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Reaction of Pyridine-*N*-Oxides with Tertiary sp^2-*N*-Nucleophiles: An Efficient Synthesis of Precursors for *N*-(Pyrid-2-yl)-Substituted *N*-Heterocyclic Carbenes

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Abstract: *N*-(Pyrid-2-yl)-substituted azolium and pyridinium salts, precursors for hybrid NHC-containing ligands, were obtained with excellent regioselectivity, employing a deoxygenative CH-functionalization of pyridine-*N*-oxides with substituted imidazoles, thiazoles, and pyridine. Unlike the traditional S_NAr-based methods, this approach provides high yields for substrates bearing substituents of different electronic nature. The utility of azolium and pyridinium salts thus prepared was also highlighted by the synthesis of pyridyl-substituted imidazolyl-2-thione, benzodiazepine as well as 2-aminopyridines.

Keywords: Pyridine *N*-oxide; *N*-Heterocyclic carbenes; Nitrogen Heterocycles; Amination; C-H functionalization

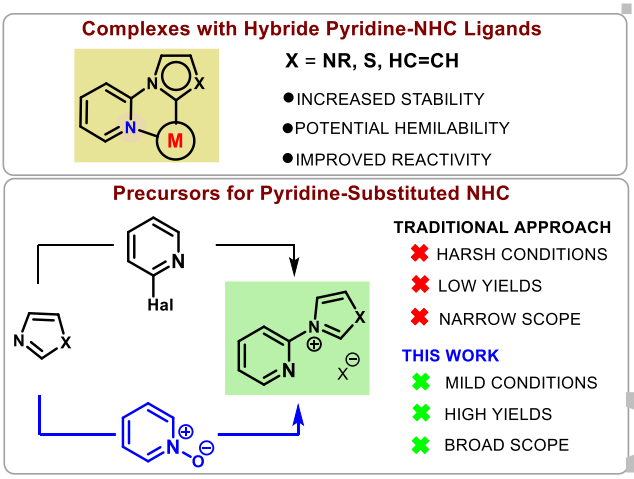

Figure 1. Traditional and our ways for synthesis of precursors for pyridyl-substituted *N*-heterocyclic carbenes.

N-Heterocyclic carbenes (NHCs) featuring high σ-donating and weak π-accepting abilities[1] are an important class of compounds that found numerous applications in organocatalysis[2] and as ligands for transition metal and main group elements.[3] Transition-metal complexes containing NHC ligands are widely used as active catalysts for fundamental organic transformations including olefin metathesis, hydrogenation transfer, various C-C bond-forming processes, etc.[4] Among others, multidentate NHCs with an appended pyrid-2-yl-type moiety bearing the donating nitrogen atom have attracted particular attention. The chelate complexes with such hybrid ligands have found wide applications due to their improved catalyst stability and their potential hemilability, which provides ease of generation of vacant coordination site and catalytically active species.[5] Besides their catalytic applications, complexes of transition metals with pyrid-2-yl-substituted NHCs have demonstrated anticancer, antimalarial, antiplasmodial, and other activities.[6] Moreover, these complexes possess unique photophysical properties and have found application in materials chemistry.[7]

Pyrid-2-yl-substituted NHCs are readily generated from the corresponding *N*-substituted azolium or pyridinium salts by deprotonation.[8] In turn, the *N*-pyridyl-substituted azolium and pyridinium salts are traditionally prepared from 2-halopyridines via a nucleophilic substitution (S_NAr) with *N*-substituted azoles and pyridine and often in low yields.[8b] The S_NAr-reactions in 2-halopyridines require high temperature (>160 °C) for substrates without strong electron-withdrawing groups, which results in a restricted functional group compatibility. At the same time, the variation of substituents on the NHC ligand would produce changes in the electronic and steric properties of the carbene moiety, providing an effective tool for fine-tuning the catalytic properties of the whole NHC-metal complex. Moreover, substituted 2-halopyridines and quinolines are difficult to prepare from the parent heterocyles as issues of poor regioselectivity and over-halogenation often arise.[9] As a result, the incorporation of halogens onto pyridines in a selective manner commonly requires multiple synthetic steps. Given wide applicability of pyridyl-substituted NHCs in catalysis, medicinal and materials chemistry, there exists a need in developing

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of an alternative synthetic method toward their precursors, which would enable a broader substrate scope and greater functional group tolerance.

A site-selective deoxygenative CH-functionalization of pyridine-*N*-oxides arguably represents a powerful strategy to access diverse pyridine structures and is recognized as an expedient and efficient alternative to nucleophilic substitution in 2-halopiridines and their transition-metal catalyzed reactions.[10] In contrast to 2-halopyridines, pyridine-*N*-oxides are straightforward to prepare from widely accessible parent pyridines via a simple oxidation process.[10a,11] Generally, electrophilically pre-activated *N*-oxides readily react with a wide range of nucleophiles under relatively mild and eco-friendly reaction conditions, yielding pyridines with a new substituent at either the C2 (predominantly) or C4 position.[10] In particular, the *N*-oxide-based strategy has been widely used for the installation of the amine functionalities into pyridines and fused pyridines, using variety of 1°, 2°, and 3° sp^3-amines as the nucleophilic agents.[12] Meanwhile, reactions of preactivated pyridine-*N*-oxides with sp^2-*N*-nucleophiles have received much less attention.[12b,m,n] Moreover, there have been no reports on the reactions with *N*-substituted imidazoles and the related compounds. If developed effectively, such reactions would provide a robust and efficient route to precursors for valuable pyridyl-substituted NHCs. Herein, we present our study of these novel C–N-bond forming reactions utilizing pyridine-*N*-oxides.

We initiated our study by examining the reaction between 2,2'-bipyridine *N*-oxide (**1a**) and 1-methylimidazole (**2a**) under different conditions. The highest yield of the imidazolium salt **3aa** was obtained when the reaction was performed in MeCN with 2 equiv of 1-methylimidazole (**2a**) and 1.5 equiv of trifluoromethanesulfonic anhydride (Tf_2O) as the activating agent at ambient temperature (Table 1, entry 1). Employing other typical activating agents (TFAA, Ac_2O, TsCl, MsCl, Ts_2O) and performing the reaction in other solvents (entries 4-6) resulted in decreasing yields. The ratio of reagents is also crucial for the reaction to proceed in high efficiency (entries 1 vs 3). Importantly, this transformation is highly site-selective at the C2 position and the regioisomeric 4-substituted product was not detected in the crude reaction mixture.

Next, the optimized reaction conditions (Table 1, entry 1) were applied to a variety of *N*-oxides bearing substituents of different electronic nature. *N*-Oxides of a variety of pyridines and quinolines with both electron-donating and electron-accepting groups were equally effective substrates, affording the imidazolium salts **3** in good to excellent yields (Scheme 1A). Remarkably, in all cases the product **3** was isolated as a single regioisomers at the C2 position, including the salt **3bb** obtained from unsubstituted pyridine-*N*-oxide. While the *N*-oxide-based strategy toward the preparation of functionalized pyridines often suffers from low 2/4-regioselectivity that limiting its

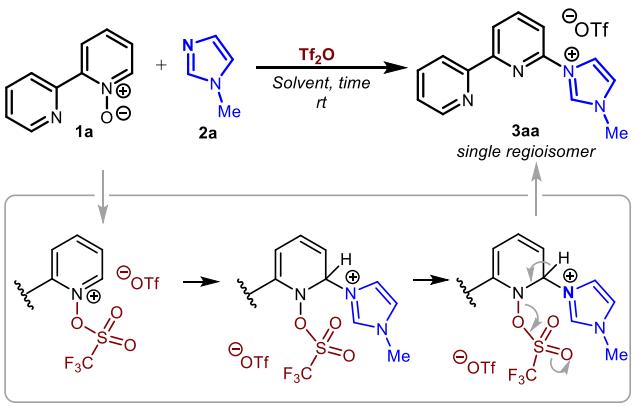

Table 1. Selected Results of Reaction Optimization.[a]

entry	**2a**:Tf_2O	solvent	time (h)	yield (%)
1	2:1.5	MeCN	4	99
2	2:1.5	MeCN	2	67
3	1.5:1.5	MeCN	4	62
4	2:1.5	DCM	4	55
5	2:1.5	toluene	4	74
6	2:1.5	THF	4	19
7	2:1.5	EtOAc	6	48

[a] The reaction was performed on 0.2 mmol (1 equiv) of 2,2'-bipyridine *N*-oxide (**1a**) in 2 mL of a solvent at rt. For more information, see the Supporting Information. Yields were determined with ^1H NMR using 1,4-dibromo-2,5-dimethylbenzene as an internal standard.

applicability,[8,12b,d] our reaction leads exclusively to the formation of 2-regioisomers regardless of the electronic nature of substituents incorporated on the pyridine ring. Moreover, no products were obtained with starting materials being almost quantitatively recovered when *N*-oxides of 2,6-dimethylpyridine, 2,6-dibromopyridine, and 2-phenylquinoline were used as the substrates under the optimized reaction conditions. However, when 3-substituted *N*-oxides derived from ethyl isonicotynate and 3,4-lutidine were employed in the transformation, mixtures of the C2 and C6 regioisomers were formed. While the C2-regioisomers are the major products in both cases, the C2/C6 proportion considerably depends on the electronic nature of the C3-substituent (**3gb** vs **3hb**).

We also explored a variety of substituted imidazoles, thiazoles and their benzannulated derivatives in the reaction (Scheme 1B). The expected azolium salts were obtained in good to high yields, in all cases, except one. Remarkably, the reaction is perfectly compatible with a 2-susbstituted imidazole (salt **3mc**) and an imidazole bearing the electron-withdrawing substituent (salt **3me**). It should be noted that derivatives of histidine were also compatible with the developed reaction conditions as demonstrated by the preparation of salts **3ld** and **3me** in good yields. Benzothiazole, however, was unreactive due its poor

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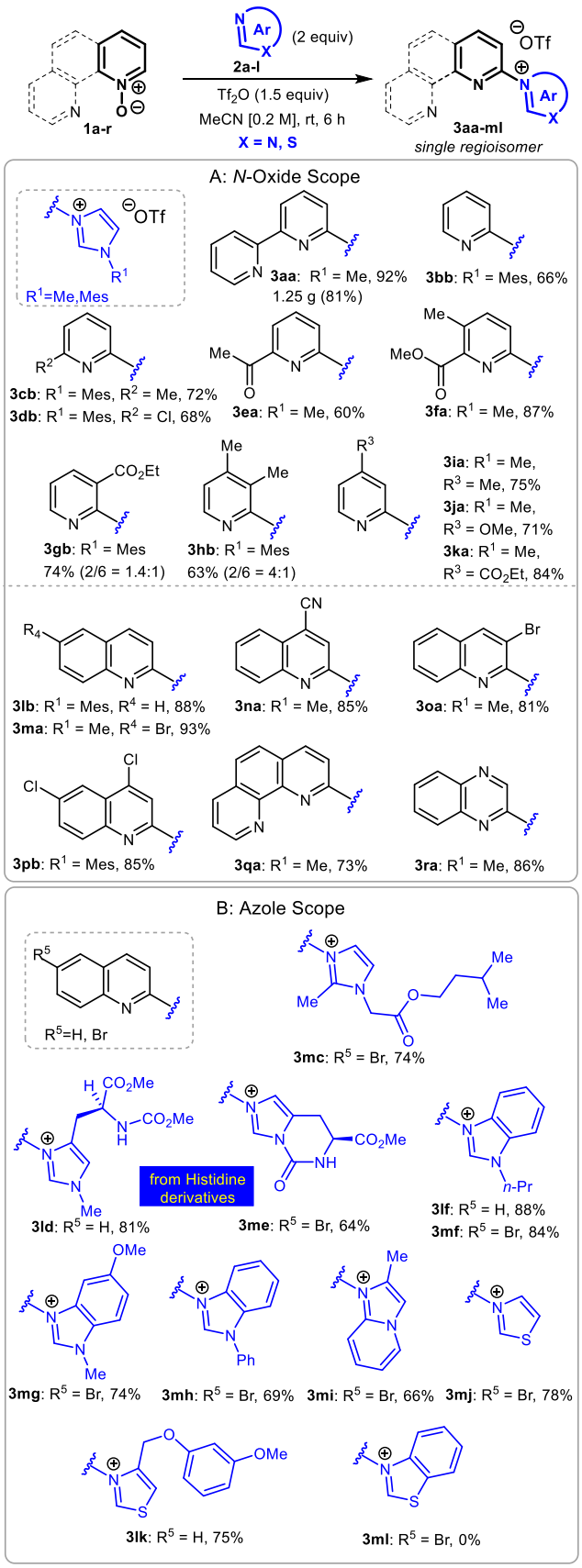

Scheme 1. Scope of *N*-oxides and azoles.[a]

Reactions were performed on 0.5 mmol of *N*-oxides. Yields and 2/6-regioisomeric ratios are reported for the isolated compounds.

nucleophilicity; only the starting *N*-oxide was almost fully recovered. Many sensitive functional groups substituent (salt **3me**). It should be noted that derivatives of histidine were also compatible with the developed reaction conditions as demonstrated by the preparation of salts **3ld** and **3me** in good yields. Benzothiazole, however, was unreactive due its poor nucleophilicity; only the starting *N*-oxide was almost fully recovered. Many sensitive functional groups remained intact under the mild reaction conditions employed, including challenging urethane (**3ld**), carbamide (**3me**) groups and a chlorine atom at the positions activated to S_NAr-reactions (**3db**, **3pb**).

Thus, azolium salts **3aa-ml** were obtained using an operationally simple procedure and, in contrast to halogenides and trifluoroacetates, were readily isolated from the reaction mixture in high purity after an aqueous workup and recrystallization. Importantly, this protocol provides access to pyridyl-substituted azolium salts which are impossible or difficult to obtain through current methods based on the S_NAr chemistry.

To further demonstrate the applicability of the protocol, we examined reactions of differently substituted pyridine-*N*-oxides with pyridine to afford the corresponding *N*-(pyrid-2-yl)-substituted pyridinium triflates. In contrast to the imidazole-based NHC complexes, their pyridine-based counterparts (pyridylidenes) are less common. However, NHCs derived by deprotonation of pyridinium salts, being stabilized by only one nitrogen atom, are particularly interested as stronger σ-donors and better π-acceptors than azol-2-ylidenes.[13] Pyridinium salts **4a-k** bearing both electron-donating and electron-withdrawing substituents on the pyridine ring were isolated in good to excellent yields employing the above-developed reaction conditions, thus demonstrating the general applicability of the method (Scheme 2). Here again, the transformation exhibits good functional group compatibility and proceeds with exceptional regiosectivity at the C2-position.

Besides their application as NHC precursors, *N*-pyridyl-substituted azolium and pyridinium salts can be used as useful reagents in organic synthesis. To demonstrate this feature, we performed several synthetic transformations (Scheme 3). First, the reaction of imidazolium triflate **3aa**, derived from 2,2'-bipyridine (**1a**) and 1-methylimidazole (**2a**), with elemental sulfur under basis conditions resulted in the formation of a tridentate ligand **5**, comprising the imidazolyl-2-thione moiety (Scheme 3A). Ligands of this type are widely used to produce metal complexes, possessing unique catalytic and redox properties.[14] Next, the quinolyl-substituted benzimidazolium salt **3mf**, obtained from quinoline-*N*-oxide (**1l**) and 1-propylbenzimidazole (**2f**), was readily transformed into the benzodiazepine derivative **6**, employing a recently developed ring opening/ring closure protocol.[15] Overall, the complex heterocyclic compound **6**, containing a structural motive of several marketed pharmaceuticals,[15,16] was obtained in two simple steps starting from two commercially available

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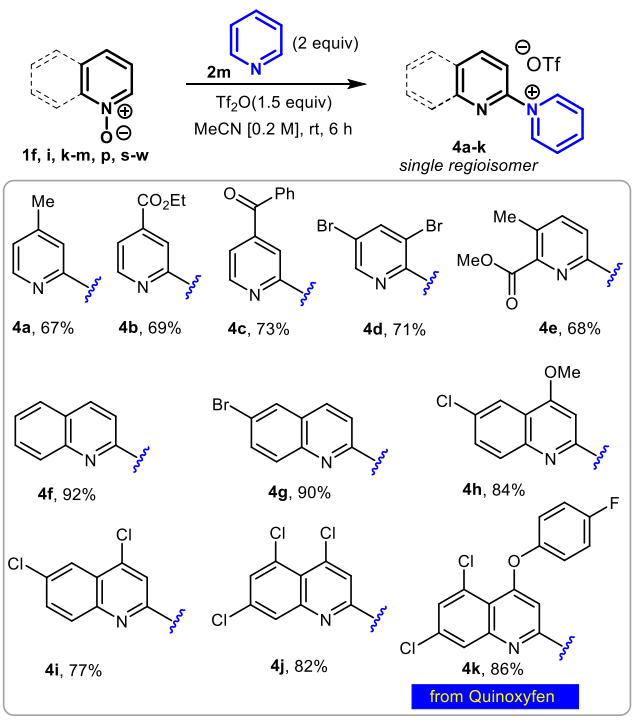


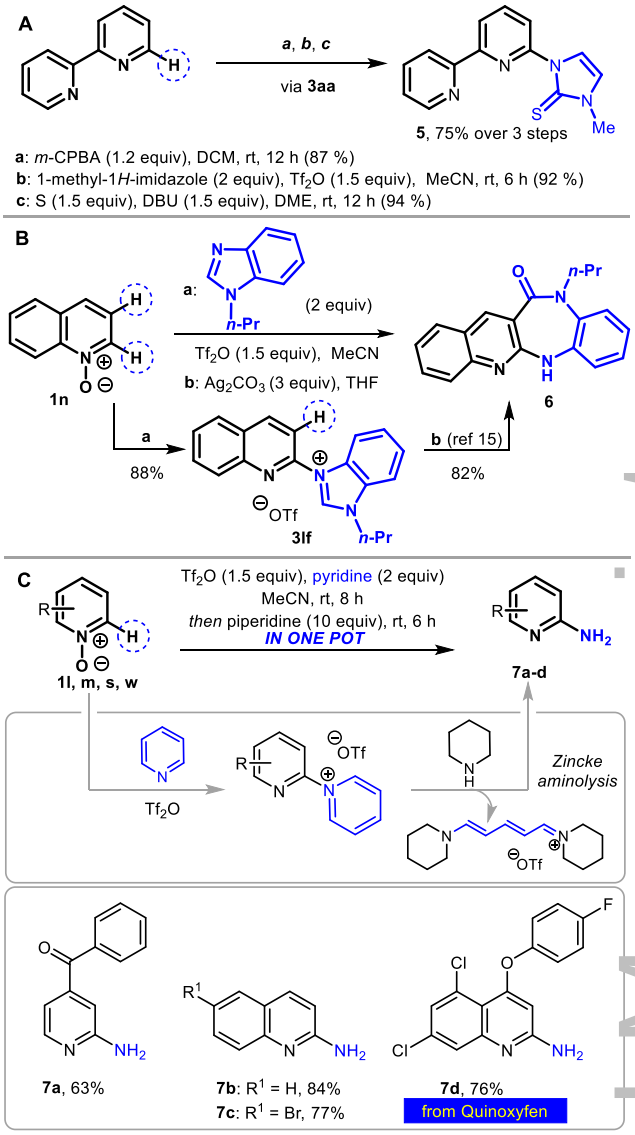
Scheme 2. Reaction of azine *N*-oxides with pyridine.[a]

[a]Reactions were performed on 0.5 mmol of *N*-oxides. Yields are reported for the isolated compounds.

compounds via a selective two-fold CH-functionalization of the quinoline ring (Scheme 3B).

Finally, we used pyridinium salts **4** for the preparation of 2-aminopyridines and 2-aminoquinolines **7** (Scheme 3C). The 2-aminopyridine structural motif is an important pharmacophore found across many known therapeutic agents.[17] While several methods to introduce the NH_2-functionality into the pyridine ring have been disclosed to date, none of them could be considered as a general approach.[12a-c,k,17b,18] The known methods suffer from significant limitations such as narrow scope, limited functional group compatibility, harsh reaction conditions, using either operationally complicated procedures or sophisticated reagent or sometimes both. Hence, our two step-one pot procedure, combining a pyridinium salt formation followed by the Zincke aminolysis,[18] to furnish 2-aminopyridines **7** represents a highly attractive alternative for the previously reported methods. Employing a site-selective deoxygenative CH-functionalization of *N*-oxides, we prepared an amino derivative of Quinoxyfen, an active ingredient of many fungicides: amine **7d** was obtained in 62% yield starting from Quinoxyfen.

In conclusion, the reaction of preactivated with Tf_2O pyridine- and quinoline-*N*-oxides with tertiary sp^2-*N*-nucleophiles (imidazoles, benzimidazoles, thiazoles, and pyridines) enables to obtain the corresponding azolium and pyridinium salts in a regioselective manner under mild conditions. The process is equally effective for substrates, containing electron-withdrawing and electron-donating



Scheme 3. Synthetic aplication.

nitriles, carbonyls, esters, and *NH*-amides. While azolium and pyridinium salts thus prepared serve as precursors for valuable *N*-(pyrid-2-yl)-substituted *N*-heterocyclic carbenes, they are also useful starting materials for the synthesis of ligands and medicinally relevant compounds.

Experimental Section

General Procedure I: Synthesis of Precursors for Pyridyl-Substituted *N*-Heterocyclic Carbenes (3aa-ml, 4a-k)

To a stirred solution of *N*-oxide (1 equiv) in MeCN (0.2 M) an azole or pyridine (2 equiv) was added in one portion. The mixture was cooled to 0 °C and Tf_2O (1.5 equiv) was added dropwise. The resulting mixture was stirred for 15 min at 0°C and 8 h at rt. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2, and washed with water, the aqueous layers were combined and extracted with CH_2Cl_2. The combined organic extracts were dried

with Na_2SO_4, and concentrated under reduced pressure to afford the product, which was purified by recrystallization from a CH_2Cl_2/Et_2O mixture.

General Procedure II: One-pot Synthesis of 2-Aminopyridines and 2-Aminoquinolines from *N*-Heterocyclic Carbenes

To a stirred solution of *N*-oxide (1 equiv) in MeCN [0.2 M] pyridine (2 equiv) was added in one portion. The mixture was cooled to 0 °C and Tf_2O (1.5 equiv) was added dropwise. The resulting mixture was stirred for 15 min at 0°C and 8 h at rt. Then, piperidine (10 equiv) was added dropwise at rt and stirring was continued for 6 h at the same temperature. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel using gradient mixtures of CH_2Cl_2 and MeOH (50:1 to 10:1) as eluents.

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UPDATE

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