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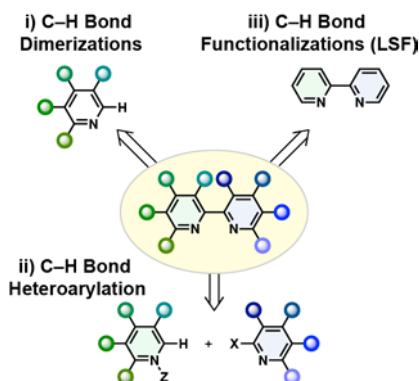
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Synthesis of 2,2'-Bipyridines through Catalytic C–C Bond Formations from C–H Bonds

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Abstract: The present review describes the homogenous catalytic methodologies for the synthesis of 2,2'-bipyridines involving C–C bond formation from C–H bond. There are three main approaches to build well-decorated 2,2'-bipyridines from C–H bond cleavage: i) the formation of C2–C2' bond *via* the dimerization of (activated) pyridines, ii) the C–H bond heteroarylation of activated pyridine, or iii) the late-stage functionalization of (activated) 2,2'-bipyridines including photoredox processes. Besides the scope and limitation of each methodologies, the relevant mechanisms of reaction are also discussed.

Keywords: C–H bond Activation • Homogeneous Catalysis • Ligand Design • N Ligands • Synthetic Methods

1. Introduction

2,2'-Bipyridines are among the most fundamental and privileged bidentate ligands in organometallic and inorganic chemistry for both catalyst and material designs.^[1] For example, 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbpy) is employed for the preparation of heteroleptic Ir(III) complexes such as Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ a well-know photoredox catalyst (Figure 1).^[2] 2,2'-Bipyridines is also a key scaffold for preparing cyclometalated complexes, such as [PtCl(Phbpy)], displaying emission features useful for the fabrication of optical devices.^[3] Moreover, chiral 2,2'-bipyridines, such as Bolm ligand, are very useful in asymmetric catalysis.^[4]

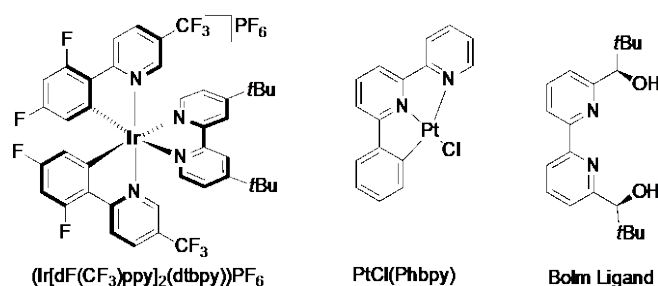


Figure 1. Representative 2,2'-Bipyridyl Ligands in Transition-Metal Catalysis and Material Sciences

Since the first synthesis in 1888 from picolinic acid,^[5] chemists have continually innovated to prepare well-decorated 2,2'-bipyridines, including asymmetrically substituted ones.^[1a] One of the most classical approaches for the synthesis of symmetrically 2,2'-bipyridines is based on reductive homocoupling of 2-halopyridines in the presence of Cu, Ni, or Pd catalysts.^[6] Asymmetrically substituted 2,2'-bipyridines can be prepared using cross-coupling reactions, *i.e.*, Stille, Negishi, Suzuki–Miyaura, Kumada, and Hiyama coupling reactions. Another possibility of the synthesis of 2,2'-bipyridines is based on the cyclization methods, namely Kröhnke cyclization^[7] and [2+2+2] cocyclotrimerization.^[8] Although these methods enable the formation of the desired symmetrically and asymmetrically substituted 2,2'-bipyridines, they suffer from a limited access of starting materials (multi-steps synthesis) and the low stability and poor reactivity of 2-halopyridines and 2-pyridyl organometallics.^[9] Since these last decades, C–H bond functionalization for the formation of C–C bond has revolutionized the synthesis of organic molecules, including 2,2'-bipyridines.^[10] Our review focus on the recent progress in catalytic cross-coupling reactions through C–H bond functionalization for the flexible access to well-decorated 2,2'-bipyridines. Among the different approaches to prepare (functionalized) 2,2'-bipyridines, there are three strategies which involves C–H bond cleavage a key step: i) the formation of C2–C2' bond *via* dimerization of (activated) pyridines, ii) the C–H bond heteroarylation of activated pyridines, or iii) late-stage functionalization of (activated) 2,2'-bipyridines (Figure 2).

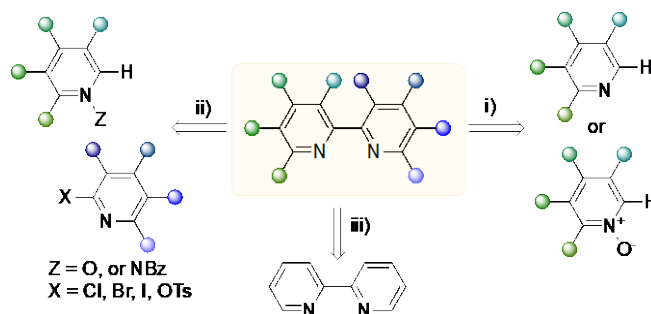


Figure 2. Synthesis of 2,2'-Bipyridines: Scope of this Review

In catalytic reactions with transition metals, the coordination ability of the 2,2'-bipyridine products remains a "problem" because it can affect, positively or negatively, the catalytic properties of the metal centers. Several strategies based on catalysts, conditions, or substrate design have been discovered to avoid such deactivation.

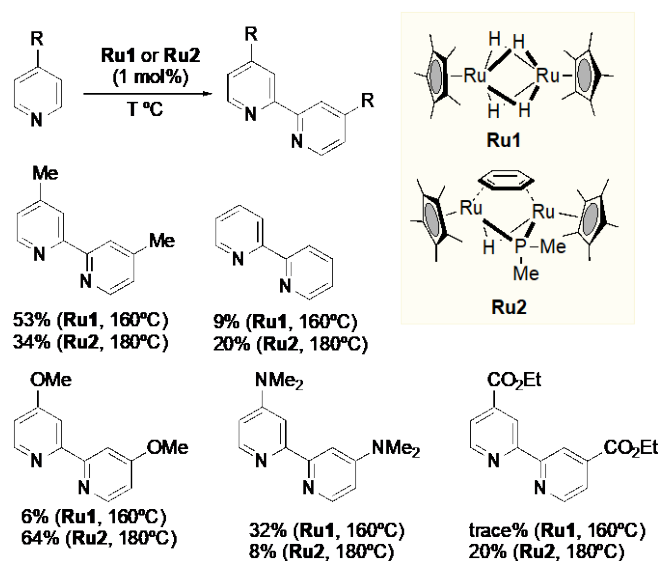
2. Dimerization of Pyridine Derivatives

The merest method of preparing 2,2'-bipyridine is the homocoupling of pyridine, initially reported with heterogeneous catalysts such as Raney's Nickel^[11] or palladium on charcoal.^[12] However, this approach is limited to the synthesis of symmetrical molecules, and the use of heterogeneous catalysts is often associated with a low functional group tolerance. Several homogeneous systems have been developed

to improve the scope of this transformation, and the dimerization of protected pyridines such as pyridine *N*-oxides was allowed reported.

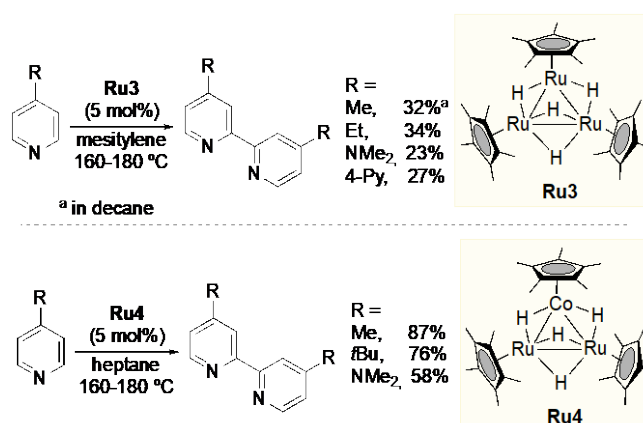
2.1. Dimerization of Pyridines

In 2007, Suzuki and co-workers reported an early example of dehydrogenative coupling of 4-substituted pyridines catalyzed by homogeneous diruthenium complexes: $\text{Cp}^*\text{Ru}(\mu\text{-H})_4\text{RuCp}^*$ (**Ru1**; $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) and $(\text{Cp}^*\text{Ru})_2(\mu\text{-PMe}_2)(\mu\text{-H})(\mu\text{-}\eta^2\text{:}\eta^2\text{-C}_6\text{H}_6)$ (**Ru2**) (Scheme 1).^[13] The phosphine-free **Ru1** complex catalyzed the dimerization of several 4-substituted pyridines and selectively produced the corresponding 4,4'-difunctionalized-2,2'-bipyridines, without the formation of by-products such as terpyridine. The μ -phosphido **Ru2** complex displayed some times better activity than **Ru1** depending on the nature of the *para*-substituent of the pyridine, *et vis versa*. The renationalization of the reactivity and the choice of catalysts is difficult to explain. It is noted that the dehydrogenative coupling of ethyl iso nicotinate is more challenging due to its lower basicity than that of other substituted pyridines.



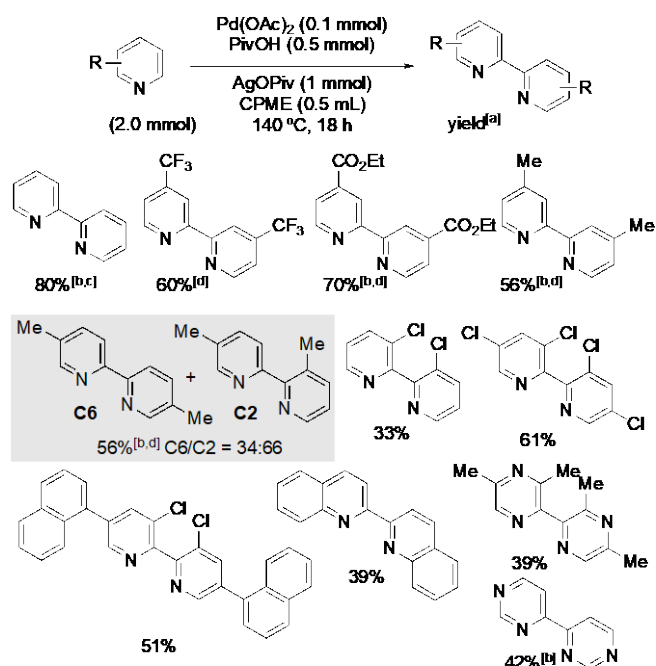
Scheme 1. Ru-Catalyzed Dehydrogenative Coupling of 4-Substituted Pyridines.

The same group has continued their efforts toward the design and synthesis of polynuclear organometallic compounds to dimerize several kinds of 4-substituted pyridines without using a sacrificial oxidant or hydrogen acceptor (Scheme 2, Top). They showed that $(\text{Cp}^*\text{Ru})_3(\mu\text{-H})_3(\mu^3\text{-H})_2$ (**Ru3**) ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) catalyzed the dimerization of 4-methylpyridine, 4-ethylpyridine, and *N,N*-dimethylpyridin-4-amine in low yield. The pyridines bearing an electron-withdrawing group are not tolerated (Scheme 2, top).^[14] In 2016, Takao and co-workers showed that the trinuclear complex composed of ruthenium and cobalt (**Ru4**) catalyzed more efficiently the dimerization of 4-methylpyridine, 4-tertbutylpyridine, *N,N*-dimethylpyridin-4-amine, but again fail with electron-poor pyridine or unsubstituted pyridine (Scheme 2, bottom).^[15]



Scheme 2. Polynuclear Organometallic Complexes-Catalyzed Dehydrogenative Coupling of 4-Substituted Pyridines

In 2019 Murakami, Itami and co-workers have developed a general and practical method for synthesizing 2,2'-bipyridines in high yields using Pd-catalyzed dehydrogenative coupling pyridine (Scheme 3).^[16] The reaction was performed using 5 mol% Pd(OAc)₂ in the presence of AgOPiv as base/oxidant in CPME (cyclopentyl methyl ether) at 140 °C. Interestingly, under these conditions, the dimerization of pyridine occurred in 80% yield. Moreover, both *para*-substituted pyridine bearing an electron-withdrawing group (*e.g.*, trifluoromethyl, ester) or an electron-donating group (*e.g.*, methyl, phenyl) underwent dimerization in high yields. *Ortho*-substituted pyridine such as α -picoline displayed a lower reactivity as the 2,2'-bipyridyl product was isolated in only 31% yield. When the reaction is performed with *meta*-substituted pyridines, a mixture of two regioisomers is observed. Interestingly, the sterically hindered 3-chloropyridines reacted preferentially at C2-positions to give the corresponding 2,2'-bipyridines with 33 to 61% yield. This regioselectivity might be explained by the high acidity of the C–H bond at the *ortho*-position of the chlorine atom; a feature communally exploited in Pd-catalyzed C–H bond arylation of polyfluororene^[17] or polychlorobenzene derivatives.^[18] The unique regioselectivity afforded a convertible platform to access various 3,3'-disubstituted-2,2'-bipyridines, a new class of axially twisted 2,2'-bipyridyl ligands. The reaction is not limited to pyridine rings, and quinolines or pyrazines are also successfully dimerized.



[a] Yield of isolated product based on Ag. [b] 0.50 mL of pyridine derivatives was used instead of CPME. [c] 0.50 mmol of 1,10-phenanthroline was added as a ligand. [d] 0.10 mmol of dtbpy was added as a ligand. [e] 36 h.

Scheme 3 Pd-Catalyzed Dehydrogenative Synthesis of 2,2'-Bipyridines via Regioselective Pyridine Dimerization

The authors proposed that the reaction is initiated from a pyridine C2-H activation by palladium(II) acetate to give pyridyl palladium

I. A second C–H bond palladation affords bis(pyridyl)palladium intermediate **II**, which undergoes reductive elimination to furnish the 2,2'-bipyridine and Pd(0). Finally, Ag salts play the role of oxidant to generate the Pd(II) catalytic active species (Figure 3).

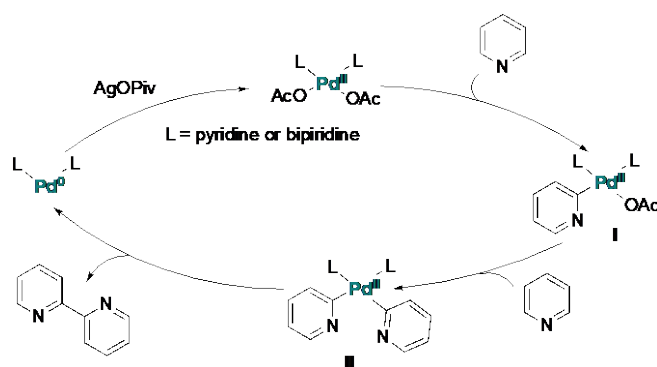
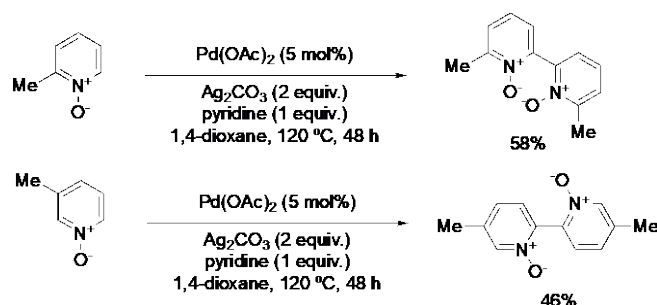


Figure 3. Proposed Mechanism for Pd-Catalyzed Pyridine Dimerization

2.2. Dimerization of Pyridine N-Oxides

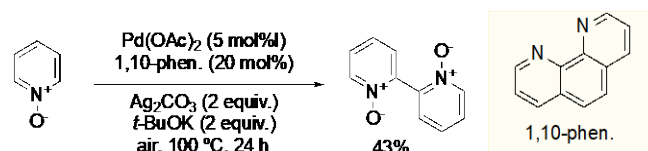
Pyridine *N*-oxides are readily available and bench-stable substrates, including in transition-metal cross-couplings. They often displayed higher reactivity in C–H bond functionalizations. In 2013, during their investigations on Pd-catalyzed oxidative C–H/C–H direct coupling of heterocyclic *N*-oxides, Kuang and co-workers reported two examples of homocoupling of pyridines *N*-oxides (Scheme 4).^[19] The treatment of 2-methylpyridine or 3-methylpyridine *N*-oxides by 5 mol% of $\text{Pd}(\text{OAc})_2$ in the presence of 2 equivalents of Ag_2CO_3 and 1 equivalent of pyridine in 1,4-dioxane at 120°C afforded the corresponding dimerized products in 58% and 46% yield, respectively. In the case of 3-methylpyridine

N-oxide, only one regioisomer is obtained from the activation at the less sterically hindered C6–H bond. It should be mentioned that no homocoupling product was observed under the above conditions when pyridine, 4-methylpyridine, 4-nitropyridine, 2-phenylpyridine, quinoline, and isoquinoline *N*-oxides were used as substrates.



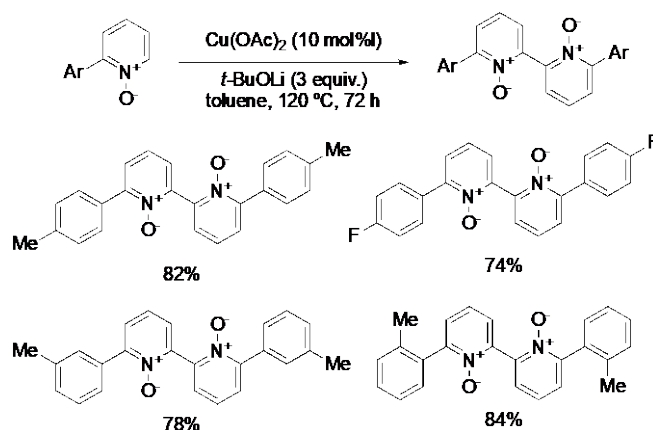
Scheme 4 Pd-catalyzed Homocoupling of Pyridine *N*-Oxides

In 2016, during their investigation on Pd-catalyzed oxidative homocoupling of 1,2,3-triazole *N*-oxides to construct bis-triazole *N*-oxides, Zhu, Liu and co-workers explored the possibility of extending the reaction to the more challenging pyridine *N*-oxide (Scheme 5).^[20] In the presence of 5 mol% Pd(OAc)₂ associated with 1,10-phenanthroline as a ligand, 1 equivalent of *t*-BuOK as a base, the pyridine *N*-oxide underwent dimerization to afford the 2,2'-bipyridine *N*-oxide product in 43% yield. Unfortunately, the authors have shown only one example in the pyridine series.



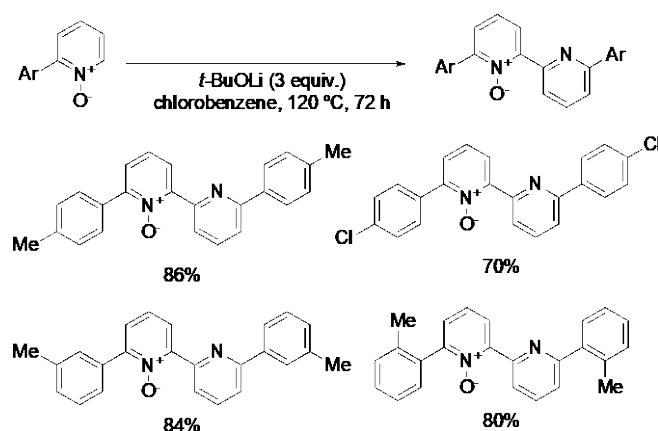
Scheme 5: Pd-Catalyzed Homocoupling of Pyridine *N*-O oxide

The dimerization of pyridine *N*-oxides is not only catalyzed by palladium. In 2017, Jain and co-workers reported the synthesis of 2,2'-homocoupled azine *N,N'*-dioxides, or azine *N*-oxides via Cu-catalyzed homocoupling reaction. The best reaction conditions for the homocoupling of 2-phenylpyridine *N*-oxide were 3.0 equivalents of *t*-BuOLi in toluene at 120 °C for 72 h in the presence of 10 mol% Cu(OAc)₂ (Scheme 6).^[21] They only studied the substitution on the aryl ring and not on the pyridine ring. The reaction with *ortho*-, *meta*- and *para*-aryl-substituted 2-arylpyridine *N*-oxides gave the corresponding *N,N'*-dioxide products.



Scheme 6: Cu-Catalyzed Homocoupling of 2-Phenylpyridine *N*-oxide Derivatives

Interestingly, they showed that when the reaction is carried out without catalytic copper, 2,2'-bipyridine *N*-monoxides were obtained instead of dioxide (Scheme 7).^[21] Similar conditions for base-promoted bipyridine *N*-monoxides synthesis from pyridine *N*-oxides were previously reported.^[22]



Scheme 7: Homocoupling of 2-phenyl pyridine *N*-oxide derivatives in the absence of copper catalysts

The authors proposed two different reaction mechanisms depending on the presence or the absence of Cu catalysts (Figure 4). First, the reaction is initiated by deprotonation of the C2-H by *t*-BuOLi to generate the lithium salt of pyridine *N*-oxide (**I**). This step is followed by transmetalation with Cu(OAc)₂ to give intermediate **II**, which undergoes oxidative coupling in the presence of air to yield the homocoupled 2,2'-bipyridine *N,N'*-dioxide. In the absence of copper acetate, the reaction follows an alternative nucleophilic aromatic substitution pathway (S_NAr), where intermediate **I** attacks another molecule of pyridine *N*-oxide to yield intermediate **III**, which loses LiOH to produce the homocoupled 2,2'-bipyridine *N*-oxide.

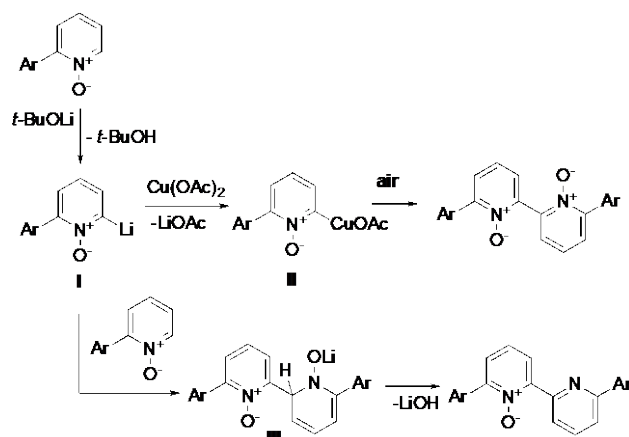
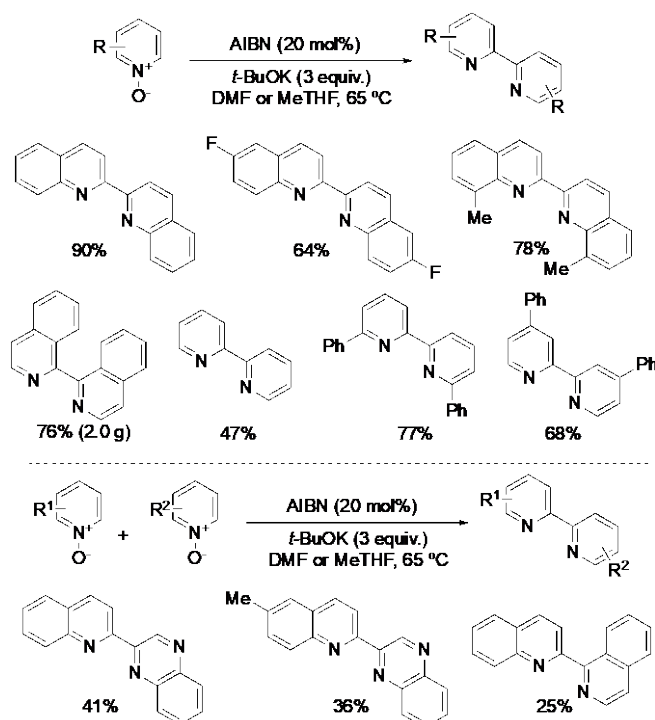


Figure 4. Proposed Mechanisms for Homocoupling of 2-Arylpyridine *N*-Oxides.

In 2016, inspired by the work of Natsume and Itai,^[23] Larionov have investigated *t*-BuOK-mediated deoxygenative homocoupling of *N*-pyridine oxides using *t*-BuOK under metal-free conditions (Scheme 8, top).^[24] It should be pointed out that the reaction directly delivers the 2,2'-bipyridine products, not the *N*-oxide or *N,N'*-dioxide products. The reactions were carried out using azoisobutyronitrile (AIBN) as a catalyst. The reaction was conducted with a broad scope and tolerates several *N*-heterocyclic systems and various substituents such as halogen substituents (F, Cl, Br) and benzylic positions. The authors have shown the applicability of this deoxygenative in gram-scale synthesis. More interestingly, the authors also succeeded the cross-coupling of two different heterocyclic *N*-oxides (Scheme 8, bottom).^[24] Although substantial amounts of homocoupling products were also formed, the reaction produced the desired asymmetrically 2,2'-bipyridine derivatives in moderate yields. This condition is

one of the unique examples of direct conversion of heterocyclic *N*-oxides to asymmetrically *N*-heterobiaryls.



Scheme 8. *t*-BuOK-Mediated Deoxygenative Homocoupling of Pyridine *N*-Oxides

The authors suggested that the reaction is initiated by the deprotonation of DMF or the C2–H of pyridine *N*-oxide to give carbanions **A** and **B** (Figure 5). Then, a single electron transfer (SET) reduction of pyridine *N*-oxide produces radical anion **D**, which adds to a second molecule of pyridine *N*-oxide to produce radical anion **E** that, after the recombination with radical **C** gives rise to intermediate **F**. Base-mediated elimination of ROH and hydroxide can then produce 2,2'-bipyridine. Alternatively, a SET reduction of anion radical **E** can produce dianion **G** that is converted to 2,2'-bipyridine *via* a stepwise base-mediated elimination of hydroxide anion.

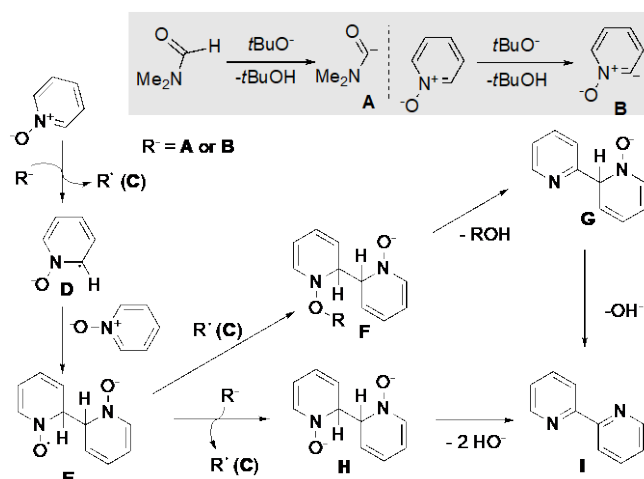


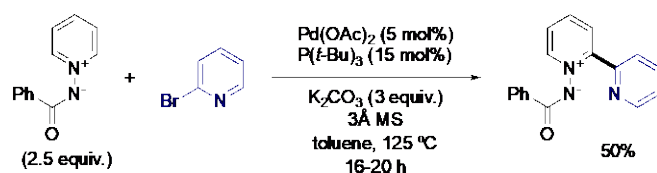
Figure 5. Proposed Mechanisms for Homocoupling of 2-Arylpyridine *N*-Oxides.

3. C–H bond Heteroarylation of Pyridine Derivatives

Pyridine remain a challenging substrate in C–H bond arylation with transition metal catalysis. Moreover, the reaction took place preferentially at C3 or C4 position,^[25] due to the electronic repulsion

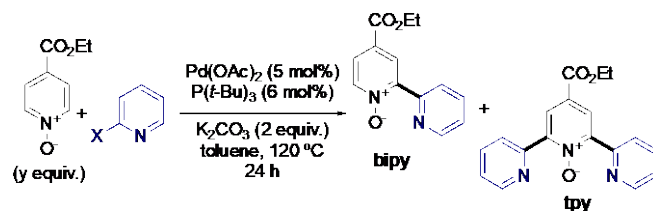
between the nitrogen lone pair and polarized C–M bond. Therefore, "protected" or "activated" pyridines shall be employed to switch the regioselectivity at the C2 position and enable the synthesis of 2,2'-bipyridines after a final deprotection step.

In 2008, Charette and co-workers reported Pd-catalyzed direct C–H bond arylation of *N*-iminopyridinium ylides with bromo(hetero)arenes at the C2-position (Scheme 9).^[26] The *ortho*-C–H bond of *N*-iminopyridinium ylides often displays higher reactivity than the *ortho*-C–H bond of pyridines avoiding chemoselectivity issues. The arylation of *N*-iminopyridinium ylides was performed using 5 mol% of Pd(OAc)₂, 15 mol% P(*t*-Bu)₃, in the presence of 3 equivalents of K₂CO₃ as a base in toluene at 125 °C. The reaction was very sensitive to water. Therefore, molecular sieves have to be employed. Only one example of heteroarylation with 2-bromopyridine has been reported affording the corresponding 2,2'-bipyridine precursor in 50% yield. The authors have demonstrated that N–N bond can be cleave under reductive conditions (e.g., Zn dust or Pt/C combined with H₂) to prepare 2-arylpyridines, but they did not report the deprotection for the synthesis of 2,2'-bipyridine derivatives.



Scheme 9 Pd-catalyzed C₂–H Bond Heteroarylation of *N*-Iminopyridinium Ylides

Since the pioneer report by Fagnou on Pd-catalyzed C–H bond arylation of pyridine *N*-oxides at C₂ position with aryl halides,^[27] an increasing number of methods for the direct arylation of arenes and heteroarenes based on transition-metal-catalyzed C–H cleavage has been developed. In 2011, Tzschucke and co-workers described Pd-catalyzed direct coupling between pyridine *N*-oxides and 2-halopyridines as the critical step of an efficient and versatile preparation of substituted 2,2'-bipyridines from readily available starting materials.^[28] This method significantly reduces the number of steps in comparison to conventional cross-coupling reactions.^[6] They demonstrated that pyridine *N*-oxides should bear an electron-withdrawing group to be reactive. Indeed reaction of equimolar amounts of 2-bromopyridine and 4-alkylpyridine *N*-oxides in the presence of 5 mol% Pd(OAc)₂ associated with 5 mol % P(*t*-Bu)₃ and 2 equivalents of K₂CO₃ in toluene failed to give detectable amounts of coupling product. In contrast, the reaction between ethyl isonicotinate *N*-oxide with 2-bromopyridine in 1.5:1 ratio affords the desired coupling product bipyridine *N*-oxide (**bipy**) in 60% yield among with 21% yield of terpyridine *N*-oxide (**tpy**)—resulting from double arylation (Scheme 10). They also evaluated the reactivity of some 2-bromopyridine-surrogate (*i.e.*, 2-chloropyridine, 2-iodopyridine, 2-pyridyl triflate, 2-pyridyl nonaflate, 2-pyridyl tosylate), but none of them outperformed 2-bromopyridine. The **bipy** / **tpy** selectivity is slightly dependent of the stoichiometry: an excess amount of ethyl isonicotinate *N*-oxide (4 equivalents) give **bipy** in 70%, while using 2.5 equivalents of 2-bromopyridine **tpy**.

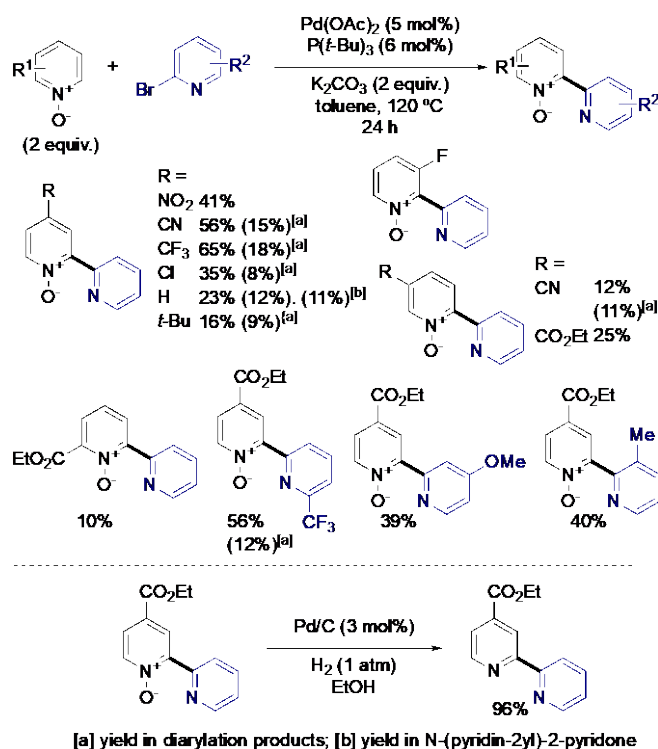


| Entry | y (equiv) | X = | bipy (%) | tpy (%) |
|------------------|-----------|-----------|----------|---------|
| 1 | 1.5 | Br | 60 | 21% |
| 2 | 1.5 | Cl | 57 | 17 |
| 3 | 1.5 | I | 14 | - |
| 4 | 1.5 | triflate | 18 | - |
| 5 | 1.5 | nonaflate | 39 | 19 |
| 6 | 1.5 | tosylate | 5 | - |
| 7 | 4 | Br | 71 | 6 |
| 8 ^[a] | 0.4 | Br | 39 | 34 |

[a] 12.5 mol% Pd(OAc)₂, 15 mol% P(*t*-Bu)₃

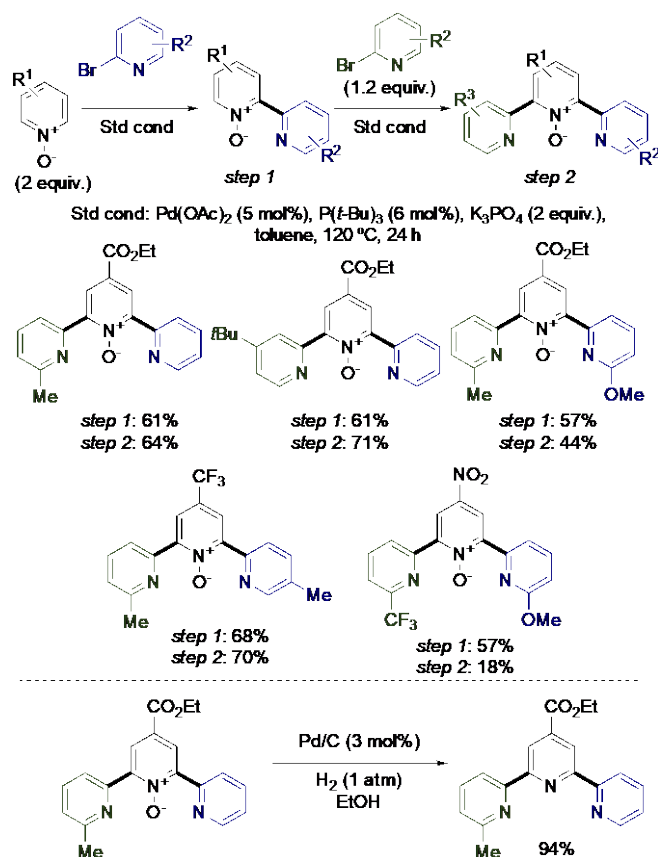
Scheme 10: Effect of the Substrate Ratio and Pseudohalide Pyridines on the Mono/Diarylation

They next explored the substrate scope of pyridine *N*-oxides and 2-bromopyridines (Scheme 11, top).^[28] Pyridine *N*-oxides bearing a *para*-electron-withdrawing substituent such as ester, nitro, cyano, trifluoromethyl, or chloro gave moderate to good yields in favor of 2,2'-bipyridine *N*-oxide products. In comparison, unsubstituted pyridine *N*-oxide gave only a 23% yield of the corresponding 2,2'-bipyridine *N*-oxide. In most cases, the authors observed the formation of diarylation products (terpyridine *N*-oxide), and with electron-rich pyridine *N*-oxides, they also observed the formation of *N*-(pyridine-2-yl)-2-pyridone. The mono arylation of *meta*-substituted pyridine *N*-oxides is more challenging as two *ortho* C–H bonds can be arylated. From 3-fluoropyridine *N*-oxide, the reaction takes place at the most acidic C-2 position (i.e., *ortho*-position of fluorine atom).^[17] From 3-cyano or 3-ester pyridine *N*-oxides, the arylation occurred at the less hindered C-6 position. *Ortho*-substituted pyridine *N*-oxides were also arylated in good yields. The nature and the position of substituent on the 2-bromopyridine seem not to have a critical effect on the reactivity. In most cases, the authors also demonstrate that the reduction of 2,2'-bipyridine *N*-oxides could be carried with hydrogen or sodium borohydride using palladium on charcoal as a catalyst in nearly quantitative (Scheme 11, bottom).^[28]



Scheme 11 top) Synthesis of Asymmetrically Substituted Bipyridine by Pd Catalyzed C-H Bond Heteroarylation of Pyridine *N*-Oxide. **bottom)** Reduction of 2,2'-Bipyridine *N*-oxides

In 2013, Tzschucke and co-workers reinvestigated this reaction to prepare asymmetrically substituted terpyridines using iterative Pd-catalyzed direct arylation of pyridine *N*-oxides (Scheme 12, top).^[29] The reaction conditions are similar to those previously reported,^[28] albeit K_3PO_4 as the base resulted in better yields than K_2CO_3 . In a first step, pyridine *N*-oxides substituted by an electron-deficient group at the *para*-position are arylated with diversely substituted 2-bromopyridines. For the second heteroarylation, 1.2 equivalent of another 2-bromopyridine derivative is employed. The second heteroarylation often seems easier to proceed to afford the asymmetrically substituted terpyridines terpyridine *N*-oxide in moderate to good yields. They also reported the synthesis of symmetrical terpyridine *N*-oxides using an excess amount of 2-bromopyridines. Finally, the authors reduced several terpyridine *N*-oxides *via* hydrogenolysis using Pd/C as a catalyst in the presence of hydrogen (Scheme 12, bottom).^[28]



Scheme 12. *top*) Preparation of Asymmetrically Substituted Terpyridines *N*-Oxides *via* Pd-catalyzed C–H Bond Heteroarylation of Pyridine *N*-Oxides. *bottom*) Reduction of terpyridine *N*-oxides

They also conducted competition experiments and kinetic studies, which agree with Hartwig and co-workers' cooperative catalysis mechanism (Figure 6).^[30] Dimeric cyclometalated complex **A** is in equilibrium with an undetected monomeric species **A'**, which induces C–H cleavage of the pyridine *N*-oxides to deliver intermediate **B**. Meanwhile, a second aryl palladium complex **D** is generated by oxidative addition of the aryl bromide to Pd(0) complex **C**. Then, transmetalation between these two aryl palladium complexes (**B** and **D**) afford the bisaryl palladium complex **E**, which undergoes fast reductive elimination to form the C2-arylated pyridine *N*-oxide and regenerate the Pd(0) catalyst **C**.

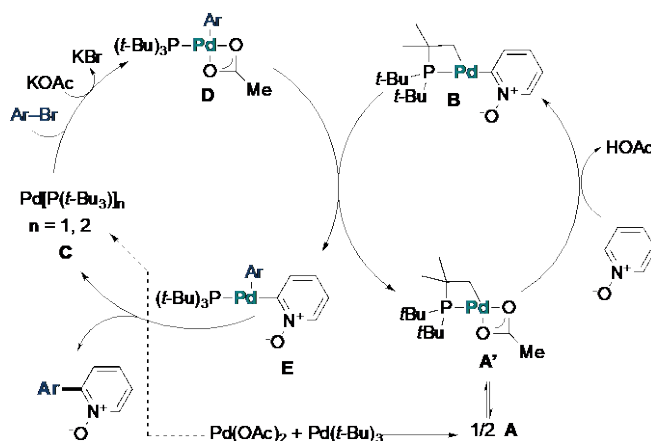


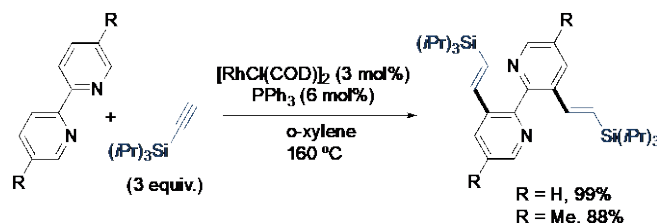
Figure 6. The Cooperative Catalysis Mechanism for the Direct Arylation of Pyridine *N*-Oxides Proposed by Hartwig.^[30]

4. Late-Stage Functionalization of 2,2'-Bipyridine Derivatives

An alternative approach to build up well-decorated 2,2'-bipyridines, instead of generating the C2-C2'-bond, involves the C-H bond functionalization of the 2,2'-bipyridine scaffolds. This late-stage functionalization simplifies the synthetic pathway and can access complexes 2,2'-bipyridines that would be time-consuming to access from simple pyridines.^[31] However, the main challenge is the strong coordination ability of the 2,2'-bipyridines. There are two pathways to achieve regioselective functionalization of 2,2'-bipyridyl C-H bond: 1) the rollover cyclometalation. Which often afford the modification of C3 and/or C3'-position(s) or 2) radical pathways to functionalize the C6 and/or C6'-position(s).

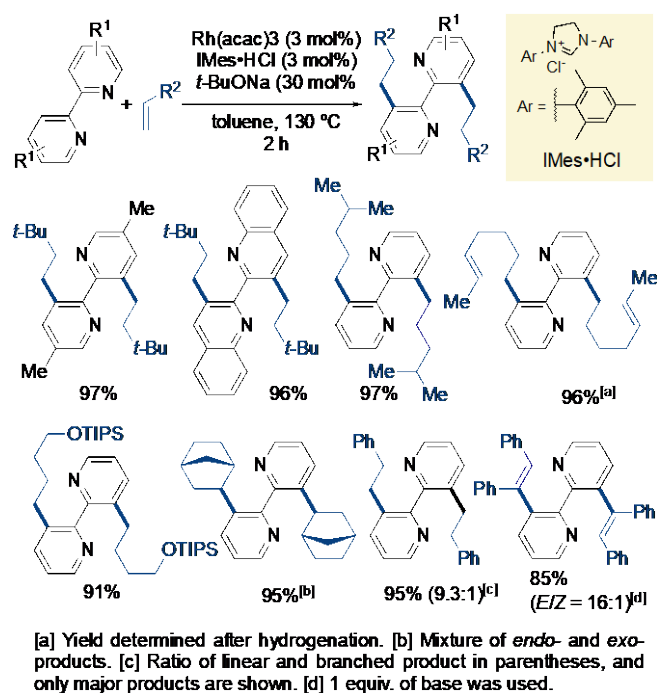
4.1 Transition Metal-Catalyzed C-H Bond Functionalizations of Bipyridines *via* "Rollover" Cyclometalation

Although bipyridines generated stable chelated with transition metal (bipy)ML_n, Miura and co-workers demonstrated in 2009 that bipyridines could be difunctionalized *via* cyclometalation (Scheme 13).^[32] The reaction of 2,2'-bipyridyl or 5,5'-dimethyl-2,2'-bipyridine with ethynyltriisopropylsilane in the presence of [RhCl(cod)]₂ and PPh₃ smoothly proceeded to give the corresponding 3,3'-dialkenylated products in good to excellent yields.



Scheme 13. Rhodium-Catalyzed Alkenylation of Bipyridine C-H Bonds with Terminal Silylacetylenes

In 2012, Chang and co-workers investigated Rh-catalyzed dialkylation of the 2,2'-bipyridyl C-H bond at C5 and C5'-positions (Scheme 14).^[33] They found that N-heterocyclic carbene (NHC, IMes) as ligand play a significant role exhibiting a strong *trans*-effect in (bipy)Rh(NHC) chelate structure, thus weakening a rhodium-pyridyl bond, which is *trans* to the bound NHC. This feature favors the rollover cyclometalation^[34] pathway enabling selective bis-functionalization of 2,2'-bipyridines and 2,2'-bisquinolines. A set of 2,2'-bipyridines were bisalkylated using 0.03 equivalent of Rh(acac)₃/2IMes-Cl ligand and 0.3 equivalent of *t*-BuONa base at 130 °C for 2 h. A wide range of aliphatic terminal alkenes, styrenes, and terminal alkenes bearing functional groups such as removable hydroxy-protecting groups were successfully employed. Notably, the hydroarylation was highly selective at the terminal olefins in the presence of an internal double bond, albeit partial isomerization was also observed. Alkenes containing strained internal double bonds such as norbornene smoothly reacted. Moreover, the reaction can be carried out using ethylene (5 atm) as alkylation reagents. The authors also extended this transformation to the hydroarylation of alkynes.



Scheme 14. Rh-Catalyzed C–H Bond Bisalkylation of Bipyridines: Rollover Cyclometalation Pathway

Based on computational calculations and experimental data, the authors proposed a mechanistic pathway of bishydroarylation depicted in Figure 7. They postulated that a Rh(I) complex ligated to tert-butoxide and NHC is the catalytically active species. Firstly, a monodentate rhodium complex **B** from the stable complex **A** ($R' = H$) via endothermic bond rupture of the stable chelate Rh-bipyridyl bond. This "rollover" decomplexation is promoted by the strong σ -donating NHC ligand (IMes) character, which weakening the *trans* Rh–N bond relative to NHC. The oxidative addition of the C–H bond is afforded Rh-hydride species **C**. Olefin insertion into Rh–H bond followed reductive elimination of a monoalkylated bipyridine **E** ($R' = CH_2CH_2R$) give the first functionalization. Finally, **E** re-enters into the second catalytic cycle by starting with a bidentate complex **F** ($R' = CH_2CH_2R$) to follow the same pathway as in the first catalytic cycle, affording the bishydroarylated product.

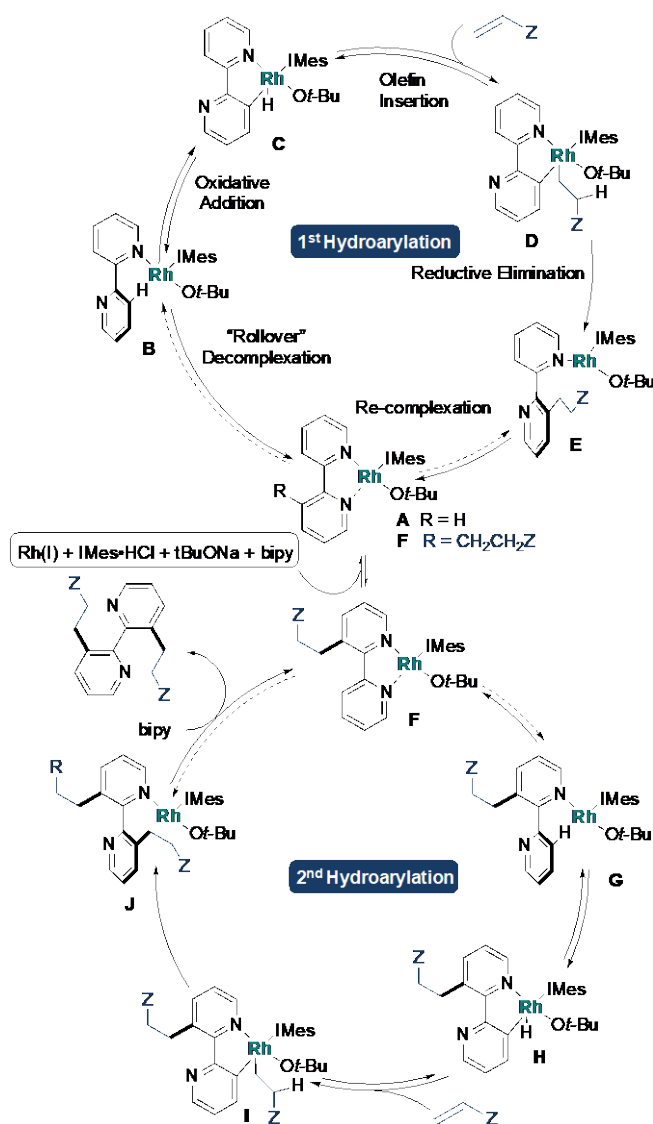
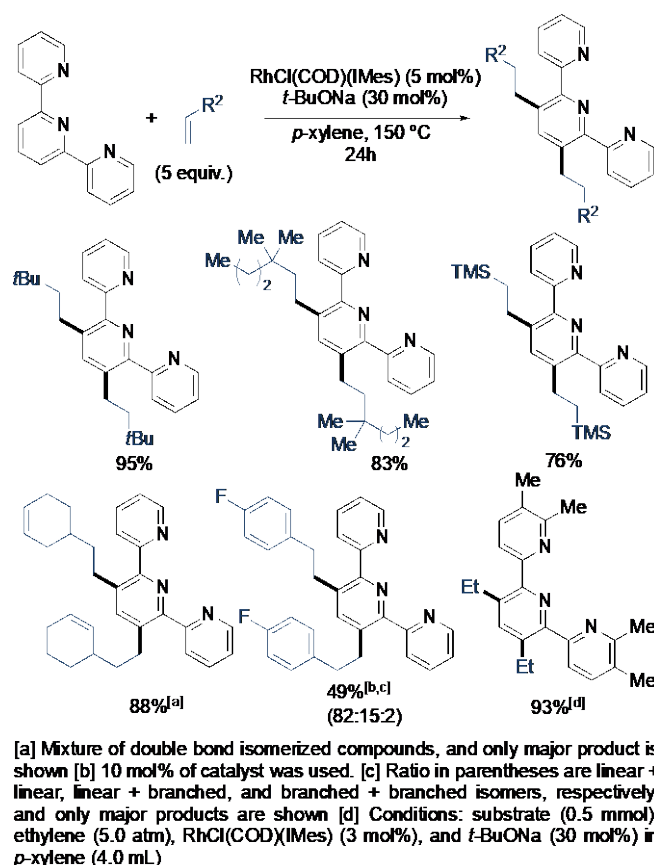


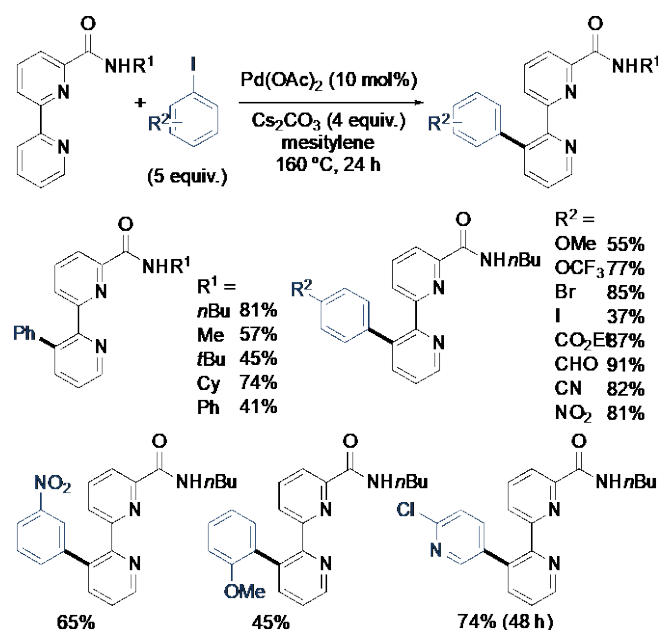
Figure 7. Proposed Mechanistic Pathway of the Rh(NHC)-Catalyzed Bishydroarylation Reaction.

In 2016, Chang used the same rollover-decomplexation strategy for the bisalkylation of terpyridine derivatives (Scheme 15).^[35] They employed this time a well-defined Rh(NHC) catalyst $[RhCl(COD)(IMes)]$ associated with *t*-BuONa. The alkylation took place at the C3 and C5-positions of the central pyridine unit. The reaction smoothly proceeded, affording a library of functionalized tridentate compounds in high yields over a broad range of alkenes, including aliphatic alkenes, styrenes, congested alkenes, and also ethylene gas. A similar mechanism to the Rh-catalyzed C–H bond bisalkylation of bipyridyl C–H bonds is proposed (Figure 7).



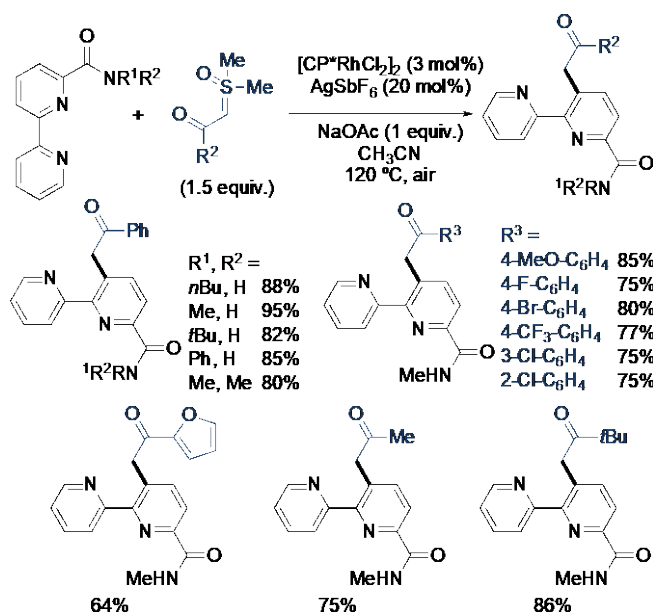
Scheme 15. Rhodium-Catalyzed C–H Alkylation of NNN tridentate Chelating Compounds *via* a Rollover Pathway

In 2016, Cheng and co-workers employed this rollover cyclometalation pathway for the C–H bond arylation of 2,2-bipyridine-6-carboxamides with aryl iodides using palladium catalysis (Scheme 16).^[36] The 2,2-bipyridine-6-carboxamides were regioselectively arylated at the C3'-position using 10 mol% Pd(OAc)₂ associated with Cs₂CO₃ (4 equivalents) in mesitylene (2 mL) at 160 °C. Notably, the primary amide group at the C6-position is required, as reaction from substrates bearing secondary amide, carboxylic acid, carboxylic ester, or 2,2-bipyridine itself failed to afford the corresponding arylated bipyridine products. Both electron-rich and electron-poor of aryl iodides were efficiently coupled, and the reaction displayed a broad functional group tolerance such as halogen (Br, I), trifluoromethoxy, carboxylic acid ester, aldehyde, ketone, cyano, nitro, and trifluoromethyl groups.



Scheme 16. Palladium-Catalyzed Site-Selective C–H Arylation of 2,2'-Bipyridine-6-carboxamides via a Rollover Cyclometalation Pathway

In 2019, the same group employed a similar strategy (*i.e.*, rollover cyclometalation pathway of 2,2-bipyridine-6-carboxamides) in Rh-catalyzed C–H acylmethylation with sulfoxonium ylides (Scheme 17).^[37] Under the optimized conditions, namely $[\text{Cp}^*\text{RhCl}_2]_2$ (3.0 mol %) as a catalyst, NaOAc (1 equiv) as a base, and AgSbF_6 as an additive in acetonitrile at 120 °C under air for 24 h, the C3 alkylated 2,2-bipyridine-6-carboxamides were isolated in good to excellent yields. In contrast with the C–H bond arylation using Pd catalysis, the functionalization took place on the pyridine unit bearing the amide group, and 2° and 3° amides could be employed. However, no reaction occurred without an amide group at the C6 position. Aryl sulfoxonium ylides holding electron-donating and electron-withdrawing groups as well as heteroaryl sulfoxonium ylides and alkanoyl sulfoxonium ylides could be employed as acylmethylation with high yields.



Scheme 17. Rh-Catalyzed Regioselective C3–H Acylmethylation of [2,2'-Bipyridine]-6-carboxamides with Sulfoxonium Ylides

The authors proposed a plausible reaction pathway (Figure 8). First, the coordination of 2,2'-bipyridine-6-carboxamides with Rh(III) forms Rh(III) complexes **A**, which undergo a reversible rollover cyclometalation to give complexes **B**. Then, the intermediates **B** are captured by the sulfoxonium ylides to generate Rh–carbene complexes **C** along with the extrusion of DMSO. The migratory insertion of complexes **C** leads to intermediates **D**. Finally, the protonolysis of **D** delivers the final product and closes the catalytic cycle.

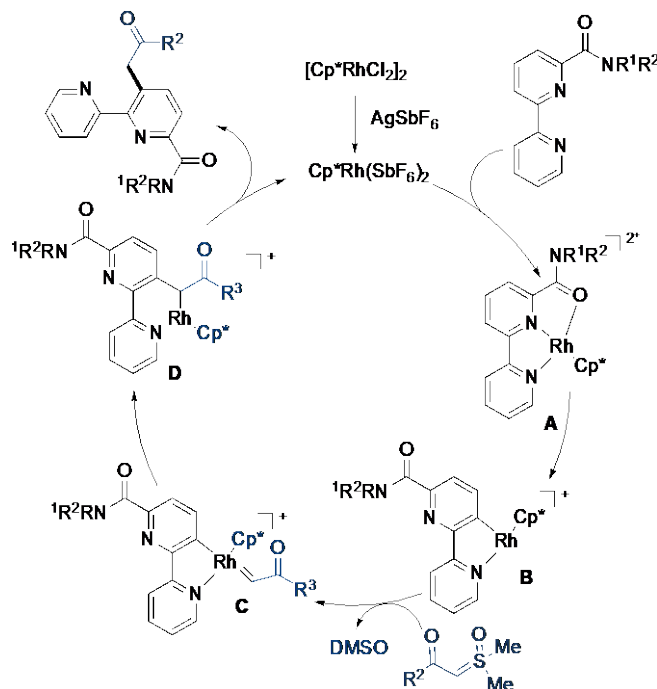
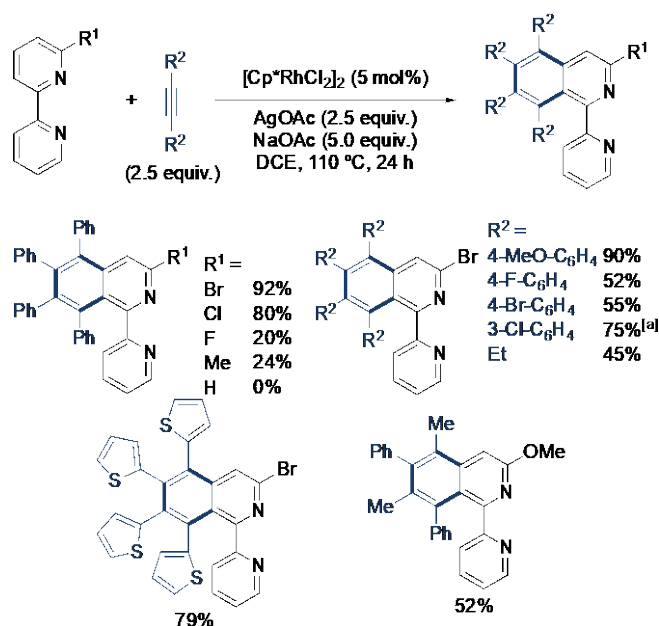


Figure 8. Plausible Catalytic Cycle for Rh-Catalyzed Regioselective C3–H Acylmethylation of [2,2'-Bipyridine]-6-carboxamides with Sulfoxonium Ylides

In 2020, Chen, Liu, Zhu, and co-workers developed a novel approach for the C–H functionalization of 2,2'-bipyridine derivatives through a rollover cyclometalation pathway (Scheme 18).^[38] The substituent at the C6 position of 2,2'-bipyridine weakened the adjacent N–Rh bond promoting the rollover cyclometalation, C–H activation, and functionalization sequence. The pyridine ring of 2,2'-bipyridine holding the C6 substituent was annulated *via* an oxidative double C–H bond alkenylation using 5 mol% $[\text{Cp}^*\text{RhCl}_2]_2$, in the presence of 2.5 equivalents of AgOAc and 5.0 equivalents of NaOAc in 1,2-dichloroethane (DCE) at 110 °C. The author shows that a substituent at the 6-position of 2,2'-bipyridine is mandatory and can be Br, Cl, F, Me, and MeO. Diarylalkynes diversely substituted by electron-donating or -withdrawing groups at the *para*- or *meta*-position of the aryl ring nicely reacted, while no reaction occurred with *ortho*-substituted diarylalkynes. Reactions with di(2-naphthyl)acetylenes, di(2-thienyl)acetylenes or hex-3-yne were also successful. Moreover, reaction with unsymmetrical alkyne (*e.g.*, prop-1-yn-1-ylbenzene) led to a single regioisomer.



Scheme 18. Rh-Catalyzed C–H Bond Functionalization of 6-Substituted 2,2'-Bipyridines with Alkynes

From experimental data and DFT calculation, the authors proposed a plausible reaction pathway (Figure 9). First, the coordination of 2,2'-bipyridine with $\text{Cp}^*\text{Rh}^{\text{III}}$ generates Rh^{III} complexes **A**, followed by rollover decomplexation (**B**) and cyclometalation to give complex **C**. Then, 1,2-insertion of alkyne into Rh –C bond forms intermediate **D**. Next, the N– Rh decomplexation with the help of the excess amount of Ag^+ induces the C–H cleavage, leading to new five-membered rhodium complex **E**. This rhodacycle intermediate can insert the second alkyne to give seven-membered rhodacycle **F** or **G**. Finally, the reductive elimination of **F** or **G** affords the annulated pyridine, and Rh^{I} is oxidized by AgOAc to regenerate the Rh^{III} active species.

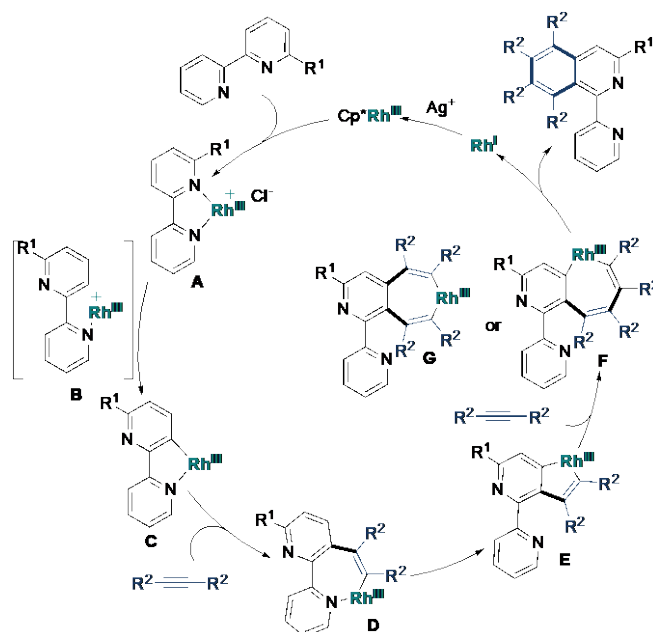


Figure 9. Proposed Mechanism for Rh-Catalyzed C–H Bond Functionalization of 6-Substituted 2,2'-Bipyridines with Alkynes

4.2 C–H Bond Functionalization of 2,2'-Bipyridines using Photoredox Catalysis

Recently, photoredox-catalyzed Minisci-type reaction has become a preferred method for the sustainable functionalization of pyridines.^[2c, 39] The reaction involves the formation of a radical, which adds to the C2 or C4 position of the pyridine ring (Figure 10). In the cases of 2,2'-bipyridines, the reaction begins with the generation of excited state catalyst *PC from ground state PC by visible-light, a single electron transfer (SET) occurs from *PC to the radical precursors leading to the formation of a free radical ($R^1\bullet$) along with the oxidized catalyst [PC^+]. Then, the radical adds to one of the protonated pyridine units at C2 or/and C4 position(s) –depending on its substitution patterns– yielding the 2,2'-dipyridine radical-cation intermediate (**A**). Then, **A** is subsequently transformed into a carbocation intermediate **B** via a SET from [PC^+] with the loss of a proton. Finally, the rearomatization gives the monofunctionalized 2,2'-bipyridine, which can undergo a second functionalization *via* a similar mechanism. As the two C6 and C6'-positions of the 2,2'-bipyridine derivatives display a similar reactivity, it is challenging to control the mono versus difunctionalizations.

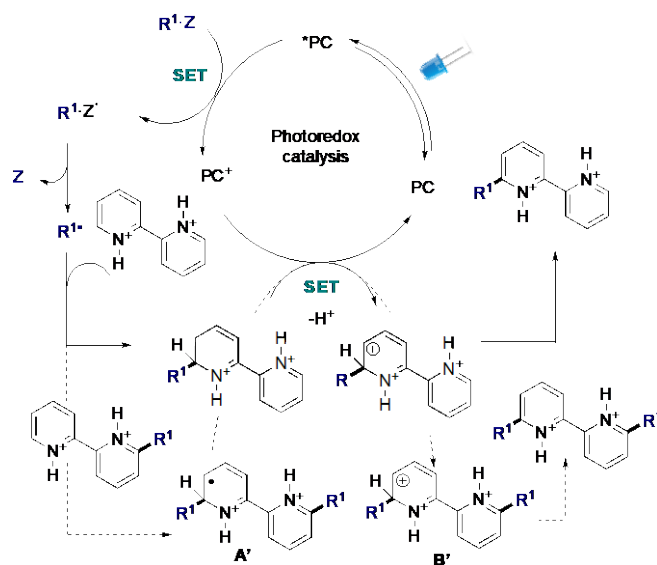
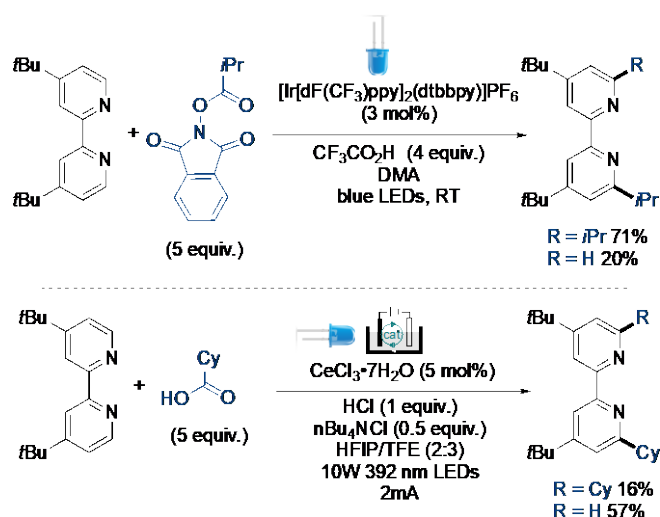


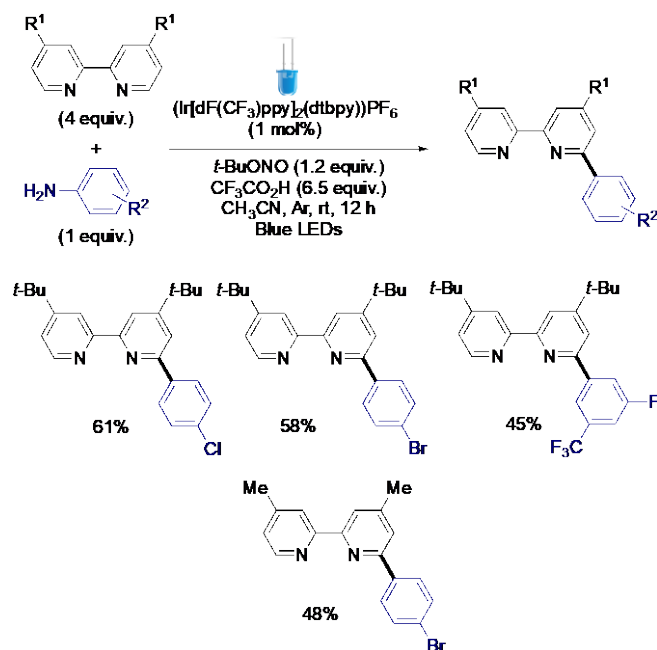
Figure 10. General Pathway for the C–H Bond Functionalization of 2,2'-Bipyridines using Photoredox catalysis

In 2017, during their investigations on C–H bond alkylation of pyridine derivatives using redox-active esters [N-(acyloxy)phthalimide] in the presence of photoredox catalysis, Shang, Fu, and co-workers described one example of alkylation of 2,2'-bipyridine (Scheme 19, top).^[40] From 4,4'-di-*tert*-butyl-2,2'-bipyridine and isobutyric acid NHPI ester (5 equivalents) in the presence of 2 mol% Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 4 equivalents of trifluoroacetic acid in DMA under irradiation at room temperature, a mixture of mono- and di alkylated 4,4'-di-*tert*-butyl-2,2'-bipyridines was obtained. The alkylation regioselectivity took place at C6 and C6'-positions. In 2020, Song, Xu, and co-workers reported one example of the oxidant-free, electrophotochemically driven C–H alkylation of 2,2'-bipyridine with carboxylic acids through H₂ evolution (Scheme 19, bottom).^[41] The optimal reaction system [namely, 5 mol% of CeCl₃•7H₂O as the catalyst, 1 equivalent of HCl as an acid additive, 0.5 equivalent of *n*Bu₄NCl as the supporting electrolyte, and a mixed solvent of HFIP/TFE (3:2) in an undivided cell exposed to 392 nm LEDs] also gives a mixture of mono- and di-alkylated products, albeit the monoalkylated 2,2'-bipyridine is obtained as the major product.

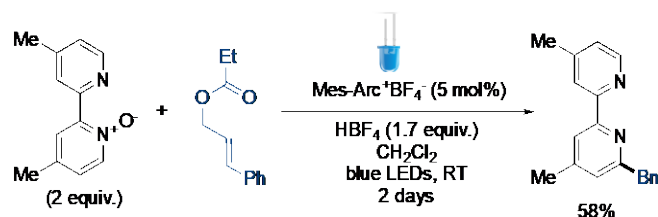


Scheme 19. Decarboxylative Alkylation of 2,2'-Bipyridines

In 2020, our group reported the synthesis of asymmetrically substituted 2,2'-bipyridines through the desymmetrization of 2,2'-bipyridines *via* two successive photoredox C–H bond functionalizations. The first step is the C–H bond arylation of 4,4'-disubstituted 2,2'-bipyridines using *in-situ* formed diazonium salts (from commercially available aromatic amines) in the presence of a photoredox catalyst under blue LEDs irradiation (Scheme 20).^[42] Besides safety concerns avoiding the manipulation of explosive aryl diazonium salts, the other main advantage to employ *in-situ* diazotization of anilines is a slower generation of the aryl radical than reactions from aryl diazonium salts favorizing the monoarylation. The coupling reaction between 4,4'-di-tert-butyl-2,2'-bipyridine (4 equivalents) or 4,4'-dimethyl-2,2'-bipyridine and diversely substituted aniline (1 equivalent) –in a mixture of CH₃CN/TFA (8:1) solvent containing 1 mol% (Ir[dF(CF₃)ppy]₂(dtbbpy))PF₆ and 1.2 equivalents of *t*-BuONO under blue LEDs irradiation– afforded the monoarylation of 2,2'-bipyridines in good yields.



Scheme 20. Synthesis of 6-Aryl-2,2'-bipyridines *via* Photoredox-Induced Meerwein Arylation with *in-situ* Diazotization of Anilines



Scheme 22. Photocatalyzed *ortho*-Alkylation of 2,2'-Bipyridine *N*-Oxide through Alkene Cleavage

The authors proposed a mechanism depicted in Figure 11. Initially, a single electron transfer occurs from the alkene to the excited photocatalyst PC* to generate a cation radical **A**. The addition of pyridine *N*-oxide to **A** generates a benzylic radical **B** which cyclizes to give rise to the aminium cation radical **C** (concerted pathway with **B** intermediate is also described). Deprotonation and intramolecular 1,2-shift of one electron afford the α -amino radical **D**. Aromatization through β -N–O bond cleavage and the protonation generates alkoxy radical **E**. The retro-aldol via β -C–C bond cleavage gives the aldehyde fragment and benzylic radical **F**, which is reduced by PC* to close the catalytic cycle.

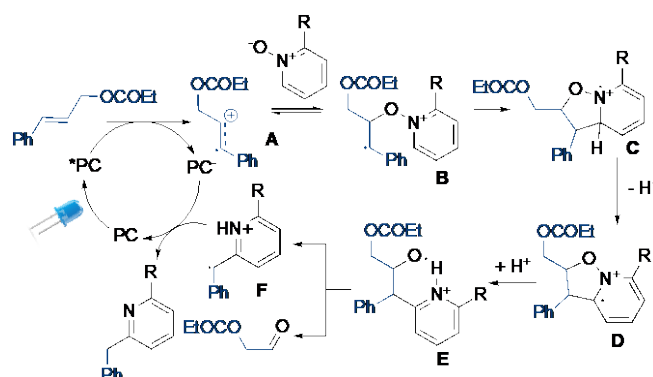
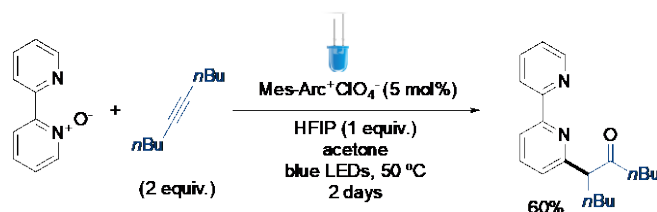


Figure 11. Proposed Mechanism for Photocatalyzed *ortho*-Alkylation of 2,2'-Bipyridine *N*-Oxide through Alkene Cleavage

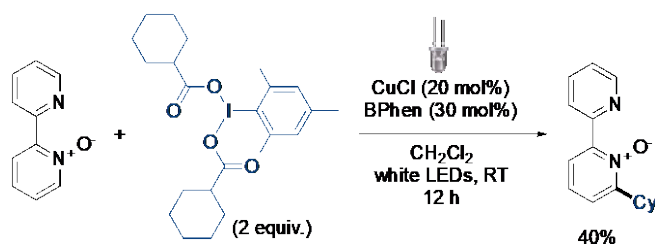
In 2019, Wu and co-workers described one example of alkylation of 2,2'-bipyridine *N*-oxide using *n*-dec-5-yne as an alkylation reagent (Scheme 23).^[45] Both starting materials were irradiated under blue LEDs in the presence of the photocatalyst 9-mesityl-10-methylacridinium perchlorate (Mes-Acr⁺ClO₄[−]). The reaction proceeded with a formal N–O atom transfer according to the alkylated 2,2'-bipyridine in 60% yield.



Scheme 23. Photoinduced Alkylation of 2,2'-Bipyridine *N*-Oxide with Alkynes under Anaerobic and Aerobic Conditions

In 2020, Loh, Tian, and co-workers reported a highly site-selective alkylation of heteroarene *N*-oxides (one example of 2,2'-bipyridine *N*-oxide) using hypervalent iodine(III) carboxylates as an alkylating agent in the presence of a cheap copper catalyst under visible light conditions (Scheme 24).^[46] In contrast with two previous protocols, the reaction afforded the C6-alkylated 2'-bipyridine *N*-oxide, not the reduced form. Cu(I) surrounded by 4,7-diphenyl-1,10-phenanthroline (BPhen) is employed as the photoredox catalyst, and its photoexcited state can reduce hypervalent iodine-(III) carboxylate to generate alkyl radical SET

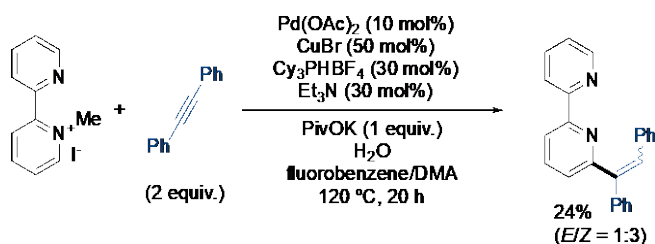
process.



Scheme 24. Decarboxylative C–H Alkylation of 2,2'-Bipyridine-*N*-Oxide by Visible Light/Copper Catalysis

In 2020, Fu, Chen, and co-workers investigated selective C2-alkenylation of pyridines with internal alkynes *via* the pyridinium salt activation strategy using Cu/Pd as dual catalysis.^[47] Besides the functionalization of pyridines, they also reported one example of the alkylation of 2,2'-bipyridine (Scheme 25). They employed a bimetallic system Pd(OAc)₂ associated with CuBr to functionalized 1-methyl-[2,2'-bipyridin]-1-ium salt. The reaction involves the C–H bond cleavage by Cu(I) to form 2-pyridiniumyl-

Cu(I) species, due to the increased acidity, followed a nucleophilic attack to the palladium coordinated alkynes. The *N*-alkyl group could be *in situ* removable *via* an *N*-dealkylation process, affording the functionalized 2,2'-bipyridine in one-pot.



Scheme 25. Pd/Cu Catalyzed C–H Alkenylation of 2,2'-Bipyridinium Salts with Alkynes

5. Conclusion

The growing interest in the field of material sciences as well as catalysis has led to the development of new eco-friendly protocols for the synthesis of various 2,2'-bipyridine derivatives. In this review, we account for the recent developments that have been achieved concerning the use of C–H bond functionalization for C–C bond formation that allow the selective formation of highly functionalized 2,2'-bipyridines. While the dimerization of pyridines is an established approach for the synthesis of 2,2'-bipyridine, only recently homogeneous catalysis has been employed to improve the functional group tolerance. However, this method remains limited to the synthesis of symmetrical 2,2'-bipyridines. A catalytic system enabling the general cross-coupling of two different pyridines in high yield and selectivity has not been discovered yet. Asymmetrically 2,2'-bipyridine derivatives can be prepared *via* C–H bond heteroarylation of pyridine derivatives with 2-halopyridines, but activated pyridines such as pyridines *N*-oxides or *N*-iminopyridinium ylides has to be employed to enhance the reactivity of the C2–H bond. The major drawback of this approach is the final deprotection to access 2,2'-bipyridines. The remarkable developments of the late-stage functionalization of bipyridines through regioselective C–H bond cleavage profoundly impact the synthesis of symmetrical and asymmetrical 2,2'-bipyridines holding versatile functional groups at different positions in an efficient and often high-yielding manner. In the near future, the combination of all these strategies among with the development of new protocols for the C–H bond activation of pyridines and 2,2'-bipyridines shall open the way of on-demand synthesis of well-decorated ligands with the desired substitution patterns allowing chemists to design novel organometallics materials or catalysts displaying better properties.



Wided Hagui obtained her Ph.D. in Chemistry in 2017 from Tunis El Manar University. During her Ph.D., she spends several months in Reims (France) with Prof Jacques Muzart and Dr. Jean Le Bras and in Rennes (France) with Dr. Henri Doucet and Dr. J.-F. Soulé to study palladium catalysis, especially C–H bond arylation of heteroarenes to synthesize polyaromatics. In 2019, she worked as a postdoctoral researcher under the guidance of Dr. Julien Boixel and Dr. J.-F. Soulé on the synthesis of asymmetrical bipyridines using photoredox catalysis for the preparation of luminescent cyclometalated platinum complexes. Since 2021, she is working as a postdoctoral scholar in Louis Fensterbank's lab at Paris-Sorbonne University.



Kiruthika Periasamy received her B.Sc (2017), M.Sc (2019) degrees from Bishop Heber College (Trichy, India), and her International Master of Molecular Catalysis & Green Chemistry (2020) from the University of Rennes 1 (France). During her master's internship, she worked under the guidance of Dr. Jean-François Soulé on the synthesis of bipyridine derivatives using photoredox reactions. She is currently a Ph.D. student under Professor Carsten Bolm at the Institute of Organic Chemistry, RWTH Aachen University (Germany). Her main research interests focus on the imination of sulfoximines in catalysis.



Jean-François Soulé received his Ph.D. from Paris-Saclay University under the supervision of Jean-Marie Beau where he develops multicomponent reactions for the synthesis of new biologically active molecules. From 2010 to 2013 he worked as a postdoctoral researcher in the group of Shū Kobayashi at the University of Tokyo (Japan) to investigate the heterogenization of nanocatalysts for applications in cross-couplings and oxidative couplings under environmentally friendly conditions. He was appointed as CNRS Researcher in 2013 at the Institut des Sciences Chimiques de Rennes (ISCR) in the team led by Henri Doucet. He obtained his « Habilitation à Diriger les Recherches » HDR in 2017. His work focuses on catalysis for regioselective C–H bond functionalizations. In 2020, he was awarded by Thieme Chemistry Journal, and he won the Jean-Pierre Sauvage Prize from the French Chemical Society (Organic Chemistry Division).

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