Heterocycles

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# Transition-Metal-Free Regioselective Alkylation of Pyridine *N*-Oxides Using 1,1-Diborylalkanes as Alkylating Reagents

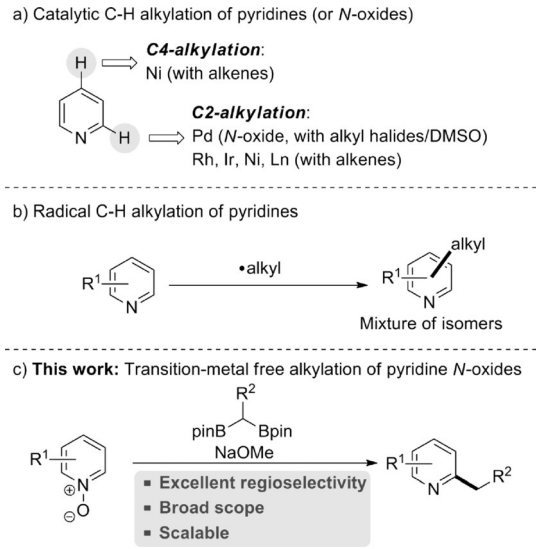
*Woohyun Jo[+], Junghoon Kim[+], Seoyoung Choi, and Seung Hwan Cho**

*Dedicated to Professor Kyo Han Ahn on the occasion of his 60th birthday*

***Abstract:*** *Reported herein is an unprecedented base-promoted deborylative alkylation of pyridine N-oxides using 1,1-diborylalkanes as alkyl sources. The reaction proceeds efficiently for a wide range of pyridine N-oxides and 1,1-diborylalkanes with excellent regioselectivity. The utility of the developed method is demonstrated by the sequential C–H arylation and methylation of pyridine N-oxides. The reaction also can be applied for the direct introduction of a methyl group to 9-O-methylquinine N-oxide, thus it can serve as a powerful method for late-stage functionalization.*

The direct alkylation of pyridines has emerged as an expedient and atom-economical strategy[1] for the preparation of alkylated pyridines which form the core structures of many biologically active compounds, pharmaceuticals, and agrochemicals.[2] Consequently, a range of metal-mediated C–H alkylation reactions of pyridines have been successfully developed using late-transition metals[1,3] and lanthanides[4] as catalysts (Scheme 1 a). The radical C–H alkylation of pyridines in the presence of photocatalysts, metal catalysts, or stoichiometric amounts of oxidants has also been extensively studied in this area of research (Scheme 1 b).[5] However, concerns regarding high costs and the presence of residual metal impurities often make these approaches unsuitable for industrial and pharmaceutical applications. Moreover, the radical approach has often resulted in the formation of an inseparable mixture of regioisomers. Thus, the development of an efficient and selective method for the alkylation, especially for the methylation,[3d,6,7] of pyridines under transition-metal-free conditions is still desirable.

The reaction of pyridine *N*-oxides with certain nucleophiles through a nucleophilic addition/elimination mechanism is a well-known approach for the preparation of functionalized pyridine compounds.[8] Although numerous methods for the introduction of functional groups such as halides, cyano, amino, phenoxy, thioalkyl, and phosphoryl into pyridine *N*-oxides have been developed,[8,9] only a limited number of examples for the C–C bond-forming reactions have been reported.[10] Specifically, the regioselective alkylation of




***Scheme 1.*** Strategies for the alkylation of pyridines or pyridine *N*-oxides. pin = pinacol.

pyridine *N*-oxides have not been well documented.[11] In 2000, Nicolaou et al. described C2-methylation reactions of pyridine *N*-oxides using Tebbe's reagent involving a nucleophilic addition/elimination process.[11a] Almqvist, Olsson,[11b,c] and Duan[11d] discovered that Grignard reagents act as facile nucleophiles in the C2 alkylation of pyridine *N*-oxides. Herein, we report the development of the transition-metal-free alkylation of pyridine *N*-oxides by employing 1,1-diborylalkanes as facile alkylating reagents (Scheme 1 c). This new process is operationally simple and works with a range of pyridine *N*-oxides and 1,1-diborylalkanes.

Recently, we[12] and others[13] have reported that 1,1-diborylalkanes can be utilized in various organic transformations under metal-catalyzed or transition-metal-free conditions. Among the reported reactions, Morken et al. described that α-borylcarbanion intermediates, generated in situ from the reaction of 1,1-diborylalkanes with an alkoxide base, could facilitate a formal $S_N2$-type alkylation with alkyl halides.[13f,g] In light of these precedents, we wondered whether the α-borylcarbanion could react with pyridine *N*-oxides in a nucleophilc aromatic substitution fashion. To test the feasibility of the idea, we initially focused on the reaction of quinoline *N*-oxide (**1a**) with diborylmethane (**2a**) in the presence potassium *tert*-butoxide in toluene at 80 °C (Table 1). To our surprise, the deoxygenated 2-methylquinoline (**3a**) was obtained as a single product, albeit in moderate yield (entry 1). Subsequent base screening (entries 2–7)

[*] W. Jo,[+] J. Kim,[+] S. Choi, Prof. Dr. S. H. Cho
Department of Chemistry and Division of Advanced Nuclear Engineering, Pohang University of Science and Technology (POSTECH), Pohang, 790-784 (Rep. of Korea)
E-mail: seunghwan@postech.ac.kr
[+] These authors contributed equally to this work.

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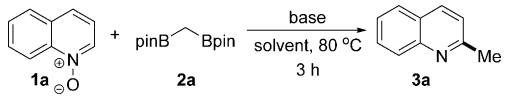
**Table 1:** Optimization study.[a]



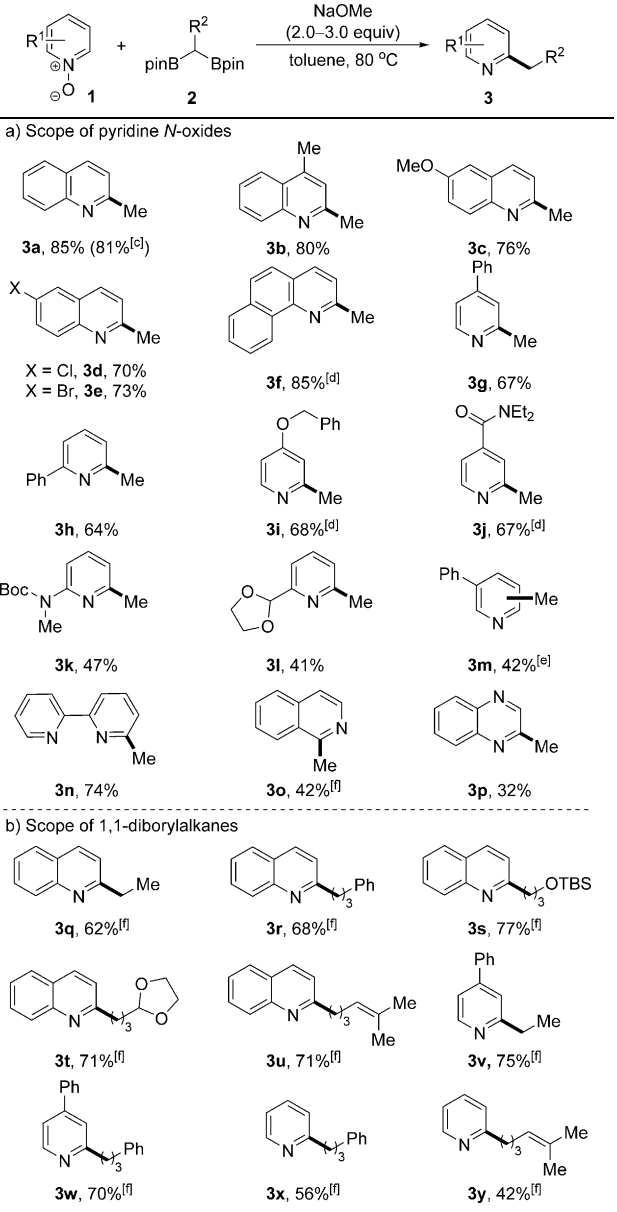

| Entry | Base | Solvent | Yield [%][b] |
|---|---|---|---|
| 1 | KO*t*Bu | toluene | 43 |
| 2 | NaO*t*Bu | toluene | 68 |
| 3 | LiO*t*Bu | toluene | 42 |
| 4 | KOMe | toluene | <1 |
| 5 | NaOMe | toluene | 87 (85)[c] |
| 6 | LiOMe | toluene | 2 |
| 7 | CsF | toluene | <1 |
| 8 | NaOMe | THF | 80 |
| 9 | NaOMe | 1,4-dioxane | 79 |
| 10[d] | NaOMe | toluene | 69 |
| 11 | – | toluene | <1 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), base (2.0 equiv), and solvent (2.0 mL) at 80 °C for 3 h. [b] Determined by $^1$H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] Yield of isolated product is given within parentheses. [d] Runs at 50 °C. THF = tetrahydrofuran.

revealed that sodium methoxide was the most effective base for the methylation reaction (entry 5). Ethereal solvents such as THF and 1,4-dioxane were also used but gave slightly lower yields (entries 8 and 9). When the reaction temperature was lowered to 50 °C, a diminished yield of **3a** was detected (entry 10). No reaction took place in the absence of a base (entry 11).

Using the optimized reaction conditions, we then explored a range of heterocyclic *N*-oxides for the methylation reaction (Table 2a). It was revealed that variously substituted quinoline *N*-oxides were methylated in good yields (**3b–e**). In the presence of 3.0 equivalents of **2a**, benzo[*h*]quinoline *N*-oxide reacted smoothly to afford **3f** in 85% yield. The present methylation proceeded well with 4- and 2-aryl-substituted pyridine *N*-oxide to give **3g** and **3h**, respectively, in good yields. The same reaction conditions were also suitable for the reactions of pyridine *N*-oxide derivatives containing various functional groups, including benzyloxy (**3i**), amide (**3j**), Boc-protected amine (**3k**), and a masked aldehyde (**3l**), while **3i** and **3j** required 3.0 equivalents of **2a** to afford satisfactory yields. When 3-phenyl pyridine *N*-oxide was used as the substrate, a 1:1 mixture of 2-methyl-5-phenylpyridine and 2-methyl-3-phenylpyridine was obtained in 42% yield (**3m**). The current protocol could also be applied to unsymmetrical 2,2′-bipyridine *N*-oxide (**3n**), thereby allowing further derivatization of the bidentate nitrogen ligand. Furthermore, other types of *N*-oxides derived from isoquinoline (**3o**) and quinoxaline (**3p**) were found to be suitable for the methylation reaction, but formation of **3o** required 3.0 equivalents of NaOMe to give a synthetically acceptable yield. Note that the methylation reaction could be easily performed on a 5.0 mmol scale without difficulty, as demonstrated in the synthesis of **3a**. Considering that the installation of methyl groups in pyridines is highly challenging and their separation from the starting material is often difficult, the current method provides a powerful tool for the methylation of pyridines and offers a simple purification process.[6,7]

**Table 2:** Substrate scope with respect to the pyridine *N*-oxides.[a,b]



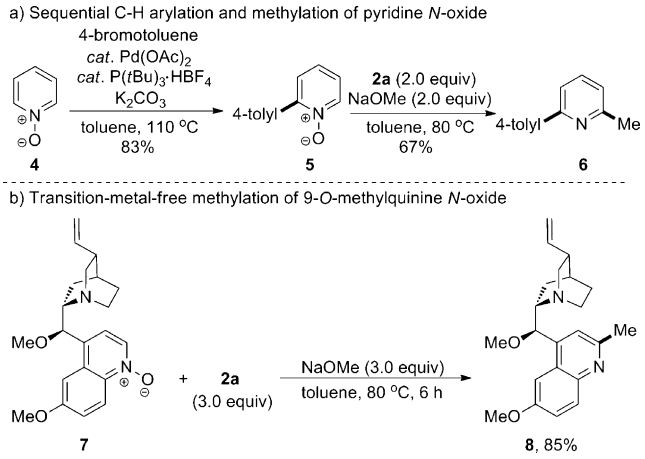

[a] Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv), NaOMe (2.0 equiv), and toluene (2.0 mL) at 80 °C for 3 h. [b] Yields of isolated products are given. [c] Yield for a 5.0 mmol reaction is given within parentheses. [d] 3.0 equiv. of **2a** were used. [e] A 1:1 mixture of 2-methyl-5-phenylpyridine and 2-methyl-3-phenylpyridine was obtained. [f] 3.0 equiv of NaOMe were used. TBS = *tert*-butyldimethylsilyl.

The optimized alkylation procedure was then applied to the reaction of a range of 1,1-diborylalkanes with quinoline or pyridine *N*-oxides in the presence of 3.0 equivalents of NaOMe (Table 2b). We found that quinoline *N*-oxide (**1a**) reacted smoothly with 1,1-diborylethane and 1,1-diborylpropylbenzene to give **3q** and **3r**, respectively, with high efficiency. Moreover, 1,1-diborylalkanes possessing a TBS-protected alcohol and a masked aldehyde underwent C2 alkylation to provide the desired products (**3s** and **3t**) in good yields. It was found that 1,1-diborylalkane bearing an alkene functional group was also compatible with the current

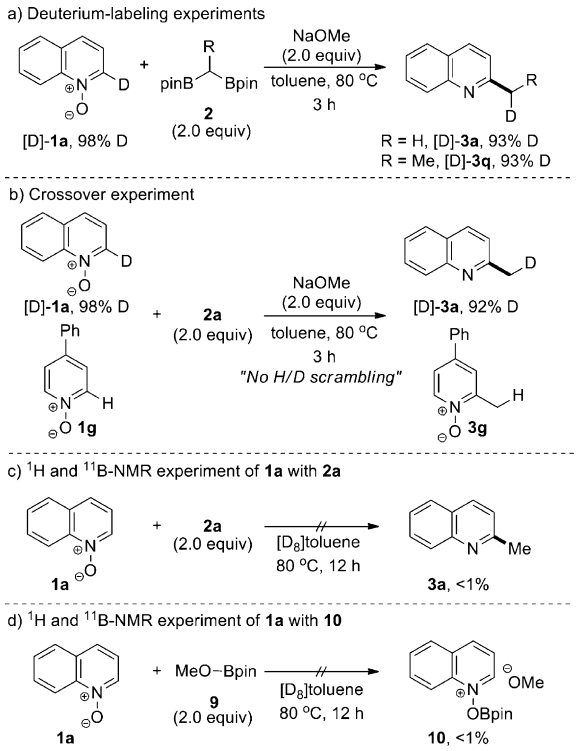
  

alkylation protocol, thus giving the product **3u** in good yield. Reactions of 4-phenyl and simple pyridine *N*-oxide could also participate in the alkylation reaction with various 1,1-diborylalkanes in good to moderate yields (**3v–y**).

With the developed protocol, we next demonstrated the synthetic utility. First, we examined a sequential C–H arylation/methylation of pyridine *N*-oxide (Scheme 2a). The palladium-catalyzed C–H arylation of pyridine *N*-oxide (**4**)




***Scheme 2.*** Synthetic utilities of the developed protocol.



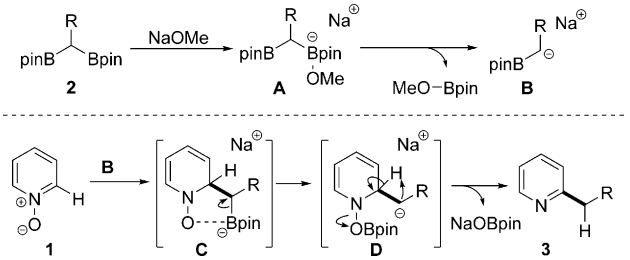

***Scheme 3.*** Preliminary mechanistic studies.

with 4-bromotoluene was achieved, under reaction conditions reported by Fagnou and co-workers, in 83% yield[14] and the produced C2-arylated product **5** was successfully subjected to the our reaction conditions, thus affording the product **6** in 67% yield (56% yield in 2 steps). We also performed the methylation of a 9-*O*-methylquinine *N*-oxide (**7**; Scheme 2b). When **7** was subjected to the reaction conditions in the presence of **2a** (3.0 equiv) and NaOMe (3.0 equiv), the methylated product **8** was formed in good yield (85%) after a prolonged reaction time (6 h). This example demonstrates the usefulness of this method for the late-stage modification of a complex *N*-heterocyclic substrate.[15]

To provide insight into the reaction mechanism, we conducted a deuterium-labeling experiment (Scheme 3a). The reaction of C2-deuterated quinoline *N*-oxide, [D]-**1a**, with diborylmethane in the presence of NaOMe gave the deuterated product [D]-**3a** with 93% incorporation of deuterium at the benzylic position. 1,1-Diborylethane also displayed a result similar to that with diborylmethane, thus showing 93% incorporation of deuterium of [D]-**3q**, indicating that the C2–H bond of quinoline *N*-oxide acts as the proton source for the protodeboronation. Additionally, when we performed a crossover experiment using a 1:1 mixture of [D]-**1a** and **1g** under the reaction conditions, no H/D scrambled products were obtained (Scheme 3b). This outcome strongly suggested that the protodeboronation occurred in an intramolecular process rather than intermolecularly.

To determine whether the boron species acted as an activating agent for the *N*-oxide to increase the electrophilicity of the C2 ring position,[9,10e] we followed the reaction between **1a** and **2a** by $^{1}$H and $^{11}$B NMR spectroscopy, without added base, in [$D_8$]toluene at 80 °C. However, no changes were detected by NMR even after prolonged reaction times (Scheme 3c). In addition, when **1a** was treated with the methoxyboronate ester **9**[16] (Scheme 3d), the quinoline *N*-oxide–Bpin complex **10** was not formed, thus indicating that a reaction mechanism involving the coordination of the *N*-oxide unit to boron, followed by intra- or intermolecular nucleophlilic attack and subsequent rearomatization/elimination of NaOBpin is unlikely.

The experimental results obtained in this study, together with precedent literature,[8] were used to propose a reaction mechanism (Scheme 4). The α-borylcarbanion intermediate **B** is initially generated by the reaction of a 1,1-diborylalkane with NaOMe via the monoborate species **A**.[13f,g] The nucleophilic attack of **B** on **1** forms the intermediate **C**. Then boron migration to the *N*-oxide is postulated to form the intermediate **D**. Finally, the internal proton transfer of C2–H to benzylic position, followed by rearomatization and elimination of NaOBpin furnishes the desired product **3**.[17]




***Scheme 4.*** Proposed reaction mechanism.

In summary, we have developed a base-promoted, transition-metal free direct alkylation of pyridine *N*-oxides employing 1,1-diborylalkanes as alkylating agents. This protocol constitutes an operationally simple and scalable strategy for the synthesis of C2-alkylated pyridine compounds. The reaction also enables the sequential C–H functionalization of pyridine *N*-oxide and rapid late-stage functionalization of complex molecules. Further studies expanding the substrate scope of both the *N*-heteroarenes and 1,1-diborylalkanes are ongoing in our laboratory.

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**Keywords:** alkylation · boron · heterocycles · transition-metal-free synthesis · regioselectivity

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