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C_6-Selective Direct Arylation of 2-Phenylpyridine *via* an Activated *N*-methylpyridinium Salt: A Combined Experimental and Theoretical Study

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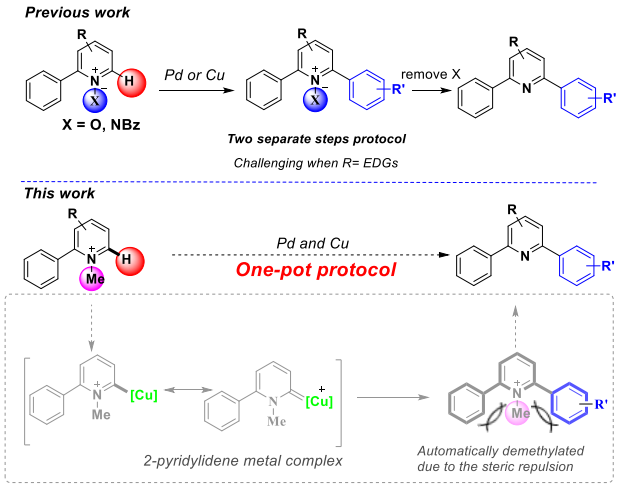
Abstract. An elegant pre-activation strategy, based on the formation of *N*-methylpyridinium iodide salts for C_6-selective direct arylation of 2-phenylpyridines using Pd/Cu cooperative catalysis, has been developed. By this methodology, a wide range of unsymmetrical 2, 6-diarylpyridines were synthesized with high reactivity and regioselectivity as well as good functional group tolerance. In particular, challenging substrates bearing electron donating groups (EDGs), such as OMe, NMe_2, were also successfully employed in this reaction. Deuterium incorporation studies revealed that the C-H bond acidity is improved significantly in *N*-methylpyridinium salts compared with their *N*-Oxide and *N*-iminopyridinium ylide counterparts, thus solving the long-standing problem associated with previous strategies for the synthesis of diaryl pyridines. Finally, the control experiments and DFT calculations supported a Pd-catalyzed and Cu-mediated mechanism in which a carbenoid copper species that is formed in-situ from *N*-methylpyridinium salts, participates in a Pd-catalyzed arylation followed by an iodide-promoted *N*-demethylation process.

Keywords: *N*-methylpyridinium; C-H arylation; Palladium; Copper; DFT

Introduction

Copper is among the first transitional metals utilized in promoting aryl-aryl bond formations, in which an intermediary aryl copper species is involved as a cross-coupling partner.[1] While 2-pyridyl copper is notoriously unstable, it has been demonstrated as an important intermediate in many successful 2-arylpyridine synthetic systems. [2]

Conventionally, the generation of 2-pyridyl copper required the presence of functionality, such as X, $B(OH)_2$ or COOH, at the C_2 position of the pyridines.[3] Due to the relatively lower acidity of the C_2-H bond, the formation of 2-pyridyl copper through direct cleavage of the pyridine C-H bond with Cu remains challenging.[4] While several Cu-catalyzed pyridine direct C-H arylations have been successfully realized based on pyridine *N*-oxide and *N*-iminopyridinium ylides,[5] the limitation of these methodologies are apparent: Firstly, the substrates



Scheme 1. Strategies for Synthesis of 2, 6-diaryl pyridines from 2-arylpyridines *via* C-H arylation.

bearing electron donating groups (EDGs) make pyridine deprotonation unfavorable and show extremely low activation reactivity.[6] Secondly, most of these strategies require additional individual steps to remove the activating groups from the target products, though some examples wherein the auto-deoxygenation occurs after C-H arylation of pyridine *N*-oxides have been reported (**Scheme 1**).[7]

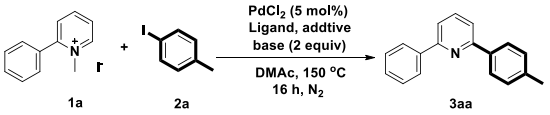
Pyridines can be easily transformed into *N*-methylpyridinium salts by methylation at the N atom. The Brönsted acidity of the adjacent pyridyl C-H bonds increases significantly and even stronger than its *N*-Oxide and *N*-iminopyridinium ylide counterparts.[8] Therefore, it would be quite appealing to explore C-H activation properties of the *N*-methylpyridinium salts. However, the instability of the *N*-methyl pyridinium salts arising from the *N*-demethylation[9] would preclude the activation of C-H bond. We envision that a pyridinium-derived copper complex can be readily achieved by deprotonation of corresponding pyridinium salts in the presence of a copper source, which then resonates to the carbenoid copper species—2-pyridylene copper complex (**Scheme 1**). It would happen to avoid the instability of pyridinium salts and smoothly participate in the following transitional-metal catalyzed reaction giving the C_2 position functionalized pyridinium salts. Importantly, these salts are prone to undergo *N*-demethylation automatically due to increased steric repulsion. Accordingly, the employment of *N*-methylpyridinium salts as an activator strategy, in combination with a copper salt or oxide, would provide a platform with unforeseen opportunities for transitional-metal catalyzed pyridine C-H functionalization. Surprisingly, however, this field has not been well developed.[10]

Unsymmetrical 2, 6-diaryl pyridines are very important structural motifs and are found in many biologically active compounds.[11] Their synthesis commonly relies on a lengthy and tedious construction of the pyridine ring.[12] Upon employing direct C-H arylation strategies, 2-arylpyridines would be good candidate substrates for the synthesis of unsymmetrical 2, 6-diarylpyridines. Yet the innate electron deficient nature of the pyridine ring leads to low reactivity.[13] Moreover, the pyridyl group, acting as a strong directing group, tends to preferentially guide the arylation to the *ortho* position of the phenyl ring,[14] To address this limitation, herein, we report the *N*-methylpyridinium salts as a new pre-activation strategy for C_6-selective arylation of 2-phenylpyridine. It provides a new synthetic methodology for the preparation of unsymmetrical 2, 6-diaryl pyridines with high regioselectivity and good functional group tolerance.

Results and Discussion

We initiated our investigation by coupling *N*-methyl-2-phenylpyridinium iodide **1a** with 4-tolyl bromide (2.0 equiv) using potassium pivalate (2.0 equiv) as base, $PdCl_2$ (5 mol %) and PPh_3 (10 mol %) as the catalyst, and Cu_2O (0.5 equiv) as additive, in *N*, *N*-dimethylacetamide (0.125 M) at 150 °C under a nitrogen atmosphere for 16 h. However, only a trace amount of the desired C_6-H arylation product **3aa** was detected. After a brief survey of various aryl reagents, we found that 4-tolyl iodide is the most efficient and gave the product in 50% yield. To our delight, the yield could be increased significantly to 75% upon increasing the pyridinium salt concentration to 1 M. The replacement of PPh_3 and $PdCl_2$ with tri-2-furylphosphine (TFP)[15] and $Pd(PhCN)_2Cl_2$ further improved the yield to 84%. Other additives, Such as CuO and Ag_2O, were inferior to Cu_2O. No product was observed in the absence of either $PdCl_2$ or Cu_2O (**Tables S1** and **S2**). It should be noted that the iodide anion of the pyridinium salts plays an important role on the reaction efficiency and switching I^- to other counter ions led to the lower yields (**Tables S3**).

Table 1. Optimization of reaction conditions.[a)]



Entry	Ligand	Additive	Concentration (M)	Yield (%)
1[b)]	PPh_3	Cu_2O	0.125	trace
2[c)]	PPh_3	Cu_2O	0.125	N.R.
3	PPh_3	Cu_2O	0.125	50
4	-	Cu_2O	0.25	59
5	-	Cu_2O	0.5	59
6	-	Cu_2O	1	73
7	PPh_3	Cu_2O	1	75
8	$AsPh_3$	Cu_2O	1	79
9	TFP	Cu_2O	1	83(84)[d)]
10	TFP	CuO	1	trace
11	TFP	CuCl	1	80
12	TFP	Ag_2O	1	42

[a)] Reaction condition: **1a** (0.5 mmol, 1.0 equiv), **2a** (1.0 mmol, 2.0 equiv), $PdCl_2$ (5 mol %), ligand (10 mol %), PivOK (1.0 mmol, 2 equiv), DMAc (0.125 M) at 150 °C for 16 h under N_2. Isolated yield determined. [b)] 1-Bromo-4-methylbenzene was used. [c)] 4-methylphenyl tosylate was used, N.R. = No reaction. [d)] $Pd(PhCN)_2Cl_2$ was used; DMAc = *N*, *N*-dimethylacetamide, PPh_3 = triphenylphosphine, TFP = tri-2-furylphosphine.

Having established the optimized reaction conditions, we next investigated the scope and limitations of this new 2, 6-diaryl pyridine synthesis. First, the scope of the (hetero) aryl iodides was tested and the results are summarized in **Table 2**. The system turned out to be applicable to a wide range of aryl iodides. The aryl iodides, irrespective of being electron rich, neutral or poor, underwent the reaction to afford the corresponding arylation products in good to excellent yields (**3aa**-**3fe**), in addition, the electron-deficient aryl bromides could also be viable

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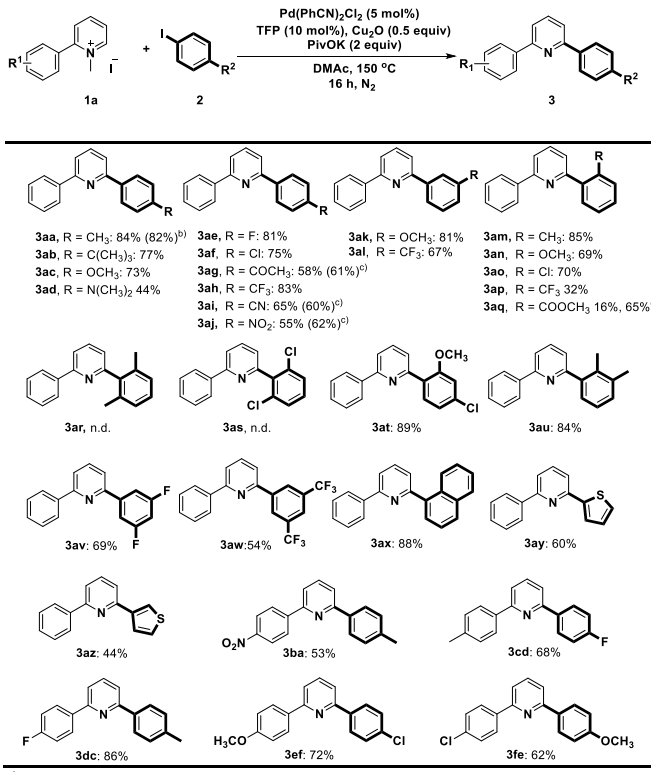
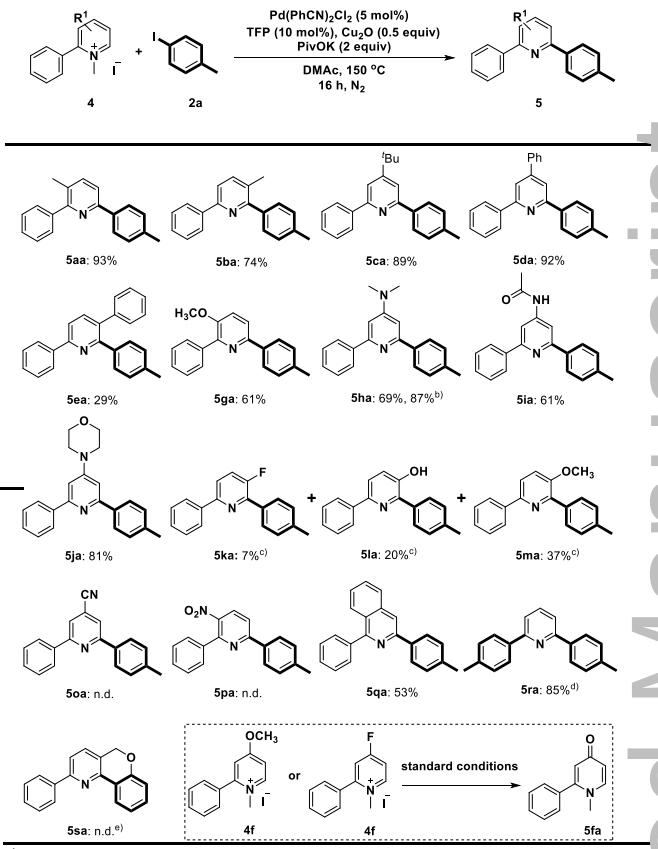
Table 2. Scope of aryl Iodides.[a)]



a) Standard reaction conditions as in **Table 1**, entry 9. Isolated yields are shown. b) isolated yield for a gram-scale reaction. c) aryl bromides were used. d) reaction was run at 100 °C.

as an arylating reagent in the present system, they exhibited similar reactivity as their iodinated counterparts (**3ag**, **3ai,** and **3aj**). Generally, the electron neutral aryl iodides gave higher yields than the electron-rich or electron-poor substrates. For example, 4-chloro-2-methoxy phenyl iodide afforded the product **3at** in 89% yield, much higher than either 2-methoxyl or 4-chloro phenyl iodide (**3af**, 75% and **3an**, 69%, respectively). This may be due to its relatively electron-neutral property, counterbalanced by the electron-donating (*ortho*-MeO) and –withdrawing (*para*-Cl) groups. Likewise, the *meta*-MeO-phenyliodide substrate gave a higher yield of product than its *ortho*- or *para*- counterpart, due to both the mesomeric and inductive effect being weaker at the *meta* position (81% for **3ak,** versus 69% and 73% for **3an** and **3ac**, respectively). The steric hindrance also had some influence on the reaction rate and the bis-*ortho*-substitution completely inhibited the reaction (**3ar** and **3as**). Importantly, the aryl iodides show good compatibility with various functional groups. Although a substrate bearing an ester group only led to a low yield of the corresponding product due to partial hydrolysis (**3aq**), the yield could be improved significantly to 65% just by lowering the temperature to 100 °C. We reasoned that the relatively low temperature retards the hydrolysis of the ester group. The reaction was also compatible with some heteroaryl compounds, such as thiophenyl iodides (**3ay**, **3az**). Finally, the order of the arylation appears to influence the yields to some extent (**3cd** versus **3dc**; **3ef** versus **3fe**). The reaction was also carried out on a gram scale without a noticeable decrease in product yield (**3aa**), highlighting the potential application of this methodology.

Table 3. Scope of substituted *N*-methyl-2-phenylpyridinium iodide. [a)]

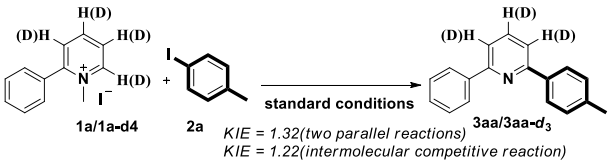


a) Standard reaction conditions as in **Table 1**, entry 9. Isolated yields are shown. b) Reaction run for 48 h. c) 5-Fluoro-1-methyl-2-phenylpyridin-1-ium iodide was used. d) 1-methylpyridin-1-ium iodide was used, 2 (1.5 mmol), Cu_2O (0.375 mmol), PivOK (1.25 mmol). e) 5-((2-iodophenoxy)methyl)-1-methyl-2-phenylpyridin-1-ium iodide was used; n.d. = not detected.

Next, the substrate scope in terms of the *N*-methyl-2-phenylpyridinium iodide was further explored by using 4-tolyl iodide as the coupling partner. We observed that the reaction outcome was dependent on the substitution pattern and the electronic nature of the pyridinium salts, and was particularly sensitive towards the electronic properties of the pyridine ring. Electron-rich substituents, such as alkyl, aryl, alkoxyl and amido groups led to the expected products in 29% to 93% isolated yields (**Table 3**, **5aa**-**5da**, **5ga**-**5ja**). Steric hindrance was responsible for the relatively lower yields for **5ba** (74%) and **5ea** (29%) in comparison with **5aa** (93%) and **5da** (92%), respectively. Especially noteworthy are the excellent yields obtained with pyridines containing very strong

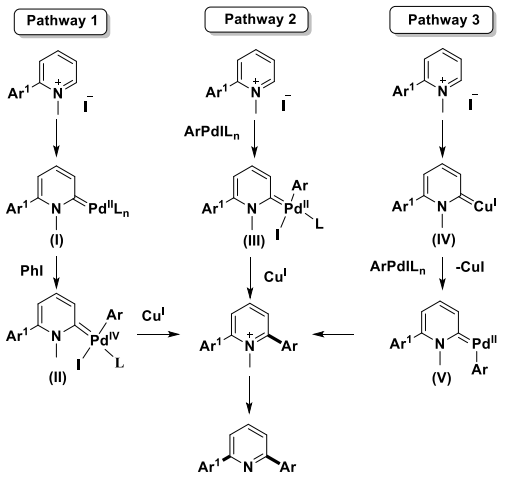
electron-donating –NR_2 groups at the *para* position (**5ha**-**5ja**), which are difficult to be arylated using the pyridine *N*-oxide strategy,[16] although a longer reaction time was required to achieve high yields. The sluggish reaction rate may be attributed to both the relatively weak Brönsted acidity of the C-H bonds and the low demethylation reactivity of the corresponding *N*-methyl diarylpyridinium salts.[17] The substitution pattern was also an influential factor in this reaction. For example, differing from the 3-methoxylpyridinium salt **4g**, the use of 4-methoxylpyridinium iodide **4f** tended to result in a nucleophilic substitution reaction with water to form a 4-pyridinone compound (**5fa**). A similar phenomenon was also observed for 4-fluoro-substituted pyridines.[18] In contrast, the reaction of the 5-fluoro-substituted 1-methy-2-phenylpyridinium iodide could successfully provide three C-H arylation compounds (**5ka**, 7%, **5la**, 20%, and **5ma** 37%) under the standard conditions. However, pyridinium substrates bearing strong electron-withdrawing substituents failed to give any of the desired products (**5oa**-**5pa**) and instead resulted in a complicated mixture, possibly due to the decomposition of such compounds *via* a nucleophilic attack pathway.[19] Of note, when *N*-methylpyridinium salt was used as the substrate, the corresponding product 2, 6-di-*p*-tolylpyridine was isolated with even higher selectivity and yield compared with our previous work.[20] Unfortunately, an attempt to realize intramolecular coupling was unsuccessful, probably because of the difficult transmetallation arising from the sterically crowded environment around in the transition state [21] (**Table 3**).

To gain insights into the reaction mechanism, deuterium labeling experiments were carried out by treating **1a** with various metal oxides, salts and bases in a solvent mixture of DMAc/D_2O (1:1) at 150 °C for 1 h under N_2 (**Table S4**). When **1a** was treated with PivOK, the deuterium incorporate selectively at C_6 position in almost quantitative yield, whereas no H/D exchange with *N*-oxides and *N*-iminopyridiniumylides[22] under the identical conditions (**Figure S7 and S8**), revealing that the *N*-methylpyridinium salt pre-activation strategy decreases the p*K*a of the C-H bonds more significantly than the other two strategies.



Scheme 2. Kinetic experiments.

Next, two competing reactions between **1a** and **1a-*d*$_4$** were conducted in a parallel or intermolecular manner, respectively, as shown in (**Scheme 2)**. Both the observed kinetic isotopic effects (KIE) of 1.32 and 1.22 indicate that the C-H bond cleavage is unlikely to be the rate-limiting step. When **1a-d1** was treated with PivOK in DMAc at 100°C for 0.5 h, a significant amount of protonated product **1a** was detected in 14% NMR yield (**Figure S10**), revealing that the cleavage of the C-H bond is reversible, thus clarifying the reason as to why the C-H cleavage is not the rate-determining step. The proton source most likely originates from the trace amount of water in DMAc.

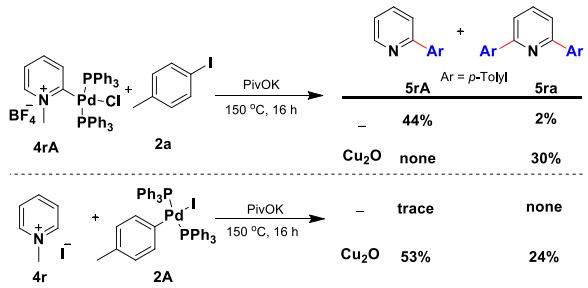


Scheme 3. Proposed three possible pathways.

To further probe the exact role of palladium and Cu_2O in the reaction, and which species coordinates with the pyridinium salt, we have proposed three possible pathways (**Scheme 3**, pathway **1**, **2**, or **3**) according to literature precedent. In pathway **1**, the pyridinium salt coordinates to palladium(II) through a base assisted concerted metallation–deprotonation (CMD) process, affording intermediate **(I)**, which then undergoes oxidative addition with PhI to form 2-pyridylidene-Pd(IV) species **(II)**.[23] From this, the arylated *N*-methyl pyridinium salt is generated *via* reductive elimination steps. The possible role of Cu_2O is to aid in removing the iodide ligands from the Pd center. Likewise, in pathway **2**, pyridinium salts also complex with Pd(II), but in this case, the Pd(II) species is generated from the oxidative addition of ArI to the in-situ formed Pd(0). Thus, arylated pyridinium salt is released from the Pd(II) instead of the Pd(IV) center. Similarly, the Cu_2O also assists in the removal of the iodide. In pathway **3**, however, Cu_2O plays quite a different role and instead reacts first with the 2-phenyl-*N*-methyl-pyridinium salt in the presence of base to yield a 2-pyridyl Cu(I) complex (**IV**), which in turn transmetalate with ArPdILn to give 2-pyridylidene-Pd(II) species(**V**), upon which the 2, 6-diaryl *N*-methylpyridinium salt is produced *via* a reductive elimination step. This pathway is widely accepted in bimetallic Pd/Cu systems.[24] Finally, the *N*-demethylation of the 2, 6-diaryl *N*-methylpyridinium salt gives the desired 2, 6-diarylpyridine.

To determine which pathway was likely operative, we synthesized two important related intermediates:

A 2-pyridyl Palladium complex **4rA**[25] and Pd(PPh$_3$)$_2$(I)(*p*-tolyl) **2A**, and conducted several experiments (**Scheme 4**). Firstly, the reaction between **4rA** and **2a** was carried out under the standard conditions with and without Cu$_2$O. Only 2% of the diarylation product (**5ra)** was detected in the absence of Cu$_2$O, along with 44% of the monoarylation product 2-(*p*-tolyl)pyridine (**5rA**). In sharp contrast, in the presence of Cu$_2$O, around 30% of the diarylation product was isolated, without any of **5rA** being detected. The comparison of these data clearly indicated that although monoarylation could occur on the 2-pyridylidene palladium intermediate *via* Pd(II)/Pd(IV) catalysis, the second C-H arylation was difficult to achieve without Cu$_2$O, proving it be essential for this step. Thus, the Cu$_2$O is believed to not only assist in removal of the halide but also enables the monoarylated *N*-methyl pyridinium salt to partake in the second C-H arylation cycle. Nevertheless, the overall yield for pathway **1** was still much lower than that obtained under the standard conditions. Thus, pathway **1** does not completely account for the outcome of this reaction.



Scheme 4. Control experiments.

In pathway **2**, *N*-methylpyridinium iodide (**4r**) was reacted with 1.0 equiv **2A** and only a trace amount of **5rA** was obtained, with no **5ra** being observed in the absence of Cu$_2$O; however, when Cu$_2$O was added, **5rA** and **5ra** were isolated in 53% and 24% yield, respectively. Cu$_2$O proved to be a prerequisite as well in this pathway.

Based on the above experimental observations, we believed the pathway **3** is most likely the operative mechanism for the reaction, although the control experimental results for which are lacking, due to our failure in obtaining the synthetically challenging 2-pyridylene copper.[26]

In order to gain a better understanding of the mechanism, density functional theory calculations, M11-L[27] with a standard 6-311+G (d,p) basis set (SDD basis set for Pd, Cu, and I) were employed to investigate the mechanism of the *N*-methylpyridinium salt arylation process. For pathway **3**, the energy profile can be divided into three sections: the copper-cycle, the palladium-cycle and the iodine-cycle. For copper-cycle (**Figure 1**), a Cu(I)-ate-complex bis(pivaloyloxy)copper **6**, known as a good C-H bond cleavage species,[28] is set to the relative zero point. It cleaves the adjacent pyridyl C-H bond of the *N*-methylpyridinium salt through a concerted metalation deprotonation (CMD) process via a six-center transition state **TS-7**,[29] with a free energy barrier of 31.3 kcal/mol to yield carbenoid copper intermediate **8**, reversibly, the presence of which was detected by the mass spectrometry in our previous work.[20b] Alternatively, the intermediate **8** could also be generated by a PivOK-promoted deprotonation process followed by a transmetalation from K to Cu[5b]. But such a deprotonation-transmetallation process can be ruled out since the free energy is as high as 35.2 kcal/mol (**Figures S 16**).

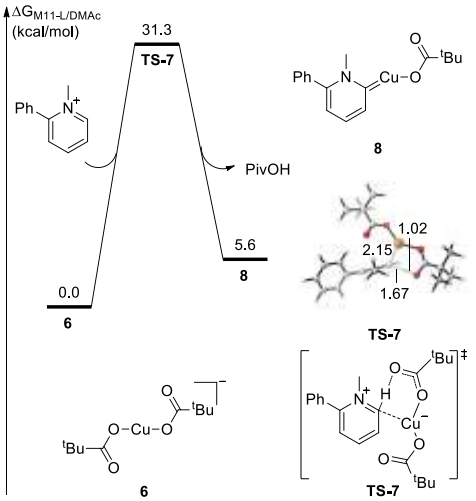


Figure 1. Calculated energy profiles of the copper cycle. The bond lengths in the geometries are given in angstroms.

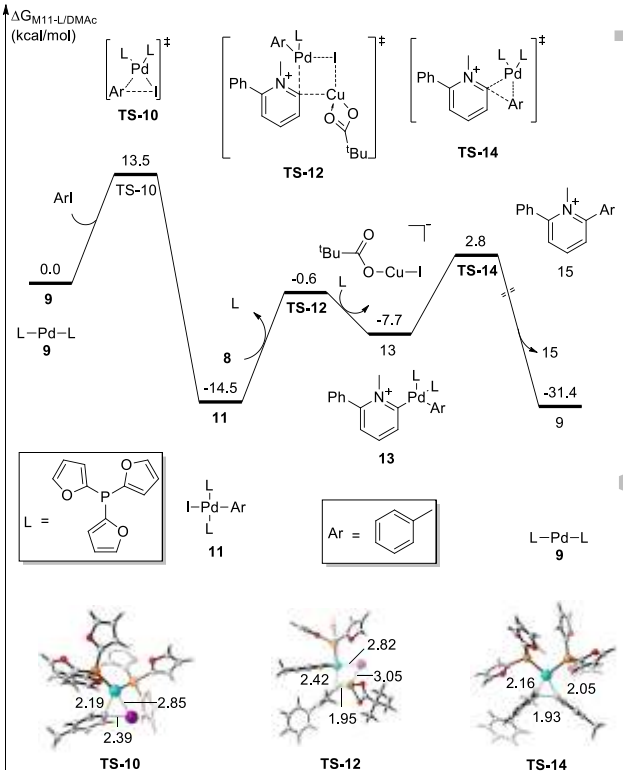


Figure 2. Calculated energy profiles of the palladium cycle. The bond lengths in the geometries are given in angstroms.

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The free energy profiles of the palladium-catalyzed cycle are shown in **Figure 2**. Bis-phosphine-coordinated Pd(0) species **9** is chosen as the relative zero point in this free energy profile. The oxidative addition with iodobenzene takes place *via* transition state **TS-10** with a free energy barrier of only 13.5 kcal/mol to form Pd(II) intermediate **11**. The transmetallation of **11** with carbenoid copper species **8** takes place *via* transition state **TS-12** with a barrier of 13.9 kcal/mol, which affords pyridylpalladium intermediate **13**. The reductive elimination of intermediate **13** releases 2, 6-diaryl *N*-methylpyridinium **15** with a free energy barrier of 10.5 kcal/mol, which regenerates the active Pd(0) species **9**. The generated 2, 6-diaryl *N*-methylpyridinium salt **15** could then demethylate in the presence of iodide. As shown in **Figure 3**, an S_N2 substitution of *N*-methylpyridinium salt **15** occurs through transition state **TS-17** to generate pyridine product **3aa** and iodomethane **18** with a free energy barrier of 31.3 kcal/mol. Subsequently, another S_N2 nucleophilic substitution with pivalate takes place *via* transition state **TS-19** to release the iodide ion and generate the methyl pivalate. Indeed, the presence of the methyl pivalate was determined by gas chromatography.

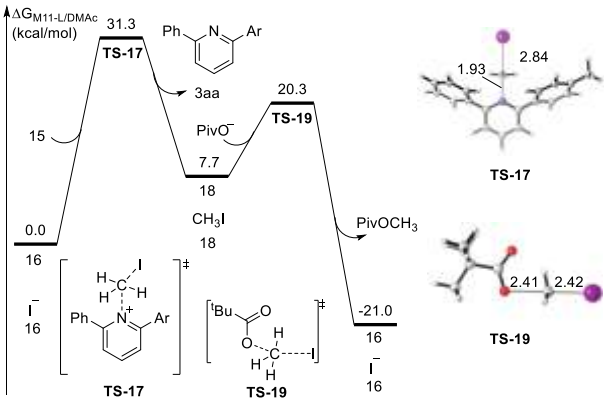

Figure 3. Calculated energy profiles of the iodine cycle for 2, 6-diaryl *N*-methylpyridinium salt. The bond lengths in the geometries are given in angstroms.

For comparison, the pathways **1** and **2** were also considered in this study, and the calculated results are summarized (**Figures S14** and **S15**). Both of the highest energies in pathways **1**[30] and **2** are higher than the overall activation free energy of the demethylation of the 2-phenyl *N*-methylpyridinium salt, which was determined to be 33.5 kcal/mol. These energetic discrepancies reveal that demethylation of the 2-phenyl *N*-methylpyridinium salt would likely take place preferentially, thus the *N*-demethylation becomes an annoying competitive side reaction. Therefore, the pathways **1** and **2** can be ruled out because the stability of the pyridinium salts cannot be guaranteed. By contrast, in pathway **3** the *N*-methylpyridinium salt could be easily transformed into the carbenoid copper species with a lower free energy barrier (31.3 kcal/mol). Therefore, pathway **3** is kinetically favorable and most likely the operative mechanism, which is consistent with conclusion of the control experimental results.

Conclusion

A new pre-activation strategy based on the formation of *N*-methylpyridinium salts for the selective C_6-H arylation of 2-phenylpyridines has been developed. This strategy has two main advantages: Firstly, the C-H bond acidity of the pyridinium salt is much higher than that in the corresponding *N*-oxides or *N*-iminopyridinium ylides, thus C-H activation reactivity is enhanced and beneficial for substrates bearing EDGs. Second, the *N*-methyl group readily departs due to the increasing steric repulsion after the C-H arylation reaction, thus obviating an additional step to remove the *N*-methyl group. This protocol provides a rapid and practical access to a wide range of unsymmetrical 2, 6-diarylpyridines with high reactivity and regioselectivity as well as good functional group tolerance. With the help of a combination of experimental and theoretical methods, the reaction mechanism has been explored. DFT calculations show that the total process of the arylation can be divided into three sections: ate-complex bis(pivaloyloxy)copper-mediated C-H bond cleavage affording a carbenoid copper, transmetallation of carbenoid copper with aryliodide-palladium following by C-C bond reductive elimination, and final demethylation under the assistance of iodide generating 2, 6-diarylpyridines. On the basis our results, *N*-methylpyridinium salts can be used as activators for new, scalable and effective strategies for the functionalization of pyridine.

Experimental Section

General Procedure for the Preparation of *N*-methylpyridinium salts

To a solution of appropriate arylpyridine (15.0 mmol, 1.0 equiv) in acetonitrile (5 mL, 3 M) was added CH_3I (8.52 g, 60.0 mmol, 4.0 equiv) under argon in a two-necked flask. The mixture was heated at 90°C for 16 h, and then cooled to room temperature. After removal of the solvent under reduced pressure to afford the crude product, which was purified by recrystallization in CH_3CN/EtOAc.

General procedures for the Synthesis unsymmetrical 2, 6-diaryl pyridines

An oven-dried 25 mL Schlenk tube equipped with magnetic stirring bar were charged with aryl iodide (1.0 mmol), appropriate *N*-methylpyridinium salt (0.5 mmol), and $Pd(PhCN)_2Cl_2$ (9.6 mg, 0.025 mmol, 5 mol %), TFP (11.6 mg, 0.05 mmol, 10 mol %), PivOK (140.0 mg, 1.0 mmol, 2 equiv), Cu_2O (36.0 mg, 0.25 mmol, 0.5 equiv). The tube was sealed and the mixture was charged with nitrogen gas three times, then dry DMAc (0.5 mL, 1 M) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at 150 °C for 16 h. After cooling to room temperature, the mixture was diluted with

ethyl acetate and filtered through a short pad of celite, the volatiles were removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give the pure products.

General Procedure for Deuterium incorporation studies

An oven-dried 25 mL Schlenk tube equipped with magnetic stirring bar was charged with appropriate starting material (0.25 mmol), and PivOK (70.0 mg, 0.5 mmol, 2.0 equiv), The tube was sealed and the mixture was charged with nitrogen gas three times, then DMAc (0.25 mL) and D_2O (0.25 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at 150 °C for 16 h. After cooling to room temperature, the mixture was diluted with CH_3CN and filtered through a short pad of celite, the volatiles were removed under vacuum and crude product was analyzed by ^1H NMR.

Computational Methods

All of the DFT calculations conducted in this study were carried out using the GAUSSIAN 09 series of programs. DFT method B3-LYP8 with a standard 6-31G(d) basis set (SDD basis set for Pd, Cu and I) was used for the geometry optimizations. The M11-L functional, proposed by Truhlar et al., was used with a 6-311+G(d,p) basis set (SDD basis set for Pd, Cu and I) to calculate the single point energies. The solvent effects were taken into consideration using single point calculations based on the gas-phase stationary points with a SMD continuum solvation model.9 The energies presented in this paper are the M11-L calculated Gibbs free energies in toluene solvent with B3-LYP calculated thermodynamic corrections.

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FULL PAPER

C_6-Selective Direct Arylation of 2-Phenylpridine *via* an Activated *N*-methylpyridinium Salt: A Combined Experimental and Theoretical Study

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