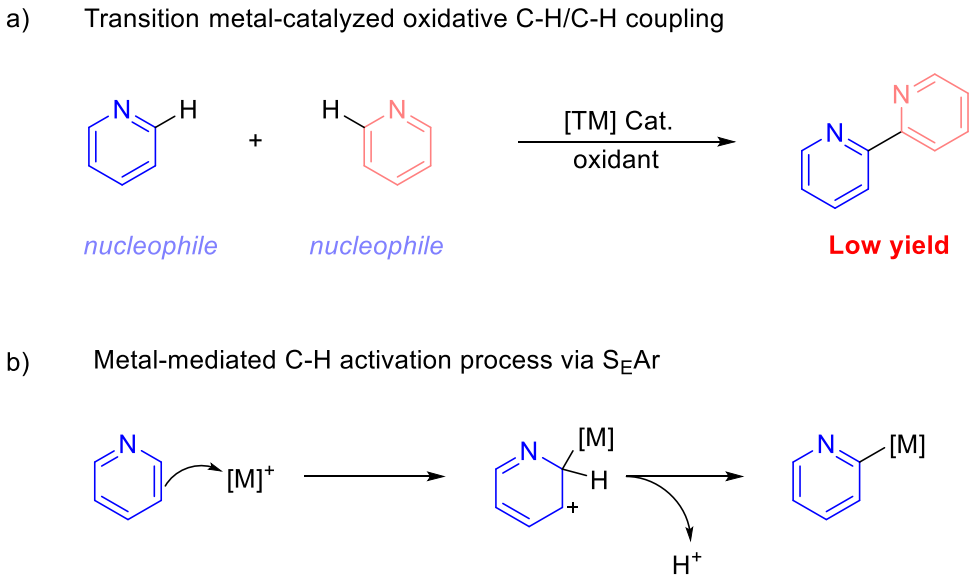


Figure 4. a) Oxidative cross-coupling of two 2-pyridyl nucleophiles. b) Electrophilic aromatic substitution process.

The problem may be avoided by using a reverse coupling approach in which 2 bromo- and 2-chloropyridines are reacted with aryl nucleophiles (Figure 5).[20] Such an approach is feasible for

only a smaller number of substrates and fails with many commercially available halogen-substituted arenes.

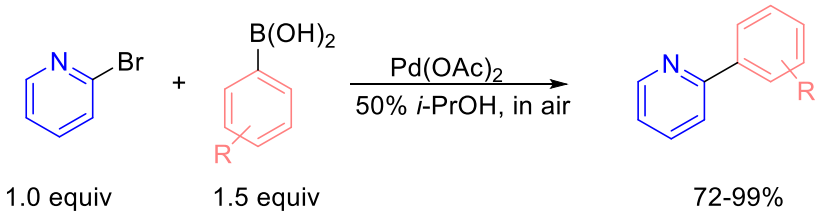


Figure 5. Suzuki-Miyaura reaction of 2-bromopyridine with aryl boronic acid.[20]

Furthermore, coupling between two pyridines is not possible by the method. Currently, the problem can be circumvented by a reductive cross-coupling strategy which can combine two electrophiles using Ullmann-type coupling reactions (Figure 6).[21,22] Although low yields are often observed with electron deficient pyridines, the reactivity can be mitigated by using catalysts possessing metals such as palladium or copper.[23,24]

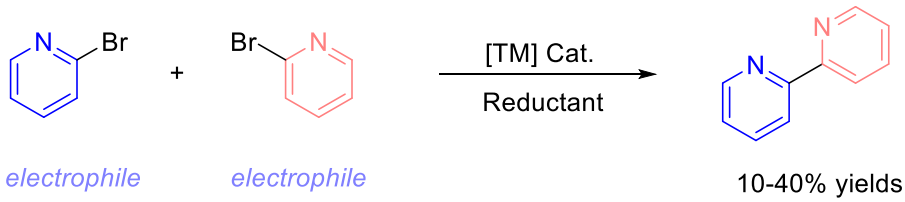


Figure 6. Ullmann-type reductive cross-coupling reaction of 2-bromopyridines.[22]

The cross-coupling between two non-symmetrical aryls containing halogens is underdeveloped in classical Ullmann reactions as it often requires the use of a significant excess of the activated aryl (Figure 7).[25,26] Moreover, the reaction temperature is crucial: above or below optimal temperature, homocoupling can prevail.[27]

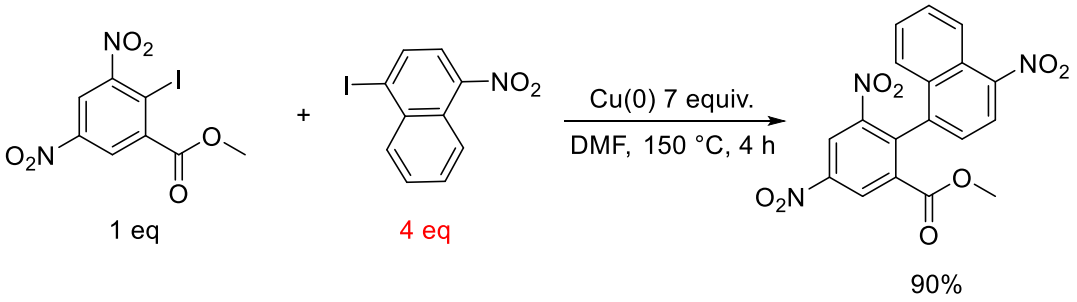


Figure 7. Unsymmetrical Ullmann cross-coupling with excess of iodo naphthalene.[26]

An attractive synthetic route to access 2-substituted pyridines is direct arylation of pyridine through metal catalyzed C-H activation by a vicinal heteroatom (Figure 8).[28,29] The method avoids pre-installation of halogens on the pyridine ring in contrast to the classical cross-coupling methods. However, as the reaction proceeds through an electrophilic aromatic substitution (S_EAr), improvements may be needed with electron deficient arenes.

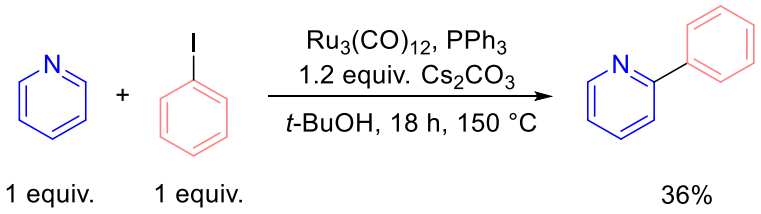
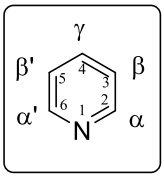


Figure 8. Metal-catalyzed C-H activation of electron-deficient heteroarenes.[29]

Given the challenges, there is a need for an efficient and reliable method for the synthesis of 2-substituted pyridines bearing carbon appendages. In the next section, we will discuss some important improvements that have been made for the methodologies cited above and some new approaches to prepare 2-substituted pyridines.

1.2 Electronic properties of pyridine



Pyridine is the simplest heterocyclic compound of the azine type with chemical formula C_5H_5N. Pyridine is analogous to benzene except a methine group is replaced by a nitrogen. Three fundamental differences exist between the two structures: 1) the diminution of the length of the C=N bond; 2) the presence of an unshared electron pair in the plane of the ring (in the sp^2 hybridized orbital of nitrogen) in place of the hydrogen, and not involved in the aromaticity of the molecule (Figure 9); 3) the presence of a strong permanent dipole, caused by the greater electronegativity of the nitrogen compared to the carbon (N → 3.0 , C → 2.5). [30]

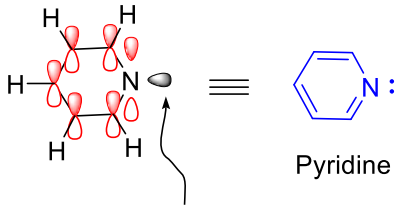


Figure 9. Structure of pyridine.

Nitrogen is more electronegative than carbon. Nitrogen can inductively drain electron density from the ring carbons and onto itself. In the mesomeric structures of pyridines (Figure 10), the electron density of the ortho and para carbons are diminished via resonance effects to exhibit fractional positive charges. As a result, the reactivity of pyridine towards nucleophilic substitution is usually favoured at the 2, 4 and 6 positions. Electrophilic substitution reaction rates on pyridine are significantly lower than on benzene.

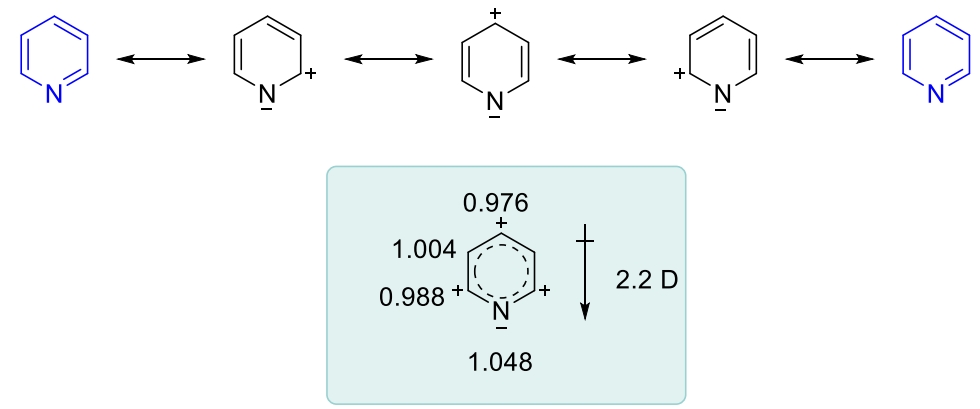


Figure 10. Mesomeric structures, electron density and permanent dipole of pyridine.[30]

Finally, due to the electron deficiency at ring carbons resulting from the polarization effect, pyridine and similar heterocycles are usually referred to as electron-poor or π-deficient arenes.[31] The HOMO of their π molecular orbitals is lower in energy compared to those of benzene (Figure 11). Consequently, the carbon atoms in pyridine are not nucleophilic.

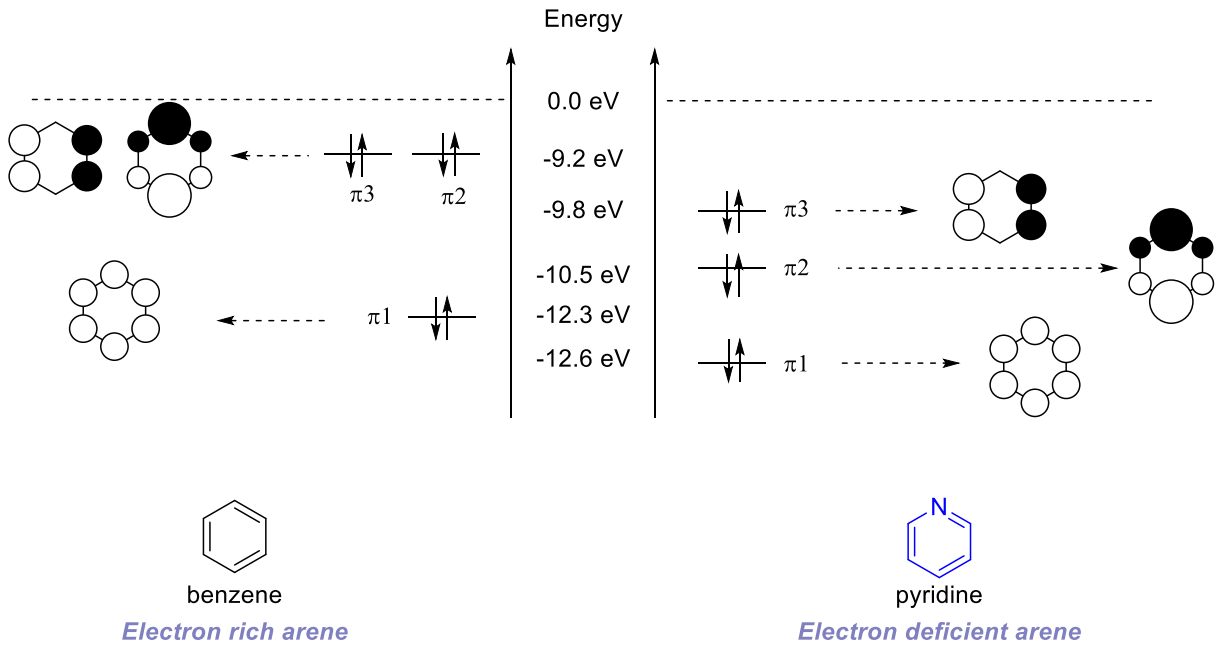


Figure 11. Energy level of π molecular orbitals of pyridine and benzene.[31]

1.3 Synthesis of pyridines with carbon substituents at position 2-

Functionalization of pyridine at the 2-position with carbon-based substituents has been known for many decades. For example, treatment of pyridine with Grignard and organolithium reagents led to the corresponding 2-substituted pyridines as cited by Hanessian and Kagotani in efforts to develop optimized conditions.[32] Alternative methods were also cited some of which will be updated in the sections below.[33–36]

In recent years, the introduction of carbon-based substituents at the 2-position of pyridine has gained importance because 2-pyridine derivatives are privileged scaffolds in many biological and pharmaceutical compounds.[4,37–41] Consequently, many methods have been developed for the synthesis of 2-subtituted pyridines, including the transition metal-catalyzed cross-coupling chemistry such as the venerable Suzuki-Miyaura reaction. In spite of the instability of 2-pyridyl boronic acid due to protodeboronation (Figure 12),[17,42] the Suzuki-Miyaura coupling reaction is still favored sometimes to the rapidly access 2-substituted pyridines.[43]

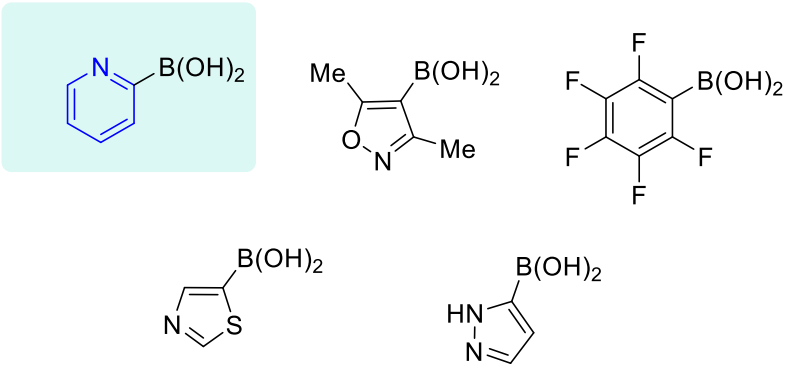


Figure 12. Unstable boronic acids due to protodeboronation.

To understand the instability of 2-pyridyl boronic acid, Lloyd-Jones studied the protodeboronation rate of 18 boronic acids by varying the pH of the solution.[17] They found that the instability is accelerated in the pH range of pH 4-8 causing the boronate zwitterionic

intermediate to decompose via fragmentation (Figure 13).[17] More specifically, the zwitterionic fragmentation is facilitated by the presence of a basic nitrogen adjacent to the boron which can stabilize the $B(OH)_3$ during C-B bond cleavage. The stronger ylidic character and the closer charge placement in the 2-pyridyl zwitterionic intermediate, both make 2-pyridyl boronates more prone to protodeboronation than 3- and 4-pyridyl boronates. However, at higher pH (pH >10), the protodeboronation rate becomes slower as the stabilizing interaction is attenuated.

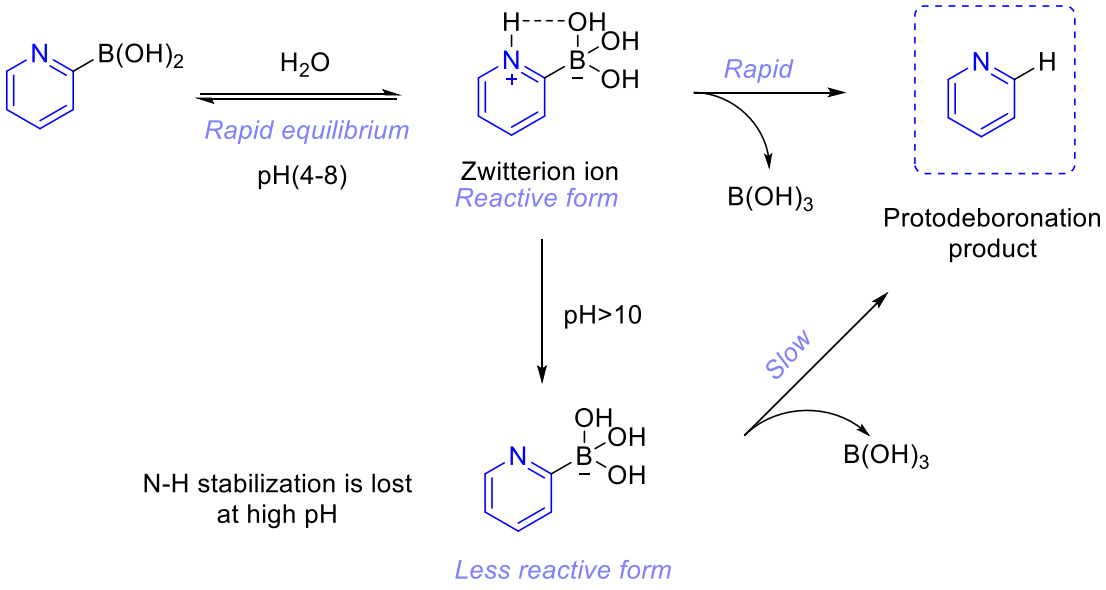


Figure 13. Mechanism of protodeboronation process for 2-pyridyl boronic acid.

After understanding the mechanism of protodeboronation process, several strategies were investigated in order to circumvent the problem. In 2006, Fu and co-workers reported an efficient $Pd/PCy_3/K_3PO_4$/dioxane/H_2O catalyst system for Suzuki-Miyaura cross-coupling of aryl halides (Figure 14).[44] By using the highly active and bulky electron-rich monophosphine ligand (PCy_3), the rate of product formation is believed to outcompete the protodeboronation process to afford the coupling product in excellent yield. However, the use of the ligand alone cannot resolve the 2-pyridyl problem efficiently, and yields can vary from 2% to 92% contingent on base and solvent.

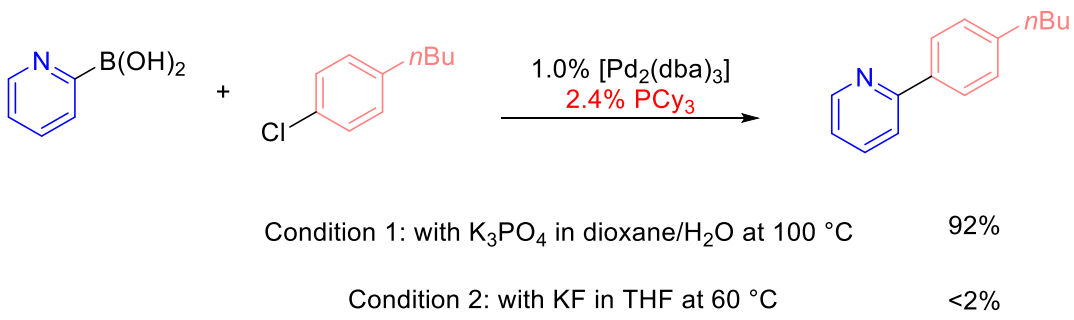


Figure 14. Efficient catalyst system for 2-pyridyl boronic acid cross-coupling reaction.

In efforts to develop active catalyst systems, Lewis acidic metal additives containing copper, silver or zinc have been used to enhance traditional cross-coupling reactions.[45–47] In 2009, Deng and co-workers reported that the coupling between 2-pyridyl boronates with diverse aryl halides was more efficient in the presence of stoichiometric copper salt additives (Figure 15a).[48] In the presence of copper salts, the 2-pyridyl boronate may undergo metal exchange to form a 2-pyridyl copper species (Figure 15b),[48] which may react more rapidly with the active Pd species than the pyridyl boronate to increase the yields of 2-aryl pyridines. Considering that boronate esters and Cu^{I} sources are commercially available and inexpensive, the method provides a practical solution to improve the low reactivity of 2-pyridyl boronates.

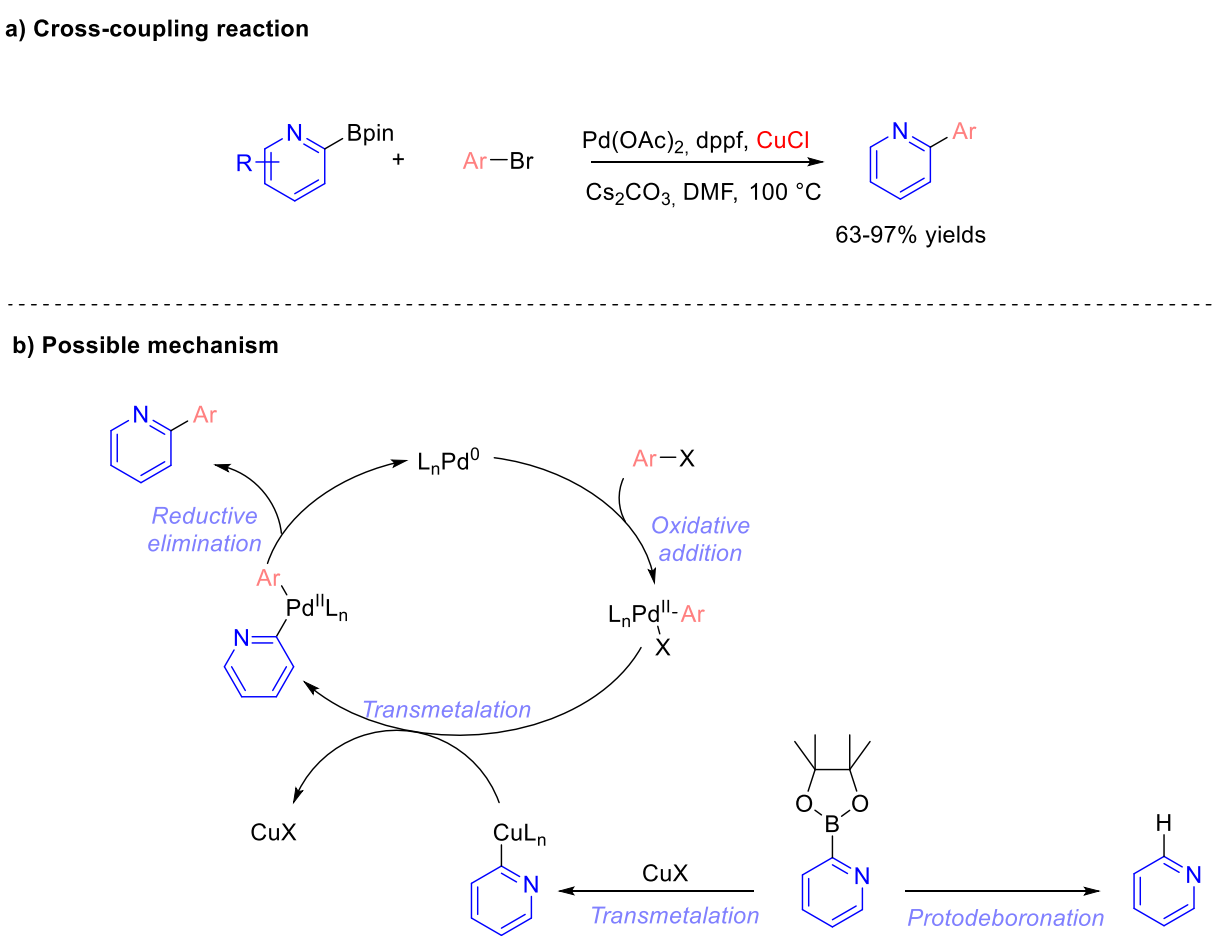


Figure 15. Reaction and mechanism of Suzuki-Miyaura cross-coupling reaction with copper salt additives.

The stability of the pyridyl boronates is also a key element in the cross-coupling reactions. In 2008, Buchwald and Billingsley proposed a general solution for Suzuki-Miyaura cross-coupling reaction of problematic 2-pyridyl nucleophiles, by using 2-pyridyl tri-isopropyl borate as substrate (Figure 16).[49] Various 2-pyridyl boron reagents were tested, but only the triol borate, lithium tri-isopropyl 2-pyridyl borate, proved to be stable and afforded a high yield. The special stability is attributed to the bulkiness of isopropyl groups that mask the boron center and render it less reactive to hydrolysis, thereby promoting "slow release" of the unstable active boron

species. However, the tolerance of functional groups can be an issue in the method, as it involves lithiation to prepare the borate species.

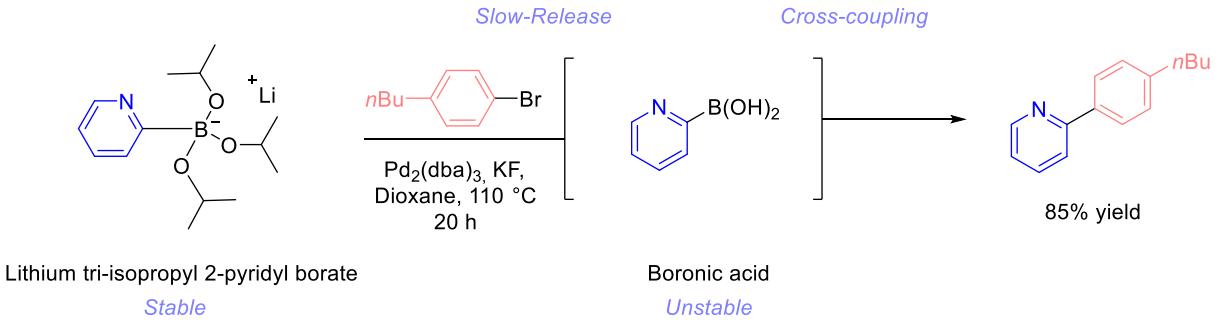


Figure 16. Cross-coupling reactions with stable lithium tri-isopropyl 2-pyridyl borate.

Although the Suzuki-Miyaura cross coupling reaction has been successfully applied to pyridyl borates and aryl/heteroaryl halides under the modified conditions, direct functionalization at the ortho position would constitute an even more efficient approach which eliminates the need for the pre-functionalization of the pyridine core and may widen substrate scope. A highly functionalized pyridine may be synthesized in fewer steps by using direct functionalization pathways.[50]

Recently, transition metal-catalyzed C-H bond functionalization methods for direct C-C bond formation toward 2-substituted pyridines have emerged.[50–52] However, due to the electron deficient character of pyridine, such functionalization remains a challenging goal due to the difficulties of electrophilic aromatic substitution pathways. The problem has been circumvented in 2005 by the group of Fagnou.[53] In their approach, the C-H activation of the pyridine nucleus was successfully achieved by conversion to the corresponding pyridine N-oxide (Figure 17). The enhanced reactivity of such a substrate is attributed to the electronic character of nitrogen when bonded to oxygen. Positions 2, 4, and 6 of pyridine N-oxides exhibit fractional negative

charges (Figure 18). The arylated pyridine N-oxide can be easily reduced to the pyridine counterpart using Pd/C and ammonium formate.

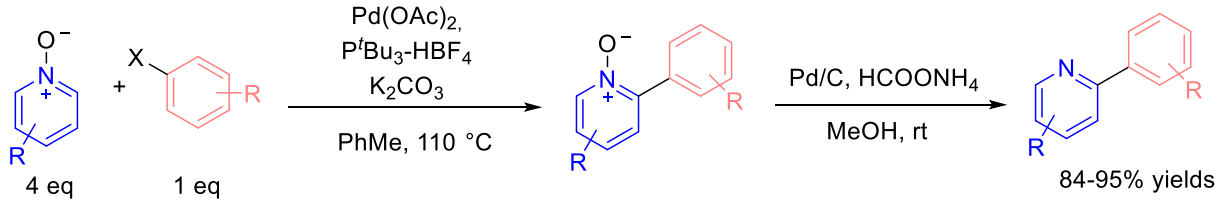


Figure 17. Palladium-catalyzed direct ortho-arylation of pyridine N-oxides.

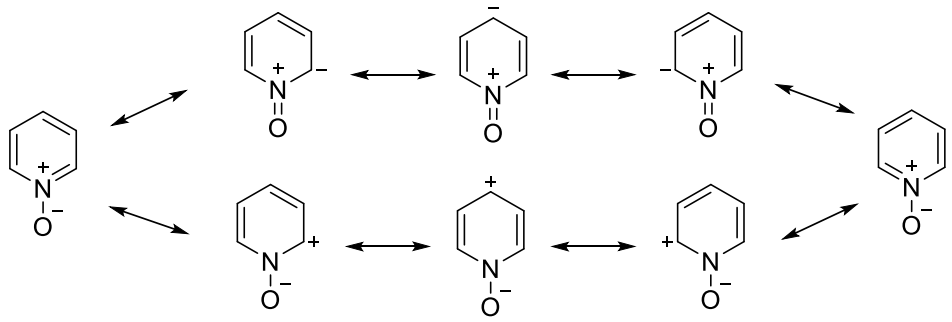


Figure 18. Mesomeric structure of pyridine N-oxide.

In 2008, Charette and co-workers developed a similar palladium-catalyzed arylation by using N-imino pyridinium ylides (Figure 19).[54] The amide functionality is a stronger Lewis base and a better directing group than the N-oxide and may favor addition to the pyridine core by complexing the palladium center and directing the C-H bond insertion. The utilisation of fewer equivalents of ylide compared to that employed with the N-oxide reactions constitutes an advantage of the approach.

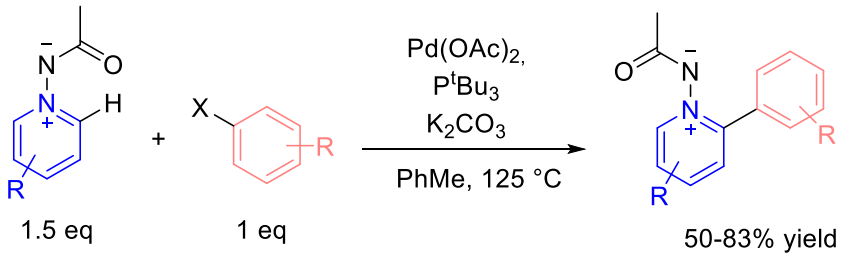


Figure 19. Palladium-catalyzed direct ortho-arylation of N-imino pyridinium ylides.

The 2, 4, 6 positions of pyridine N-oxide can also have electrophile character in the presence of strong organometallics such as Grignard reagents. The nucleophilic addition of a Grignard reagent to pyridine N-oxide has been known for many years.[55–57] However, the method is prone to chemo-selectivity problems[56], and the formation of intermediate ring-opened product 2,4-dienal oxime, which requires a further treatment with acetic anhydride at high temperature (120 °C) to regenerate the substituted pyridine ring (Figure 20).[58]

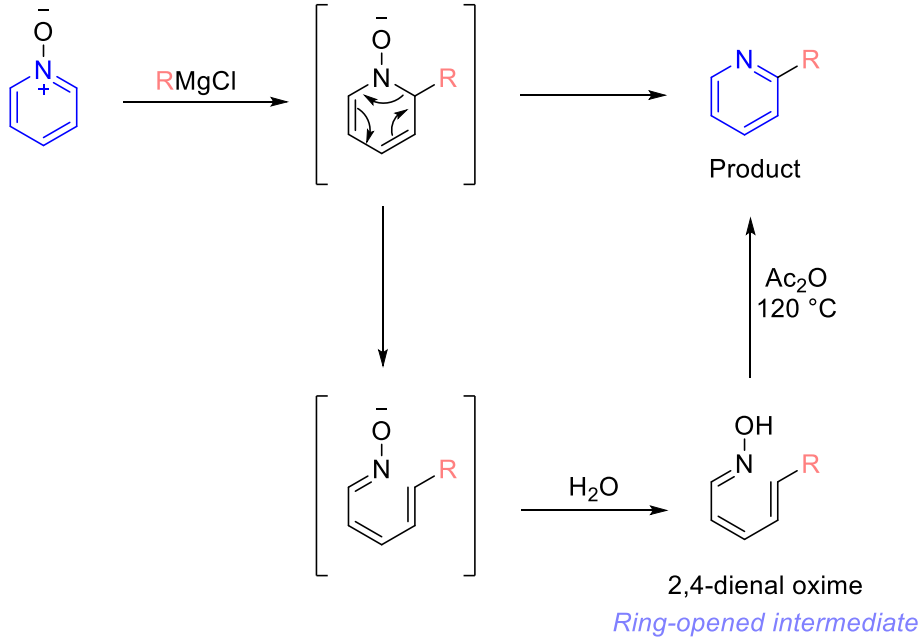


Figure 20. Nucleophile addition of Grignard reagent to pyridine N-oxide.

In 2010, Almqvist and Olsson revised the field and reported a mild chemoselective method towards 2-substituted pyridines by using Grignard reagents (Figure 21).[59] In the work, the 2-substituted pyridine is formed in a single-step through Grignard addition at low temperature, which prevents the formation of the ring-opened products. A work-up with methanol and an acylating agent such as trifuoroacetic anhydride (TFAA) reduced the dihydropyridine N-oxide to afford the corresponding 2-aryl pyridine in good yields.

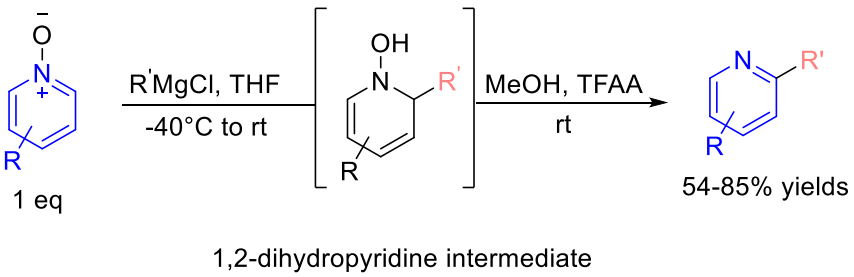


Figure 21. Nucleophile addition of Grignard reagent to pyridine N-oxide.

An efficient alkylation of N-oxides with benzyltrimethylsilane was also reported by Vorbrüggen (Figure 22).[34] The oxygen anion can attack on the silyl center and liberate the alkyl nucleophile, which can undergo a nucleophile addition on the electrophilic C-2 position of the pyridine ring. Then the trimethylsilanol is eliminated by a rearomatization process affording 2-benzylpyridine in 70% yield.[34]

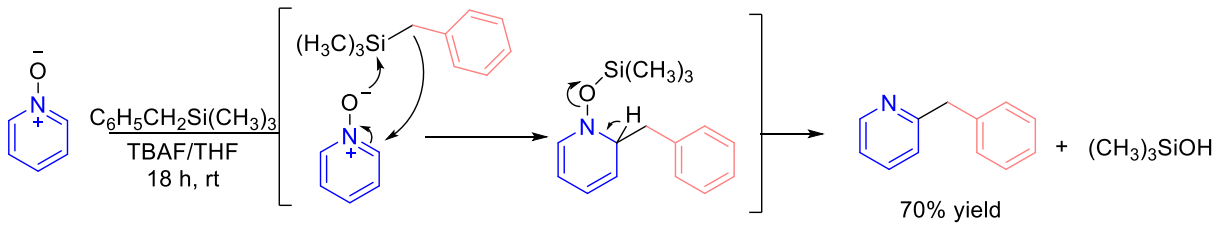


Figure 22. Alkylation of N-oxides with benzyltrimetylsilane.

Finally, 2-alkyl pyridines can be also obtained by a regioselective addition of Grignard reagents to other N-activated pyridinium intermediates such as N-acyl pyridinium and N-methoxycarbonyl pyridinium salts (Figure 23).[60,61]

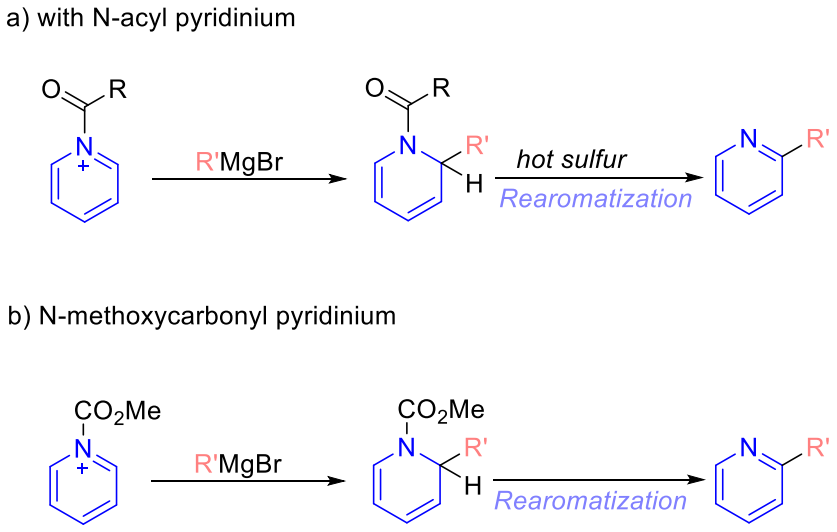


Figure 23. Alkylation of N-activated pyridiniums with Grignard reagents.

Although pyridine N-oxides seem to be versatile substrates for pyridine functionalization, the necessity of two additional steps for the activation of the pyridine core and unmasking of the arylated product, narrows the substrate scope. Thus, the use of pyridines directly would clearly represent the ideal situation in terms of both cost and simplicity.

Except for the now historically noteworthy examples limited to pyridine and free radical mediated substitutions reactions,[62–64] methods for the direct arylation of pyridine have not been adequately explored. In 2008, Ellman reported a Rh(I)-catalyzed arylation of pyridines and quinolines with aryl bromides at 175 °C in dioxane leading to 2,6-disubstitution in good yields (Figure 24).[65] In the method, a bulky alkyl substituent is necessary in the 2-position of the pyridine for efficient coupling. The steric interactions provided by the 2-position substituent may limit binding of rhodium to the nitrogen. However, the necessities of a large excess of pyridine substrate and high temperature remain limitations of the approach. It is noteworthy that with a Pd catalyst, the 3-arylation product was observed instead of the desired 2-substituted pyridine.

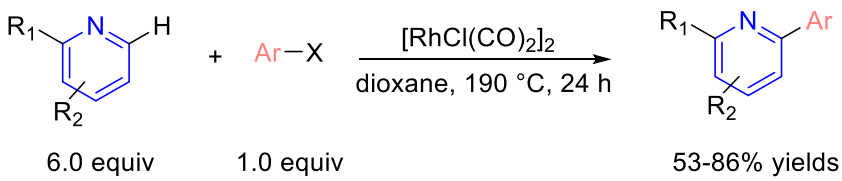


Figure 24. Rh-catalysed direct arylation of pyridines.

Itami has achieved direct coupling of pyridine with aryl iodides in the presence of KO*t*Bu under microwave conditions (Figure 25).[66] In the work, a series of alkoxide reagents such as NaO*t*Bu, LiO*t*Bu, KOMe, and KOH were tested, but none afforded the coupling product under the same conditions. The special reactivity of KO*t*Bu to promote coupling reactions is of significance because it avoids the addition of any exogenous transition metal species. However, the poor regioselectivity is the main limitation of the approach.

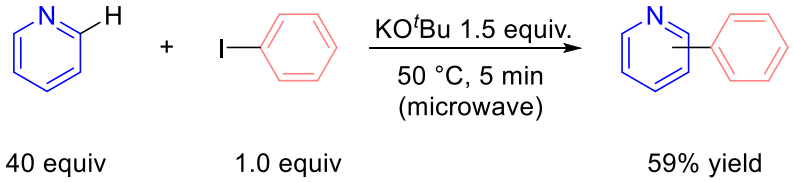


Figure 25. Potassium t-butoxide promoted direct arylation of pyridine.

In 2013, You and coworkers developed a palladium-catalyzed double C-H activation method for 2-pyridine cross-coupling reactions (Figure 26a).[67] In the reaction, a stoichiometric quantity of an oxidant such as a silver salt is required to oxidize the Pd^0 and close the catalytic cycle. Neither coupling partner needs to be functionalized and both can coordinate on the palladium through C-H activation (Figure 26b). The resulting complex can then undergo reductive elimination to form the desired product in a good yield. However, the use of a large excess of pyridine remains the main limitation.

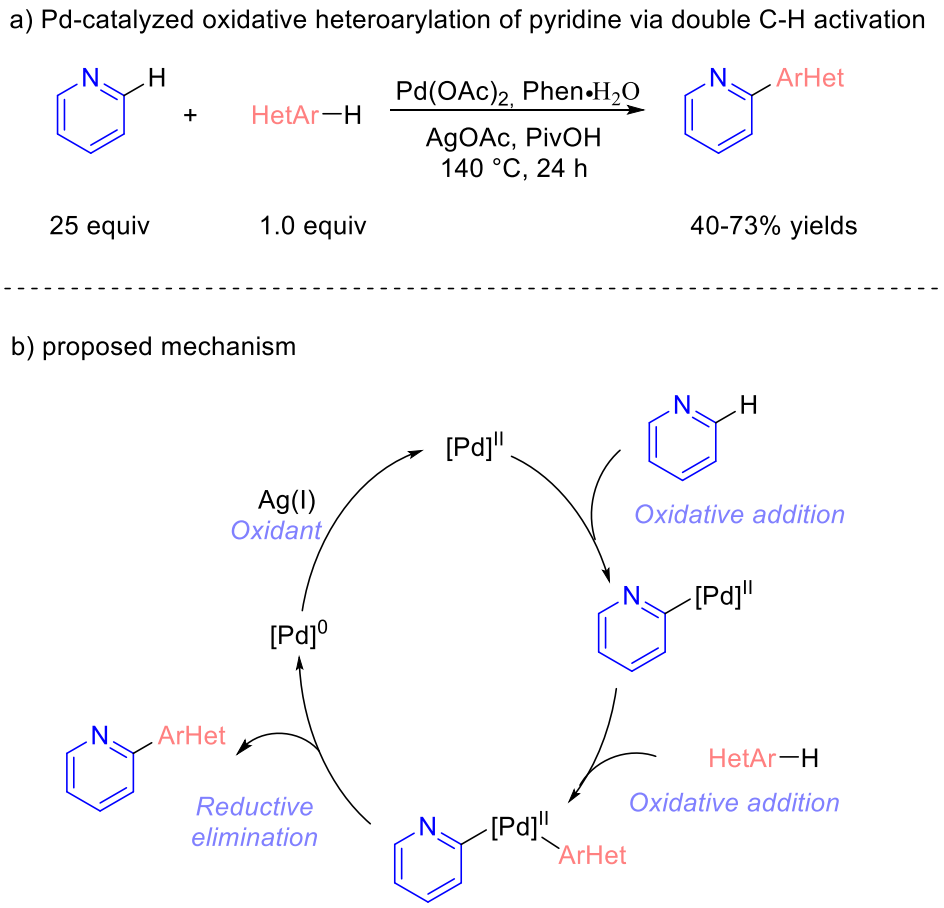


Figure 26. Palladium-catalysed oxidative cross-coupling reactions and mechanism.

Aside from the improvements of the classical methods, transition metal-catalyzed desulfinative cross-coupling has recently been considered as a potential approach to cross-coupling chemistry.[68] In 2017, Willis and co-workers reported the palladium-catalyzed cross-coupling reactions of 2-pyridyl sulfinates with (hetero)aryl halides to afford 2-aryl pyridines in good yields (Figure 27).[69] Compared with the corresponding boron-derived reagents, the sulfinates are shown to be easier to prepare and more stable under coupling reaction conditions. Moreover, the ability to couple efficiently with cheaper and less active aryl chlorides enables the preparation of a broad range of 2-linked pyridines. The synthesis of heteroaryl pyridines by the method constitutes an advantage over the classical methods.

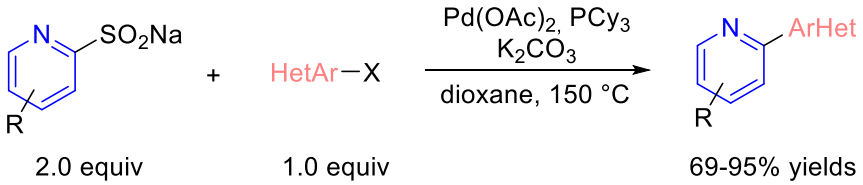


Figure 27. Pd-catalyzed cross-coupling of 2-pyridyl sulfinates.

Detailed mechanistic studies by the Willis group in 2020, indicate that the use of potassium carbonates was a key to achieve good yields of products (Figure 28).[70] They demonstrated that the potassium can undergo a cation exchange with the sodium sulfinate salt which accelerates the transmetalation step, while the carbonate moiety can trap the SO_2 byproduct which can disrupt the catalysis by coordinating to the palladium center. They also showed that the rate-determining step of the reaction is the rate of SO_2 extrusion because of the formation of a five-membered ring palladacycle with the 2-pyridyl sulfinate, which is thermodynamically stable. Thus, the need of an electron-withdrawing group on the pyridine ring to weaken the Pd-N bond or using high temperature is necessary for the Pd-N bond cleavage and the extrusion of SO_2. Although 2-pyridyl sulfinates are potential coupling partners in cross-coupling reactions, they still have some issues such as difficult purification for more complex sulfinate salts due to their anionic character.

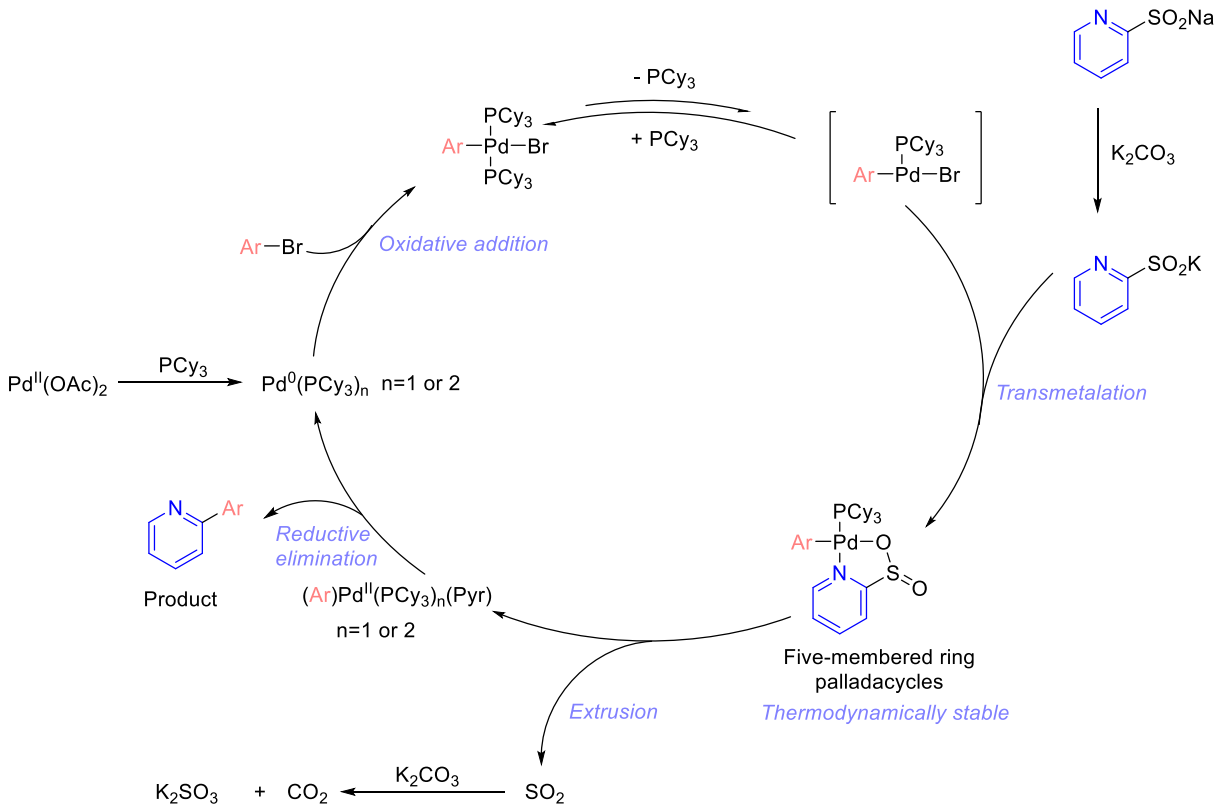


Figure 28. General mechanism of desulfinative cross-couplings.[70]

To circumvent the problems, Willis studied allylsulfones as latent sulfinate coupling partners in palladium-catalyzed cross-coupling reactions (Figure 29).[71] Because of the neutral nature of the molecule, the purification problem was resolved. The Pd catalyst can generate the π-allyl-Pd intermediate and the active sulfinate, which will engage in the cross-coupling process. The resulting Pd (0) can be regenerated by interception of the π-allyl-Pd intermediate with a nucleophile thereby allowing the cross-coupling to proceed.

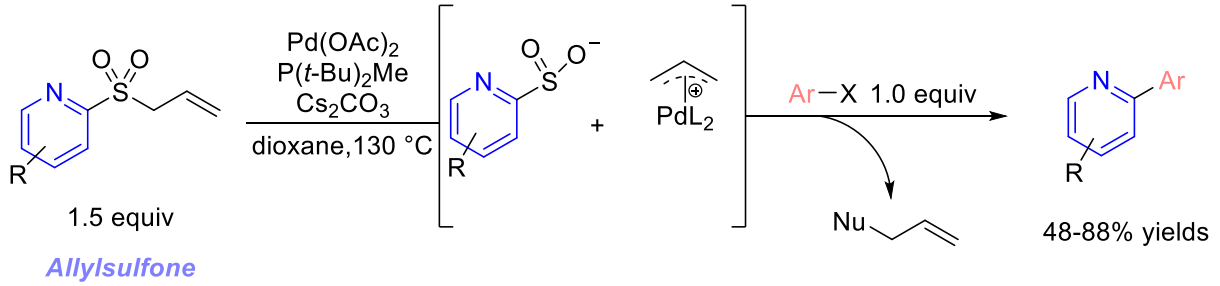


Figure 29. Palladium-catalyzed desulfinative cross-coupling of 2-pyridyl allylsulfone.[71]

Sulfinates can also be employed as the electrophilic coupling partners in Mizoroki− Heck[72], Suzuki−Miyaura[73], and Hiyama[74] cross-coupling processes. Furthermore, sulfinates can also undergo efficiently nucleophilic aromatic substitution with organometallic reagents. In 2019, the Hu group reported a transition metal-free desulfinative cross-coupling of heteroaryl sulfinates with Grignard reagents in an S_NAr process, to afford 2-substituted pyridine in good yields (Figure 30a).[75] A patent (No. U.S. 7,560,563) disclosed the same reactivity between 2-pyridyl sulfones and organolithium reagents at -78 °C (Figure 30b).[76]

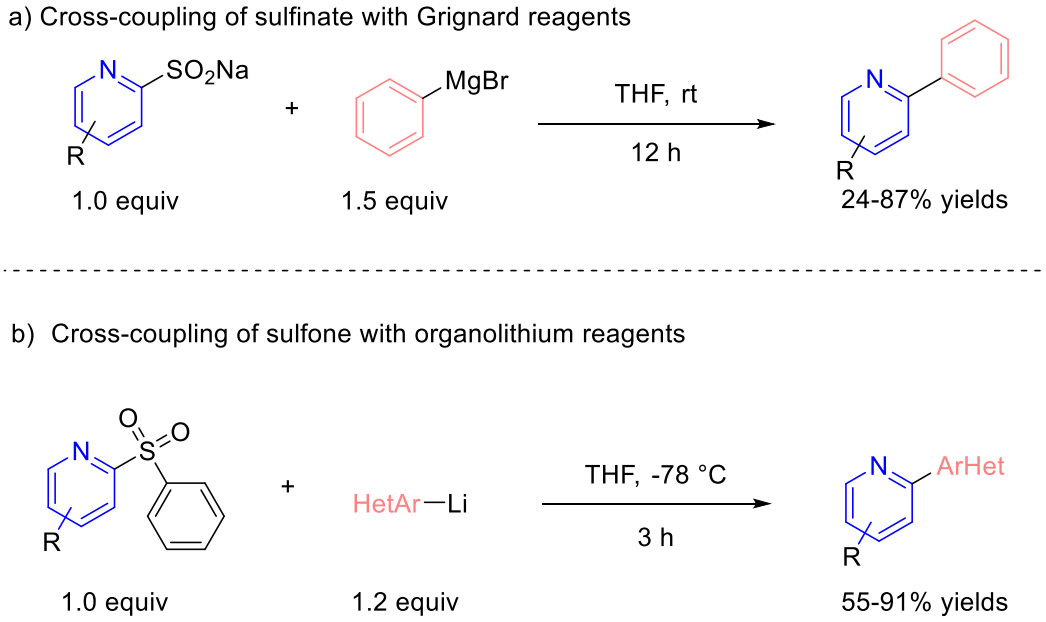


Figure 30. Nucleophilic aromatic substitution of organometallics with 2-pyridyl sulfinates and 2-pyridiyl sulfones.

A similar cross-coupling reaction between 2-pyridyl sulfonate esters and organometallic reagents was reported by Hanessian and Kagotani in 1987, giving access to 2-alkyl and 2-arylpyridines within short reaction times in good yields (Figure 31).[32]

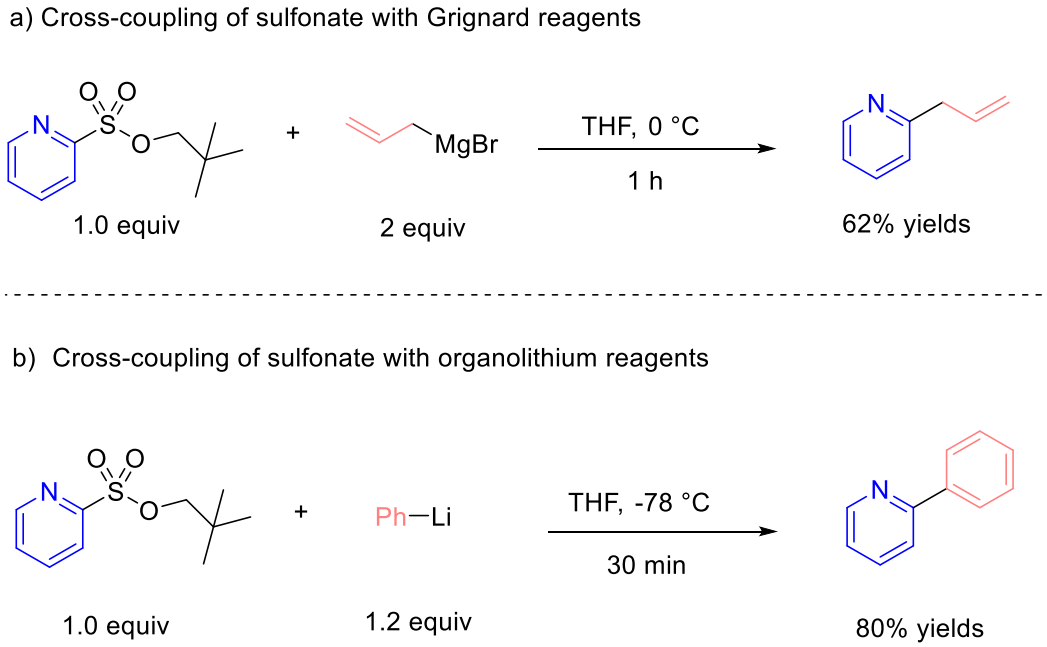


Figure 31. Nucleophilic aromatic substitution of organometallics with sulfonate.[32]

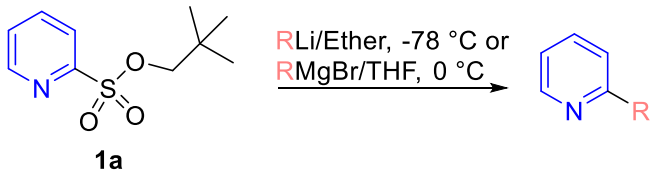
Finally, sulfur-containing organic molecules not only have great utilisations in organic synthesis, which can serve as useful building blocks and versatile functional group for further manipulations[77]. Sulfonyl chlorides[78] and sulfonyl hydrazides[79], are efficiently used in transition metal catalyzed for desulfinative cross-coupling reactions to synthesize heterobiaryl products. The objective of the project is to revise the reactivity of 2-pyridyl sulfonate esters with organometallic reagents and to expand their utilisation in cross-coupling reactions, in order to develop a mild, scalable, and transition metal-free desulfinative cross-coupling approach to access 2-substituted pyridines.

Chapter 2. Direct arylation of 2-pyridyl sulfonates with organolithium reagents

2.1 2-Pyridyl sulfonate esters

The inception of the project dates back to over 30 years ago, when Hanessian and Kagotani reported the reaction of neopentyl 2-pyridyl sulfonate with organometallic reagents to produce the corresponding 2-substituted pyridines (Table 1).[32] In an independent study, primary and secondary 2-pyridyl sulfonate esters of aliphatic alcohols reacted with $MgBr_2$ at 0 °C to afford the corresponding bromides.[80]

Table 1.Direct arylation of neopentyl 2-pyridyl sulfonate with organolithium reagents.[32]



1a

Product No.	R	Reaction conditions		Yield (%)
		Reagent (equiv.)	Temp.(°C)/ Time (h)	
2a	*n*-C_4H_9	RLi (2)	-78/0.5	68%
2c	C_6H_5	RLi (1.2)	-78/0.5	80%

Intrigued by the effective reactivity of the 2-pyridyl sulfonate ester **1a**, we deemed it worthy to expand on the prior results as an alternative cross-coupling method to prepare carbon-substituted pyridines at the 2-position.

2-Pyridyl sulfonate esters can be prepared in high yield by treatment of an alcohol with 2-pyridyl sulfonyl chloride. The latter reagent has been known for some time[32,80] but only sporadically

used. Obtained as a white powder, pyridyl sulfonyl chloride has good shelf life especially if stored at 0 °C. Originally it was prepared by bubbling chlorine gas into a solution of pyridine 2-thiol in concentrated hydrochloric acid.[32] However, in the study, we adopted a more practical method by using sodium hypochlorite solution as chlorine source (Figure 32).[81]

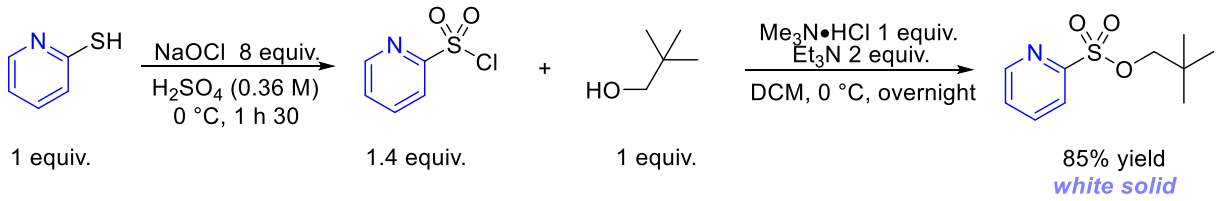
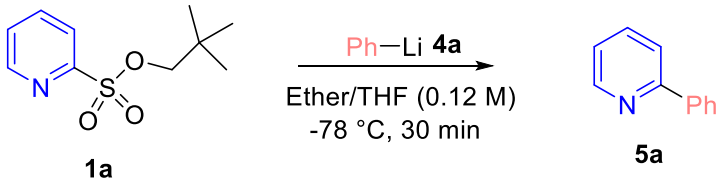


Figure 32. Synthesis of neopentyl 2-pyridyl sulfonates.

To explore S_NAr-type reactions at the 2-position, we began our investigation with the crystalline neopentyl 2-pyridyl sulfonate (**1a**). Treatment with 3 equivalents of phenyl lithium in THF at -78 °C led to the desired 2-phenyl pyridine (**5a**) in 84% yield within 30 min. Relative to ether, THF was found to be the better solvent with regard to reactivity and solubility (Table 2).

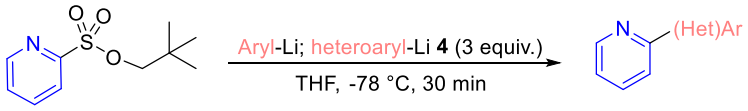
Table 2. Optimization of the conditions for phenyl lithium reaction.



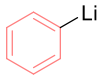
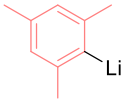
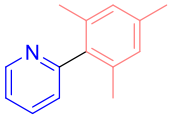
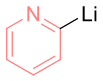
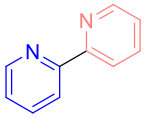
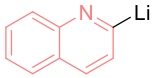
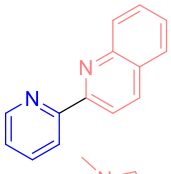
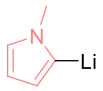
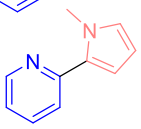
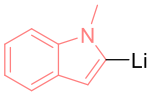
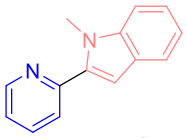
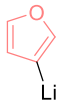
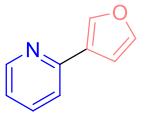
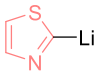
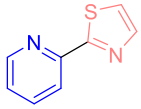
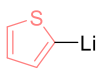
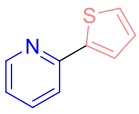
Entry	Ph-Li	Solvent	yield
1	1.2 equiv.	Ether	26%+ 62% SM
2	1.2 equiv.	THF	29% + 60% SM
3	2 equiv.	Ether	70% +18% SM
4	2 equiv.	THF	72% + 16% SM
5	3 equiv.	Ether	80%
6	3 equiv.	THF	84%

We then studied the coupling reaction of neopentyl 2-pyridyl sulfonate (**1a**) with various alkyl, aryl and heteroaryl organolithium compounds in order to gain information about the potential and scope of the reaction. Various organolithium reagents were screened using the optimized conditions as shown in Table 3. Thus, the Li/Br exchange of bromo aryl compounds was firstly performed at -78 °C to obtain the aryl lithium species (**4a-4i**). Inverse addition of 3 equivalents of organolithium reagent (1 M) into the solution of the neopentyl 2-pyridyl sulfonate (**1a**) at -78 °C afforded the desired products (**5a-13**). The procedure worked smoothly only for the reactions with phenyl lithium (**4a**) (Table 3, entry 1) and 2-pyridyl lithium (**4c**) (Table 3, entry 3), leading to the desired products (**5a, 7**) in excellent yields.

Table 3. Preliminary cross-coupling studies of neopentyl 2-pyridyl sulfonate with organolithium reagents.



1a **5a-13**

Entry	Organolithium reagent		(concentration/ addition mode)	Product		Yield%[a]
1		**4a**	1.8 M (clear solution)/ inverse addition		**5a**	84%
2		**4b**	a) 1 M (precipitation)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**5b**	0%[b] 0%[b]
3		**4c**	a) 1 M (clear solution)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**7**	92% 72%
4		**4d**	a) 1 M (precipitation)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**8**	0%[b] 52%[c]
5		**4e**	a) 1 M (precipitation)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**9**	46%[d] 29%[e]
6		**4f**	a) 1 M (precipitation)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**10**	0%[b] 0%[b]
7		**4g**	a) 1 M (clear solution)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**11**	0%[b] 0%[b]
8		**4h**	a) 1 M (clear solution)/ inverse addition b) 0.1 M (clear solution)/ direct addition c) 0.1 M (clear solution)/ direct addition		**12**	0%[b] 0%[b] 0%[b,f]
9		**4i**	a) 1 M (clear solution)/ inverse addition b) 0.1 M (clear solution)/ direct addition		**13**	0%[b] 0%[b]

[a] Isolated yield. [b] Starting material was recovered intact. [c] Also isolated 55% of 2,2'-biquinoline dimer and 3% of 2-butyl-1,2-dihydro-2,2'-biquinoline. [d] With 6 equiv. of N-methyl pyrrole-Li. Also isolated 33% of 2-((1-methyl-1H-pyrrol-2-yl)sulfonyl)pyridine. [e] With 6 equiv. of N-methyl pyrrole-Li. Also isolated 9% 2-((1-methyl-1H-pyrrol-2-yl)sulfonyl)pyridine and 60% of starting material. [f] With 5 equiv. of thiazolyl-Li.

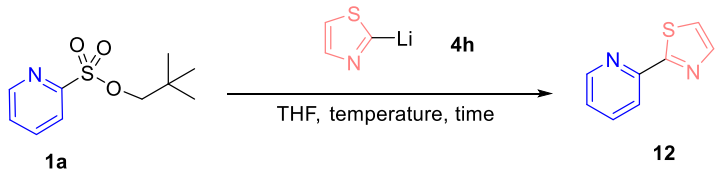
Results showed that the reactions with other heteroaryl lithiums were unsatisfactory as most of the reactions did not achieve a full conversion, and in some cases no reaction occurred (Table

3, entry 2a-9a) using the inverse addition strategy (addition of a concentrated organolithium solution 1 M into a diluted 2-pyridyl sulfonate solution). Low conversion with certain organolithium solutions (**4b**, **4d**-**4f)** may be due to precipitation at high concentration (1 M), which complicated precision in handling the reagent. Therefore, we decided to use a direct addition mode whereby the 2-pyridyl sulfonate was added into a diluted and clear organolithium solution for the problematic cases.

Addition of neopentyl 2-pyridyl sulfonate (**1a**) into a dilute and clear solution of 3 equivalents of 2-quinolyl lithium (**4d)**, led to 52% of the desired product (**8**) together with a dimerized 2,2'-biquinoline (Table 3, entry 4b). In the reaction with 2-pyridyl lithium (**4c**)**,** the yield of product **7** decreased from 92% to 72% (Table 3, entry 3b). For lithium solutions (**4d, 4g-4h**) which were not stable at room temperature and could be potentially quenched during syringe transfer, direct addition was preferred over the inverse addition mode (Table 3, entry 4, 7-8). In our hands, use of a cannula for lithium solution addition was not applicable on a 0.174 mmol scale. In the cases of N-methyl indole lithium (**4f**), 3-furyl lithium (**4g**), 2-thiazolyl lithium (**4h**) and 2-thienyl lithium (**4i**), neither addition mode afforded a detectable coupling product, and the neopentyl 2-pyridyl sulfonate (**1a**) was recovered unchanged after reaction at -78 °C even with excess reagents (Table 3, entry 6-9). The same result was obtained with mesityl lithium (**4b**) and may be due to steric effects (Table 3, 2b). All the organolithium reagents reacted with benzaldehyde under similar conditions.

In order to solve the coupling issues with the oxygen and sulfur containing heteroaryl lithiums, 2-thiazolyl lithium (**4h**) was selected as the testing substrate because of its ease of preparation. Different conditions have been screened to understand the influence of parameters such as temperature, mode of addition and number of equivalents of reagent (Table 4).

Table 4.Optimization of the conditions for coupling reaction with 2-thiazolyl lithium.



1a **12**

Entry	Concentration of lithium solution	Equivalent	Temperature	Time	Product Yield [a]	Recovered starting material [a]
1	0.66 M	2	-78 °C	1 h	0%	87%
2	0.66 M	4	-78 °C	1 h	0%	85%
3	0.15 M	2	-78 °C to 0 °C	30 min	45%[b]	0%
4	0.15 M	2	-78 °C to 0 °C	1 h	7%[b]	83%
5	0.15 M	4	-78 °C to 0 °C	1 h	12%[b]	72%
6	0.15 M	2	-78 °C to -40 °C	1 h	27%[b]	36%
7	0.15 M	4	-78 °C to -40 °C	30 min	47%[b]	0%
8	0.32 M	2	-78 °C to -40 °C	1 h	33%[b]	32%
9	0.32 M	4	-78 °C to -40 °C	30 min	49%[b]	0%

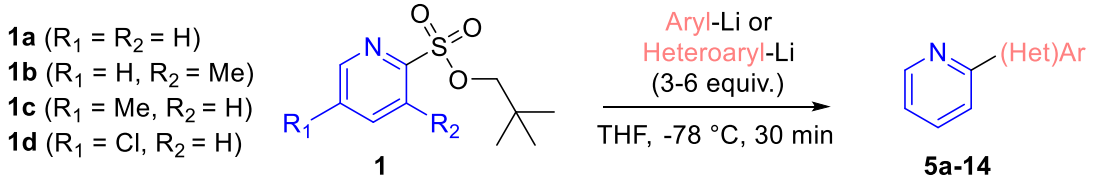
[a] Isolated yield. [b] Dimeric 2,2'-bithiazole was also isolated.

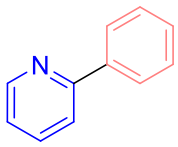
A solution of neopentyl 2-pyridyl sulfonate (**1a**) was added dropwise into a 2-thiazolyl lithium (**4h**) solution. Different equivalents of organolithium, and other parameters were evaluated. The temperature seemed to be the primary factor that governed the reaction. The product **12** was not formed at low temperature (-78 °C), even at high concentration and more equivalents of organolithium reagents (Table 4, entry 1-2), but was obtained at 0 °C with 2 equivalents of 2-thiazolyl lithium (**4h**), affording 2-thiazolyl 2-pyridine (**12**) in 45% yield accompanied by the dimeric 2,2'-bithiazole (Table 4, entry 3). Unfortunately, due to the stability of the thiazolyl

lithium, the reaction was not repeatable at 0 °C and the starting material (**1a**) remained unreacted most times (Table 4, entry 4-5). The problem was circumvented by lowering the temperature to -40 °C (Table 4, entry 6). Four equivalents of 2-thiazolyl lithium (**4h**) were needed to have a full conversion (Table 4, entry 7). The concentration effect of organolithium was also evaluated by doubling the concentration to 0.32 M. Although no improvement was observed and same results were obtained (Table 4, entry 8-9), the conditions in entry 9 were selected to study other heteroaryl lithiums.

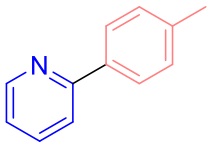
The organolithium reagents (**4a-4i**) were reacted with neopentyl 2-pyridyl sulfonate (**1a**) using the optimized conditions (Table 5).

Table 5.(Hetero)aryl-Li addition reactions to neopentyl 2-pyridyl sulfonate.

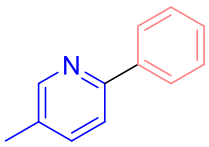




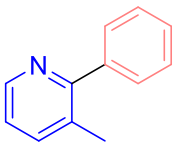
5a
84%(3 equiv.)



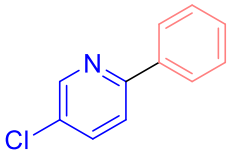
5c
84%(4 equiv.)



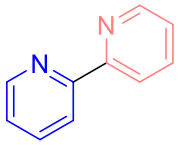
6a
51% (5 equiv.)



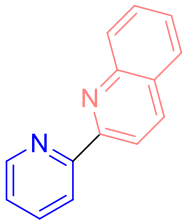
6b
90%(3 equiv.)



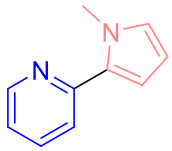
6c
74%(3 equiv.)



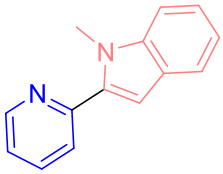
7
92% (3 equiv.)



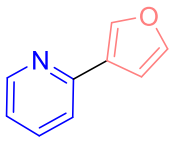
8
67%[a] (4 equiv.)[a]



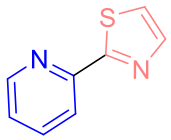
9
30%(6 equiv.)[b]



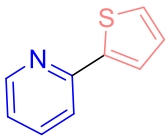
10
42% (4 equiv.)[c]



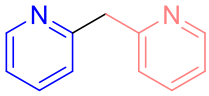
11
65%(4 equiv.)[c]



12
49%[c](4 equiv.)[c,d]



13
37%[d] (6 equiv.)[c,e]



14
85% (4 equiv.)

[a] Dimeric 2,2'-biquinoline was also isolated. [b] 40% starting material and 15% pyridyl N-methyl pyrrole sulfone were also isolated. [c] Reaction run at -40 °C. [d] Dimeric 2,2'-bithiazole was also isolated. [e]12% pyridyl thiophene sulfone were also isolated.

All examined aryl organolithiums showed good nucleophilicity toward the C-2 position of the neopentyl 2-pyridyl sulfonate (**1a**) and delivered the expected biaryl products (**5a, 5c**) in

excellent yields at -78 °C. In the case of *p*-tolyl lithium, one more equivalent of lithium reagent was required to have a full conversion. Treatment of **1a** with 2-pyridyl lithium (**4c**) afforded the coupled product 2,2'-bipyridine (**7**) in an excellent yield (92%). Other pyridine derivatives were less effective at -78 °C. For example, 2-quinolyl lithium (**4d**) required 4 equivalents to furnish pyridine **8** in moderate yield (67%) accompanied by 2,2'-biquinoline dimer. N-Methyl pyrrole lithium (**4e**) reacted sluggishly at -78 °C even with 6 equivalents of the lithium reagent, affording pyridine **9** in a low yield (30%), accompanied by 40% of recovered sulfonate (**1a**) and 15% of pyridyl N-methyl pyrrole sulfone (**17**). The reaction with the benzylic nucleophile picolinyl lithium proceeded smoothly to afford pyridine **14** in excellent yield (85%).

For other heterocyclic nucleophiles such as 3-furyl lithium (**4g**), N-methyl indole lithium (**4f**) and 2-thienyl lithium (**4i**), cross-coupled products **10**-**11**, **13** were isolated in good to modest yield by applying the condition used for 2-thiazolyl lithium (at -40 °C). Interestingly, in the reaction with 2-thienyl lithium (**4i**), sulfone species **18** was again detected and isolated in 12% yield.

2-Pyridyl sulfonates (e.g., **1b**-**1d**) bearing a variety of substituents such as chloride and methyl group at meta positions were also prepared and reacted with phenyl lithium (**4a**) to give substituted pyridines **6a**-**6c**. Pyridines **6a**-**6c** were not synthesized efficiently in a recent article which reported a similar cross-coupling process involving 2-pyridyl sulfinate and Grignard reagents as coupling partners, in the absence of transition-metal catalysts.[75] 5-Chloro-2-phenyl pyridine (**6c**) was formed in 74% yield under our condition by treatment with the corresponding 2-pyridyl sulfonate (**1d**) at -78 °C. Phenyl lithium (**4a**) added successfully into the more crowded C-2 position of 2-pyridyl sulfonate **1b**, affording 3-methyl-2-phenyl pyridine (**6b**) in excellent yield (90%). However, the reaction with neopentyl 5-methylpyridine-2-sulfonate (**1c**) was quite

sluggish under the condition even with 5 equivalents of organolithium reagents, affording 5-methyl-2-phenylpyridine (**6c**) in a moderate yield (51%). One possible reason is that the methyl is an electron donating group which can enrich the electron density of the pyridine core, and thus make it less electrophilic to the nucleophilic addition. It is of interest that no regioisomers were observed, and attack of nucleophiles occurred exclusively at the C-2 position of the 2-pyridyl sulfonates**.**

To explore some mechanistic aspects of the reaction, dansyl chloride was added before workup of the reaction between neopentyl 2-pyridyl sulfonate (**1a**) and phenyl lithium (**4a**) in order to trap the alkoxide (Figure 33). However, the expected neopentyl dansyl sulfonate was not observed by the TLC under UV light in comparison with a reference sample.

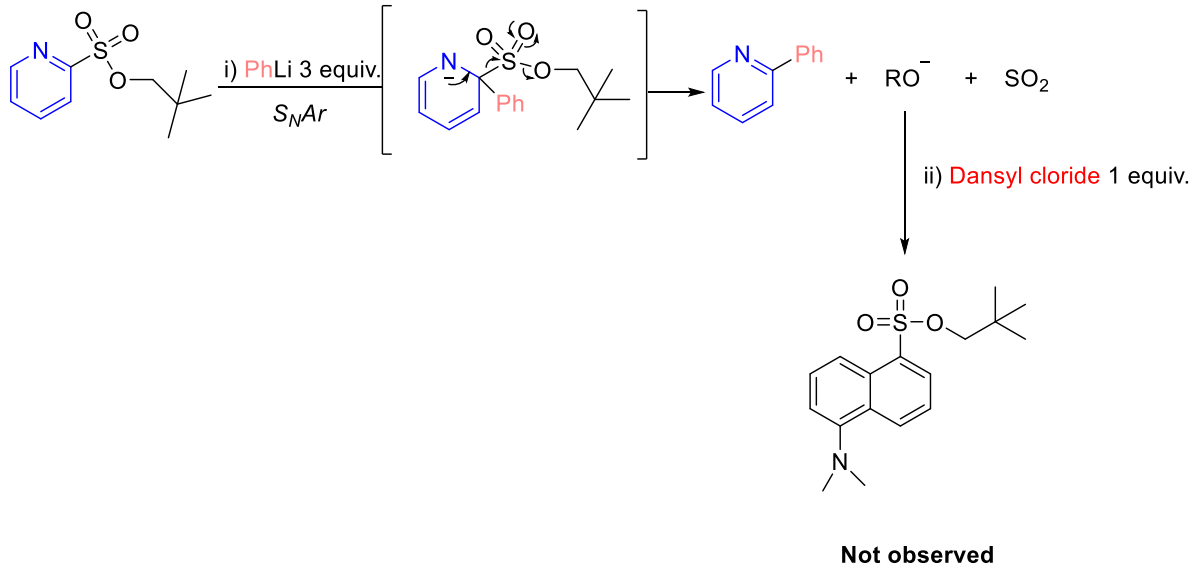


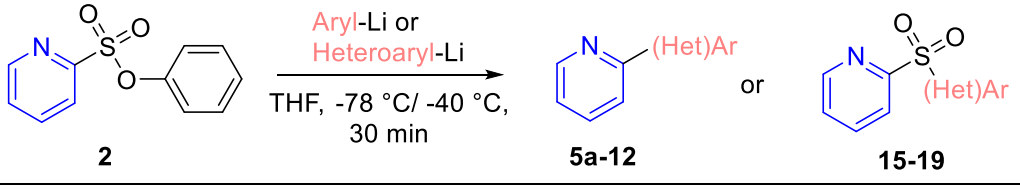
Figure 33. Test with dansyl chloride.

2.2 Phenyl 2-pyridyl sulfonate

To increase the reactivity of heteroaryl lithium reagents toward 2-pyridyl sulfonates, we changed the neopentyl alcohol part of the sulfonate to a more electron withdrawing group such as phenol, in order to render the sulfonate a better leaving group.

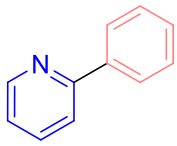
A series of aryl and heteroaryl lithiums were reacted with phenyl 2-pyridyl sulfonate (**2**) under optimized conditions (Table 6). The nucleofugality of the sulfonate moiety does not seem to have an important effect on the reactivity of the coupling reactions. The yields of 2-phenyl pyridine (**5a**), 2-tolyl pyridine (**5c**), and bipyridine (**7**) were comparable to those obtained with the neopentyl 2-pyridyl sulfonate (**1a**) (Table 6). An equivalent of phenol was isolated from the reactions. 2-Thiazolyl lithium (**4h**) reacted smoothly this time at -78 °C, but instead of affording the desired pyridine **12**, 2-thiazolyl 2-pyridyl sulfone (**15**) was isolated in 84% yield. Similar sulfone products (e.g., **16**-**18**) were also obtained in good to modest yields from reactions with 3-furyl lithium (**4g**), 2-thienyl lithium (**4i**) and N-methyl pyrrole lithium (**4e**) under similar conditions. However, at higher temperature (-40 °C), the cross-coupled products **10**-**12** were obtained in modest yields.

Table 6. (Hetero)aryl-Li addition reactions to phenyl 2-pyridyl sulfonate.

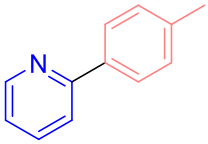


2 **5a-12** **15-19**

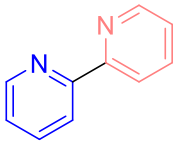
Reaction at -78 °C



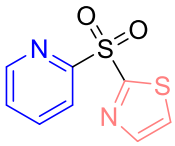
5a
81%(3 equiv.)



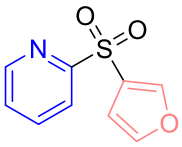
5c
86%(4 equiv.)



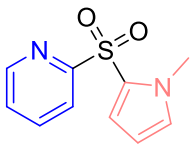
7
89% (3 equiv.)



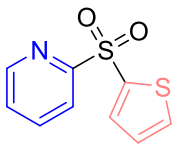
15
84% (3 equiv.)



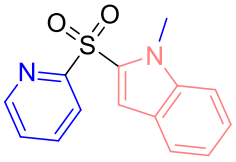
16
76% (3 equiv.)



17
73% (4 equiv.)

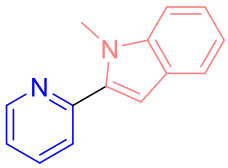


18
52% (6 equiv.)

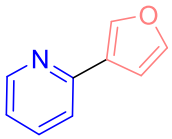


19
0%[c] (6 equiv.)

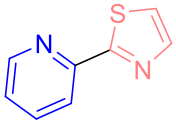
Reaction at -40 °C



10
37%[a] (4 equiv.)



11
52%[a] (4 equiv.)



12
46%[a,b] (4 equiv.)

[a] Reaction runs at -40 °C. [b] Dimeric 2,2'-bithiazole was also isolated. [c] 83% of starting material was recovered.

In order to test if a sulfone was a reactive intermediate, 2-thiazolyl 2-pyridyl sulfone (**15**) was treated with 3 equivalents of 2-thiazolyl lithium (**4h**) under the same conditions (Figure 34b). Interestingly, the yield of 2-thiazolyl pyridine (**12**) was comparable to that obtained with 2-pyridyl sulfonates **1a** and **2**, accompanied by 2,2'dithiazole dimer (Figure 34b).

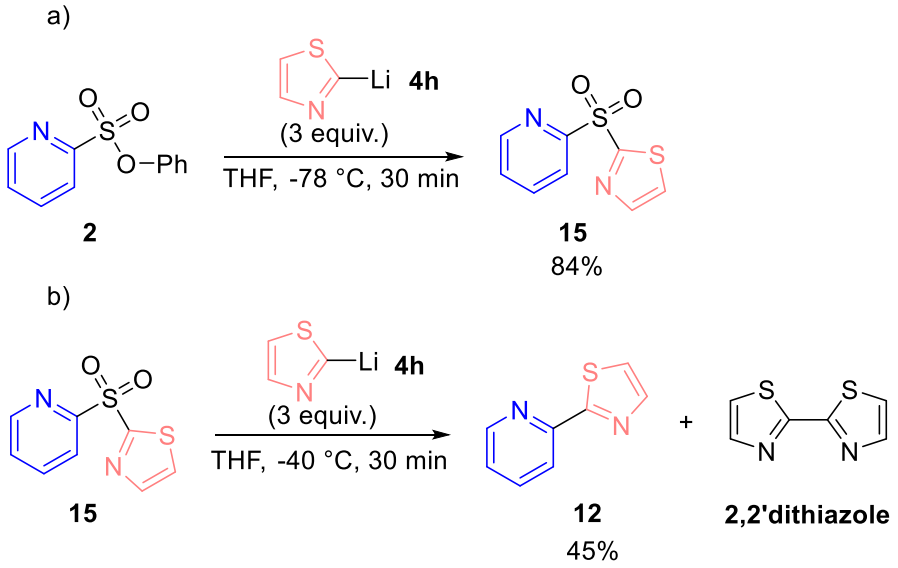


Figure 34. Reactivity between 2-thiazolyl lithium with phenyl 2-pyridyl sulfonate and 2-thiazolyl 2-pyridyl sulfone.

The result led us to wonder whether the coupling reaction between 2-pyridyl sulfonates and organolithium reagents could proceed through a sulfone intermediate, as the softer heteroaryl lithiums may have a preference to attack on the sulfur atom of the pyridyl sulfonate ester. Thus, the reaction may initially proceed to give the heteroaryl 2-pyridyl sulfone. At higher temperature, the excess of the organolithium reagent could react further to afford the coupled product. The detection of N-methyl pyrrole sulfone **17** and thienyl sulfone **18** from the previous reactions with neopentyl 2-pyridyl sulfonate (**1a**) support the assumption. However, no sulfone **19** was observed at -40 °C employing N-methyl indole lithium (**4f**), but cross-coupled product **10** was isolated from reaction higher temperature in 37% yield.

2.3 Phenyl 2-pyridyl sulfone

In order to exclude the possibility that 2-pyridyl sulfone was an intermediate of the coupling reaction, several experiments were conducted. Firstly, 1.2 equivalents of phenyl lithium (**4a**) were added to a solution of **2** at -78 °C, and afforded 2-phenyl pyridine (**5a**) in 31% yield

together with 58% yield of recovered starting material **2**. No sulfone product was detected. It can be concluded that the reaction of 2-pyridyl sulfonates with phenyl lithium (**4a**) involves an S_NAr process (Figure 35).

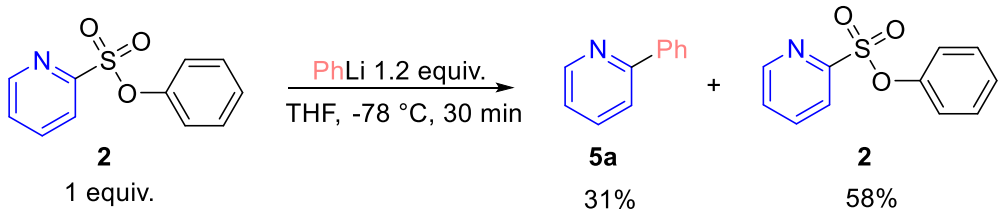
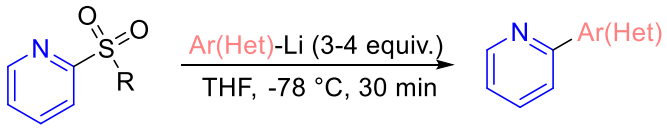


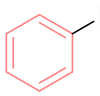
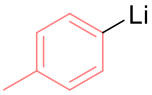
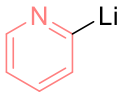
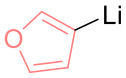
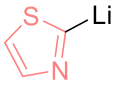
Figure 35. Test with 1.2 equiv. of PhLi.

We also reacted neopentyl and phenyl 2-pyridyl sulfonates (**1a** and **2**) as well as phenyl 2-pyridyl sulfone (**3**) with phenyl lithium (**4a**) under the same conditions (3 equiv. PhLi, THF, -78 °C, 30 min) (Table 7, entry 1). All three reactions afforded 2-phenyl pyridine (**5a**) in a similar yield of 80-84% without trace of phenyl sulfone (**3**) (Table 7, entry 1).

Table 7. Comparing reactivity of sulfonates and sulfone with Ar(Het) Li.



1a-3 **5a-12**

Entry	Ar(Het)-Li		Product Yield % R= neopentyl alcoholate **1a**	R= phenolate **2**	R= phenyl **3**	
1		**4a**	84% (3 equiv.)	81% (3 equiv.)	80% (3 equiv.)	**5a**
2		**4j**	84% (4 equiv.)	86% (4 equiv.)	93% (3 equiv.)	**5c**
3		**4c**	92% (3 equiv.)	89% (3 equiv.)	86% (3 equiv.)	**7**
4		**4g**	65%[a,b] (4 equiv.)	52%[a,c] (4 equiv.)	66%[a] (3 equiv.)	**11**
5		**4h**	49%[a,d] (4 equiv.)	46%[a,d] (4 equiv.)	65%[a] (3 equiv.)	**12**

[a] Reaction runs at -40°C. [b] 6% of starting material and 2% of 2-(furan-3-ylsulfonyl)pyridine were isolated when using 3 equiv. of furan-3-yllithium. [c] 9% of 2-(furan-3-ylsulfonyl)pyridine were isolated when using 3 equiv. of furan-3-yllithium. [d] Dimeric 2,2'-bithiazole was also isolated.

To further evaluate the difference of reactivity between sulfonate **1a** and sulfone **3** in such coupling chemistry, we reacted a 1:1 mixture of both starting materials in THF with 2.5 equivalents of phenyl lithium (**4a**) at -78 °C (Figure 36). We noted that the reactivity with phenyl lithium (**4a**) was quite similar and a nearly equal quantity of both starting materials was recovered indicating an S_NAr process in both cases.

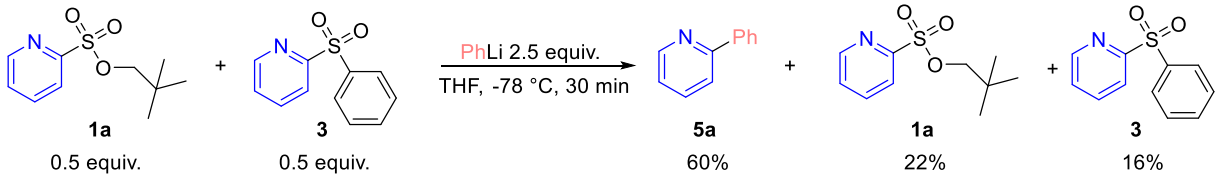


Figure 36. Reactivity of neopentyl 2-pyridyl sulfonate and phenyl sulfone with PhLi.

The reactivity of sulfonates **1a, 2** and sulfone **3** with 2-pyridyl lithium (**4c**) were similar and afforded the coupled bipyridine **7** in 86-92% yields (Table 7, entry 3). Less equivalents of *p*-tolyl lithium (**4j**) were needed for sulfone **3** to react to full conversion (Table 7, entry 2).

To further compare their reactivity, a 1:1 mixture of neopentyl 2-pyridyl sulfonate (**1a**) and phenyl 2-pyridyl sulfone (**3**) in THF was treated again with 2.5 equivalents of *p*-tolyl lithium (**4j**) at -78 °C (Figure 37).

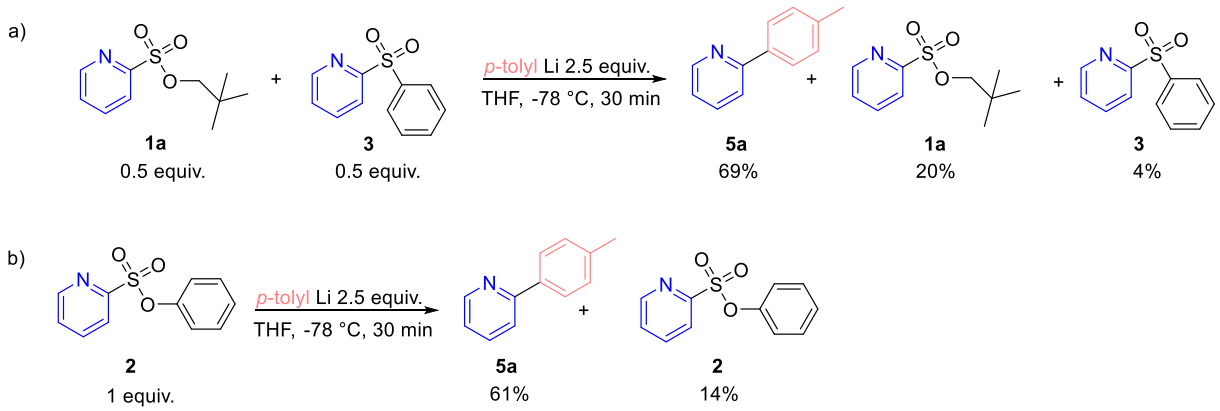


Figure 37. *p*-Tolyl Li addition to sulfonates and sulfone.

The spot of sulfone **3** disappeared more rapidly than that of sulfonate **1a** on the TLC plate. We recovered 4% yield of the phenyl 2-pyridyl sulfone (**3**) and 20% yield of the neopentyl 2-pyridyl sulfonate (**1a**). The lower reactivity of *p*-tolyl lithium toward pyridyl sulfonate **1a** compared to pyridyl sulfone **3** raises doubts whether the reaction is proceeding through the sulfone intermediate. No sulfone was observed when phenyl 2-pyridyl sulfonate (**2**) reacted with 2.5

equivalents of *p*-tolyl lithium, affording 61% yield of aryl pyridine **5c** and 14% yield of recovered starting material (**2**).

We then proceeded to compare the reactivity of 2-pyridyl sulfonates **1a**, **2** and 2-pyridyl sulfone **3** with heteroaryl lithium reagents to examine if the sulfone is the reactive intermediate since sulfone intermediate was detected in the reactions of phenyl 2-pyridyl sulfonate (**2**) with most of the heteroaryl lithium reagents at -78 °C (Table 6). A small quantity of 3-furyl 2-pyridyl sulfone (**16**) was observed when 2-pyridyl sulfonates **1a**, **2** were reacted with 3 equivalents of 3-furyl lithium (**4g**) at -40 °C (Table 7, Entry 4). More equivalents of 3-furyl lithium were needed for the reaction of the sulfonates to go to full conversion, compared to the phenyl 2-pyridyl sulfone (**3**) reaction indicating that the formation of sulfone may be a secondary reaction in the chemistry between 2-pyridyl sulfonates **1a** and **2** and heteroaryl lithium reagents. Especially in the reaction of phenyl 2-pyridyl sulfonate (**2**), sulfones may be formed more easily than in the reaction with neopentyl 2-pyridyl sulfonate (**1a**) at -40 °C (Table 7, Entry 4). Curiously, in the reaction of phenyl 2-pyridyl sulfone (**3**) with 3 equivalents of 2-thiazolyl lithium (**4h**) at -40 °C, the dimeric 2,2' dithiazole product was not observed and the pyridine thiazole **12** was isolated in 65% yield (Table 7, entry 5). To explore some mechanistic details for the formation of the dimerized product, a solution of 2-thiazolyl lithium (**4h**) was treated alone at -40 °C to see if the dimer would form. However, no trace of the dimer product was observed.

2.4 Plausible mechanism

There are three plausible pathways for bond cleavage of neopentyl and phenyl 2-pyridyl sulfonates, and 2-pyridyl sulfones with organolithium reagents (Figure 38). In pathway (a), the organolithium reagent can effect a nucleophilic substitution on the neopentyl carbon bearing a sulfonyl group, which is a good leaving group. However, the C-O cleavage appears not to be operative in our cases since the attack on the neopentyl and phenyl groups is intrinsically not favored. Pathway (b) corresponds to an S_NAr type reaction, in which the organolithium adds to the activated electrophilic C-2 position of pyridine and displaces the leaving group leading to the coupled products in the Table 5. The same mechanism has been also proposed by Hu et al. in their transition metal-free coupling reaction between a 2-pyridyl sulfinate and Grignard reagents.[75] Pathway (c) leading to the substituted 2-pyridyl sulfones seems to be in vigor only in the reaction of phenyl 2-pyridyl sulfonate (**2**) with softer heteroaryl lithium such as N-methyl pyrrole, furyl, thiazolyl and thienyl lithiums (**4e** and **4g-i)** at low temperature (-78°C) (Table 6). One possible explanation is that the lithium reagents are less reactive at -78 °C and do not undergo an S_NAr process. They can, however, displace the phenolate part of the phenyl 2-pyridyl sulfonate (**2**) at -78 °C, to afford the pyridyl sulfones (**15-18**) in good to modest yield. Aryl and heteroaryl lithium reagents can also attack the 2-pyridine carbon of phenyl 2-pyridyl sulfone (**3**) with release of lithium phenyl sulfinate.

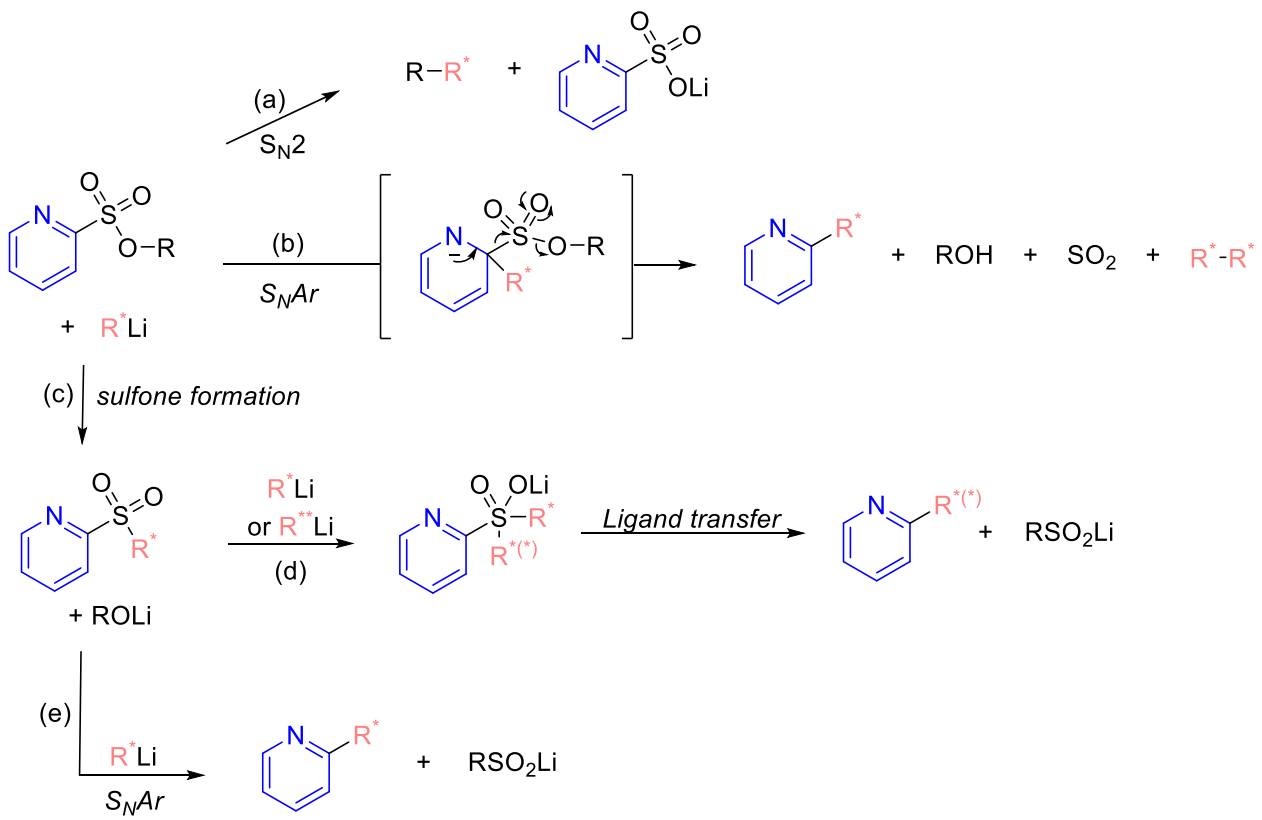


Figure 38. Possible bond cleavage pathways of 2-pyridyl sulfonates.

To form a heterobiaryl sulfone such as thiazolyl pyridyl sulfone (**15**), the S_NAr process can occur by the organolithium reacting either at the pyridine carbon or at the thiazole carbon because 2,2'-bithiazole was isolated from the reaction using thiazolyl lithium (**4h**). To demonstrate the possibility, the thiazolyl 2-pyridyl sulfone (**15**) was treated with 4 equivalents of PhLi (**4a**) at -78 °C to furnish the phenyl 2-pyridine (**5a**) as the only detectable product in 78% yield (Figure 39a). With 2 equivalents of PhLi (**4a**) at -40 °C , a mixture of three adducts consisting of the 2-phenyl pyridine (**5a**) (65%), 2-thiazolyl pyridine (**12**) (13%) and 2-phenyl thiazole (**20**) (11%) was obtained (Figure 39b).

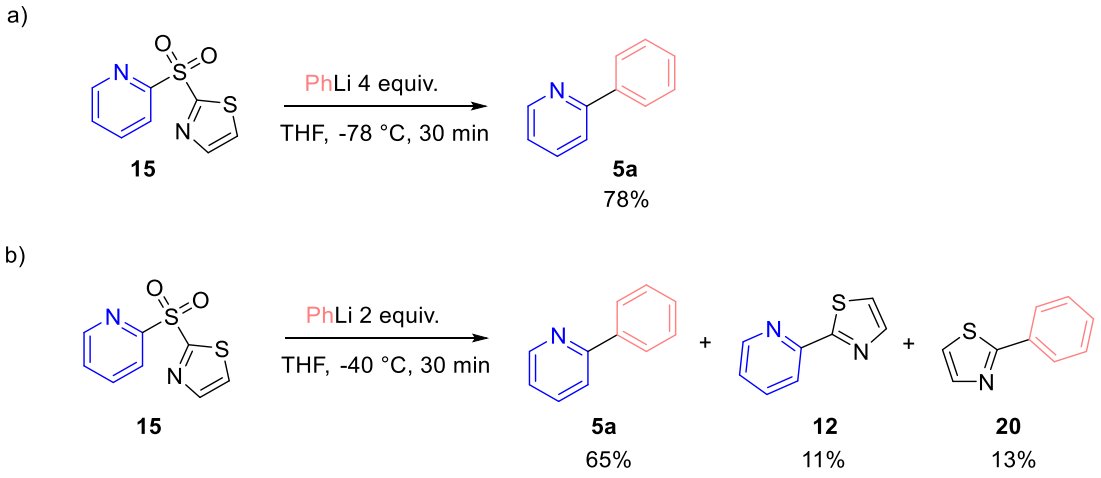


Figure 39. Reactivity between thiazolyl pyridyl sulfone and PhLi.

The formation of 2-thiazolyl pyridine (**12**) was surprising since this meant extrusion of SO_2 in the process of combining two heteroaryls. This type of desulfinative coupling reaction of pyridyl sulfone was only known in a nickel-catalyzed reaction at high temperature (150 °C) to furnish biaryls (Figure 40).[82]

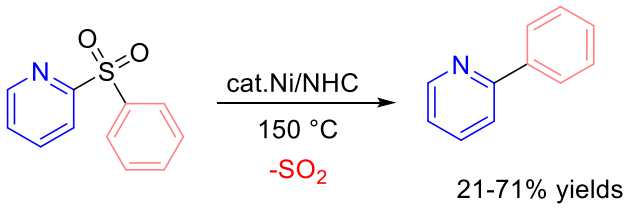


Figure 40. Transformation of phenyl 2-pyridyl sulfone into 2-phenyl pyridine via extrusion of SO_2.

Another possibility is through a ligand coupling reaction of a pentacoordinate hypervalent σ-sulfurane intermediates (Figure 41).[83] These species are usually unstable due to the expanded valence-shell and tend to resume their normal valency by extruding a pair of ligands from the hypervalent atom in order to form a stable octet sulfur compound. Normally, the two extruded ligands are one from an axial position and the other from an equatorial position as their orbitals can overlap easily in the trigonal bipyramid structure of σ-sulfurane intermediates.

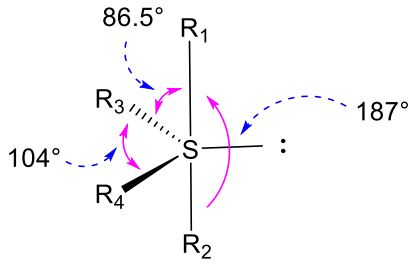


Figure 41. Structure of σ-sulfurane and bond angles.

In fact, ligand coupling reactions which proceed within a σ-sulfurane intermediate have been known for many decades, especially in the reaction between a sulfoxide and Grignard reagents.[83] The general mechanism of such transformation consist of 3 steps.[84] Firstly, the Grignard reagent attacks a sulfoxide opposite to the sulfinyl oxygen to occupy the axial position of the sulfurane intermediate. Then, a reversible pseudorotation process will allow the sulfurane to adopt the most stable conformation depending on the electronic and steric effects of its ligands (Figure 42).[84] Normally electron rich and sterically large ligands will occupy an equatorial position to minimize the destabilisation. Finally, the axial ligand will couple preferentially with one equatorial ligand due to overlapping of orbitals to form the coupling product.

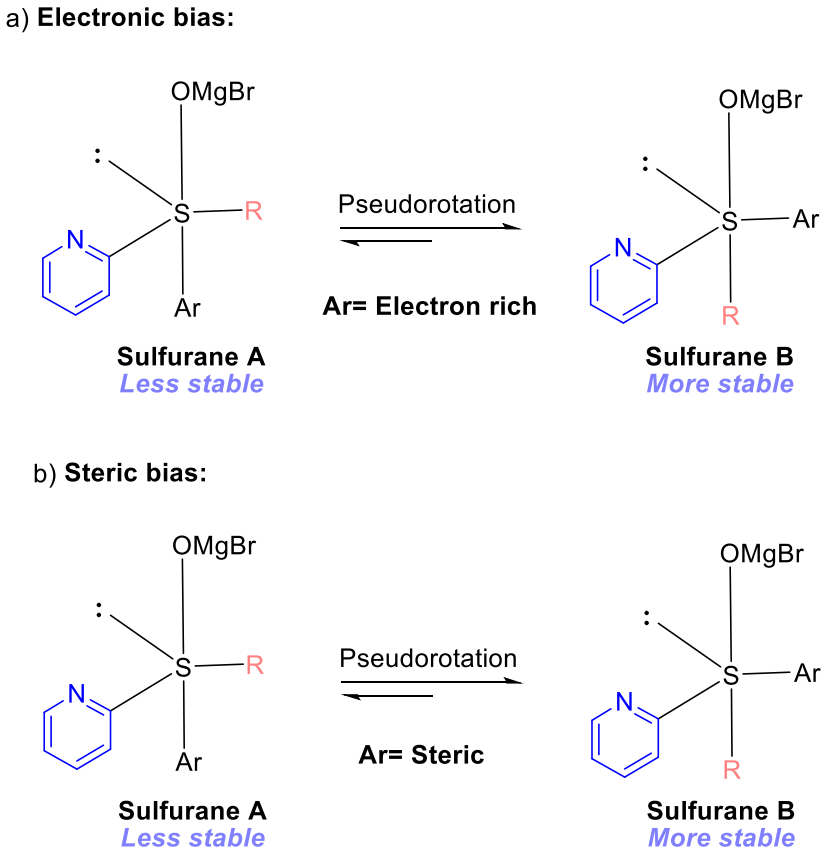


Figure 42. Electronic and steric bias of sulfurane.

Interestingly, in some cases the ligand coupling reaction can proceed faster than the pseudorotation within the sulfurane intermediate.[85] In a reaction between a deuterated benzyl 2-pyridyl sulfoxide and a benzyl magnesium chloride at room temperature, the significant difference of yield of benzyl pyridine (88%) and dideuterobenzyl pyridine (12%) shows that the ligand coupling reaction is faster (Figure 43).

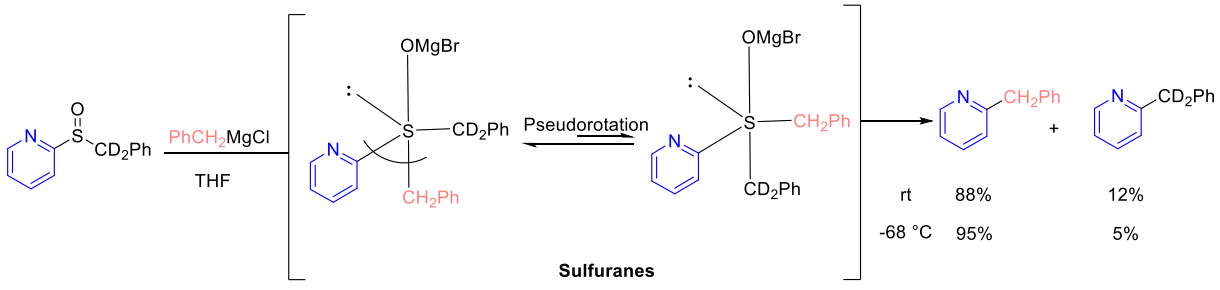


Figure 43. Ligand coupling reaction of sulfoxide with benzyl Grignard.[85]

However, there are also cases in which pseudorotation proceeds faster than ligand coupling.[86] For example, in the reaction of phenyl 2-pyridyl sulfoxide with benzyl magnesium bromide (Figure 44a), or in the reaction of benzyl 2-pyridyl sulfoxide with phenyl magnesium bromide (Figure 44b), the ligand coupling always takes place between 2-pyridyl and benzyl groups. This means that regardless of the nature of the nucleophile which attacks the sulfur atom from an axial orientation, pseudorotation prefers to place the benzyl group on an axial position for easier ligand coupling with the 2-pyridyl group.

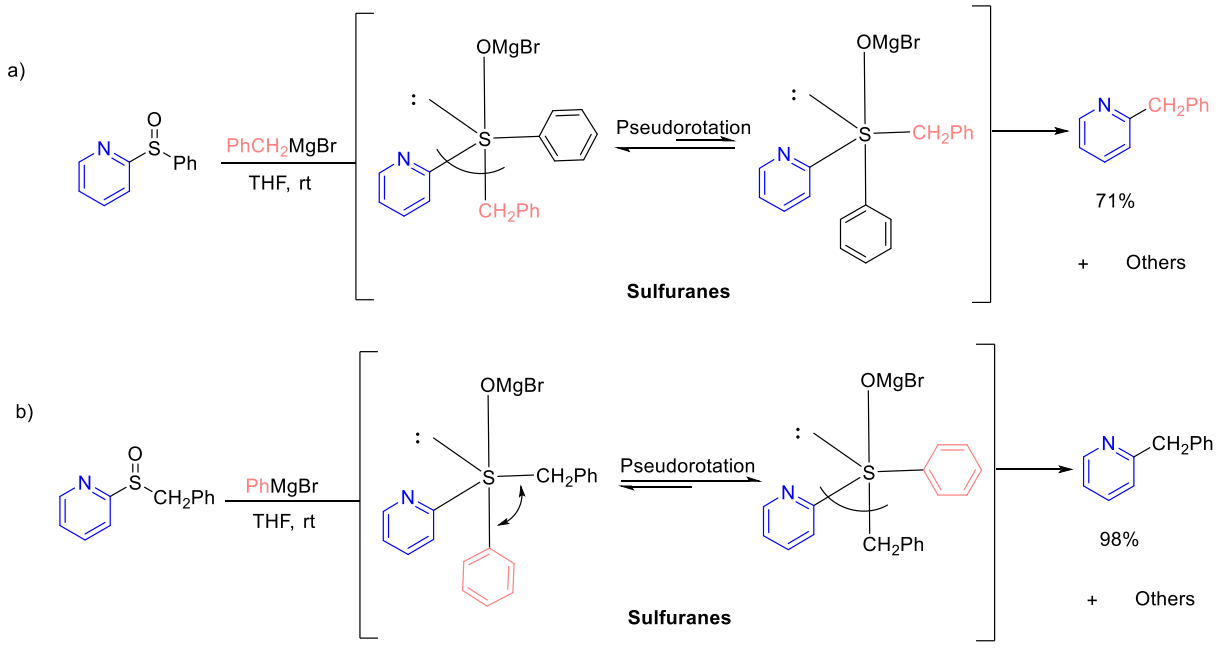


Figure 44. Reaction of sulfoxides with Grignard reagents.[86]

Ligand exchange chemistry could also occur in the reaction between sulfoxides and Grignard reagents, by way of a σ-sulfurane intermediate.[35] In the reaction between a methyl 2-pyridyl sulfoxide and phenyl magnesium bromide at room temperature (Figure 45), the initial ligand exchange forms 2-pyridylmagnesium bromide, which in the subsequent step can further react with the original sulfoxide to afford 2,2'-dipyridyl, the ligand coupling product, in 41% yield. However, no general conclusion can be drawn on the relationship between these three processes

(ligand coupling, pseudorotation and ligand exchange) in such reactions, until additional kinetic measurements are made for coupling reaction with various ligands .[83]

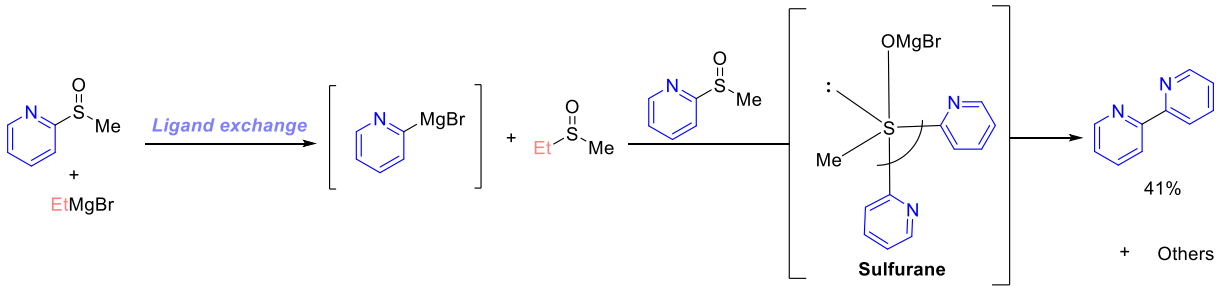


Figure 45. Ligand exchange reaction between sulfoxides and Grignard reagent.[35]

Although the ligand coupling reactions for sulfone substrates are not well known, it is still observed in a reaction of an acetylenic sulfone with *n*-butyllithium (Figure 46). [87]

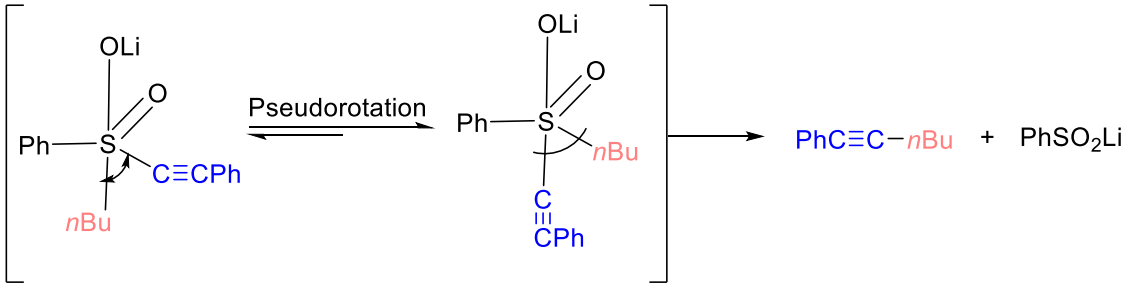


Figure 46. Ligand coupling reaction of a sulfone.

In the reaction of thiazolyl 2-pyridyl sulfone (**15**) with PhLi (**4a**) at -40 °C (Figure 47), the lithium reagent may initially attack from the axial position of the sulfone to form a sulfurane A, then a reversible pseudorotation will place the electron rich phenyl on the equatorial position and thiazole on the aixal position, to have the stable conformation as in sulfurane B. Then the interaction between the axial thiazole with equatorial pyridine would afford the thiazolyl pyridine ligand coupling product (**12**).

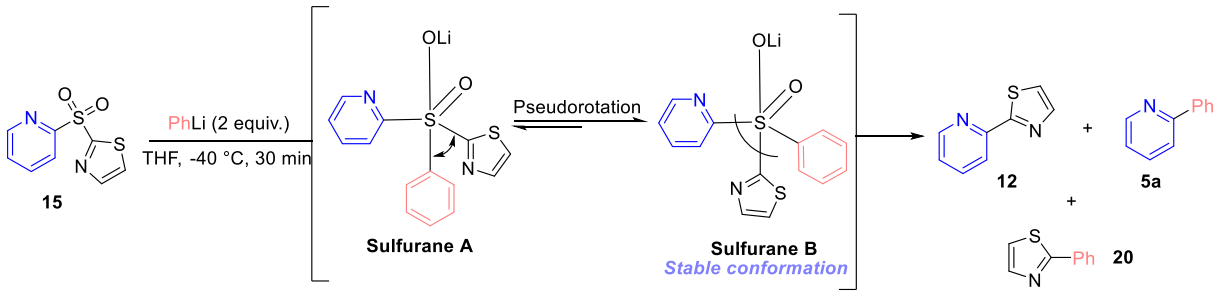


Figure 47. Addition of PhLi to thiazolyl sulfone via ligand coupling process.

To further test the ligand coupling reaction, phenyl 2-pyridyl sulfonate (**2**) was treated with 1.5 equivalents of PhMgBr (Figure 48, Eq. 1). Although no reaction took place at -78 °C, the phenyl sulfone (**3**) was obtained in 68% yield within 1 h at 0 °C, indicating that the Grignard reagents attack preferentially at the sulfur atom and with elimination of the phenolate. The same reaction was repeated with 3 equivalents of PhMgBr (Figure 48, Eq.2), and led to a mixture of three adducts consisting of the 2-phenyl pyridine (**5a**) (42%), 4-phenylpyridyl 2-phenyl sulfone (**21**) (10%) and the bis-phenyl sulfone **22** (7%). The formation of 2-phenyl pyridine (**5a**) could either proceed via an S_NAr type reaction or a ligand coupling reaction. The formation of 4-phenylpyridyl 2-phenyl sulfone (**21**) was not too surprising as Grignard reagents are known to add to the 2-, and 4-position of the pyridine. There are approaches using bulky pyridinium salts to block intentionally the C-2 position of the pyridine, to synthesize the 4-substituted pyridine using Grignard reagents.[88,89] The formation of the bis-phenyl sulfone (**22**) could result from a ligand exchange process by replacing the electronegative ligand with PhMgBr to form a pyridyl MgBr which can further react with the original sulfonate (**2**) to form a 2,2'-sulfonyldipyridine or a bipyridine product. However, they were not detected. Finally, the treatment of phenyl 2-pyridyl sulfone (**3**) directly under the same conditions led to **5a** (62%), **21** (15%) and **22** (11%) (Figure 48, eq. 3), leading to the conclusion that the reaction of the phenyl 2-pyridyl sulfonate

(**2**) initially proceeds to give the phenyl 2-pyridyl sulfone (**3**), which in the presence of excess Grignard reagent reacts further.

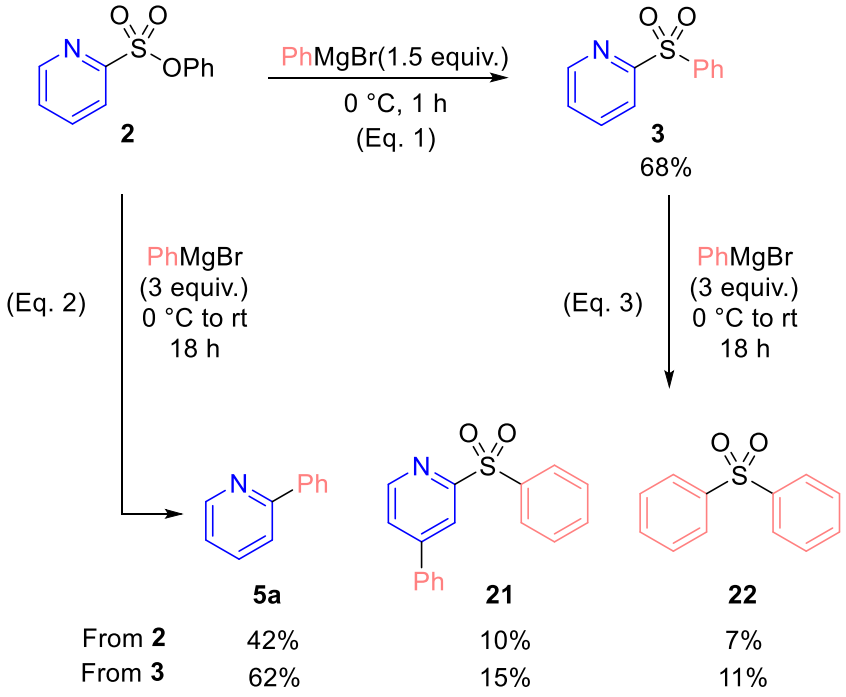


Figure 48. Reaction of phenyl sulfonate with Grignard reagents

2.5 Conclusion

In summary, we were successful in the synthesis of 2-substituted pyridines by treatment of neopentyl 2-pyridyl sulfonates (**1a-1d**) and phenyl 2-pyridyl sulfonate (**2**) with aryl and (hetero)aryl lithium reagents in THF at -78 °C (or -40 °C). The nucleofugality of the sulfonate moiety did not have an important effect on the reactivity of the coupling chemistry and both reactions with sulfonates and sulfone were completed within 30 minutes using 3-6 equivalents of the lithium reagent in good yields (Table 5, Table 7). The results suggest an S_NAr reaction pathway for organolithium reactions. Formation of sulfone could be seen especially in the reactions between phenyl 2-pyridyl sulfonate (**2**) and heteroayl lithium reagents at low temperature (-78 °C), presumably by attack of the softer hetero lithium reagents to the sulfur

atom with phenolate elimination. Experiments indicates that sulfones result from secondary reactions at high temperature (-40 °C). In contrast, Grignard reagents attack preferentially on the sulfur atom of the pyridyl sulfonate and sulfone, and both the S_NAr pathway and ligand coupling process may be involved. More detailed mechanistic studies are currently being carried out in our laboratory to shed light on these possibilities.

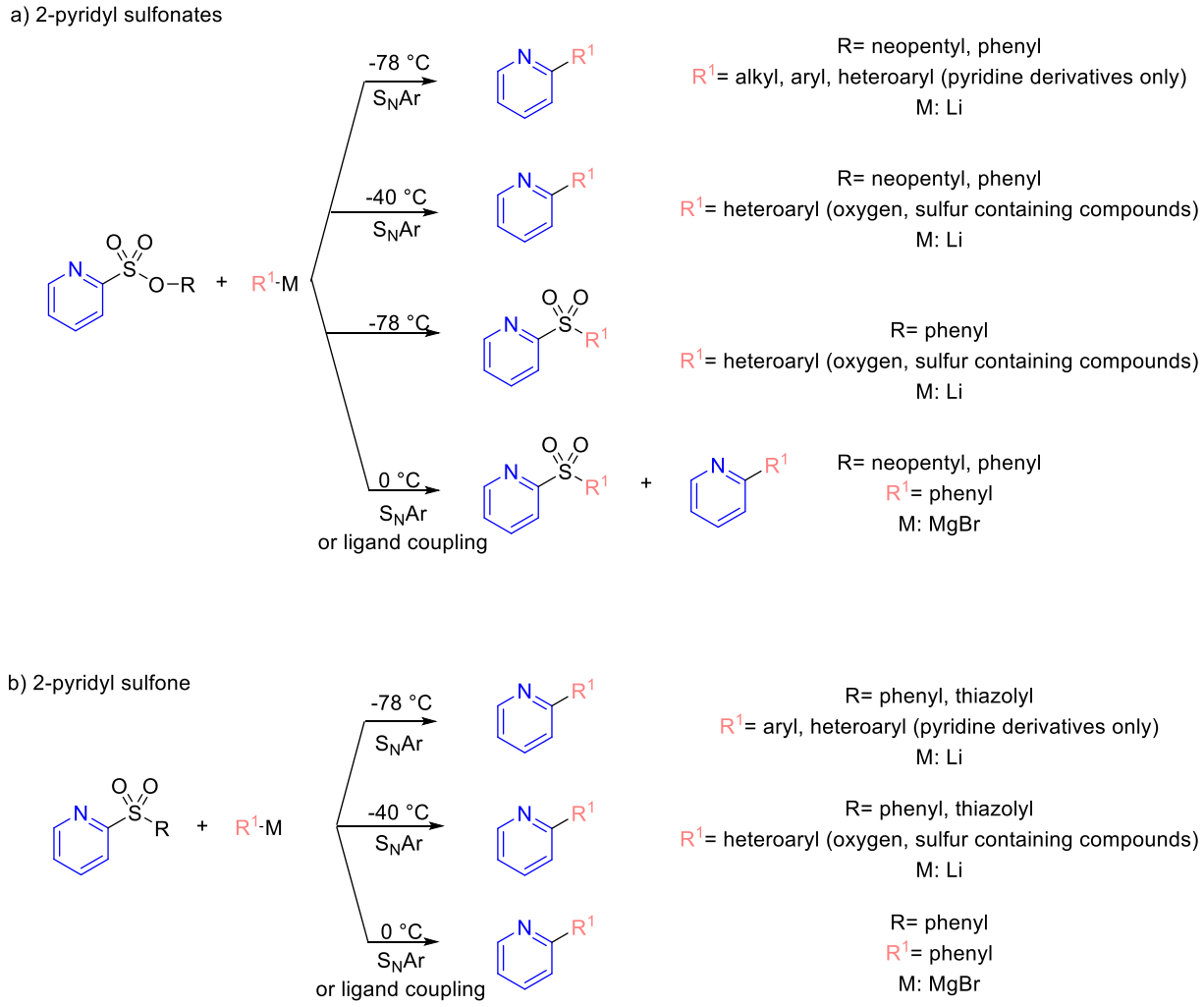
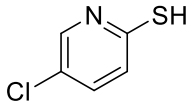


Figure 49. General trends for the reaction of 2-pyridyl sulfonates and sulfone with organometallic reagents.

2.6 Experimental procedures

General information. Unless otherwise noted, all the reactions were carried out using standard Schlenk techniques. Glassware was oven (135 °C) or flame-dried prior to use. Anhydrous dichloromethane, diethyl ether and THF were obtained using solvent purification systems. All other solvents and reagents were used as received. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica plates (SIL 60, G-25, UV254) and were visualized using a UV lamp (254 nm) or revealed with proper stains. NMR spectra were recorded on Bruker AV-300, ARX-400, AV-400 or AV-500 spectrometers with complete proton decoupling for nuclei other than ^{1}H. ^{1}H and ^{13}C chemical shifts are reported in parts per million with the solvent resonance as the internal standard ($CDCl_3$, ^{1}H: δ 7.26 ppm, ^{13}C: δ 77.16 ppm). Coupling constants are reported in Hertz (Hz). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sept = septuplet, dd = double doublet, dt = double triplet, ddd = double double doublet, dtt = double triple triplet, m = multiplet, br = broad. Spectra were analyzed and processed using MestReNova. High Resolution Mass Spectrometry (HRMS) analyses were performed at the Centre Régional de Spectrométrie de Masse de l'Université de Montréal. Phenyl 2-pyridyl sulfonate (**2)** was synthesized according to literature procedure.[90]

General procedure to prepare thiol compounds

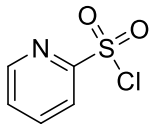


5-chloropyridine-2-thiol

To a solution of 5-chloropyridin-2(1H)-one (600mg, 4.6 mmol) in anhydrous toluene (55 mL), Lawesson reagent (1g, 2.3 mmol) was added and the mixture was stirred for 4 h at 124 °C (oil bath temperature). The mixture was cooled to rt and was left standing without stirring overnight.

Precipitated product 5-chloropyridine-2-thiol was then filtered off to give pale yellow crystals in 68% yield. Product was used without further purification. 3-Methylpyridine-2-thiol (62% yeild) and 5-methylpyridine-2-thiol (69% yield) were also made by this way from their starting material 3-methylpyridin-2(1H)-one and 5-methylpyridin-2(1H)-one respectively.

General procedure to prepare sulfonyl chloride compounds

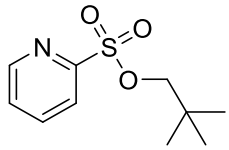


pyridine-2-sulfonyl chloride

To a 500 mL three-neck flask equipped with a thermometer and a sodium hydroxide trap, 9 mmol (1 g) of pyridine 2-thiol and 25 mL of concd H_2SO_4 were added. The mixture was cooled to 0 °C using an ice bath and treated dropwise with 35.4 mL of sodium hypochlorite. The temperature should be kept under 15 °C during the addition. The mixture was kept at 0 °C for 1h, and extracted with DCM (3 times). The organic layered was combined, dried with Na_2SO_4, filtered and evaporated in vacuum to a residue which was used without further purification. 3-Methylpyridine-2-sulfonyl chloride, 5-methylpyridine-2-sulfonyl chloride, and 5-chloropyridine-2-sulfonyl chloride were also made by this way with their thiol counterparts.

General procedure for sulfonate synthesis

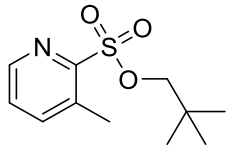
Neopentyl 2-pyridyl sulfonate (1a)



A solution of pyridine-2-sulfonyl chloride (470.7 mg, 2.65 mmol, 1.4 equiv.) in 4 mL of dichloromethane was treated at 0 °C with trimethylamine hydrochloride (180.6 mg, 1.89 mmol, 1 equiv.) and triethylamine (0.53 mL, 3.78 mmol, 2 equiv.). A solution of neopentyl alcohol

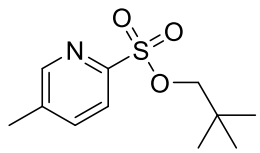
(166.6 mg, 1.89 mmol, 1 equiv.) in 2.5 mL of dichloromethane was added to the reaction mixture. After stirring overnight at 0 °C, water was added to the reaction mixture, which was extracted with dichloromethane (3x). The organic layer was combined washed with water and brine, dried with $MgSO_4$, filtered and evaporated. The residue was purified on silica gel using hexane/EtOAc = 80/20 as eluent affording **1a** as a white solid (368 mg, 85%). ^{1}H NMR (400 MHz, CDCl3) δ 8.84 – 8.67 (m, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.96 (td, J = 7.7, 1.7 Hz, 1H), 7.57 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 4.03 (s, 2H), 0.93 (s, 9H) ppm. ^{13}C NMR (75 MHz, CDCl3) δ = 155.0, 150.4, 138.3, 127.6, 123.3, 82.1, 32.0, 26.1 ppm. HRMS (ESI) calcd. for $C_{10}H_{16}NO_3S$ $(M+H)^+$ 230.0845, found 230.0844.

Neopentyl 3-methylpyridine-2-sulfonate (1b)



Following the general procedure, **1b** was isolated as a colorless oil (290 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.6, 1.7, 0.7 Hz, 1H), 7.73 (ddd, *J* = 7.8, 1.6, 0.7 Hz, 1H), 7.45 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.97 (s, 2H), 2.69 (s, 3H), 0.96 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 146.6, 141.4, 134.1, 127.4, 81.7, 32.0, 26.2, 19.1 ppm. HRMS (ESI) calcd. for $C_{11}H_{18}NO_3S$ $(M+H)^+$ 244.1002, found 244.0993.

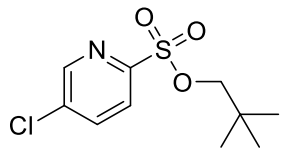
Neopentyl 5-methylpyridine-2-sulfonate (1c)



Following the general procedure, **1c** was isolated as a white solid (373 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (dt, *J* = 2.3, 0.8 Hz, 1H), 8.00 – 7.86 (m, 1H), 7.80 – 7.64 (m, 1H), 3.98 (s,

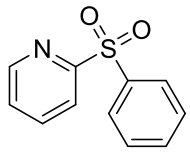
2H), 2.45 (s, 3H), 0.92 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.1, 150.8, 138.4, 138.3, 123.0, 81.7, 32.0, 26.1, 18.7 ppm. HRMS (ESI) calcd. for $C_{11}H_{18}NO_3S$ $(M+H)^+$ 244.1002, found 244.0992.

Neopentyl 5-chloropyridine-2-sulfonate (1d)



Following the general procedure, **1d** was isolated as a white solid (420 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.00 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.92 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.03 (s, 2H), 0.94 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 152.9, 149.4, 137.9, 136.6, 124.2, 82.4, 32.0, 26.1 ppm. HRMS (ESI) calcd. for $C_{10}H_{15}ClNO_3S$ $(M+H)^+$ 286.0275, found 286.0270.

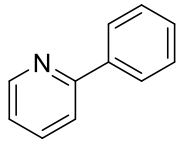
Phenyl 2-pyridyl sulfone (3)



A round-bottom flask was charged with 2-chloropyridine (0.83 mL, 8.807 mmol, 1 equiv.), thiophenol (0.98 mL, 9.504 mmol, 1.1 equiv.) and DMF (6.8 mL), followed by K_2CO_3 (1.46 g, 10.6 mmol, 1.2 equiv.), heated to 110 °C and stirred for 20 h. The heterogeneous mixture was filtered. The filter cake was washed with DMF. The filtrate containing the crude sulfide was concentrated and transferred to a new flask. The oxidation to sulfone was carried out by adding 2.3 equiv. of *m*CPBA in DCM (0.1 M) and stirring for 5 hours. The conversion of the sulfide to the sulfoxide and sulfone was monitored by low-res MS. Saturated aqueous solution of Na_2SO_3 was added and the organic phase was separated and washed with saturated aqueous solution of

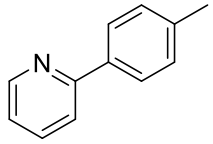
$NaHCO_3$. The combined organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 80/20 as eluent affording **3** (1.5 g, 80%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.20 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.12 – 8.02 (m, 2H), 7.92 (td, *J* = 7.8, 1.7 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.57 – 7.49 (m, 2H), 7.45 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 150.6, 139.0, 138.3, 133.9, 129.3, 129.1, 127.1, 122.3 ppm. HRMS (ESI) calcd. for $C_{11}H_{10}NO_2S$ $(M+H)^+$ 220.0427, found 220.0426.

2-Phenylpyridine (5a)



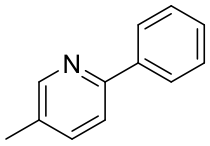
A -78°C solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (1.16 mL) was treated dropwise with a 1.8 M solution of PhLi (0.29 mL, 0.522 mmol, 3 equiv), stirred for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **5a** (23 mg, 84%) as a yellow oil. From **2** and **3**, **5a** was isolated in 81% and 80% yield respectively following the same conditions. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (dt, *J* = 4.8, 1.6 Hz, 1H), 8.12 – 7.92 (m, 2H), 7.82 – 7.67 (m, 2H), 7.59 – 7.34 (m, 3H), 7.32 – 7.14 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.6, 149.8, 139.5, 136.9, 129.1, 128.9, 127.1, 122.2, 120.7 ppm. HRMS (ESI) calcd. for $C_{11}H_{10}N$ $(M+H)^+$ 156.0808, found 156.0812.

2-(*p*-Tolyl)pyridine (5c)



A 1 M solution of *p*-tolyl lithium was prepared by stirring an equimolar mixture of *n*BuLi and 1-bromo-4-methylbenzene in THF at -78 °C for 1 h. A -78 °C solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 1 M solution of tolyl lithium (0.35 mL, 0.349 mmol, 2 equiv.), stirred for 20 min, treated with another 2 equivalents of the tolyl lithium solution and stirred for 10 min. The reaction was then quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 9:1 as eluent affording **5c** (25 mg, 84%) as a yellow oil. From **2** and **3**, **5c** was isolated in 86% and 93% yield respectively following the same conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dt, *J* = 5.0, 1.4 Hz, 1H), 7.98 – 7.84 (m, 2H), 7.76 – 7.65 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.19 (ddd, *J* = 6.1, 4.9, 2.4 Hz, 1H), 2.41 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 149.6, 139.1, 136.8, 136.7, 129.6, 126.9, 121.9, 120.4, 21.4 ppm. HRMS (ESI) calcd. for $C_{12}H_{12}N$ $(M+H)^+$ 170.0964, found 170.0956.

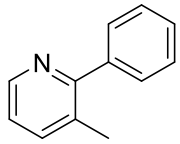
5-Methyl-2-phenylpyridine (6a)



A -78 °C solution of **1c** (42.3 mg, 0.174 mmol, 1 equiv.) in THF (1.16 mL) was treated dropwise with a 1.8 M solution of PhLi (0.29 mL, 0.522 mmol, 3 equiv.), stirred for 20 min, treated with another 2 equivalents of the PhLi solution, stirred for 10 min, quenched with water and extracted

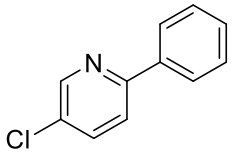
with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **6a** (15 mg, 51%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.46 (m, 1H), 8.02 – 7.93 (m, 2H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.55 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.46 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.44 – 7.36 (m, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 150.0, 139.3, 137.6, 131.8, 128.9, 128.8, 126.9, 120.3, 18.3 ppm. HRMS (ESI) calcd. for $C_{12}H_{12}N$ $(M+H)^+$ 170.0964, found 170.0958.

3-Methyl-2-phenylpyridine (6b)



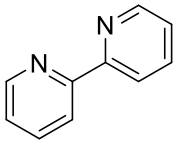
A -78 °C solution of **1b** (42.3 mg, 0.174 mmol, 1 equiv.) in THF (1.16 mL) was treated dropwise with a 1.8 M solution of PhLi (0.29 mL, 0.522 mmol, 3 equiv.), stirred for 30 min, quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 8/2 as eluent affording **6b** (26 mg, 90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.43 (m, 1H), 7.60 – 7.56 (m, 1H), 7.55 – 7.50 (m, 2H), 7.48 – 7.42 (m, 2H), 7.42 – 7.36 (m, 1H), 7.18 (dd, *J* = 7.7, 4.7 Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 147.0, 140.6, 138.7, 131.0, 129.0, 128.3, 128.0, 122.2, 20.2 ppm. HRMS (ESI) calcd. for $C_{12}H_{12}N$ $(M+H)^+$ 170.0964, found 170.0957.

5-Chloro-2-phenylpyridine (6c)



A -78 °C solution of **1d** (45.9 mg, 0.174 mmol, 1 equiv.) in THF (1.16 mL) was treated dropwise with a 1.8 M solution of PhLi (0.29 mL, 0.522 mmol, 3 equiv.), stirred for 30 min, quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **6c** (24.5 mg, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 2.5, 0.8 Hz, 1H), 8.01 – 7.89 (m, 2H), 7.79 – 7.62 (m, 2H), 7.54 – 7.38 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 148.6, 138.3, 136.6, 130.8, 129.4, 129.0, 127.0, 121.3 ppm. HRMS (ESI) calcd. For $C_{11}H_9ClN$ $(M+H)^+$ 190.0418, found 190.0413.

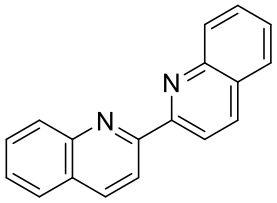
2,2'-Bipyridine (7)



A 1 M solution of pyridine-2-yllithium was prepared by stirring an equimolar mixture of *n*BuLi and 2-bromopyridine in THF at -78 °C for 30 minutes. A -78 °C solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 1 M solution of pyridine-2-yllithium (0.35 mL, 0.35 mmol, 2 equiv.), stirred for 20 min, treated with another equivalent of 1 M pyridine-2-yllithium solution and stirred until complete disappearance of **1a** (10 min). The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was

purified on silica gel using hexane/EtOAc = 85/15 as eluent affording **7** (25 mg, 92%) as white solid. From **2** and **3**, **7** was isolated in 89% and 86% yield respectively following the same conditions. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 2H), 8.39 (dt, *J* = 8.0, 1.1 Hz, 2H), 7.81 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 2H), 7.36 – 7.23 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 149.3, 137.1, 123.9, 121.2 ppm. HRMS (ESI) calcd. for $C_{10}H_9N_2$ $(M+H)^+$ 157.0760, found 157.0754.

2-(Pyridin-2-yl)quinoline (8)

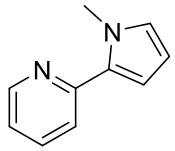


A -78 °C solution of 2-bromoquinoline (145 mg, 0.696 mmol, 4 equiv.) in THF (6.7 mL) was treated dropwise with a 2.5 M solution of *n*BuLi (0.28 mL, 0.696 mmol, 4 equiv.), stirred for 30 min. A solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise to the mixture and stirred at -78 °C for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 85/15 as eluent affording **8** (24 mg, 67%, Rf: 0.3 (hexane/EtOAc, 8:2)) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 – 8.72 (m, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.6 Hz, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.95 – 7.83 (m, 2H), 7.75 (ddd, *J* = 8.4, 6.7, 1.5 Hz, 1H), 7.57 (td, *J* = 7.4, 6.8, 1.1 Hz, 1H), 7.38 (dd, *J* = 7.5, 5.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 156.2, 149.3, 148.0, 137.1, 137.0, 129.9, 129.7, 128.4, 127.8, 126.9, 124.2, 122.0, 119.1 ppm. HRMS (ESI) calcd. for $C_{14}H_{11}N_2$ $(M+H)^+$ 207.0917, found 207.0916.

2,2'-biquinoline (51 mg, Rf: 0.5 (hexane/EtOAc, 8:2) were also isolated as yellow solid, mp 192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, *J* = 8.6 Hz, 2H), 8.35 (dd, *J* = 8.7, 0.8 Hz, 2H), 8.25 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.90 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.78 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 2H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 148.0, 136.9, 130.1, 129.7, 128.6, 127.8, 127.1, 119.6 ppm; HRMS (ESI) calcd. for $C_{18}H_{13}N_2$ $(M+H)^+$ 257.1073, found 257.1066.

Literature data for 2,2'-biquinoline: yellow solid, mp 193-195 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 (d, 2H, J = 8.8 Hz), 8.33 (d, 2H, J = 8.4 Hz), 8.24 (d, 2H, J= 8.4 Hz),. 7.89 (d, 2H, J = 8.0 Hz), 7.72 (m, 2H), 7.57 (m, 2H) ppm.[91]

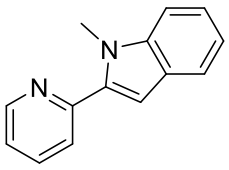
2-(1-Methyl-1H-pyrrol-2-yl) pyridine (9)



A 0.6 M solution of (1-methyl-1H-pyrrol-2-yl)lithium was prepared by stirring an equimolar mixture of *n*BuLi and 2-bromopyridine in THF at -78 °C for 30 min, then at 0 °C for 1 h. A -78 °C solution of **1a** (40 mg, 0.174mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 0.6 M solution of (1-methyl-1H-pyrrol-2-yl)lithium (0.87 mL, 0.52 mmol, 3 equiv.), stirred for 30 min, treated with another 3 equivalents of (1-methyl-1H-pyrrol-2-yl)lithium solution and stirred for another 30 min at -78 °C. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (9:1 hexane/ EtOAc) affording **9** (5.8 mg, 30 %, Rf: 0.45 (hexane/EtOAc, 8:2)) as yellow liquid, and the starting material (16 mg, 40%, Rf: 0.3 (hexane/EtOAc, 8:2)). The side product 2-((1-methyl-

1H-pyrrol-2-yl) sulfonyl) pyridine (**17**) (5.8 mg, 15%, Rf: 0.1 (hexane/EtOAc, 8:2)) was also isolated as yellow solid with eluent hexane/ EtOAc= 7/3. Data for **9**: ^{1}H NMR (300 MHz, Chloroform-d) δ 8.80 – 8.58 (m, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.91 (td, J = 7.8, 1.7 Hz, 1H), 7.45 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.03 (dd, J = 4.1, 1.9 Hz, 1H), 6.85 (t, J = 2.2 Hz, 1H), 6.18 (dd, J = 4.1, 2.5 Hz, 1H), 4.01 (s, 3H) ppm; ^{13}C NMR (101 MHz, Chloroform-d) δ 152.5, 148.4, 136.4, 132.1, 126.5, 121.6, 120.3, 110.9, 107.7, 36.9 ppm; HRMS (ESI) calcd. for $C_{10}H_{11}N_2$ $(M+H)^+$ 159.0917, found 159.0912. Data for 2-((1-methyl-1H-pyrrol-2-yl) sulfonyl) pyridine (**17**): ^{1}H NMR (400 MHz, Chloroform-d) δ 8.85 – 8.44 (m, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.90 (td, J = 7.8, 1.7 Hz, 1H), 7.45 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.02 (dd, J = 4.1, 1.9 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.17 (dd, J = 4.1, 2.5 Hz, 1H), 4.00 (s, 3H) ppm; ^{13}C NMR (101 MHz, Chloroform-d) δ 160.0, 150.1, 138.2, 130.7, 126.7, 126.2, 121.3, 120.2, 108.6, 36.5 ppm; HRMS (ESI) calcd. for $C_{10}H_{11}N_2O_2S$ $(M+H)^+$ 223.0536, found 223.0529.

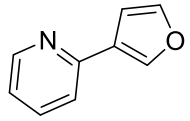
1-Methyl-2-(pyridin-2-yl)-1H-indole (10)



A -78 °C solution of 1-methyl-1*H*-indole (93.1 mg, 0.696 mmol, 4 equiv.) in anhydrous THF (0.8 mL) was treated dropwise with a 1.7 M solution of *t*BuLi (0.41 mL, 0.696 mmol, 4 equiv.), stirred for 5 min and the resulting solution was allowed to warm up to room temperature for 1 h. The mixture was cooled to -40 °C and a solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise over 20 min. The mixture was allowed to warm up to 0 °C gradually. After 10 minutes, the reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and

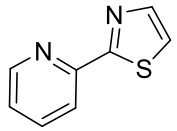
concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 9/1 affording **10** (15.2 mg, 42%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.79 – 7.70 (m, 2H), 7.67 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.29 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.88 (d, *J* = 0.8 Hz, 1H), 4.09 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 149.0, 139.5, 138.9, 136.9, 127.6, 123.8, 122.8, 121.9, 121.1, 120.1, 110.0, 103.8, 32.1 ppm. HRMS (ESI) calcd. for $C_{14}H_{13}N_2$ $(M+H)^+$ 209.1073, found 209.1064.

2-(Furan-3-yl)pyridine (11)



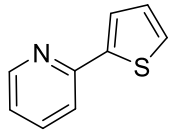
A -78 °C solution of 3-bromofuran (102.3 mg, 0.696 mmol, 4 equiv.) in THF (1.9 mL) was treated dropwise with a 2.5 M solution of *n*BuLi (0.28 mL, 0.696 mmol, 4 equiv.), stirred for 2 h. A solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise to the mixture and stirred at -40 °C for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 9/1 affording **11** (16.4 mg, 65 %) as a pale-yellow volatile oil. From **2** and **3**, **11** was obtained with 52% and 66% yield respectively following the same conditions. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.02 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.65 (td, *J* = 7.7, 1.9 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.12 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.89 (dd, *J* = 1.9, 0.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 149.8, 144.0, 141.3, 136.7, 127.2, 121.8, 120.2, 108.7 ppm. HRMS (ESI) calcd. for C_9H_8NO $(M+H)^+$ 146.0600, found 146.0598.

2-(Pyridin-2-yl)thiazole (12)



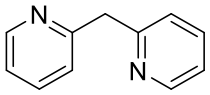
A -78 °C solution of 2-bromothiazole (114.2 mg, 0.696 mmol, 4 equiv.) in THF (1.9 mL) was treated dropwise with a 2.5 M solution of *n*BuLi (0.28 mL, 0.696 mmol, 4 equiv.), stirred for 30 min. A solution of **11a** (40 mg, 0.174 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise to the mixture and stirred at -40 °C for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using DCM/acetone = 99/1 affording **12** (13.8 mg, 49%, Rf: 0.28 hexane/EtOAc, 8:2)) as a white solid and 2,2'-bithiazole (14 mg, Rf: 0.3 hexane/EtOAc, 8:2)). From **2** and **3**, **12** was obtained with 46% and 65% yield respectively following the same conditions. Data for **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.9 Hz, 1H), 8.20 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.92 (d, *J* = 3.2 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44 (d, *J* = 3.2 Hz, 1H), 7.32 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 151.5, 149.6, 144.2, 137.3, 124.6, 121.6, 119.8 ppm; HRMS (ESI) calcd. for $C_8H_7N_2S$ $(M+H)^+$ 163.0325, found 163.0324. Data for 2,2'-bithiazole: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 3.2 Hz, 2H), 7.44 (d, *J* = 3.1 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 144.0, 121.1 ppm. HRMS (ESI) calcd. for $C_6H_5N_2S_2$ $(M+H)^+$ 168.9889, found 168.9881.

2-(Thiophen-2-yl)pyridine (13)



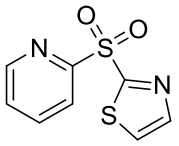
A 1 M solution of thiophen-2-yllithium was prepared by stirring an equimolar mixture of *n*BuLi and 2-bromothiophene in THF at -78 °C for 5 minutes and then at rt for 3 h. A -40 °C solution of **1a** (40 mg, 0.174mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 1 M solution of thiophen-2-yllithium (0.52 mL, 0.52 mmol, 3 equiv.), stirred 30 min, treated with another 3 equivalents of thiophen-2-yllithium, stirred for 30 min at -40 °C and 10 min at rt. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **13** (10.4 mg, 37%, Rf: 0.4 hexane/EtOAc, 8:2)) as a white solid. 2-(Thiophen-2-ylsulfonyl) pyridine (**18**) (4.7mg, 12%, Rf: 0.1 hexane/EtOAc, 8:2) was also isolated. Data for **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.54 (m, 1H), 7.75 – 7.64 (m, 2H), 7.63 – 7.58 (m, 1H), 7.40 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.15 (ddd, *J* = 6.7, 4.9, 1.7 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.7 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.4, 149.3, 144.2, 137.3, 128.3, 128.0, 125.2, 122.1, 119.2 ppm; HRMS (ESI) calcd. for C_9H_8NS $(M+H)^+$ 162.0372, found 162. 0367. Data for 2-(thiophen-2-ylsulfonyl) pyridine (**18**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dt, *J* = 4.7, 1.2 Hz, 1H), 8.19 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.94 (td, *J* = 7.8, 1.7 Hz, 1H), 7.86 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.73 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 150.6, 139.7, 138.3, 135.5, 135.3, 128.0, 127.2, 121.9 ppm; HRMS (ESI) calcd. for $C_9H_8NO_2S_2$ $(M+H)^+$ 225.9991, found 225.9983.

Di(pyridin-2-yl)methane (14)



A 1 M solution of pyridin-2-ylmethyl lithium was prepared by stirring an equimolar mixture of *n*BuLi and 2-methylpyridine in THF at -78 °C for 1 h and then at 0 °C for 30 min. A -78 °C solution of **1a** (40 mg, 0.174 mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 1 M solution of pyridin-2-ylmethyl lithium dropwise (0.35 mL, 0.35 mmol, 2 equiv.), stirred for 20 min, treated with another 2 equivalents of pyridin-2-ylmethyl lithium solution and stirred until complete disappearance of **1a** (10 min). The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using DCM/MeOH = 95/5 as eluent affording **14** (25 mg, 85%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 5.1, 1.8 Hz, 2H), 7.62 (td, *J* = 7.7, 1.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 7.6, 4.9 Hz, 2H), 4.36 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 149.5, 136.7, 123.7, 121.6, 47.4 ppm. HRMS (ESI) calcd. for $C_{11}H_{11}N_2$ $(M+H)^+$ 171.0917, found 171.0922.

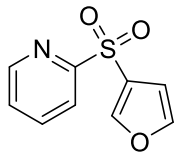
2-(Pyridin-2-ylsulfonyl)thiazole (15)



A -78 °C solution of 2-bromothiazole (209.1 mg, 1.275 mmol, 3 equiv.) in THF (3.5 mL) was treated dropwise with a 2.5 M solution of *n*BuLi (0.51 mL, 1.275 mmol, 3 equiv.), stirred for 30 min. A solution of **2** (100 mg, 0.425 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise to the mixture and stirred at -78 °C for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and

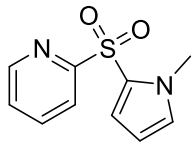
concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 85/15 affording **15** (80.6 mg, 84%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.70 (m, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.77 (d, *J* = 3.0 Hz, 1H), 7.55 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 156.7, 150.8, 145.5, 138.5, 128.0, 127.2, 123.7 ppm. HRMS (ESI) calcd. for $C_8H_7N_2O_2S_2$ $(M+H)^+$ 226.9944, found 226.9937.

2-(Furan-3-ylsulfonyl)pyridine (16)



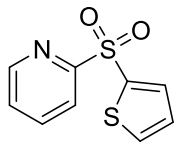
A -78 °C solution of 3-bromofuran (73.7 mg, 0.522 mmol, 3 equiv.) in THF (1.4 mL) was treated dropwise with a 2.5 M solution of *n*BuLi (0.21 mL, 0.522 mmol, 3 equiv.), stirred for 2 h. A solution of **2** (41 mg, 0.174 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise to the mixture and stirred for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 7/3 affording affording 27.7 mg (76 %) of **16** as a white solid.^{1}H NMR (400 MHz, Chloroform-d) δ 8.73 – 8.65 (m, 1H), 8.19 – 8.08 (m, 2H), 7.94 (td, J = 7.8, 1.7 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.48 (s, 1H), 6.78 (d, J = 1.8 Hz, 1H) ppm.^{13}C NMR (101 MHz, Chloroform-d) δ 158.6, 150.4, 147.9, 144.8, 138.2, 127.2, 126.7, 121.7, 109.5 ppm. HRMS (ESI) calcd. for $C_9H_8NO_3S$ $(M+H)^+$ 210.0219, found 210.0209.

2-((1-Methyl-1H-pyrrol-2-yl)sulfonyl)pyridine (17)



A 0.6 M solution of (1-methyl-1H-pyrrol-2-yl)lithium was prepared by stirring an equimolar mixture of *n*BuLi and 2-bromopyridine in THF at -78 °C for 30 min, then at 0 °C for 1h. A -78 °C solution of **2** (41 mg, 0.174mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 0.6 M solution of (1-methyl-1H-pyrrol-2-yl)lithium (0.58 mL, 0.348 mmol, 2 equiv.), stirred for 20 min, treated with another 2 equivalents of (1-methyl-1H-pyrrol-2-yl)lithium solution and stirred until complete disappearance of **2**. Then the reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layer was dried over Na_2SO_4, filtered nd concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (7:3 hexane/EtOAc) affording 28.3 mg (73 %) of **17** as yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.85 – 8.44 (m, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.90 (td, J = 7.8, 1.7 Hz, 1H), 7.45 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.02 (dd, J = 4.1, 1.9 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.17 (dd, J = 4.1, 2.5 Hz, 1H), 4.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-d) δ 160.0, 150.1, 138.2, 130.7, 126.7, 126.2, 121.3, 120.2, 108.6, 36.5 ppm. HRMS (ESI) calcd. for $C_{10}H_{11}N_2O_2S$ $(M+H)^+$ 223.0536, found 223.0529.

2-(Thiophen-2-ylsulfonyl)pyridine (18)

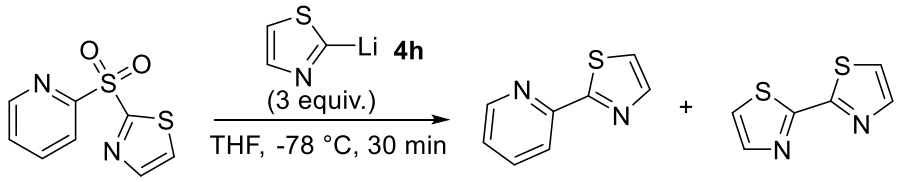


A 1M solution of thiophen-2-yllithium was prepared by stirring an equimolar mixture of *n*BuLi and 2-bromothiophene in THF at -78 °C for 5 min and then at rt for 3 h. A -78 °C solution of **2**

(41 mg, 0.174mmol, 1 equiv.) in THF (1.1 mL) was treated dropwise with the 1 M solution of thiophen-2-yllithium (0.52 mL, 0.52 mmol, 3 equiv.), stirred for 30 min, treated with another 3 equivalents of thiophen-2-yllithium solution and stirred for 30 min at -78 °C. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (9:1 hexane/ EtOAc) affording 20mg (52%) of **18** as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (dt, *J* = 4.7, 1.2 Hz, 1H), 8.19 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.94 (td, *J* = 7.8, 1.7 Hz, 1H), 7.86 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.73 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H) ppm.^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.9, 150.5, 139.6, 138.2, 135.3, 135.2, 127.9, 127.0, 121.8 ppm. HRMS (ESI) calcd. for $C_9H_8NO_2S_2$ $(M+H)^+$ 225.9991, found 225.9983.

2.7 Supplementary reactions

Reaction of 15 with thiazol-2-yllithium

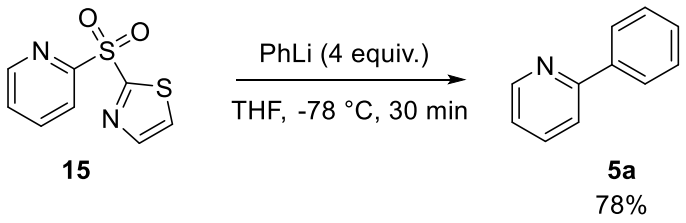


15 **12** 45%

A -78 °C solution of 2-bromothiazole (57.1 mg, 0.348 mmol, 2 equiv.) in THF (1 mL) was added dropwise with a 2.5 M solution of *n*BuLi (0.14 mL, 0.348 mmol, 2 equiv.), stirred for 30 min. A solution of **15** (39.4 mg, 0.174 mmol, 1 equiv.) in THF (0.7 mL) was added dropwise to the mixture and stirred for 30 min at -40 °C. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and

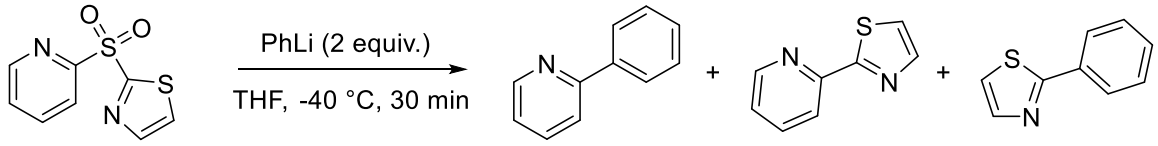
concentrated *in vacuo*. The residue was purified on silica gel using DCM/Acetone = 99/1 affording **12** (12.7 mg, 45%) and 13.8 mg of 2,2'-bithiazole.

Reaction of 15 with phenyl lithium



15 **5a** 78%

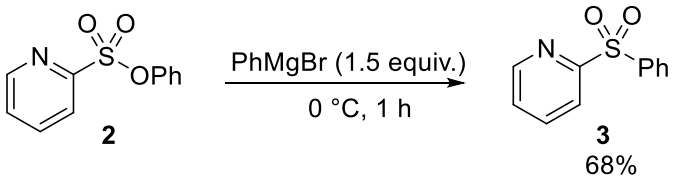
A -78 °C solution of **15** (39.4 mg, 0.174 mmol, 1 equiv.) in THF (1.16 mL) was treated dropwise with a 1.8 M solution of PhLi (0.19 mL, 0.348 mmol, 2 equiv.), stirred for 20 min, treated with another 2 equivalents of PhLi solution and stirred until complete disappearance of **15**. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **5a** (23 mg, 84%) as a yellow oil.



15 **5a** 65% **12** 11% **20** 13%

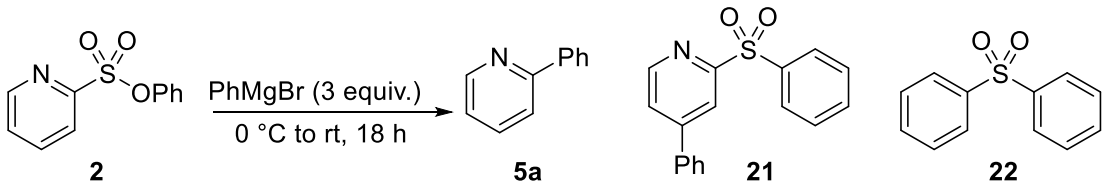
A -78 °C solution of **15** (39.4 mg, 0.174 mmol, 1 equiv.) in THF (1.26 mL) was treated dropwise with a 1.8 M solution of PhLi (0.19 mL, 0.348 mmol, 2 equiv.). The mixture was warmed to -40 °C and stirred for 30 min. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording 23 mg (65%) of **5a**, 3.1 mg (11%) of **12**, and 3.6 mg (13%) of **20**.

Reaction of 2 with PhMgBr



2 **3**
68%

A 0 °C solution of **2** (41 mg, 0.174 mmol, 1 equiv.) in THF (0.6 mL) was treated dropwise with a 1 M solution of PhMgBr (0.26 mL, 0.26 mL, 1.5 equiv.), stirred for 1 h. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **3** (26 mg, 68%).



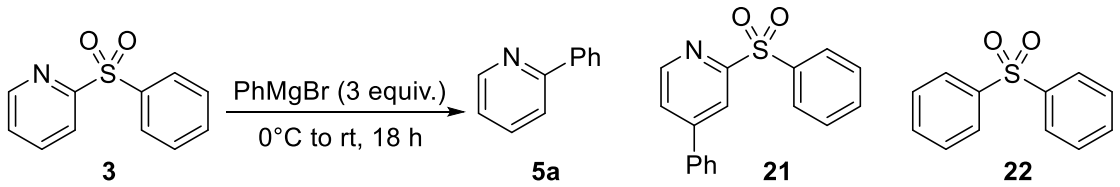
2 **5a** **21** **22**
42% 10% 7%

A 0 °C solution of **2** (41 mg, 0.174 mmol, 1 equiv.) in THF (0.6 mL) was treated dropwise with a 1 M solution of PhMgBr (0.52 mL, 0.52 mmol, 3 equiv.), stirred for 1h and warmed up to room temperature for 18h. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on silica gel using hexane/EtOAc = 9/1 as eluent affording **5a** (42%), **21** (10%) and **22** (7%).

Data for 4-phenyl-2-(phenylsulfonyl)pyridine (**21**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 5.0 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.14 – 8.04 (m, 2H), 7.71 – 7.59 (m, 4H), 7.59 – 7.48 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 151.1, 151.1, 139.1, 136.6, 133.9, 130.3, 129.6,

129.3, 129.1, 127.3, 124.6, 120.2 ppm; HRMS (ESI) calcd. for $C_{17}H_{14}NO_2S$ $(M+H)^+$ 296.0740, found 296.0729.

Data for sulfonyldibenzene (**22**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.59 (m, 4H), 7.51 – 7.42 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 131.2, 129.5, 125.0 ppm; HRMS (ESI) calcd. for $C_{12}H_{11}O_2S$ $(M+H)^+$ 219.0474, found 219.0480.



Following the same conditions as above with **3**, the following product distribution was obtained: **5a** (62%), **21** (15%) and **22** (11%).

References

(1) Agledal, L.; Niere, M.; Ziegler, M. The Phosphate Makes a Difference: Cellular Functions of NADP. *Redox Report*. Taylor & Francis February 1, **2010**, pp 2–10. https://doi.org/10.1179/174329210X12650506623122.

(2) Baumann, M.; Baxendale, I. R. An Overview of the Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles. *Beilstein J. Org. Chem.* **2013**, *9* (1), 2265–2319. https://doi.org/10.3762/bjoc.9.265.

(3) MDDR: MDL Drug Data Registry, by MDL InformationsSystems, Inc; San Leandro, California, USA

(4) Henry, G. D. De Novo Synthesis of Substituted Pyridines. *Tetrahedron*. **2004**, 60 (29), 6043–6061. https://doi.org/10.1016/j.tet.2004.04.043.

(5) Guan, A. Y.; Liu, C. L.; Sun, X. F.; Xie, Y.; Wang, M. A. Discovery of Pyridine-Based Agrochemicals by Using Intermediate Derivatization Methods. *Bioorganic Med. Chem.* **2016**, *24* (3), 342–353. https://doi.org/10.1016/j.bmc.2015.09.031.

(6) Kaes, C.; Katz, A.; Hosseini, M. W. Bipyridine: The Most Widely Used Ligand. A Review of Molecules Comprising at Least Two 2,2′-Bipyridine Units. *Chem. Rev.* **2000**, *100* (10), 3553–3590. https://doi.org/10.1021/cr990376z.

(7) Campeau, L. C.; Rousseaux, S.; Fagnou, K. A Solution to the 2-Pyridyl Organometallic Cross-Coupling Problem: Regioselective Catalytic Direct Arylation of Pyridine N-Oxides. *J. Am. Chem. Soc.* **2005**, *127* (51), 18020–18021. https://doi.org/10.1021/ja056800x.

(8) Bailey, T. R. Unsymmetrical Heterobiaryl Synthesis. A Highly Efficient Palladium-Catalyzed Cross-Coupling Reaction of Heteroaryl Trialkylstannanes with Aryl Halides. *Tetrahedron Lett.* **1986**, *27* (37), 4407–4410. https://doi.org/10.1016/S0040-4039(00)84964-3.

(9) Luzung, M. R.; Patel, J. S.; Yin, J. A Mild Negishi Cross-Coupling of 2-Heterocyclic Organozinc Reagents and Aryl Chlorides. *J. Org. Chem.* **2010**, *75* (23), 8330–8332.

https://doi.org/10.1021/jo1018798.

(10) Hodgson, P. B.; Salingue, F. H. The Preparation of a Stable 2-Pyridylboronate and Its Reactivity in the Suzuki-Miyaura Cross-Coupling Reaction. *Tetrahedron Lett.* **2004**, *45* (4), 685–687. https://doi.org/10.1016/j.tetlet.2003.11.068.

(11) Molander, G. A.; Ellis, N. Organotrifluoroborates: Protected Boronic Acids That Expand the Versatility of the Suzuki Coupling Reaction. *Acc. Chem. Res.* **2007**, *40* (4), 275–286. https://doi.org/10.1021/ar050199q.

(12) Billingsley, K. L.; Buchwald, S. L. A General and Efficient Method for the Suzuki–Miyaura Coupling of 2-Pyridyl Nucleophiles. *Angew. Chem.* **2008**, *120* (25), 4773–4776. https://doi.org/10.1002/ange.200801465.

(13) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. Copper-Facilitated Suzuki Reactions: Application to 2-Heterocyclic Boronates. *Org. Lett.* **2009**, *11* (2), 345–347. https://doi.org/10.1021/ol802556f.

(14) Perkins, J. R.; Carter, R. G. Synthesis of Programmable Tetra-Ortho-Substituted Biaryl Compounds Using Diels-Alder Cycloadditions/Cycloreversions of Disubstituted Alkynyl Stannanes. *J. Am. Chem. Soc.* **2008**, *130* (11), 3290–3291. https://doi.org/10.1021/ja7113486.

(15) Denmark, S. E.; Smith, R. C.; Chang, W. T. T.; Muhuhi, J. M. Cross-Coupling Reactions of Aromatic and Heteroaromatic Silanolates with Aromatic and Heteroaromatic Halides. *J. Am. Chem. Soc.* **2009**, *131* (8), 3104–3118. https://doi.org/10.1021/ja8091449.

(16) Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131* (20), 6961–6963. https://doi.org/10.1021/ja901416p.

(17) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. Protodeboronation of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: PH-Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **2016**, *138* (29), 9145–9157. https://doi.org/10.1021/jacs.6b03283.

(18) Blakemore, D. Suzuki-Miyaura Coupling. In *RSC Drug Discovery Series*; Royal Society of Chemistry, **2016**; Vol. 2016-Janua, pp 1–69. https://doi.org/10.1039/9781782622086-00001.

(19) Yang, Y.; Lan, J.; You, J. Oxidative C−H/C−H Coupling Reactions between Two (Hetero)Arenes. *Chem. Rev.* **2017**, *117* (13), 8787-8863. https://doi.org/10.1021/acs.chemrev.6b00567.

(20) Liu, C.; Yang, W. A Fast and Oxygen-Promoted Protocol for the Ligand-Free Suzuki Reaction of 2-Halogenated Pyridines in Aqueous Mediaw. *Chem.Commun*. **2009,** 6267–6269. https://doi.org/10.1039/b912364d.

(21) Li, H.; Oppenheimer, J.; Smith Iii, M. R.; Maleczka, R. E. Improved Synthesis of Electron Deficient Bipyridines. *Tetrahedron Lett*. **2016**, *57* (21) 2231-2232. https://doi.org/10.1016/j.tetlet.2016.04.023.

(22) Rajalakshmanan, E.; Alexander, V. Synthesis of Dimethylbipyridines by the Reductive Coupling of 2-Halomethylpyridines with Nickel Catalyst. *Synth. Commun.* **2005**, *35* (6), 891–895. https://doi.org/10.1081/SCC-200051056.

(23) Schultz, D. M.; Sawicki, J. W.; Yoon, T. P. An Improved Procedure for the Preparation of $Ru(Bpz)_3(PF_6)_2$ via a High-Yielding Synthesis of 2,2'-Bipyrazine. *Beilstein J. Org. Chem.* **2015**, *11* (1), 61–65. https://doi.org/10.3762/bjoc.11.9.

(24) Coe, B. J.; Peers, M. K.; Scrutton, N. S. Syntheses and Electronic and Optical Properties of Complexes of the Bis(2,2′-Bipyrazyl)Ruthenium Unit. *Polyhedron* **2015**, *96*, 57–65. https://doi.org/10.1016/j.poly.2015.04.028.

(25) Tang, J.; Fan, F.; Cong, X.; Zhao, L.; Luo, M.; Zeng, X. Reductive Cross-Coupling between Unactivated C(Aryl)−N and C(Aryl)−O Bonds by Chromium Catalysis Using a Bipyridyl Ligand. *J. Am. Chem. Soc* **2020**, *142* (29), 12834-12840. https://doi.org/10.1021/jacs.0c05730.

(26) Suzuki, H.; Enya, T.; Hisamatsu, Y. Synthesis and Characterization of Some Nitrobenzanthrones: Suspected New Mutagens in Atmospheric Environment. *Synthesis (Stuttg).* **1997**, *1997* (11), 1273–1276. https://doi.org/10.1055/s-1997-1352.

(27) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl−Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction. *Chem. Rev.* **2002**, *102* (5), 1359–1470. https://doi.org/10.1021/cr000664r.

(28) Ritleng, V.; Sirlin, C.; Pfeffer, M. Ru-, Rh-, and Pd-Catalyzed C-C Bond Formation Involving C-H Activation and Addition on Unsaturated Substrates: Reactions and Mechanistic Aspects. *Chem. Rev.* **2002**, *102* (5), 1731–1769. https://doi.org/10.1021/cr0104330.

(29) Godula, K.; Sezen, B.; Sames, D. Site-Specific Phenylation of Pyridine Catalyzed by Phosphido-Bridged Ruthenium Dimer Complexes: A Prototype for C-H Arylation of Electron-Deficient Heteroarenes. *J. Am. Chem. Soc.* **2005**, *127* (11), 3648–3649. https://doi.org/10.1021/ja042510p.

(30) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell, **2010**, pp. 7.

(31) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH GmbH, **2003**, pp. 271

(32) Hanessian, S.; Kagotani, M. A Novel Regiospecific Synthesis of 2-Substituted Pyridines. *Synth.* **1987**, *1987* (4), 409–411. https://doi.org/10.1055/s-1987-27967.

(33) Richey, H. G.; Farkas, J. Reactions of Diethylmagnesium - Ethyllithium Solutions with Pyridine. *Tetrahedron Lett.* **1985**, *26* (3), 275–278. https://doi.org/10.1016/S0040-4039(01)80795-4.

(34) Vorbrüggen, H.; Krolikiewcz, K. Conversion of Heterocyclic N-Oxides into α-Alkylated Heterocycles Trimethylsilanol as Leaving Group - IV. *Tetrahedron Lett.* **1983**, *24* (9), 889–890. https://doi.org/10.1016/S0040-4039(00)81556-7.

(35) Kawai, T.; Furukawa, N.; Oae, S. A Convenient Preparation of Bipyridines through Ligand Coupling Reaction with A-Sulfurane Formed by Treatment of Methyl 2-Pyridyl Sulfoxide with Grignard Reagents. *Tetrahedron Lett.* **1984**, *25* (24), 2549–2552. https://doi.org/10.1016/S0040-4039(01)81228-4.

(36) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. Highly Regioselective α-Allylation of N-(Alkoxycarbonyl)Pyridinium Salts by Means of Allyltin Reagents. *J.*

Org. Chem. **1985**, *50* (2), 287–288. https://doi.org/10.1021/jo00202a031.

(37) Andersson, H.; Almqvist, F.; Olsson, R. Synthesis of 2-Substituted Pyridines via a Regiospecific Alkylation, Alkynylation, and Arylation of Pyridine N-Oxides. *Org. Lett.* **2007**, *9* (7), 1335–1337. https://doi.org/10.1021/ol070184n.

(38) Abass, M. Fused Quinolines. Recent Synthetic Approaches to Azoloquinolines. A Review. *Heterocycles*. April 1, **2005**, pp 901–965. https://doi.org/10.3987/REV-04-592.

(39) Fang, A. G.; Mello, J. V.; Finney, N. S. Exploiting the Versatile Assembly of Arylpyridine Fluorophores for Wavelength Tuning and SAR. *Org. Lett.* **2003**, *5* (7), 967–970. https://doi.org/10.1021/ol0272287.

(40) Davies, I. W.; Marcoux, J. F.; Reider, P. J. A General [3 + 2 + 1] Annulation Strategy for the Preparation of Pyridine N-Oxides. *Org. Lett.* **2001**, *3* (2), 209–211. https://doi.org/10.1021/ol006831r.

(41) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59* (10), 4443–4458. https://doi.org/10.1021/acs.jmedchem.5b01409.

(42) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. Base-Catalyzed Aryl-B(OH)2 Protodeboronation Revisited: From Concerted Proton Transfer to Liberation of a Transient Aryl Anion. *J. Am. Chem. Soc.* **2017**, *139* (37), 13156–13165. https://doi.org/10.1021/jacs.7b07444.

(43) Fyfe, J. W. B.; Watson, A. J. B. Recent Developments in Organoboron Chemistry: Old Dogs, New Tricks. *Chem*. Elsevier Inc July 13, **2017**, pp 31–55. https://doi.org/10.1016/j.chempr.2017.05.008.

(44) Kudo, N.; Perseghini, M.; Fu, G. C. A Versatile Method for Suzuki Cross-Coupling Reactions of Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **2006**, *45* (8), 1282–1284. https://doi.org/10.1002/anie.200503479.

(45) Chen, K.; Peterson, R.; Math, S. K.; Lamunyon, J. B.; Testa, C. A.; Cefalo, D. R. Lithium Trihydroxy/Triisopropoxy-2-Pyridylborate Salts (LTBS): Synthesis, Isolation, and Use in Modified Suzuki-Miyaura Cross-Coupling Reactions. *Tetrahedron Lett.* **2012**, *53* (36),

4873–4876. https://doi.org/10.1016/j.tetlet.2012.06.145.

(46) Chen, J.; Cammers-Goodwin, A. 2-(Fluorophenyl)Pyridines by the Suzuki-Miyaura Method: Ag2O Accelerates Coupling over Undesired Ipso Substitution (S_NAr) of Fluorine. *Tetrahedron Lett.* **2003**, *44* (7), 1503–1506. https://doi.org/10.1016/S0040-4039(02)02793-4.

(47) Budiman, Y. P.; Friedrich, A.; Radius, U.; Marder, T. B. Copper-Catalysed Suzuki-Miyaura Cross-Coupling of Highly Fluorinated Aryl Boronate Esters with Aryl Iodides and Bromides and Fluoroarene−Arene Π-Stacking Interactions in the Products. *ChemCatChem* **2019**, *11* (21), 5387–5396. https://doi.org/10.1002/cctc.201901220.

(48) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. Copper-Facilitated Suzuki Reactions: Application to 2-Heterocyclic Boronates. *Org. Lett.* **2009**, *11* (2), 345–347. https://doi.org/10.1021/ol802556f.

(49) Billingsley, K. L.; Buchwald, S. L. A General and Efficient Method for the Suzuki-Miyaura Coupling of 2-Pyridyl Nucleophiles. *Angew. Chem. Int. Ed.* **2008**, *47* (25), 4695–4698. https://doi.org/10.1002/anie.200801465.

(50) Li, B. J.; Yang, S. D.; Shi, Z. J. Recent Advances in Direct Arylation via Palladium-Catalyzed Aromatic C-H Activation. *Synlett* **2008**, *2008* (7), 949–957. https://doi.org/10.1055/s-2008-1042907.

(51) Kakiuchi, F.; Kochi, T. Transition-Metal-Catalyzed Carbon-Carbon Bond Formation via Carbon-Hydrogen Bond Cleavage. *Synthesis*. © Georg Thieme VerlagStuttgart ˙ New York October 1, **2008**, pp 3013–3039. https://doi.org/10.1055/s-2008-1067256.

(52) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem. Int. Ed.* **2009**, *48* (28), 5094–5115. https://doi.org/10.1002/anie.200806273.

(53) Campeau, L. C.; Rousseaux, S.; Fagnou, K. A Solution to the 2-Pyridyl Organometallic Cross-Coupling Problem: Regioselective Catalytic Direct Arylation of Pyridine N-Oxides. *J. Am. Chem. Soc.* **2005**, *127* (51), 18020–18021.

https://doi.org/10.1021/ja056800x.

(54) Larivée, A.; Mousseau, J. J.; Charette, A. B. Palladium-Catalyzed Direct C-H Arylation of N-Iminopyridinium Ylides: Application to the Synthesis of (±)-Anabasine. *J. Am. Chem. Soc.* **2008**, *130* (1), 52–54. https://doi.org/10.1021/ja710073n.

(55) Kato, T.; Yamanaka, H. Reaction of Pyridine and Quinoline N-Oxides with Phenylmagnesium Bromide. *J. Org. Chem.* **1965**, *30* (3), 910–913. https://doi.org/10.1021/jo01014a061.

(56) Van Bergen, T. J.; Kellogg, R. M. Reactions of Aryl Grignard Reagents with Pyridine 1-Oxide. The Structure of the Addition Products. *J. Org. Chem.* **1971**, *36* (12), 1705–1708. https://doi.org/10.1021/jo00811a034.

(57) Schiess, P.; Ringele, P. Grignard Reaction with Pyridine-N-Oxide. *Tetrahedron Lett.* **1972**, *13* (4), 311–312. https://doi.org/10.1016/S0040-4039(01)84310-0.

(58) Andersson, H.; Almqvist, F.; Olsson, R. Synthesis of 2-Substituted Pyridines via a Regiospecific Alkylation, Alkynylation, and Arylation of Pyridine N-Oxides. *Org. Lett.* **2007**, *9* (7), 1335–1337. https://doi.org/10.1021/ol070184n.

(59) Andersson, H.; Sainte-Luce Banchelin, T.; Das, S.; Olsson, R.; Almqvist, F. Efficient, Mild and Completely Regioselective Synthesis of Substituted Pyridines. *Chem. Commun.* **2010**, *46* (19), 3384–3386. https://doi.org/10.1039/c000748j.

(60) Comins, D. L.; Abdullah, A. H. Regioselective Addition of Grignard Reagents to 1-Acylpyridinium Salts. A Convenient Method for the Synthesis of 4-Alkyl(Aryl)Pyridines. *J. Org. Chem.* **1982**, *47* (22), 4315–4319. https://doi.org/10.1021/jo00143a028.

(61) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. On the Regioselectivity of the Reaction of N-Methoxycarbonylpyridinium Chloride with Grignard Reagents: Highly Regioselective Synthesis of 2-Substituted N-Methoxycarbonyl-1,2-Dihydropyridines. *Tetrahedron Lett.* **1983**, *24* (17), 1801–1804. https://doi.org/10.1016/S0040-4039(00)81774-8.

(62) Fraenkel, G.; Cooper, J. W.; Fink, C. M. One-Step Synthesis of 2-SubstitutedN-Ethoxycarbonyl-1,2-Dihydropyridines. *Angew. Chem. Int. Ed.* Engl. **1970**, *9* (7), 523–

523. https://doi.org/10.1002/anie.197005231.

(63) Lyle, R. E.; Marshall, J. L.; Comins, D. L. The Reaction of 1-Acylpyridinium Salts with Grignard and Organocadmium Reagents. *Tetrahedron Lett.* **1977**, *18* (12), 1015–1018. https://doi.org/10.1016/S0040-4039(01)92816-3.

(64) Lyle, R. E.; Comins, D. L. Regioselective Nucleophilic Addition to 3,4-Lutidine. *J. Org. Chem.* **1976**, *41* (20), 3250–3252. https://doi.org/10.1021/jo00882a007.

(65) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(I)-Catalyzed Direct Arylation of Pyridines and Quinolines. *J. Am. Chem. Soc.* **2008**, *130* (45), 14926–14927. https://doi.org/10.1021/ja8059396.

(66) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. Potassium T-Butoxide Alone Can Promote the Biaryl Coupling of Electron-Deficient Nitrogen Heterocycles and Haloarenes. *Org. Lett.* **2008**, *10* (20), 4673–4676. https://doi.org/10.1021/ol8019764.

(67) Liu, B.; Huang, Y.; Lan, J.; Song, F.; You, J. Pd-Catalyzed Oxidative C-H/C-H Cross-Coupling of Pyridines with Heteroarenes. *Chem. Sci.* **2013**, *4* (5), 2163–2167. https://doi.org/10.1039/c3sc50348h.

(68) Garnier-Amblard, E. C.; Liebeskind, L. S. Transition Metal-Catalyzed Desulfitative Coupling of Thioorganic Compounds with Boronic Acids. In *Boronic Acids*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2011**; Vol. 2, pp 363–391. https://doi.org/10.1002/9783527639328.ch7.

(69) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. Pyridine Sulfinates as General Nucleophilic Coupling Partners in Palladium-Catalyzed Cross-Coupling Reactions with Aryl Halides. *Chem. Sci.* **2017**, *8* (6), 4437–4442. https://doi.org/10.1039/c7sc00675f.

(70) De Gombert, A.; McKay, A. I.; Davis, C. J.; Wheelhouse, K. M.; Willis, M. C. Mechanistic Studies of the Palladium-Catalyzed Desulfinative Cross-Coupling of Aryl Bromides and (Hetero)Aryl Sulfinate Salts. *J. Am. Chem. Soc.* **2020**, *142* (7), 3564–3576. https://doi.org/10.1021/jacs.9b13260.

(71) Markovic, T.; Murray, P. R. D.; Rocke, B. N.; Shavnya, A.; Blakemore, D. C.; Willis, M.

C. Heterocyclic Allylsulfones as Latent Heteroaryl Nucleophiles in Palladium-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2018**, *140* (46), 15916–15923. https://doi.org/10.1021/jacs.8b09595.

(72) Zhou, X.; Luo, J.; Liu, J.; Peng, S.; Deng, G. J. Pd-Catalyzed Desulfitative Heck Coupling with Dioxygen as the Terminal Oxidant. *Org. Lett.* **2011**, *13* (6), 1432–1435. https://doi.org/10.1021/ol200101x.

(73) Cheng, K.; Yu, H. Z.; Zhao, B.; Hu, S.; Zhang, X. M.; Qi, C. Palladium-Catalyzed Desulfitative Cross-Coupling of Arylsulfinates with Arylboronic Acids. *RSC Adv.* **2014**, *4* (101), 57923–57928. https://doi.org/10.1039/c4ra07455f.

(74) Cheng, K.; Hu, S.; Zhao, B.; Zhang, X. M.; Qi, C. Palladium-Catalyzed Hiyama-Type Cross-Coupling Reactions of Arenesulfinates with Organosilanes. *J. Org. Chem.* **2013**, *78* (10), 5022–5025. https://doi.org/10.1021/jo302791q.

(75) Wei, J.; Liang, H.; Ni, C.; Sheng, R.; Hu, J. Transition-Metal-Free Desulfinative Cross-Coupling of Heteroaryl Sulfinates with Grignard Reagents. *Org. Lett.* **2019**. https://doi.org/10.1021/acs.orglett.8b03918.

(76) Turner, K. A Review of U.S. Patents in the Field of Organic Process Development Published During June and July 2009. *Org. Process Res. Dev.* **2009**, *13* (6), 1046–1058. https://doi.org/10.1021/op900261t.

(77) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: New York, **1996**.

(78) Rao Volla, C. M.; Vogel, P. Iron-Catalyzed Desulfinylative C-C Cross-Coupling Reactions of Sulfonyl Chlorides with Grignard Reagents. *Angew. Chem. Int. Ed.* **2008**, *47* (7), 1305–1307. https://doi.org/10.1002/anie.200704858.

(79) Yang, F.-L.; Ma, X.-T.; Tian, S.-K. Oxidative Mizoroki-Heck-Type Reaction of Arylsulfonyl Hydrazides for a Highly Regio- and Stereoselective Synthesis of Polysubstituted Alkenes. *Chem. Eur. J.* **2012**, *18* (6), 1582–1585. https://doi.org/10.1002/chem.201103671.

(80) Hanessian, S.; Kagotani, M.; Komaglou, K. Design and Reactivity of Organic Functional Groups - 2-Pyridylsulfonates as Nucleofugal Esters: Remarkably Mild Transformations

into Halides and Olefins. *Heterocycles* **1989**, *28* (2), 1115–1120. https://doi.org/10.3987/COM-88-S134.

(81) Boibessot, T.; Bénimèlis, D.; Jean, M.; Benfodda, Z.; Meffre, P. Synthesis of a Novel Rhizobitoxine-Like Triazole-Containing Amino Acid. *Synlett* **2016**, *27* (19), 2685–2688. https://doi.org/10.1055/s-0036-1588300.

(82) Takahashi, F.; Nogi, K.; Yorimitsu, H. Intramolecular Desulfitative Coupling: Nickel-Catalyzed Transformation of Diaryl Sulfones into Biaryls via Extrusion of SO 2. *Org. Lett.* **2018**, *20* (20), 6601–6605. https://doi.org/10.1021/acs.orglett.8b02972.

(83) Oae, S. LIGAND COUPLING THROUGH HYPERVALENT INTERMEDIATES. REACTION OF HETEROARYL SULFOXIDES WITH ORGANOMETALLICS REAGENTS AND THEIR IMPLICATIONS. *Phosphorous Sulfur Relat. Elem.* **1986**, *27* (1–2), 13–29. https://doi.org/10.1080/03086648608072755.

(84) Dean, W. M.; Šiaučiulis, M.; Storr, T. E.; Lewis, W.; Stockman, R. A. Versatile C(Sp^2)−C(Sp^3) Ligand Couplings of Sulfoxides for the Enantioselective Synthesis of Diarylalkanes. *Angew. Chem. Int. Ed.* **2016**, *55* (34), 10013–10016. https://doi.org/10.1002/anie.201602264.

(85) Oae, S.; Takeda, T.; Kawai, T.; Furukawa, N. LIGAND COUPLING AND PSEUDOROTATION IN THE REACTION OF ALKYL 2-PYRIDYL SULFOXIDE WITH GRIGNARD REAGENTS. *Phosphorous Sulfur Relat. Elem.* **1987**, *34* (3–4), 133–137. https://doi.org/10.1080/03086648708074317.

(86) Oae, S.; Kawai, T.; Furukawa, N. Ligand Coupling through σ-Sulfurane - Complete Retention of Configuration of 1-Phenylethyl Group in the Reaction of 1-Phenylethyl 2-Pyridyl Sulfoxide with Grignard Reagent1. *Tetrahedron Lett.* **1984**, *25* (1), 69–72. https://doi.org/10.1016/S0040-4039(01)91150-5.

(87) Smorada, R. L.; Truce, W. E. Reactions of Arylsulfonylacetylenes with Organolithium and Grignard Reagents: A New Synthesis of Acetylenes. *J. Org. Chem.* **1979**, *44* (19), 3444–3445. https://doi.org/10.1021/jo01333a049.

(88) Akiba, K. ya; Iseki, Y.; Wada, M. Facile Synthesis of 4-Substituted Pyridines Using

Grignard Reagents. *Tetrahedron Lett.* **1982**, *23* (38), 3935–3936. https://doi.org/10.1016/S0040-4039(00)87747-3.

(89) Akjba, K. Y.; IsEKI, Y.; Wada, M. A Convenient Method for the Regioselective Synthesis of 4-Alkyl(Aryl)Pyridines Using Pyridinium Salts. *Bull. Chem. Soc. Jpn.* **1984**, *57* (7), 1994–1999. https://doi.org/10.1246/bcsj.57.1994.

(90) Li, B.; Guo, D.-D.; Guo, S.-H.; Pan, G.-F.; Gao, Y.-R.; Wang, Y.-Q. Palladium-Catalyzed C−H Functionalization of Phenyl 2-Pyridylsulfonates. *Chem. Asian J.* **2017**, *12* (1), 130–144. https://doi.org/10.1002/asia.201601413.

(91) Verniest, G.; Wang, X.; De Kimpe, N.; Padwa, A. Heteroaryl Cross-Coupling as an Entry toward the Synthesis of Lavendamycin Analogues: A Model Study. *J. Org. Chem.* **2010**, *75* (2), 424–433. https://doi.org/10.1021/jo902287t.