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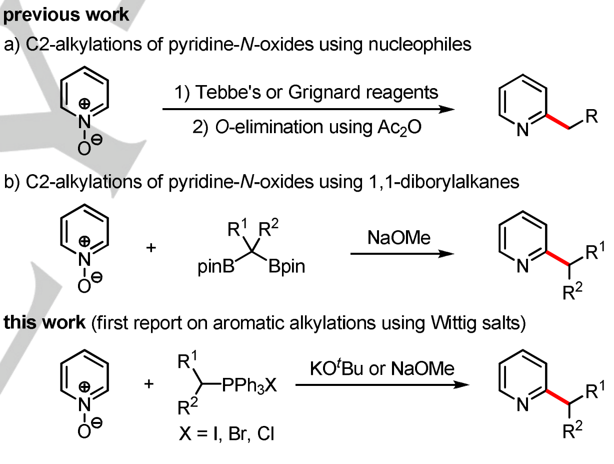
Reductive C2-Alkylation of Pyridine- and Quinoline-*N*-Oxides Using Wittig Reagents

Sangil Han,[a,†] Prashant Chakrasali,[b,c,†] Jihye Park,[a] Hyunjung Oh,[a] Saegun Kim,[a] Kyuneun Kim,[b,c] Ashok Kumar Pandey,[a] Sang Hoon Han,[a] Soo Bong Han,*[b,c] and In Su Kim*[a]

Abstract: The ability to alkylate pyridines and quinolines is important for their further development as pharmaceuticals and agrochemicals, and for other purposes. Herein we describe the unprecedented reductive alkylations of pyridine- and quinoline-*N*-oxides using Wittig reagents. A wide range of pyridine- and quinoline-*N*-oxides was used to provide a variety of C2-alkylated pyridines and quinolines with excellent site selectivities and functional-group compatibilities. The sequential C–H functionalizations of pyridine- and quinoline-*N*-oxides highlight the utility of the developed method. Detailed labeling experiments were performed in order to understand the mechanism of this process.

The ability to C–H alkylate a pyridine is attractive from the perspectives of organic and medicinal chemistry because alkylated pyridines have remarkable therapeutic potentials.[1] In particular, C2-methylated pyridines and quinolines are recognized as ubiquitous heterocyclic core units that are found in a variety of pharmaceuticals and agrochemicals.[2] Over the past few decades, a range of transition-metal-mediated C–H alkylation reactions of pyridines have been intensively studied.[3] In addition, much attention has been directed toward radical-mediated C–H alkylations of pyridines using metal catalysts, photocatalysts, and stoichiometric oxidants.[4] However, from a synthetic point of view, the formation of residual metal impurities and inseparable regioisomers can pose additional barriers to industrial and pharmaceutical applications. Therefore, it is highly desirable to develop mild and selective methods for the construction of C2-alkylated pyridine derivatives under metal-free conditions. Pyridine-*N*-oxides have been used as synthetic precursors for the formation of C2-functionalized pyridine derivatives.[5] A variety of synthetic transformations using halo, cyano, amino, phenoxy, thioalkyl, and phosphoryl groups have been disclosed. However, regioselective C2-alkylations of pyridine-*N*-oxides have rarely been described. For example, Nicolaou et al. reported the C2-methylations of pyridine-*N*-oxides using Tebbe's reagent (Scheme 1).[6] Grignard reagents have also been used to prepare C2-alkylated pyridines through nucleophilic additions to pyridine-*N*-oxides followed by elimination.[7] Very recently, Cho and coworkers demonstrated site-selective alkylations of pyridine-*N*-oxides using 1,1-diborylalkanes as alkylating reagents, to give C2-alkylated pyridines.[8]

The Wittig reaction, which is based on the reaction of an aldehyde or ketone with a phosphonium ylide, is ranked among the most important reactions for C–C bond formation.[9] In addition, Wittig reagents have also been used as C-nucleophiles in Michael additions and other alkylation reactions.[10] Moreover, phosphonium salts have been applied to organocatalytic Mannich-type processes to afford aza-Morita–Baylis–Hillman adducts.[11] However, to the best of our knowledge, there are no reports on C–H alkylation reactions of (hetero)aromatic compounds using Wittig reagents. Herein, we describe the transition-metal-free C–H alkylations of pyridine- and quinoline-*N*-oxides using phosphonium salts as alkylating reagents to furnish C2-alkylated pyridines and quinolines.



previous work

a) C2-alkylations of pyridine-*N*-oxides using nucleophiles

b) C2-alkylations of pyridine-*N*-oxides using 1,1-diborylalkanes

this work (first report on aromatic alkylations using Wittig salts)

Scheme 1. Metal-free site-selective C–H alkylations of pyridine-*N*-oxides.

Our study was initiated by examining the coupling of 2,2'-bipyridine-*N*-oxide (**1a**) with methyltriphenylphosphonium bromide (**2a**) under alkaline conditions, as summarized in Table 1. We were pleased to observe that **1a** coupled with **2a** in the presence of KO^{t}Bu (2 equiv.) in toluene at 80 °C to provide the deoxygenated 6-methyl-2,2'-bipyridine (**3a**) in 51% yield (Table 1, entry 1). However, other bases such as NaO^{t}Bu, NaOMe, and DBU were less effective in this transformation (Table 1, entries 2–4). Interestingly, MTBE (*t*-butyl methyl ether) as the solvent is unique in its ability to facilitate the coupling reaction to afford the C2-methylated pyridine derivative **3a** in 66% yield (Table 1, entries 5–7). In addition, this reaction can be extended to other methyltriphenyl phosphonium salts, such as MePPh$_3$Cl (**2b**) and MePPh$_3$I (**2c**). Notably, MePPh$_3$I (**2c**) was found to deliver our desired product **3a** in 73% yield (Table 1, entry 9). Increasing amount of KO^{t}Bu to 3 equiv. provided a comparable yield (74%), as shown in entry 10. The best result was obtained by treatment with 2 equiv. of KO^{t}Bu in MTBE at 110 °C under an atmosphere of N$_2$ to afford **3a** in 81% yield (Table 1, entry 11).

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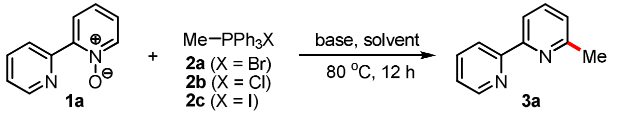
Table 1. Selected optimization of reaction conditions.[a]



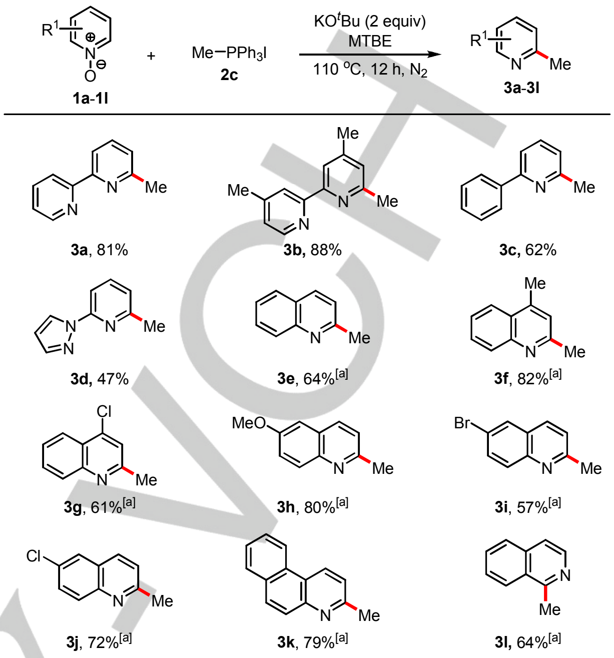
entry	base (equiv.)	MePPh$_3$X	solvent	yield[b]
1	KO^{t}Bu (2)	**2a**	toluene	51
2	NaO^{t}Bu (2)	**2a**	toluene	18
3	NaOMe (2)	**2a**	toluene	36
4	DBU (2)	**2a**	toluene	N.R.
5	KO^{t}Bu (2)	**2a**	THF	53
6	KO^{t}Bu (2)	**2a**	Et$_2$O	49
7	KO^{t}Bu (2)	**2a**	MTBE	66
8	KO^{t}Bu (2)	**2b**	MTBE	40
9	KO^{t}Bu (2)	**2c**	MTBE	73
10	KO^{t}Bu (3)	**2c**	MTBE	74
11[c]	KO^{t}Bu (2)	**2c**	MTBE	81

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), base (quantity noted), solvent (2 mL) at 80 °C for 12 h under N$_2$ in a pressure tube. [b] Isolated percent yield by flash column chromatography. [c] This reaction was carried out at 110 °C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. MTBE = *t*-butyl methyl ether.

With the optimized reaction conditions in hand, the scope of the reaction was examined with a variety of pyridine- and quinoline-*N*-oxides and MePPh$_3$I (**2c**) (Table 2). To our delight, 2,2′-bipyridine-*N*-oxide **1b** was smoothly coupled with MePPh$_3$I (**2c**) to provide the unsymmetrical dipyridyl compound **3b** in 88% yield with complete site-selectivity. Notably, this transformation can readily be used to prepare unsymmetrical dipyridyl ligands.[12] In addition, 2-phenyl pyridine-*N*-oxide (**1c**) was favored in this transformation, furnishing the C2-methylated pyridine **3c** in good yield. This reaction was also applicable to pyrazole-containing pyridine-*N*-oxide **1d**, albeit with relatively decreased reactivity. Moreover, this reaction is only not limited to pyridine-*N*-oxides. Under modified reaction conditions, a variety of quinoline-*N*-oxides **1e**−**1k** were converted into C2-methylated quinoline derivatives **3e**−**3k** in moderate to high yields. Finally, isoquinoline-*N*-oxide **1l** also underwent C−H methylation to give **3l** in 64% yield. The regioselectivity at the C1-position was particularly noteworthy, and is possibly ascribable to the higher electrophilicity of the benzylic iminium carbon.

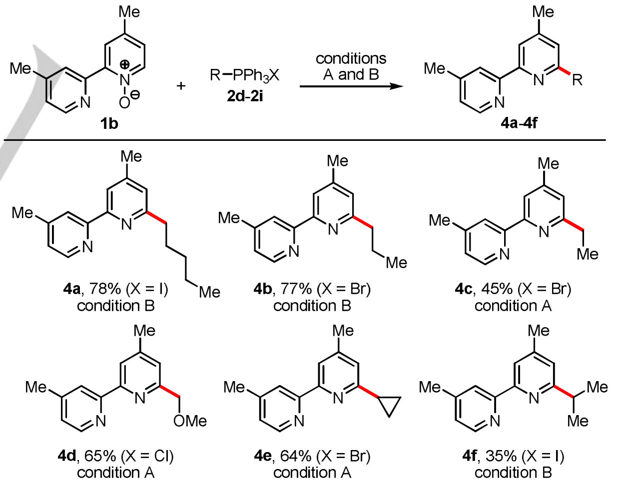
Inspired by these results, we further investigated the C−H alkylation reaction of pyridine-*N*-oxide **1b** with a variety of phosphonium salts **2d**−**2i** under the optimal reaction conditions (Table 3). Linear alkyl phosphonium salts **2d**−**2f** were smoothly coupled with **1b** to give the C6-alkylated products **4a** (78%), **4b** (77%), and **4c** (45%), respectively. The current protocol could be applied to the alkoxymethyl phosphonium salt **2g**, which furnished **4d** in 65% yield. Moreover, cyclopropyl and branched-alkyl phosphonium salts **2h** and **2i** were also compatible with the current reaction conditions.[13]

Table 2. Scope of pyridine and quinoline *N*-oxides.[a]



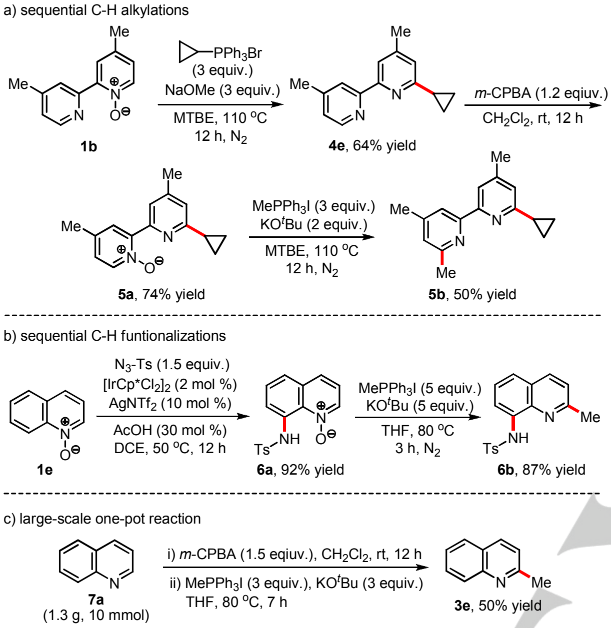
[a] Reaction conditions: **1e**−**1l** (0.2 mmol), **2c** (0.6 mmol), KO^{t}Bu (3 equiv.), THF (2 mL), 80 °C, 3 h under N$_2$ in pressure tubes.

Table 3. Scope of alkyl phosphonium salts.[a]

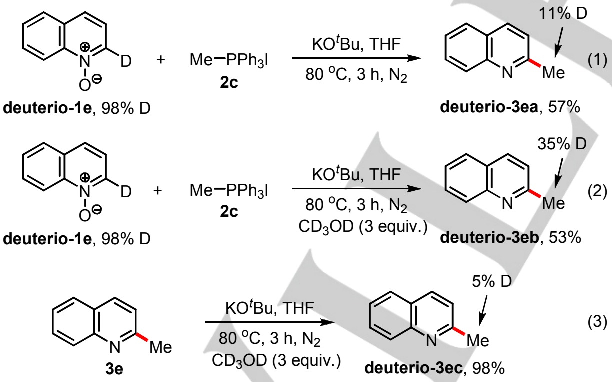


[a] Reaction conditions: condition A: **1b** (0.2 mmol), **2f**−**2h** (0.6 mmol, 3 equiv.), NaOMe (3 equiv.), MTBE (2 mL), 110 °C, 12 h under N$_2$ in pressure tubes. condition B: **1b** (0.2 mmol), **2d**, **2e** and **2i** (0.8 mmol, 4 equiv.), KO^{t}Bu (4 equiv.), MTBE (2 mL), 110 °C, 12 h under N$_2$ in pressure tubes.

To highlight the utility of this protocol, a series of synthetic transformations were performed, as shown in Scheme 2. First, we envisaged the sequential syntheses of unsymmetrical 2,2′-dipyridyl ligands using our developed protocol. To our delight, 2,2′-bipyridine-*N*-oxide **1b** was readily converted into our desired product **5b**. Moreover, the Ir(III)-catalyzed C–H functionalization[14] of **1e** with tosyl azide provided C8-aminated quinoline-*N*-oxide **6a**, which was subjected to C–H methylation conditions to afford the 8-aminoquinoline derivative **6b** in 87% yield. Moreover, scale-up of one-pot reaction involving **7a** resulted in the direct formation of 2-methylquinoline (**3e**) in 50% yield.



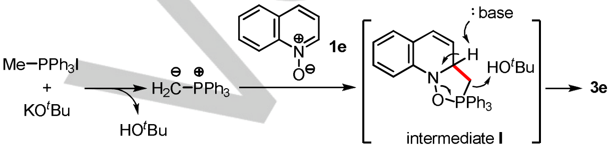
Scheme 2. One-pot and sequential transformations.



Scheme 3. Mechanistic investigation.

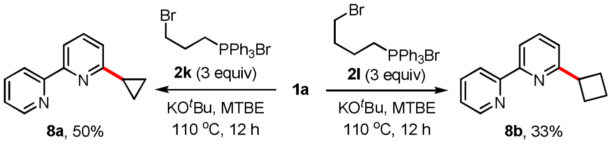
To gain mechanistic insight into this process, a series of labeling experiments were performed (Scheme 3). Treatment of **deuterio-1e** with $MePPh_3I$ (**2c**) resulted in 11% deuterium incorporation on the methyl group of the product, **deuterio-3ea** (eq. 1). The reaction of **deuterio-1e** with **2c** in the presence of CD_3OD also resulted in 35% deuterium incorporation on the methyl group (eq. 2). In addition, the methyl group on compound **3e** was partially deuterated using CD_3OD under the standard reaction conditions (eq. 3). These results suggest that the intramolecular migration of the C2-deuterium might be completely excluded in the reaction pathway, and the formation of a phosphonium ylide as an intermediate might be involved.

With the above mechanistic information in mind, a plausible reaction pathway is outlined in Scheme 4. Initially, the phosphonium salt ($MePPh_3I$) reacts with KO^{t}Bu to form the phosphonium ylide, which subsequently undergoes an intermolecular [3+2] annulation reaction to afford intermediate **I**. Finally, aromatization by an external base leads to the formation of the C2-methylated product **3e**. The eliminated triphenylphosphine oxide was observed by ^{1}H NMR spectroscopy of the crude reaction product in each cases.



Scheme 4. Proposed reaction mechanism.

To further confirm whether phosphonium ylides are potential intermediates in this process or not, we performed the reaction of **1a** with bromoalkylphosphonium salts under the standard reaction conditions (Scheme 5). To our delight, cyclopropylated and cyclobutylated pyridine derivatives **8a** and **8b** were formed. This observation is rationalized through the initial formation of phosphonium ylides from the bromoalkylphosphonium salts **2k** and **2l** that then undergo cyclization to afford cyclopropyl and cyclobutyl phosphonium salts, which then further react with a base to generate the corresponding ylide intermediates.



Scheme 5. Alkylation using bromoalkyl phosphonium salts.

In conclusion, we disclosed the unique reactivities of phosphonium salts in the C–H alkylations of pyridine- and quinoline-*N*-oxides. This protocol provides a facile route to the formation of C2-alkylated pyridine and quinoline derivatives under mild reaction conditions. High levels of site selectivity and functional-group tolerance were observed. In particular, the scaled-up one-pot reactions and sequential C–H transformations of pyridine- and quinoline-*N*-oxides highlight the utility of the developed method. A number of labeling experiments were carried out to understand the mechanism of this transformation.

Acknowledgements

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Keywords: Alkylation • Methylation • Pyridine-*N*-oxide • Regioselectivity • Wittig reagent

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Entry for the Table of Contents

Key Topic: Alkylation of pyridine-*N*-oxides

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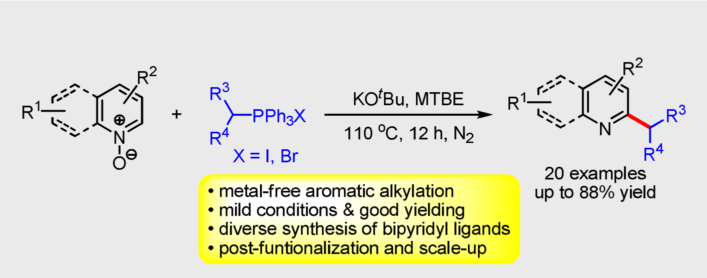

Sangil Han, Prashant Chakrasali, Jihye Park, Hyunjung Oh, Saegun Kim, Kyuneun Kim, Ashok Kumar Pandey, Sang Hoon Han, Soo Bong Han, and In Su Kim**

Page No. – Page No.

Reductive C2-Alkylation of Pyridine- and Quinoline-*N*-Oxides Using Wittig Reagents

Alkylated pyridines & quinolines: The unprecedented reductive alkylation of pyridine- and quinoline-*N*-oxides using Wittig reagents is described. A wide range of pyridine- and quinoline-*N*-oxides was used to provide a variety of C2-alkylated pyridines and quinolines with excellent site selectivities and functional-group compatibilities.