SUBSTITUENT EFFECTS ON THE SYNTHESIS AND REACTIVITY OF 2-BENZYLOXYPYRIDINIUM TRIFLATE DERIVATIVES

A THESIS

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

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MASTER OF SCIENCE

BY

TAYYEBEH BAKHSHEH

DR. PHILIP A. ALBINIAK - ADVISOR

BALL STATE UNIVERSITY

MUNCIE, INDIANA

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Abstract

2-benzyloxy-1-methylpyridinium triflate (Bn-OPT) has recently been investigated as a new benzylation reagent to transfer benzyl groups to a variety of oxygen nucleophiles under relatively neutral and mild conditions. The reaction using Bn-OPT requires stirring at 80 °C for 24 hours to generate the corresponding benzyl ether. The benzylation reaction potentially proceeds through an $S_N1$-like pathway generating the benzyl cation and the corresponding anion as intermediates. Previous studies have shown that using an electron donating groups (such as para-methoxy) on the benzyl ring affects the decomposition of the triflate salt and the reaction occurs at significantly lower temperature and time due to the stabilization of the benzyl cation. This project focuses on using electron withdrawing groups (EWGs) on the pyridyl ring which affects the stability of the anion and lowers the reaction temperature.

The synthetic strategy for the various derivatives follows the original Bn-OPT synthesis. EWGs affect the stability of this reagent at room temperature; therefore it was decided to transfer benzyl group by \textit{in situ} formation of 2-benzyloxypyridinium salt derivatives except for weak EWG. Three different categories of electron withdrawing groups were chosen to investigate the chemical reactivity of this reagent as well as the feasibility of the proposed idea: nitro and trifluoromethyl groups as strong deactivators, cyano as a substituent with medium effect, and chloro on the fifth and sixth positions to the nitrogen atom as a weak deactivator. These have been studied, and the results will be compared to the original reagent without using electron withdrawing groups. The successful installation helps support our theory using EWGs on pyridyl ring to lower the temperature of the benzylation reaction as well as the reaction time.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄</td>
<td>Lithium Aluminum Hydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BnO</td>
<td>Benzyloxy</td>
</tr>
<tr>
<td>OTHP</td>
<td>Tetrahydropyranyl ether</td>
</tr>
<tr>
<td>OMOM</td>
<td>Methoxymethyl ether</td>
</tr>
<tr>
<td>CSI</td>
<td>Chlorosulfonyl isocyanate–sodium hydroxide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Ddichloro-5,6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>Bn-OPT</td>
<td>2-Benzyloxy-1-methylpyridinium trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluromethanesulfonic acid</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>MeOTf</td>
<td>Methyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
</tbody>
</table>
t tert

EWG Electron-withdrawing group

C Celsius

CF₃ Trifluoromethyl

CN Cyano

TLC Thin Layer Chromatography

DMF N,N-Dimethylformamide

DMSO Dimethylsulfoxide

CH₂Cl₂ Dichloromethane

Et₂O Diethyl ether

ref. Reference

g gram(s)

h hour(s)

d day(s)

equiv. equivalent

eq. equivalent

ml milliliter
M molar
Me methyl
min minute(s)
mol moles
mp melting point
ppm part(s) per million
s singlet
d doublet
t triplet
m multiplet
RT room temperature
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Chapter 1

Background Information
1. Introduction

1.1 Protective groups

Organic synthesis has reached a remarkable level of competence and even the most complex molecules are accessible. The prerequisites for this success are both the availability of a wide range of efficient synthetic methods and the reagents. The complex synthetic intermediates and products contain, in general, a multiplicity of functional groups, most of which must be blocked and, at an appropriate point in the synthesis, liberated.

When a chemical reaction needs to be performed in a selective manner at one reactive site in a multifunctional molecule, all other sites that are reactive to the same chemical environment must be temporarily blocked by rendering them inert. For example, consider the following reaction (Scheme 1.1), making a keto alcohol from a keto ester:

![Scheme 1.1: Reduction of a Ketoester to an Alcohol Required a Protecting Group](image)

The overall transformation required is a reduction of an ester to a primary alcohol. Lithium Aluminum Hydride, LiAlH₄, is a common reagent used for these reductions, but it will also
reduce the ketone as well which is not desired. The solution to this problem is to mask the ketone with a protecting group and change the reactivity so that no undesired reactions take place. In this example, we can protect the ketone \textbf{1.1} as an acetal \textbf{1.3}, which doesn't react with LiAlH$_4$. The acetal is then called a protecting group for the carbonyl. This step is the formation or installation of the protecting group onto the desired functional group, rendering the functional group inert in the second step. Then \textbf{1.3} can be reduced to the primary alcohol (\textbf{1.4}) which is known as the transformation step. Finally the acetal is removed by reacting it with an aqueous acid, revealing the original carbonyl which is called the deprotection or cleavage step. From this example it can be seen that protecting one or more functional groups requires at least two (protection-deprotection) or more additional steps in the overall synthesis but it allows the opportunity for selective synthesis of molecules that would not be otherwise possible.

A protecting group could be called ideal when it fulfills the following criteria: 1) the protecting group should react with the desired functional group in a selective manner and produce product in high yield 2) the other functional groups in the desired molecule must not be reacted 3) the protected compound should have good stability when stored for a long time and be stable under all the conditions used during the synthesis, including those of the purification steps 4) It should have a minimum number of functional group to avoid side reaction during the course of the main reaction 5) at the time of deprotection, it should be cleavable under very mild conditions in a highly selective manner and in high yield; other protecting groups present in the molecule and unprotected functionalities should not be affected by the cleavage conditions.
1.2 Benzyl Ethers

The benzyl group plays a central role in protecting many groups for alcohols, carboxylic acids, amines, and diols which can be present as ethers, esters, urethanes, carbonates, or benzylidene acetals. Benzyl ethers are among the most popular alcohol protecting groups due to their stability in a wide range of reaction conditions and mild cleavage protocols. They are stable in both aqueous acidic and basic solutions which can easily remove many protecting groups. Very strong acids will deprotect the benzyl ether, but traditional acidic conditions (like aqueous pH=1) causes no problems. Whereas other protecting groups such as the tetrahydropyranyl ethers (OTHP) and methoxymethyl ethers (OMOM) deprotect easily under these conditions. The OBn are unreactive toward most metal hydride reducing agents and mild oxidizing agents. In addition, various reactivity and chemical differentiability can be obtained by different substituted benzyl ethers.

1.2.1 Deprotection of Benzyl Ethers

A variety of methods have been developed for the removal of benzyl ethers, depending on the other functional groups of the molecule. Deprotection is normally performed as a palladium-catalyzed hydrogenation, forming the C-H (1.6) and O-H (1.7) bonds in their respective places (Scheme 1.2). This is a very gentle method of deprotection which is due to the fact the benzyl substrate are excellent for oxidative addition reactions of Pd\(^0\) or Ni\(^0\). Scheme 1.2 shows an example of a selective deprotection of benzyl ether in the presence of another protecting group, OTHP group which are generally stable with respect to hydrogenolysis.
The addition of Lewis acids such as FeCl$_3$ (Scheme 1.3a),$^5$ MgBr$_2$ (Scheme 1.3b)$^6$ or CrCl$_2$/LiI$^7$ and lithium naphthalenide$^8$ are other methods of deprotection of the benzyl group, avoiding the catalytic hydrogenolysis.

Chlorosulfonyl isocyanate–sodium hydroxide (CSI) has also been developed in the activation of benzyl ether to form N-chlorosulfonyl-N-benzylcarbamate (1.13), which is easily cleaved by NaOH to form the alcohol (Scheme 1.4a).$^9$–$^{11}$ As an alternative method, 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) was reported to be a good reagent for deprotection in the presence or absence of water (Scheme 1.4b).$^{12}$–$^{14}$
1.3 Synthesis of Benzyl Ethers

Benzyl ethers can be generated from alcohols by the Williamson Ether Synthesis under basic conditions, using trichloroacetimidates in the presence of acids,\textsuperscript{15,16} or using 2-Benzylxyloxy-1-methylpyridinium triflate (Bn-OPT).\textsuperscript{17–19}

The Williamson reaction is widely used in both laboratory and industrial synthesis, and remains the simplest and most popular method of preparing ethers. These reactions involve an alkoxide (1.17) that reacts with a primary alkyl halide (1.18) via an S\textsubscript{N}2 mechanism (Scheme 1.5). Since alkoxide ions are highly reactive, this method often competes with the base-catalyzed elimination of the alkylating agent. The nature of the leaving group as well as the reaction conditions (particularly the temperature and solvent) can have a strong effect on which is favored. In particular, some structures of alkylating agent can be particularly prone to elimination.
For substrates that are not stable to basic conditions, the use of benzyl trichloroacetimidate allows for protection under acidic conditions. Trichloroacetimidates were first prepared and thoroughly investigated by Cramer and his group in the late fifties. This reagent has been successfully employed in the use of the benzylation of carbohydrates, lactams, and p-hydroxy esters.

The conversion of imidate structure (1.21) to the stable amide by protonation at the nitrogen of the benzyl trichloroacetimidate seems to be a main driving force in benzylation, which needs to be activated by a strong acid like trifluoromethanesulfonic acid (TfOH) or trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 1.6). In addition, the trichloromethyl group as an electron-withdrawing group will enhance the reactivity of the imidate as a leaving group.

Both methods of benzyl ether formation, Williamson ether synthesis and coupling with trichloroacidimate, offer an effective and established way for protecting an alcohol functional group. Simple alcohols with little to no functionality could be protected by either technique.
However, these procedures can sometimes be problematic with multifunctional substrates due to extreme pH. A mild and pH-neutral method could be more effective to generate benzyl ethers in more complex molecular systems.

1.4 Benzyloxyypyridinium Triflates (Bn-OPT)

2-Benzyl oxy-1-methylpyridinium triflate (Bn-OPT) is a relatively new reagent which allows for protection of alcohols under relatively neutral conditions.17–19 Bn-OPT (1.23) is a white crystalline solid compound which is stable at room temperature and can be easily prepared. No acidic or basic activators are required for the benzyl transfer reaction, which takes place upon warming under mild conditions when alcohol substrates are present.

![Scheme 1.7: Synthesis of Benzyloxyypyridinium Triflate](image)

The synthesis of 1.23 (Scheme 1.7) is a two-step synthesis: 2-chloropyridine (1.21) undergoes nucleophilic aromatic substitution and the chloro is replaced by benzyl alcohol in the first step. The second step is the methylation of the nitrogen atom using methyl triflate (MeOTf).19 Strong electrophiles, like methyl triflate, are very reactive and they react by following the \( S_N2 \) mechanism.

Dudley and Albinia have developed novel synthetic methods for O-protected ether17–19 and esters26 using Bn-OPT and investigated its mechanisms.27,28 A wide range of structurally varied
alcohols has been used to provide the corresponding benzyl ether by using Bn-OPT (Table 1.1). For primary and secondary alcohols, yields are typically higher than 70%. Benzylation of tertiary alcohols and phenols are more challenging substrates.

![Chemical structure](image)

Table 1.1: Synthesis of Benzyl Ethers using Bn-OPT

<table>
<thead>
<tr>
<th>Ethers</th>
<th>Yield %</th>
<th>Ethers</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO(\rightarrow)O(\rightarrow)OH</td>
<td>93</td>
<td>OAc(\rightarrow)OH</td>
<td>96</td>
</tr>
<tr>
<td>HO(\rightarrow)CO(\rightarrow)Me</td>
<td>75</td>
<td>TBDPSO(\rightarrow)O(\rightarrow)O</td>
<td>72</td>
</tr>
<tr>
<td>PivO(\rightarrow)H(\rightarrow)Ot-Bu</td>
<td>95</td>
<td>PhO(\rightarrow)Ph(\rightarrow)OBn</td>
<td>73</td>
</tr>
</tbody>
</table>

Bn-OPT is suitable for the benzylation of acids under relatively mild and neutral conditions. Et\(_3\)N, a weak base, is used for estrification of alcohol to activate the carboxylic acids as well as a phenylcarbenium scavenger to block further reaction after the consumption of the carboxylic acid. Benzylation of carboxylic acids proceeds in high yield and in the presence of alcohols, phenols, and other functional groups (Table 1.2).
Bn-OPT is an ideal alternative for some alcohols because of the neutral conditions. In some cases, the only way to benzylate the alcohol was to use Bn-OPT. Table 1.3 shows some examples of molecules where benzylation would not occur using alternative methods.
Table 1.3: Application of Bn-OPT

Molecule 1.40 is frequently seen as chiral building blocks for the construction of a variety of synthetic intermediates in total synthesis.\(^\text{29}\) It can undergo transesterification, acetate migration, or hydrolysis under both the Williamson ether synthesis and trichloroacetimidate reaction conditions. In the case of molecule 1.41,\(^\text{30}\) the initial attempt of protecting the hydroxyl group resulted in the decomposition or only low yields of the desired tris-PMB ether despite trying a variety of different acid catalysts (TfOH, La(OTf)\(_3\), BF\(_3\).OEt\(_2\), Ph\(_3\)CBF\(_4\)) with para-methoxybenzyl(PMB)-trichloroacetimidate. Little improvement was observed using basic conditions with PMB-Cl/Br and NaI. The 72% yield of tris-PMB ether has been obtained using PMB-lepidine in the presence of MeOTfs. For 1.42, the use of this alkylating agent was
necessary, as other conventional alkylating agents resulted in alkylation of only the thiourea sulfur atom.\textsuperscript{31}

**Scheme 1.8**: Different Versions of Pyridinium Triflate Transfer Reagents; Dashed line shows the bond to be broken

Other versions of this reagent such as \(\text{t-butoxy (1.43)}\) and \(\text{allyloxy (1.44)}\) pyridinium triflate (ongoing project in Albiniak’s lab) have been developed to transfer the corresponding groups to the alcohols or carboxylic acids (Scheme 1.8). The reactivity of these different reagents varies. The reaction conditions must be adjusted to fit the reactivity of the transferring groups. The high reactivity of \(\text{t-butyl and para methoxybenzyl (PMB)}\)\textsuperscript{32} triflate salts require that the transferring reactions be conducted under low temperature (0 °C to room temperature). These derivatives have been generated \textit{in situ} and trapped with alcohols to overcome the limited stability of these reagents. The PMB lepidine (1.45) ether was used to increase the solubility of PMB-transfer reagents in PhCF\textsubscript{3}.\textsuperscript{28} Harsher reaction conditions such as increasing the temperature to 100 °C must be used to accomplish this reaction with halobenzyl (1.46) groups which are less reactive.\textsuperscript{33}
The transformation of methyl group (1.47) which is completely unreactive did not occur under the same reaction condition as the original reagent at 80 °C.\textsuperscript{18}

### 1.4.1 Reaction Mechanism

Two basic mechanistic extremes of alkylation are generally accepted: the first-order nucleophilic substitution (S\textsubscript{N1}) and the second-order nucleophilic substitution (S\textsubscript{N2}). The typical S\textsubscript{N1} and S\textsubscript{N2} reaction mechanisms are shown in Scheme 1.9. In an S\textsubscript{N1} substitution reaction, the first step is the formation of a benzyl carbocation intermediate and the corresponding anion. This takes place slowly and represents the rate-limiting step. The covalently bonded adduct is rapidly formed from this intermediate and the nucleophile. The stability of the carbocation and nature of the leaving group determine the reactivity of the electrophile. The S\textsubscript{N2} reaction involves an attack of the electrophilic carbon atom by a nucleophile from the opposite site of the leaving group. These types of reactions are dependent on steric accessibility.

**Scheme 1.9:** Two Basic Mechanistic Extreme Pathways for the Substitution Reaction

The earliest observational evidence for the decomposition of Bn-OPT by a S\textsubscript{N1} mechanism involved the formation of diarylmethane byproducts during the reaction of 1.23 with alcohols.
which was interpreted by the Friedel–Crafts-type products (Scheme 1.10).\textsuperscript{27} Further studies have been performed by heating Bn-OPT in the absence of other nucleophiles at 80 °C for 24 hours in various aromatic solvents such as anisole, toluene, benzene, and bromobenzene. The corresponding diarylmethanes are obtained in excellent yields (>93%) for electron-rich arenes such as anisole, and in good yields (72% yield) for less activated arenes such as bromobenzene.

![Scheme 1.10](image)

**Scheme 1.10:** Reaction of the Bn-OPT with Electro\textsuperscript{1.53}n-rich Arenes

Friedel-Crafts alkylation usually involves treating the aromatic compounds with an alkyl halide and a Lewis acid like AlCl\textsubscript{3}\textsuperscript{34}. The Lewis acid removes the chloride atom from the alkyl halide (1.54), which then releases the corresponding cation (1.56) for the alkylation reaction shown in Scheme 1.11a.

![Scheme 1.11](image)

**Scheme 1.11:** a) Traditional Friedel-Crafts Reaction; b) Friedel–Crafts Reaction of Bn-OPT with Electron-rich Arenes
A Lewis acid is required for the formation of a carbocation-like species in Friedel–Crafts reactions because of the relatively limited nucleophilicity of the aromatic compounds. The observance of the Friedel–Crafts-type products in the absence of Lewis acid or other activating agent, therefore, supports the thermal decomposition of 1.23 and the formation of the phenylcarbenium species (1.48) for the benzylation reaction as shown in Scheme 1.11b.

It is well-established that the stability of a carbocation increases as the number of hyperconjugating alkyl groups attached to the carbon is increased (1° < 2° < 3°). Allylic and benzylic carbocations show even greater stability due to conjugation with π or lone-pair electrons. When the benzyl-group is replaced by t-butyl (1.54) in this reagent, the resulting carbocation (3°) is more stable and hence lower the transition-state energy and the reaction temperature to 0 °C (Scheme 1.12a). On the other hand, methyl carbocation (1°) is an unstable carbocation. It was also observed that the methoxypyridinium triflate did not transfer a methyl group under similar reaction conditions (Scheme 1.12b). Since methyl groups are great substrates for the SN2 type mechanism, this data was interpreted so that the mechanism does not proceed via SN2.

\[ \text{Scheme 1.12: Transferring a) t-butyl b) Methyl Groups to an Alcohol Using Pyridinium Triflate} \]
An important method in determining the mechanism of a particular reaction is to study how the rate of the reaction varies by altering a substituent on the reactant. By measuring how the various substituent groups affect the rate of reaction, one can gain insight as to whether the reaction proceeds through a cationic, or an anionic transition state. Substituents which donate electrons density into the ring make the formation of the carbocation easier whereas substituents that withdraw electron density from the system will impede the formation of a carbocation. Based on these results, thermal decomposition of benzyloxypyridinium triflate generates a reactive benzyl electrophile which can be trapped with alcohols or other nucleophiles.

The S_N1 reaction involves a carbocation intermediate and the corresponding anion (Scheme 1.9). The effects of various substituents on the benzyl ring on the stability of the carbocation have been investigated. Previous experiments have shown that an electron deactivating group such as halogens on the benzyl ring reduce the stability of the carbocation and the temperature of transferring reaction was elevated to 100 °C (Scheme 1.13a) compared to the benzylation reaction occurring at 80 °C (Scheme 1.13b).33 Whereas para-methoxy, an strong electron donating substituent, significantly decreases the reaction temperature by stabilizing the carbocation and the transformation reaction occurs at 0 °C to room temperature (Scheme 1.13c).32
However, the effect of substituents on the anion intermediate has not been studied so far. It is believed that an electron withdrawing group increases the stability of the anion by reducing the electron density on the ring. The goal of this project was to investigate the influence of electron acceptor substituents on the benzylation reaction using the pyridinium triflate derivatives.
References:


(2) Kocienski, P. J. *Protecting groups*; Thieme, 2005.


Chapter 2

Results and Discussion
2.1 Introduction

This project has focused on the introduction of electron withdrawing substituents on the pyridyl ring to investigate the reactivity of the benzylation reaction. Based on previous investigations of different versions of the pyridinium triflate, the mechanism of the benzylation reaction was proposed to be more like a S_N1 pathway with the benzyl cation and corresponding anion acting as the intermediate 2.2 (Scheme 2.1a). It has also been shown that the introduction of an electron donating substituent, such as a methoxy group on the benzyl ring 2.4, reduces the ‘transferring reaction’ temperature to room temperature by stabilizing the intermediate carbocations (Scheme 2.1b). It was expected that electron acceptor groups 2.5 assist in the transformation of the benzyl group into nucleophiles by stabilizing the anionic intermediate (Scheme 2.1c). Using an electron withdrawing group on the pyridyl ring will not be incorporated in the group being transferred, enabling the transferring reaction to proceed at lower temperatures in a shorter amount of time.

Three different categories of electron withdrawing groups were chosen to investigate the chemical reactivity of this reagent as well as the feasibility of the proposed idea: NO_2 and CF_3 groups as strong deactivators, CN as a substituent with medium effect, and Cl on the meta or ortho positions as a weak deactivator. These have been studied, and the results will be compared to the original reagent without using electron withdrawing groups.
The first focus was on the transferring reaction of a methyl group to a nucleophile. It was thought this reagent would be easy to prepare in order to test the feasibility of the main idea. A secondary focus involved the synthesis and investigation of the effects of electron deactivating groups on the original benzyl reagent. This was studied thoroughly and we were able to compare our results with the original version of this reagent.

Derivatives were designed with a functional group in either the third or fifth positions (ortho and para positions to the oxygen atom) on the pyridyl ring. These positions were chosen because the stabilizing effect of the electron withdrawing group on the anion is larger than from the second and fourth positions. The manner in which electron withdrawing substituents influence the stability of the anion of a pyridyl ring is shown in Scheme 2.1c. Charge stabilization is greatest when the electron withdrawing group is bonded to one of the negatively charged carbons of the pyridyl anion intermediate. Placing the substituent on the second position is too close to the nitrogen and may impart steric hindrance, masking the electronic effects as well.
The synthetic strategy for the various derivatives follows the original Bn-OPT synthesis. Although the chemical reactivity of pyridine derivatives with electron withdrawing groups is different, its synthesis is expected to proceed in the same mechanistic manner. The proposed synthesis for all derivatives is shown in Scheme 2.2.

![Scheme 2.2: Synthesis of Pyridinium Triflate Salt Derivatives (2.9) and the Benzylation Reaction](image)

EWG: a) 5-NO$_2$  b) 5-CF$_3$  c) 3-CF$_3$  d) 5-Cl  e) 6-Cl  f) 5-CN

It was already mentioned in chapter one that pyridinium triflate salt 2.9 can be prepared in two steps (Scheme 2.2). The replacement of the halogen by a nucleophile involves an intermediate anion which is stabilized by the electronegative nitrogen in the pyridyl ring. Then pyridine attacks electrophiles through its nitrogen atom. The introduction of electron withdrawing substituents is expected to influence the chemical reactivity of the pyridine in different ways. They increase the reactivity of the pyridine ring as an electrophile by lowering the electron density of the ring. Therefore the first step in Scheme 2.2 becomes easier. On the other hand, they reduce the nucleophilicity of the pyridine nitrogen, thereby increase the activation energy required for the methylation of the nitrogen (Scheme 2.3 solid line). It was expected that this type of substituent reduces the activation energy of the anion intermediates and mutually the cation species (Scheme 2.1a). This project was designed to improve the reactivity of the original reagent using electron withdrawing substituents and find an appropriate balance between the activation energy required for the methylation reaction on nitrogen and the transferring reaction.
Previous experiments have shown the transferring tertiary alkyl and allyl groups (on-going projects) as well as the benzyl group and its derivatives\textsuperscript{1-4} to a nucleophile occurs in high yield due to the stability of the intermediate carbocation. However, all attempts to transfer methyl groups to a nucleophile were not successful. It was believed that improving the stability of the anion makes it a better leaving group and helps the substitution reaction on the methyl group through S\textsubscript{N}2-type reaction. Using electron withdrawing substituents on the pyridyl ring pulls electron density from the ring and stabilizes the negative charge through a combination of inductive and resonance effects. If the substitution reaction on the methyl group could be performed by stabilizing the pyridyl anion species, we would be able to expand the utility of this reagent to a variety of primary and secondary alkyl groups. The transferring reaction would occur through different pathways. A stable anion leaving group makes ionization process much easier in S\textsubscript{N}1 reactions and it is also a very good leaving group in S\textsubscript{N}2 reactions.
Since methyl cations are particularly unstable, a strong electron withdrawing group such as a nitro group was chosen to convert the anion into a better leaving group. The anion can leave allowing the methyl group to transfer to a nucleophile. Therefore a nitration reaction on pyridine was attempted using reagents available in the lab. The nitration reaction on the pyridine is an electrophilic aromatic substitution. Electrophilic attack on a carbon atom of pyridine is particularly difficult due to the electron-deficient character of the pyridine ring. However, one strongly donating substituent such as methoxy could cancel out the effect of the nitrogen to a first approximation.

2.2 Synthesis of 2-methoxypyridine

The first attempt in the synthesis of nitropyridine derivatives was the substitution of a methoxy group on the second position using 2-chloropyridine 2.11 in order to activate the ring and facilitate the nitration reaction of pyridine. 2-chloropyridine is more reactive than pyridine towards nucleophile at the second position.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>18-crown-6</th>
<th>Solvent</th>
<th>Temp (°C), Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>Toluene</td>
<td>112 (24h)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.01 equiv</td>
<td>Toluene</td>
<td>112 (24h)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.05 equiv</td>
<td>Methanol</td>
<td>65 (24h)</td>
<td>57*</td>
</tr>
<tr>
<td>4</td>
<td>0.05 equiv</td>
<td>Methanol</td>
<td>65 (24h)</td>
<td>84*</td>
</tr>
</tbody>
</table>

*Table 2.1: Yields (isolated) for the Synthesis of 2-Methoxypyridine.  
*Removal of methanol prior to the work up
This reaction has been performed under different conditions to generate 2-methoxypyridine 2.12 (Table 2.1). The reaction mixture was refluxed in toluene overnight with or without 18-crown-6 (entries 1 and 2). No product was observed in the crude NMR. The product was lost either by the decomposition at a high temperature in the reaction mixture or using reduced pressure below 250 mm Hg in the rotary evaporation apparatus to remove toluene. 2-Methoxypyridine 2.12 is a volatile compound and evaporates at a pressure below 250 mbar. When the reaction was performed at 65 °C in methanol without using toluene, good yields are obtained (entry 4). The only difference between entries 3 and 4 is the removal of methanol prior to the work up (entry 3) or after that (entry 4).

Carbon atoms on pyridine ring are less reactive towards electrophile than benzene due to the electronegativity of N. When pyridines are activated by an electron-donating substituent such as methoxy group, they can undergo the electrophilic aromatic substitution on ortho and para positions in relation to the activating group.

2.3 Nitration of 2-methoxypyridine

The nitration reaction on the pyridine is an electrophilic aromatic substitution. All attempts at the nitration of 2-methoxypyridine 2.12 were unsuccessful (Scheme 2.2).

\[ \text{MeO} \quad \text{H}_2\text{SO}_4, \text{HNO}_3 \quad \text{MeO} \]

\[ \text{MeO} \quad \text{H}_2\text{SO}_4, \text{HNO}_3 \quad \text{MeO} \]

Scheme 2.2: The Nitration Reaction of 2-Methoxypyridine
This reaction was conducted in two different methods. The first time, a mixture of the starting material and sulfuric acid was prepared and then the concentrated nitric acid was slowly dripped into the reaction flask at 0 °C. The second time, a mixture of concentrated nitric acid and the sulfuric acid was prepared at 0 °C, then 2-methoxypyridine was slowly added into the reaction flask. Neither reaction resulted in any amount of product. Similar attempts were made at a higher temperature (50 °C) for 2.5 days. The starting material was recovered from the reactions even at higher temperature.

The treatment of pyridine with the mixture of HNO₃ and H₂SO₄ results in the protonation of the nitrogen atom generating the pyridinium ion 2.14 (Scheme 2.3). Pyridine itself is not very reactive towards electrophiles and the pyridinium ion is even more unreactive. 3-Nitropyridine can be obtained with dinitrogen pentoxide in sulfur dioxide solution generating N-nitropyridinium ion intermediates when treated with water to give 3-nitropyridines in a good yield.⁵,⁶

A nitration addition was attempted on 2-methoxypyridine using reagents available in the lab, although it was not successful. A procedure using dinitrogen pentoxide in sulfur dioxide solution to make 2.13 nitropyridine derivatives was obtained. However, due to the costs of the reagents, the lack of guarantee that the product would even form, and the possibility that there would be a
mixture of derivatives making the purification process harder, it was decided to purchase 2-chloro-5-nitropyridine from a commercial retailer to save us time and money.

2.4 Synthesis of 2-methoxy-5-nitropyridine

The next attempt was the synthesis of 2-methoxy-5-nitropyridine 2.13 from 2-chloro-5-nitropyridine 2.7a using the procedure obtained from the synthesis of 2-methoxypyridine 2.12 in order to test the transformation of a methyl group to a nucleophile using this version of pyridinium triflate. This order of reactions would allow us to circumvent the unsuccessful nitration reaction.

\[
\text{Cl} \quad \text{NO}_2 \quad \xrightarrow{\text{KOH, MeOH, 18-Crown-6}} \quad \text{MeO} \quad \text{NO}_2
\]

The progress of the first reaction shown above (Table 2.2) was monitored by TLC. By the end of workday, there was still some starting material not consumed by the reaction so the reaction was left to stir overnight at reflux. The next morning, the product spot had disappeared. No new spot formed based on the TLC plate and \(^1\text{H}\) NMR. The next reaction was conducted at lower temperature yielding 24% of the desired product (entry 2). It is believed that methanol should be added slowly to the reaction mixture in order to improve the yield based on the results of later

<table>
<thead>
<tr>
<th>entry</th>
<th>Temp (°C), Time</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65 (24 h)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0 (0.5 h), RT (0.5 h)</td>
<td>24%</td>
</tr>
</tbody>
</table>

Table 2.2: Yields (isolated) for the Synthesis of 2-Methoxy-5-nitropyridine

The progress of the first reaction shown above (Table 2.2) was monitored by TLC. By the end of workday, there was still some starting material not consumed by the reaction so the reaction was left to stir overnight at reflux. The next morning, the product spot had disappeared. No new spot formed based on the TLC plate and \(^1\text{H}\) NMR. The next reaction was conducted at lower temperature yielding 24% of the desired product (entry 2). It is believed that methanol should be added slowly to the reaction mixture in order to improve the yield based on the results of later
experiments. It was attempted to make the salt version of 2.13 in small scale from what has been made to test the feasibility of the idea.

2.5 Synthesis of 2-methoxy-5-nitro-1-methylpyridinium trifluoromethanesulfonate

Alkylation of 2-methoxy-5-nitropyridine 2.13 with methyl triflate was followed by the synthetic strategy for the original Bn-OPT reagent. Although the 2-methoxypyridinium triflate is not a benzyl alcohol derivative, its synthesis is expected to proceed in the same manner.

This reaction was performed in an ice bath starting with 1.25 equivalent of methyl triflate (Scheme 2.5). After two hours, the reaction progress was monitored by TLC which showed that the reaction was not complete. An additional 10 µl MeOTf (0.13 equiv) was added to the reaction mixture to push the reaction forward. After 0.5 hour, the reaction mixture was filtered to isolate the precipitant from the liquid. Based on analysis of the NMR spectrum, the precipitate was a mixture of the desired product and the starting compound. After removing the solvent from the filtrate, only the starting compound was observed in 1H NMR spectrum. The methylation reaction of the original Bn-OPT was conducted at 0 °C for less than 2h resulted in high yield of product. Further studies are required at higher temperature to optimize this reaction.
An electron deactivating group was expected to reduce the nucleophilicity of the pyridine nitrogen. A strong electron acceptor group such as nitro will considerably slow down the reaction rate of an electrophile with the nitrogen. So the methylation reaction of 2-benzyloxy-5-nitropyridine was not successful.

We were not able to test the substitution reaction on the methyl group because the synthesis of 2.16 was in low yield. This reaction was more complicated than anticipated, and therefore we moved on to the synthesis of the benzyl derivatives, instead of improving the synthesis of 2.13, in order to investigate the effects of electron withdrawing groups on the reactivity of this reagent. The next experiments will categorize the synthesis of various compounds with each step based on Scheme 2.2. Step one in Scheme 2.2 is the synthesis of 2-benzyloxy of pyridine derivatives.
2.6 Synthesis of 2-benzyloxy-5-nitropyridine

The first derivative investigated contained a strong electron withdrawing NO₂ group at the fifth position of the pyridyl ring.

\[
\text{BnOH} + \text{Cl-N-O₂} \rightarrow \text{KOH, Toluene} \rightarrow \text{NO₂} 
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Base</th>
<th>18-Crown-6</th>
<th>Solvent</th>
<th>Temp (°C), Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>-</td>
<td>Et₂O</td>
<td>0 (1h), RT (2h)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>-</td>
<td>Et₂O</td>
<td>0 (1h), RT (24h), 35 (3h)</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>KOH</td>
<td>0.04 equiv</td>
<td>Toluene</td>
<td>120 (24h)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>KOH</td>
<td>0.14 equiv</td>
<td>Toluene</td>
<td>120 (24h)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>-</td>
<td>Et₂O (dried)</td>
<td>0 (1h), RT (2h)</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>NaH</td>
<td>-</td>
<td>DMF</td>
<td>RT (24h)</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>KOH</td>
<td>0.05 equiv</td>
<td>DMF-Toluene</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>KOH</td>
<td>-</td>
<td>Toluene</td>
<td>0 (1h), RT (1h)</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>KOH</td>
<td>-</td>
<td>Toluene</td>
<td>0 (1h), RT (1h)</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2.3: Yields (isolated) for the Synthesis of 2-Benzylloxy-5-nitropyridine

The overall yields for the synthesis of 2-benzyloxy-5-nitropyridine have shown in Table 2.3. This reaction was conducted under different conditions varying the nature of the base, solvent, temperature, reaction time, and mixing of the reagents. 18-Crown-6 was not used for entry 1 and 2. A mixture of sodium hydride and diethyl ether was stirred in a two-necked round bottom flask at 0 °C. Then benzyl alcohol, 2-chloro-5-nitropyridine, and one half of solvent were added to the first flask (entry 1). The solution quickly changed to dark brown in color. For entry 2, we decided to separate the alcohol and pyridine compound. NaH, 2.7a, and one half of diethyl ether were stirred in two-necked round bottom flask at 0 °C. Then a mixture of benzyl alcohol and the
rest of solvent were added to this flask via a syringe. The solution still changed to dark brown in color quickly. It was thought that some heat may be required. Other attempts at higher temperature to improve the yield were not successful. No product was formed when the reaction mixture was refluxed in toluene for 24 hours (entry 3 and 4). Another attempt using dried diethyl ether to avoid the moisture in the reaction flask did not improve the yield (entry 5). \(2.7a\) (0.3 M) is not soluble in diethyl ether, instead DMF was used to solubilize it. A mixture of \(2.7a\) and DMF was added drop-wise to a flask containing the benzyl alcohol and DMF (entry 6). The solution changed from yellow to dark brown in color. The crude NMR has shown more than 60% of the desired product, but the isolated yield was still low after purification with column chromatography. 2-Chloro-5-nitropyridine was diluted in DMF and toluene to slow down the rate of its addition into the benzyl alcohol. The crude NMR showed the desired product above 70% but the yield was still low (26%) after it was purified via column chromatography (entry 7). It was assumed that that product was lost during the purification process via column chromatography. Two experiments were conducted with the same procedure except the crude mixture of one was purified via recrystallization (entry 8) and the other one using silica gel via column chromatography (entry 9). Recrystallization was more effective than column chromatography. This reaction takes place very fast generating lots of heat. It was assumed this experiment needs to a temperature cooler than 0 °C to get the higher yield. Further studies might need on the purification of the crude mixture to optimize the yield.
2.7 Synthesis of 2-benzyloxy-5-(trifluoromethyl)pyridine

Nitro group is a very strong activator group; therefore it was decided to test the proposed idea with CF₃ group as strong electron withdrawing group which is slightly weaker than nitro group. It was expected that high electron density on oxygen atom in nitro substituent might interfere with the methylation reaction in the second step to make the salt derivatives 2.9 as well (Scheme 2.2).

![Chemical structure of 2-benzyloxy-5-(trifluoromethyl)pyridine]

<table>
<thead>
<tr>
<th>entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C), Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>Et₂O</td>
<td>0 (1h), RT (24h), 35 (2d)</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>DMF</td>
<td>0 (1h), RT (24h), 50(2d)</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>DMF</td>
<td>0 (1h), RT (1h)</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 2.4: Yields (isolated) for the Synthesis of 2-Benzyloxy-5-(trifluoromethyl)pyridine

Several attempts have been made to improve the yield including different methods of the addition of reactants (Table 2.4). A good yield was obtained when 2-chloro-5-(trifluoromethyl)pyridine was added very slowly over 0.5 hour to a mixture of benzyl alcohol and NaH. 2-Hydroxy-3-(trifluoromethyl)-1-methylpyridinium triflate can be isolated in organic layer via filtration of the organic phase after extraction, without further purification.
Column chromatography was attempted to purify the mixture but it did not work very well. A small amount of ethyl acetate was used to dissolve the crude mixture which may interfere in some way.

### 2.8 Synthesis of 2-benzyloxy-3-(trifluoromethyl)pyridine

A substituent on the third and fifth positions was anticipated to have the same impacts on the rate of reactions based on the contributing resonance structures for the intermediate (Scheme 2.1c). The same reactivity was observed for CF₃ group on the third and fifth positions.

The same conditions as CF₃ on the fifth position was used to synthesize 2-benzyloxy-3-(trifluoromethyl)pyridine 2.8c yielding 70% of the desired product which is a colorless oil.
2.9 Synthesis of 2-benzyloxy-5-chloropyridine

Chloro was chosen to explore the effects of a weak electron withdrawing group on the chemical reactivity of pyridine.

![Chemical Reaction](image)

Electron withdrawing groups enhance the reactivity of the pyridine carbon atom towards a nucleophile and reduce the reaction temperature. Since chloro is a weak electron withdrawing group, this reaction was conducted at temperature between the temperature required for pyridine without electron withdrawing group (111 °C) and with strong deactivating group (0 °C for NO₂ or CF₃). Results are shown in Table 2.5. A minimum of 0.05 equiv of 18-crown-6 was found to be necessary for complete consumption of the alcohol substrates. Future studies will need to optimize the reaction conditions to find the best temperature and the minimum amount of time. 24 hours is not required for this reaction based on previous information from the pyridine without or with electron withdrawing substituent. A yield higher than 90% was obtained at 60 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>18-crown-6</th>
<th>Temp (°C), Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>45 (4d)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>60 (4d)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>45 (24h)</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
<td>60 (24h)</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>60 (24h)</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 2.5: Yields (isolated) for the Synthesis of 2-Benzylloxy-5-chloropyridine
in small scale, 100 mg (entry 5), or in large scale, 1 gram (entry 6), in the presence of 18-crown-6.

2.10 Synthesis of 2-benzyloxy-6-chloropyridine

2,6-Dichloropyridine was used to synthesis the 2-benzyloxy derivative replacing only one of the chlorines. Overall yields for the synthesis of 2-benzyloxy-6-chloropyridine are shown in Table 2.6.

\[
\text{\begin{tabular}{|c|c|c|c|c|}
\hline
entry & 2,6-Dichloropyridine & 18-crown-6 & Temp (°C), Time & Yield% \\
\hline
1 & 1.2 equiv & - & 45 (3d) & - \\
2 & 1.2 equiv & - & 60 (3d) & - \\
3 & 1.2 equiv & 0.05 & 45 (24h) & 80 \\
4 & 1.1 equiv & 0.2 & 60 (24h) & 83 \\
5 & 1.1 equiv & 0.05 & 45 (24h) & 90 \\
\hline
\end{tabular}}
\]

*Table 2.6: Yields (isolated) for the Synthesis of 2-Benzyloxy-6-chloropyridine*

A higher yield was obtained at 45 °C comparing to the 5-chloro derivatives because of two chloros with the same chemical reactivity. Although the highest yield was obtained at 60 °C, this reaction was performed in large scale (1 g) at 45 °C because of the less formation of the by-product. The second attempt (in larger scale, entry 5) resulted in a higher yield (90%). It was difficult to isolate the desired compound via column chromatography. Spots associated to the product and the by-product were close together on TLC plate. The first attempts to isolate the
desired compound resulted in the low yield of the pure compound (less than 65%) and more than 30% of the mixture. The byproduct was volatile and can be easily removed under high vacuum without affecting the overall yield which made the purification process easier.

2.11 Synthesis of 2-benzyloxy-5-cyanopyridine

A CN substituent, a moderate electron acceptor group, was chosen to investigate the reactivity of this derivative on the transferring reaction and give us a broader perspective about the effects of this type of substituent on the transformation reaction.

\[
\text{BnOH} + \begin{array}{c}
\text{CN} \\
\text{Cl}
\end{array} \rightarrow \begin{array}{c}
\text{CN} \\
\text{CN}
\end{array} \quad \text{KOH, Toluene} \rightarrow \begin{array}{c}
\text{CN} \\
\text{BnO}
\end{array} \]

<table>
<thead>
<tr>
<th>entry</th>
<th>Temp (°C), Time</th>
<th>Product Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115 (1h)</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>80 (2h)</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>50 (2h)</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>40 (2h)</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>25(2h)</td>
<td>99</td>
</tr>
</tbody>
</table>

*Table 2.7:* Yields (isolated) for the Synthesis of 2-Benzyloxy-5-cyanopyridine

The best yield was obtained at room temperature without observing any by-product (Table 2.7). As the temperature increased to 115 °C, the amount of by-product increased according to the crude proton NMR. We were unable to identify the by-product; however it is a liquid and evaporates under high vacuum. No by-product was observed at 40 °C as well. 2-Hydroxy5-
cyano-1-methylpyridinium triflate is soluble in organic layer and can be isolated directly by filtration of the organic phase after extraction, without further purification.

The overall yields and the optimal temperature for the synthesis of 2-benzyloxypyridine derivatives have shown in Table 2.8 as well as the pyridine without electron withdrawing groups.

These reactions were completed in less than 2h except for chloros (entry 2 and 3) which needs to be investigated further. The series of substituents influence the temperature of the benzyloxy substitution on the second position of pyridine derivatives in similar ways. The reaction temperature decreases with electron withdrawing groups compared to the normal pyridine (entry 1). The same trend was observed with the range of weak (chloro, entry 2 and 3) to very strong (nitro, entry 7) electron withdrawing ability. The reaction temperature reduces to 60 °C for chloro, room temperature for cyano, and 0 °C for CF3 and nitro groups. As it was expected
electron withdrawing groups increase the reactivity of the pyridine carbon atom towards a nucleophile by lowering the electron density of the ring. Yields greater than 70% were obtained with chloro (weak), cyano (medium), and even CF$_3$ with strong electron deactivating effects. A good yield, 59%, was obtained for nitro which is believed that this reaction needs to perform at a temperature cooler than 0 °C to get the higher yield which was not possible in our lab. No 18-crown-6 was needed for strong electron withdrawing groups, which confirm an increase in the reactivity of 2.7 compared to other substituents (entry 5, 6, and 7).

The next step is the preparation of the salt derivatives using these electron withdrawing groups (Scheme 2.2).

### 2.12 Synthesis of 2-benzyloxy-1-methyl-5-nitropyridinium triflate

Synthesis of 2-benzyloxy-1-methylpyridinium triflate 2.9a presented significant problems.

![Scheme 2.2](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>MeOTf</th>
<th>Temp (°C), Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>0 (2h)</td>
</tr>
<tr>
<td>2</td>
<td>3.7</td>
<td>25(1h), 35(1h), 45(1h), 55(1h), 65(1h), 75(1h)</td>
</tr>
</tbody>
</table>

*Table 2.9: Reaction Conditions for the Synthesis of 2-Benzylloxy-1-methyl-5-nitropyridinium Triflate*
The first attempt to synthesize this reagent was performed in an ice bath starting with 1.2 equivalent of the methyl triflate (Table 2.9, entry 1). After one hour, the reaction progress was monitored by TLC which showed that the reaction was not complete. An additional 10 µl MeOTf (0.19 equiv) was added to the reaction mixture to complete the reaction. After one hour, the reaction mixture was filtered to isolate the precipitant from the liquid. According to the proton NMR, there was no desired product in either the precipitate or the filtrate. A strong electron withdrawing group such as nitro will considerably reduce the nucleophilicity of the nitrogen therefore the methylation reaction of 2-benzyloxy-5-nitropyridine was not completed at 0 °C. It was also attempted to find the temperature required for the formation of the salt. Since this reagent has a spot on the base line, the reaction progress was monitored via TLC looking for the lower temperature a spot on the base line appears and the highest temperature the spot of pyridine compound disappeared. The reaction temperature was raised 10 °C every hour. After one hour at room temperature there was no spot on the base line. At 35 °C a spot on the base line appeared and the total consumption of the starting material was seen at 75 °C on TLC plate. The proton NMR of the reaction mixture showed the decomposition of the product after one hour at 75 °C.
2.13 2-benzyloxy-1-methyl-5-(trifluoromethyl)pyridinium triflate

The oxygen atom in nitro substituent might alkylate in the presence of methyl triflate, therefore it was decided to make the salt with CF₃ group to remove the probability of this condition and understand better the effect of a strong EWG on the chemical reactivity of this reagent.

\[
\begin{array}{c}
\text{BnO} \quad \text{CF}₃ \\
\text{N} \\
\text{MeOTf, PhCF}_₃ \\
\end{array}
\xrightarrow{\text{MeOTf, PhCF}_₃} 
\begin{array}{c}
\text{BnO} \\
\text{TfO} \\
\text{Me} \\
\text{CF}₃ \\
\end{array}
\]

\[2.8b \rightarrow 2.9b\]

<table>
<thead>
<tr>
<th>entry</th>
<th>MeOTf</th>
<th>Temp (°C), Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7 equiv</td>
<td>RT(4h)</td>
</tr>
<tr>
<td>2</td>
<td>4 equiv</td>
<td>RT(1h), 35(1h), 45(1h)</td>
</tr>
<tr>
<td>3</td>
<td>1.4 equiv</td>
<td>35 (28h)</td>
</tr>
</tbody>
</table>

Table 2.10: Reaction Conditions for the Synthesis of 2-Benzyl

The first attempt to synthesize this reagent was performed at room temperature with 1.7 equivalent of methyl triflate (Table 2.10, entry 1). The reaction progress was monitored by TLC which showed that it was not complete after three hours. 10 µl MeOTf (0.2 equiv) was added to the reaction mixture to complete the reaction. The reaction mixture filtered the precipitant after an hour. According to the proton NMR, there was a mixture of product and starting material. It was tried to find the lowest temperature required for the formation of the salt and the highest temperature where the decomposition of this reagent might occur (entry 2). The reaction temperature raised 10 °C every hour. After one hour at room temperature there was no spot on the base line. At 35 °C a spot on the base line appeared and the total consumption of the starting material was seen at 45 °C on TLC plate. From the crude 1H NMR spectra of using 4 equivalent
of MeOTf, it was apparent two new products were formed, along a small amount of unreacted starting 2-benzyloxy-5-(trifluoromethyl)pyridine. The proton NMR of this reagent with CF₃ on the 3-position showed a mixture of either two different products or the product and starting material as well. The last reaction was attempted to investigate the stability of this reagent during the purification process (entry 3). We were not able to obtain a pure compound by filtration; therefore recrystallization was attempted using hexane and ethyl acetate at 70 °C which was not successful. So it was attempted to transfer the benzyl group by in situ formation of this reagent followed by immediate decomposition and reaction with the ROH nucleophile.

### 2.14 2-benzyloxy-5-chloro-1-methylpyridinium triflate

The synthesis of this compound was straight forward and followed the original Bn-OPT synthesis. A slight variation is made at temperature with this derivative with the electron withdrawing substituent.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>MeOTf</th>
<th>Temp (°C), Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 equiv</td>
<td>RT(1h), 40 (1h)</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>1.3 equiv</td>
<td>RT(5h)</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>1.3 equiv</td>
<td>30 (4h)</td>
<td>83</td>
</tr>
</tbody>
</table>

*Table 2.11:* Yields (isolated) for the Synthesis of 2-Benzyloxy-5-chloro-1-methylpyridinium Triflate
The complete consumption of the pyridine substrate was seen after a few hours at room temperature which is slightly higher than the same reaction with 2-benzylloxypyridine (Table 2.11). Nucleophilicity of the nitrogen slightly decreases with chloro which is a weak deactivating substituent. We were able to isolate this compound by filtration and then the removal of the solvent under high vacuum. The salt appeared to be stable at room temperature for up to two days and can be stored for a longer time at low temperature (refrigerator).

2.15 2-benzyloxy-6-chloro-1-methylpyridinium triflate

The chemical reactivity of chlorines on the fifth and sixth positions was anticipated to be almost the same in the absence of other factors.

Attempts at the preparation of this compound 2.9e were unsuccessful even at higher temperature (Scheme 2.7). After addition of MeOTf at 0 °C, the reaction mixture was stirred at room temperature for 1.5 hours, followed by 1.5 hours at 35 °C and 5 hours at 45 °C. A mixture of the desired product and the starting pyridine substrate was observed in the crude proton NMR. It is believed that steric hindrance affects the nucleophilicity of the nitrogen. The benzyl and chloro groups were hindering its approach to the methyl electrophile, making the nitrogen a weak nucleophile. Alkylation with MeOTf resulted in no salt precipitation even after it was stored at low temperature (refrigerator).
An electron deactivating group was expected to reduce the nucleophilicity of the pyridine nitrogen, thereby increase the activation energy of the methylation reaction (Scheme 2.3). A strong electron acceptor group such as nitro will considerably slow down the reaction rate of an electrophile with the nitrogen. Attempts at the methylation of 2-benzyloxypyridine with strong electron deactivating groups were unsuccessful. It was also observed that electron withdrawing groups affects the stability of the salt derivatives. We were able to prepare the salt with chloro substituent, a weak electron accepter group, and store it at low temperature. Although, attempts to isolate the salt stable with strong electron withdrawing group were not successful, the benzylation reaction was conducted by *in situ* formation of the salt to test the feasibility of the proposed idea.
2.16 Benzylation Reaction with CF₃ substituent on the 5-position

CF₃ substituent was used first to explore the effects of a strong electron withdrawing group on the benzylation reaction because the oxygen atom in nitro group might interfere with the methylation reaction.

![Reaction Diagram]

These reactions were conducted under argon atmosphere to avoid the reaction between MeOTf and the moisture in the air (Table 2.12). The complete consumption of the starting pyridine compound was not achieved in excess amount of MeOTf. The pyridine substrate 2.8b, 38%, was still remaining after four hours at 50 °C (entry 6). Table 2.6 shows the percentages of pyridine derivatives 2.8b were recovered in different reaction conditions when there is a CF₃ on the 5-
position. The CF₃ group is a strong electron withdrawing group which significantly reduces the nucleophilicity of the nitrogen causing the increase of the activation energy of the methylation reaction. It was believed that electron withdrawing groups help the transferring reaction by lowering the activation energy of the anion intimidate. According to this information, a strong electron withdrawing group would not be a good option to reduce the temperature of the benzylolation reaction. The reason is that the formation of the salt should be done *in situ* and needs a high temperature resulting in either the decomposition of this reagent or side reactions. Further studies may require and perform this experiment at 50 °C longer (24h) to prove the obtained yield. But we can conclude that the highest yield (55%) was obtained at temperature about 40-45 °C based on these results and those from CF₃ on the 3-position which has almost the same effect on the reactivity of this reagent.
2.17 Benzylolation Reaction with CF$_3$ substituent on the 3-position

Overall yields for the synthesis of benzylethers using CF$_3$ group on the third position are shown in Table 2.13. The same pattern was observed as CF$_3$ on the fifth position.

![Chemical structure](image)

Table 2.13: Yields (isolated) for the Benzylolation Reaction by in situ Formation of the Salt with CF$_3$ Substituent on the 3-position

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>Pyridine derivative</th>
<th>MeOTf</th>
<th>Temp(°C), time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>1.2 eq.</td>
<td>23, 2 weeks</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>1.3 eq.</td>
<td>35, 66h</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>1.3 eq.</td>
<td>45, 74h</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>1.3 eq.</td>
<td>55, 72h</td>
<td>20</td>
</tr>
</tbody>
</table>

The yield was improved as the temperature increased to 45 °C where the best yield (56%) was obtained. Although it was seen peaks assigned to the pyridine substrate in crude NMR, no mass associated to them was recorded. Attempts to improve the yield by increasing the reaction time were not successful. According to the TLC plate, the reaction did not show any progress after the first day. It is believed that no methyl triflate was present after one day because of the high reactivity of it.
2.18 Benzylation Reaction Using Nitro Group

Based on information from benzylation reactions of this reagent derivative with CF$_3$ groups on the 3 and 5 positions, it was decided to run the benzylation reaction with nitro group at 40 °C (Scheme 2.8).

![Scheme 2.8: The Benzylation Reaction by in situ Formation of the Salt with Nitro Substituent](image)

One significant problem encountered involved the total consumption of the starting pyridyl compound. MeOTf is a very reactive reagent. It was thought that it reacts with the nitrogen on pyridyl ring quickly. Crude NMR shows small amount of the pyridine substrate was still remaining after 17 hours at 40 °C. Another problem was met to load the sample on silica gel during the purification process. It was solved by the filtration of the polar compound (a pale yellow solid) and loading the filtrate on silica gel after removing the solvent. 2-Hydroxy-1-methylpyridinium triflate is a polar compound and very soluble in water. It was found that a strong electron withdrawing group, nitro group, decreases the solubility of this reagent in water in a way that it can be isolated in organic layer. The pure compound was obtained directly by filtration of the organic phase after extraction, without further purification.
2.19 Benzylation Reaction Using Cyano Group

The cyano group acts as a medium activator on pyridine ring. The benzylation reaction was attempted by *in situ* formation of the salt and the results were shown in Table 2.14.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>Pyridine derivative</th>
<th>MeOTf</th>
<th>Temp(°C), time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>1.5 eq.</td>
<td>26, 24h</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>1 eq.</td>
<td>1.1 eq.</td>
<td>1.5 eq.</td>
<td>45, 24h</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>1 eq.</td>
<td>1.2 eq.</td>
<td>1.5 eq.</td>
<td>45, 12h</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>1 eq.</td>
<td>1.2 eq.</td>
<td>1.5 eq.</td>
<td>55, 12h</td>
<td>47</td>
</tr>
</tbody>
</table>

*Table 2.14: Yields (isolated) for the Benzylation Reaction by *In Situ* Formation of the Salt with Cyano Substituent on the 5-position*

At room temperature, the starting pyridine compound was not totally consumed after 24 hours. A pure product was obtained at room temperature (entry 1). A side reaction occurred at higher temperature generating byproducts. Based on proton NMR, three peaks at 3.3 (methyl ether), 4.08, and 4.5 (CH₂ of benzyl group) associated to the byproduct were observed after running column chromatography along with the desired product. Although the complete consumption of the starting pyridine compound was observed after 12 hours at 45 °C on TLC, a small amount of it was recovered through column chromatography (entry 3). The pyridone byproduct was not dissolved in water, but it dissolved in CH₂Cl₂ during extraction of the organic layer.
2.20 Benzylation Reaction Using 5-Chloropyridinium Triflate Derivative

2-Benzoyloxy-5-chloropyridinium triflate, 2.9d, was the only salt isolated and stored in refrigerator among these electron withdrawing substituents.

\[
\text{\begin{align*}
\text{O} & \quad \text{O} \\
& \quad \text{OH} \\
2.17 &
\end{align*}}
\text{ } + 
\text{ } \begin{align*}
\text{BnO} & \quad \Phi & \quad \text{Cl} \\
\text{Me} & \quad \text{TfO} & \quad & \text{PhCF}_3 \\
2.9d & 
\end{align*}
\text{ } \xrightarrow{\text{PhCF}_3} 
\text{\begin{align*}
\text{O} & \quad \text{O} \\
& \quad \text{OBn} \\
2.18 &
\end{align*}}
\]

This reaction was conducted at different temperature. Overall yields for the benzylation reaction using 2.9d are shown in Table 2.14. No desired product was observed at room temperature and at 35 °C after 24 hours according to the TLC plate. Good yields (higher than 80%) were obtained at temperature above 60 °C for 24 hours (entry 4-6) which support the proposed idea that electron withdrawing group can improve the reactivity of the original reagent by stabilizing the anion intermediate. In addition, the chloro might be a good substituent to transfer the benzyl group at temperature 20 °C lower than the original reagent with comparable yields. The temperature required for this reaction to meet the activation energy is between 55 and 65 °C according to the

<table>
<thead>
<tr>
<th>entry</th>
<th>Temp(°C), time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 (24h)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>35 (24h)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>55 (21h)</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>60 (24h)</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>65 (21h)</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>75 (21h)</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 2.15: Yields (isolated) for the Benzylation Reaction Using 5-Chloropyridinium Triflate Derivative

48
obtained yield. Recrystallization of 2.9d was attempted at 45 °C using hexane and methanol. Slow decomposition of the salt was observed at room temperature (25 °C).

A strong electron withdrawing group has a negative influence on the reactivity of this reagent derivative by decreasing the nucleophilicity of the nitrogen. However a weak electron withdrawing group such as chloro helps the transferring reaction and slightly lowers the reaction temperature. Further studies are required for cyano group, a medium electron withdrawing group. The reaction was certainly complete at lower temperature in a shorter amount of time, but the yield is not comparable with the original reagent.

### 2.21 Results and Conclusions

The optimal temperature and yields for each step for different substituents are shown in Table 2.16 as well as those of the normal pyridine without any substituents (entry 1).

Although electron withdrawing groups enhance the reactivity of the first step and lower the temperature, an increase at the temperature of the second step was observed to get the optimal conditions which limit the yields as well as the affectivity of strong electron withdrawing substituents.

A weak electron withdrawing group, chloro (entry 2), allowed for efficient benzyl transfer to occur at 60 °C, 20 °C less than the original reagent in high yield. Therefore the proposed idea is feasible and the electron withdrawing group will reduce the temperature of the transferring reaction by stabilizing the anion intermediate.
The reaction was certainly complete at lower temperature in a shorter amount of time using medium electron withdrawing group, but the yield is not comparable with the original reagent (entry 4). A side reaction occurred at temperature higher than the room temperature which needs further studies to improve the yield. A strong electron withdrawing group significantly decreases the nucleophilicity of the nitrogen resulting in a huge activation energy barrier for the second step (entry 5, 6, and 7). Increasing the reaction temperature and time was attempted to get the total consumption of the starting pyridine compounds with strong EWG which was unsuccessful. The starting pyridine compounds were recovered at 55 °C after 24 hours. The stability of the salt 2.9 limits the reaction temperature

EWGs affect the stability of the salt 2.9 compound. The chloro salt was the only salt isolated and stored in the refrigerator among these substituents. Recrystallization was attempted and the

<table>
<thead>
<tr>
<th>entry</th>
<th>EWG</th>
<th>Temp (°C), Time for Compound 2.8</th>
<th>Yield % of 2.8</th>
<th>Temp (°C), Time for Triflate Salt 2.9</th>
<th>Yield % of 2.9</th>
<th>Temp (°C), Time for Benzylation 2.18</th>
<th>Yield % of 2.18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>111(2h)</td>
<td>95</td>
<td>0(1h)</td>
<td>99</td>
<td>80(24h)</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>5-Cl</td>
<td>60 (24h)</td>
<td>90</td>
<td>23(5h)</td>
<td>92</td>
<td>60(24h)</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>6-Cl</td>
<td>60 (24h)</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5-CN</td>
<td>25(2h)</td>
<td>99</td>
<td>45 (24h)</td>
<td>In situ</td>
<td>26 (24h)</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>5-CF3</td>
<td>0 (1h), RT</td>
<td>75</td>
<td>40(18h)</td>
<td>In situ</td>
<td>40(18h)</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>3-CF3</td>
<td>0 (1h), RT</td>
<td>75</td>
<td>45(72h)</td>
<td>In situ</td>
<td>45(72h)</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>5-NO2</td>
<td>0 (1h), RT</td>
<td>59</td>
<td>40</td>
<td>In situ</td>
<td>40</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 2.16: Yields (isolated) for Different Steps of Generating the Salt 2.9, and the Benzylation Reaction to Form 2.18
decomposition of the chloride salt was observed at room temperature. Other versions of this reagent were unstable at lower temperature (refrigerator).

EWGs decrease the solubility of the pyridone byproducts in water. Filtration works to separate the pyridone compound with strong EWGs from the organic layer. Other pyridone derivatives may purify with a polar wash through column chromatography.

2.22 Future Work

Other medium EWGs might be attempted to improve the yield of the benzylation reaction at lower temperature in a shorter amount of time.

For cyano group, it would be interesting to run experiments and add the alcohol after the consumption of the pyridine compound which may improve the yield.

It was difficult to monitor the consumption of the alcohol by TLC plate because of non-UV-reactive properties of the alcohol when the benzylation reaction was tried by the in situ formation of the salt. Using a UV-active alcohol makes the project easier in particular for students with not enough practical experience as well as being sure about the amount of time for the reaction completion.

Other alcohol substrates would be attempted to understand better the effects of EWGs on the benzylation reaction.

2.23 Summary Statement

The effects of a EWG on synthesis and reactivity of 2-benzyloxy-1-methylpyridinium triflate 2.9 have been investigated to target the second generation of the original Bn-OPT reagent that would
allow for the benzylation of alcohols at lower temperature in a shorter amount of time. The introduction of electron withdrawing substituents influences the chemical reactivity of the pyridine in different ways. They reduce the nucleophilicity of the nitrogen on the pyridine ring, thereby an increase in the reaction temperature was required for the methylation of the nitrogen. On the other hand, these substituents convert the anion into a better leaving group by pulling the electron density from the ring and facilitate the substitution reaction. The salt with a weak electron withdrawing group, chloro, helps the transferring reaction and lowers the reaction temperature up to 20 °C in high yield. The reaction was complete at lower temperature in a shorter amount of time using a medium electron withdrawing group, cyano group, but the yield is not comparable with the original reagent. An increase at the temperature of the methylation reaction was observed to get the optimal conditions which limit the yields as well as the affectivity of strong electron withdrawing substituents such as NO₂ and CF₃ groups. Therefore the proposed idea is feasible and the electron withdrawing group will reduce the temperature and time of the transferring reaction by stabilizing the anion intermediate.

References

Chapter 3

Experimental
General Information

Analytical Data: Nuclear Magnetic Resonance (NMR) spectra were recorded on JEOL (300 MHz) or (400 MHz) instruments. Proton (\(^1\)H) chemical shifts, reported in parts per million (ppm), are referenced to known resonances of the residual protonated solvent.

Solvents: Trifluorotoluene was dried by distillation and stored over 4 Å sieves. All other solvents were used directly from the manufactures without additional purification.

Purification: Flash column chromatography was performed with Dynamic Adsorbents Inc. Standard Grade Silica Gel (32-63 Å porosity). Thin Layer Chromatography (TLC) was performed utilizing Sorbent Technologies UV254 polyester backed silica gel plates with fluorescent indicator. Developed plates were visualized under 254 nm UV light, or stained with iodine, p-anisaldehyde solution.

Reagents: General Reaction Procedure: Glassware, NMR tubes, stir bars, needles, and syringes were dried overnight in an oven heated to 120 °C and cooled to room temperature in desiccators over CaSO\(_4\). All reactions were performed under argon (Ar) unless specified otherwise. Low boiling solvents were evaporated by a Buchi Roto-vapor-R under vacuum (~ 7 mm Hg) via a water aspirator pump followed by high vacuum (~ .5 mm Hg) via an oil pump.

Reference: All procedures are referenced to my first lab-notebook and the page number. TB-1-17 refers to the initials of my name, number of the lab-notebook, and the page number respectively.
2-methoxypyridine (2.12): (TB-1-17) 2-chloropyridine (5ml, 53.77 mmol, 1 equiv) and the methanol (11 ml, 271.84 mmol, 5 equiv) were placed through a 10 ml and 20 ml syringe, respectively, into a three-necked, 50-mL, round-bottom flask with a magnetic stirring bar. KOH (85%) (10.683 g, 190.39 mmol, 3.5 equiv) and 18-crown-6 (0.7850 g, 2.97 mmol, 0.05 equiv) were added to the mixture. The reaction mixture was heated at reflux (65 °C) for 17h, and then cooled to room temperature and separated. Distilled water (25 ml) was added to the reaction mixture and transferred to a 100-mL separatory funnel. Then the organic solution was extracted with diethyl ether (25 mL), washed 3 times with brine (10 ml), dried over Na₂SO₄ and the solvent was removed under reduced pressure on a rotary evaporator (down to 250 mm Hg) to leave a colorless oil. The product was then purified via a vacuum distillation using the Kugelrohr apparatus (a short-path distillation) which was set at 80 mm Hg and the distillation occurred at 110 °C. The last bulb containing the clean product was transferred to a flask using CH₂Cl₂ and rotovaped down to 40 mm Hg for about 5 minutes and then put under high vacuum for 10 seconds to remove all of the solvent to yield 4.93 g, 45.18 mmol (84%); a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, J=4.8 Hz, J=1.1 Hz, 1H), 7.56 (td, J=8.6 Hz, J=1.8 Hz, 1H), 6.84-6.89 (m, 1H), 6.7 (apparent d, J=8.6 Hz, 1H), 3.9 (s, 3H). ¹³C NMR (75MHz, CDCl₃) δ 52.9, 110.7, 116.3, 138.5, 146.7, 163.9; IR (thin film): 3013, 2979, 1601, 1571, 1469, 1310, 1287, 1019, 810, 778 cm⁻¹.
2-methoxy-5-nitropyridine (2.13): (TB-1-25) A procedure identical to the one described for 2a was used; 2-chloro-5-nitropyridine (0.5034, 3.17 mmol, 1 equiv), KOH (85%) (0.673 g, 11.99 mmol, 3.8 equiv), 18-crown-6 (0.0515 g, 0.195 mmol, 0.06 equiv), and methanol (1.2 ml, 47.3 mmol, 15 equiv). The white precipitate was purified via column chromatography using 34.5 g silica gel (100 times of actual yield) and a 79:1 ratio of hexane to ethyl acetate to yield 0.1217 g, 0.79 mmol (24%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.09 (d, $J$=2.6 Hz, 1H), 8.35 (dd, $J$=9.2 Hz, $J$=3.0 Hz, 1H), 6.83 (d, $J$=9.2 Hz, 1H), 4.06 (s, 3H); $^{13}$C NMR (75MHz, CDCl$_3$) δ 54.7, 111.1, 133.7, 139.3, 144.7, 167.2; IR (thin film): 3095, 2962, 1605, 1575, 1489, 1347, 1300, 999, 845, 766 cm$^{-1}$. 
2-benzyloxy-5-(trifluoromethyl)pyridine (2.8b): (TB-1-33) benzyl alcohol (0.61 ml, 5.89 mmol, 1.06 equiv) and NaH (60%) (0.2637 g, 6.595 mmol, 1.2 equiv) and 2 ml DMF were placed in a three-necked, 25-mL, round-bottom flask with a magnetic stirring bar. The mixture was cooled to 0 °C in an ice bath. In another flask (5 ml round bottom), 2-chloro-5-(trifluoromethyl)pyridine (1.0023 g, 5.51 mmol, 1 equiv) and 2 ml DMF were stirred for 5 minutes and then this mixture was slowly added dropwise via syring to the first flask, stirred for one hour at 0 °C and then the ice bath was removed, allowed the reaction mixture to warm to room temperature. After 1 hour it was complete on TLC. The organic layer was extracted with distilled water (10 ml) and methylene chloride (10 ml, 3 times), dried over Na₂SO₄ and the solvent was removed under reduced pressure on a rotary evaporator (down to 15 mm Hg). The white precipitate was purified via recrystallization using petane to yield 1.0426 g, 4.12 mmol (75%). Melting point: 62-63 °C, ¹H NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H), 7.78 (dd, J=8.8 Hz, J=2.6 Hz, 1H), 7.44-7.48 (m, 2H), 7.31-7.42 (m, 3H), 6.88 (d, J=8.8 Hz, 1H), 5.43 (s, 2H); ¹³C NMR (75MHz, CDCl₃) δ 68.3, 111.4, 120.2 (q, J=33.2 Hz), 124.0 (q, 269.1 Hz), 128.1, 128.5 135.7 (q, J=2.8), 136.6, 144.9 (q, 4.0 Hz), 165.5; IR (thin film): 3037, 2960, 1611, 1574, 1455, 1329, 1299, 1113, 977, 841, 755 cm⁻¹.
2-benzylloxy-5-nitopyridine (2.8a): (TB-1-37) A procedure identical to the one described for 2d was used; 2-chloro-5-nitropyridine (0.1023 g, 0.645 mmol, 1 equiv), benzyl alcohol (0.082 ml, 0.791 mmol, 1.2 equiv), and KOH (85%) (0.1363 g, 2.43 mmol, 3.8 equiv). The white precipitate was purified via recrystallization using hexane and ethyl acetate to yield 0.0879 g, 0.38 mmol (59%). Melting point: 105-106 °C, ¹H NMR (400 MHz, CDCl₃) δ 9.10 (d, J=2.6 Hz, 1H), 8.37 (dd, J=8.9 Hz, J= 2.9 Hz, 1H), 7.44-7.48 (m, 2H), 7.33-7.43 (m, 3H), 6.88 (d, J=9.2 Hz, 1H), 5.49 (s, 2H); ¹³C NMR (75MHz, CDCl₃) δ 69.1, 111.4, 128.1, 128.3, 128.5, 133.9, 135.8, 139.5, 144.6; IR (thin film): 3096, 2963, 1604, 1576, 1486, 1344, 1276, 1121, 983, 834, 766 cm⁻¹.
2-benzylxy-3-(trifluoromethyl)pyridine (2.8c): (TB-1-34) A procedure identical to the one described for 2d was used; benzyl alcohol (0.61 ml, 5.89 mmol, 1.06 equiv), 2-chloro-3-(trifluoromethyl)pyridine (1.0413 g, 5.57 mmol, 1 equiv), NaH (60%) (0.2491 g, 6.23 mmol, 1.1 equiv); The product (colorless oil) was purified via column chromatography using 11 g silica gel (10 times of actual yield) and a 199:1, and 49:1 ratio of hexane to ethyl acetate to yield 1.0152 g, 4.01 mmol (70%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.32 (apparent d, J=6.8 Hz, 1H), 7.88 (apparent d, J=7.2 Hz, 1H), 7.44-7.49 (m, 2H), 7.28-7.41 (m, 3H), 6.98 (apparent t, J=6.8 Hz, 1H), 5.52 (s, 2H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 67.8, 113.5 (q, J=32.8 Hz), 116.1, 123.0 (q, J=270.2 Hz), 127.2, 127.7, 128.4, 136.4 (q, J=5.2 Hz), 136.7, 150.4, 160.2; IR (thin film): 3034, 2956, 1585, 1440, 1330, 1297, 1117, 1035, 803, 776 cm$^{-1}$. 
2-benzyloxy-5-chloropyridine (2.8d): (TB-1-67) A procedure identical to the one described for 2d was used; benzyl alcohol (0.504 g, 4.66 mmol, 1 equiv), 2, 5-dichloropyridine (0.775 g, 5.237 mmol, 1.1 equiv), KOH (85%) (0.9564 g, 14.49 mmol, 3 equiv), 18-crown-6 (0.060 g, 0.225 mmol, 0.05 equiv); white precipitate 0.9343 g, 4.25 mmol (90%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (d, J=2.6 Hz, 1H), 7.53 (dd, J=8.8 Hz, J=2.6 Hz, 1H), 7.42-7.47 (m, 2H), 7.30-7.41 (m, 3H), 6.76 (d, J=8.8 Hz, 1H), 5.35 (s, 2H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 67.9, 112.2, 124.2, 127.92, 127.95, 128.4, 136.9, 138.5, 145.1, 161.9; IR (thin film): 3032, 2926, 1590, 1470, 1355, 1276, 1109, 1007, 992, 825, 736 cm$^{-1}$. 
2-benzyloxy-6-chloropyridine (2.8e): (TB-1-66) A procedure identical to the one described for 2d was used; benzyl alcohol (0.0439 g, 0.406 mmol, 1 equiv), 2, 6-dichloropyridine (0.0665 g, 0.446 mmol, 1.1 equiv), KOH (85%) (0.158 g, 2.4 mmol, 4 equiv), 18-crown-6 (0.0054 g, 0.021 mmol, 0.05 equiv); colorless oil; 0.0735 g, 0.33 mmol (83%). 1H NMR (400 MHz, CDCl₃) δ 7.47 (t, J=7.7 Hz, 1H), 7.4 (apparent d, J=7.0 Hz, 2H), 7.25-7.36 (m, 3H), 6.92 (d, J=7.8 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 5.3 (s, 2H); ¹³C NMR (75MHz, CDCl₃) δ 68.3, 109.4, 116.5, 128.0, 128.2, 128.4, 136.5, 140.7, 148.2, 163.2; IR (thin film): 3032, 2947, 1590, 1559, 1435, 1296, 1160, 985, 902, 787 cm⁻¹.
2-benzyloxy-5-cyanopyridine (2.8f): (TB-1-87) benzyl alcohol (0.052 g, 0.481 mmol, 1.1 equiv), 2-Chloro-5-cyanopyridine (0.059 g, 0.426 mmol, 1 equiv) were placed in a 5 ml vial with a magnetic stirring bar. KOH (85%) (0.141 g, 2.97 mmol, 6 equiv), 18-crown-6 (0.0052 g, 0.020 mmol, 0.05 equiv) and 1.4 ml toluene were added to the mixture at room temperature. After 2 hours 10 ml of distilled water was added to the reaction mixture and transferred to a 50-mL separatory funnel. Then the organic solution was extracted with 10 mL of CH₂Cl₂, washed with 10 ml brine (2 times), dried over Na₂SO₄ and the solvent was removed under reduced pressure on a rotary evaporator (down to 15 mm Hg). The white solid was purified via column chromatography using 4.3 g silica gel (50 times of actual yield) and a 99:1 and 39:1 ratio of hexane to ethyl acetate to yield 0.0886 g, 0.42 mmol (99%). ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 7.77 ( apparent d, J=8.8 Hz, 1H), 7.40-7.44 (m, 2H), 7.31-7.39 (m, 3H), 6.85 (d, J=8.8, 1H), 5.4-5.5 (s, 2H); ¹³C NMR (75MHz, CDCl₃) δ 68.5, 102.5, 111.98, 117.1, 128.0, 128.2, 128.5, 136.0, 141.0, 151.8, 165.3; IR (thin film): 3060, 2927, 2225, 1598, 1489, 1451, 1295, 1009, 947, 830, 726 cm⁻¹.
2-benzyloxy-5-chloro-1-methylpyridinium trifluoromethanesulfonate (2.9d): (TB-1-74) 2-benzyloxy-5-chloropyridine (0.0.626 g, 2.85 mmol, 1 equiv), and trifluorotoluene (9.5 ml) were placed in a three-necked, 25-mL, round-bottom flask equipped with an argon bubbler inlet, rubber septum and a magnetic stirring bar by temporary removal of the septum. The mixture was cooled to 0 °C in an ice bath. Methyl triflate was slowly added drop-wise via syring to the flask and then the ice bath was removed. After 5 hours at room temperature, a white solid was filtered and dried under vacuum to get 1.0055g, 2.62 mmol (92%): ^1^H NMR (400 MHz, DMSO-D_6) δ 9.1-9.2 (s, 1H), 8.6-8.7 (d, 1H), 7.9-8.0 (d, 1H), 7.5-7.6 (d, 2H), 7.4-7.5 (m, 3H), 5.6-5.7 (s, 2H), 3.9-4.0 (s, 3H); IR (thin film): 3078, 3038, 1636, 1583, 1523, 1393, 1323, 1256, 1156, 1014, 895, 834, 740 cm⁻¹.
Benzylation Reaction by *in situ* Formation of the Salt

(TB-1-48) The alcohol (0.062 g, 0.516 mmol, 1 equiv.), 2-benzyloxy-5-nitropyridine (0.132 g, 0.573 mmol, 1.1 equiv.), and trifluorotoluene (1.5 ml) were placed in a 5-mL vial equipped with an argon bubbler inlet, rubber septum and overhead mechanical stirrer by temporary removal of the septum. Methyl triflate was slowly added drop-wise (1 or 2 drops per minutes) via syring to the vial, and then increased the temperature to 40 °C. After 2 hour there were two layers in the reaction mixture and the bottom layer was a little darker, redish, than the top one. The organic layer was extracted with distilled water (10 ml) and methylene chloride (10 ml, 3 times), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure on a rotary evaporator (down to 15 mm Hg). The desired product was purified via column chromatography using 5.5 g silica gel (50 times of theoretical yield) and a 49:1 and 9:1 ratio of hexane to ethyl acetate to isolate 0.0518 g (48%) colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.2-7.3 (m, 5H), 4.5(s, 2H), 3.5-3.6 (m, 8H), 3.4(s, 3H)
Appendices