Reaction Between Grignard Reagents and Heterocyclic N-oxides
Synthesis of Substituted Pyridines, Piperidines and Piperazines

Hans Andersson
Title
Reaction Between Grignard Reagents and Heterocyclic N-oxides – Synthesis of Substituted Pyridines, Piperidines and Piperazines

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Abstract
This thesis describes the development of new synthetic methodologies for preparation of bioactive interesting compounds, e.g. substituted pyridines, piperidines or piperazines. These compounds are synthesized from commercially available, cheap and easily prepared reagents, videlicet the reaction between Grignard reagents and heterocyclic N-oxides.

The first part of this thesis deals with an improvement for synthesis of dienal-oximes and substituted pyridines. This was accomplished by a rapid addition of Grignard reagents to pyridine N-oxides at rt. yielding a diverse set of substituted dienal-oximes. During these studies, it was observed that the obtained dienal-oximes are prone to ring-close upon heating. By taking advantage of this, a practical synthesis of substituted pyridines was developed.

In the second part, an ortho-metalation of pyridine N-oxides using Grignard reagents is discussed. The method can be used for incorporation of a range of different electrophiles, including aldehydes, ketones and halogens. Furthermore, the importance for incorporation of halogens are exemplified through a Suzuki–Miyaura coupling reaction of 2-iodo pyridine N-oxides and different boronic acids. Later it was discovered that if the reaction temperature is kept below -20 °C, the undesired ringopening can be avoided. Thus, the synthesis of 2,3-dihydropyridine N-oxide, by reacting Grignard reagents with pyridine N-oxides at -40 °C followed by sequential addition of aldehyde or ketone, was accomplished. The reaction provides complete regio- and stereoselectivity yielding trans-2,3-dihydropyridine N-oxides in good yields. These intermediate products could then be used for synthesis of either substituted piperidines, by reduction, or reacted in a Diels–Alder cycloaddition to give the aza-bicyclo compound.

In the last part of this thesis, the discovered reactivity for pyridine N-oxides, is applied on pyrazine N-oxides in effort to synthesize substituted piperazines. These substances are obtained by the reaction of Grignard reagents and pyrazine N-oxides at -78 °C followed by reduction and protection, using a one-pot procedure. The product, a protected piperazine, that easily can be orthogonally deprotected, allowing synthetic modifications at either nitrogen in a fast and step efficient manner. Finally, an enantioselective procedure using a combination of PhMgCl and (-)-sparteine is discussed, giving opportunity for a stereoselective synthesis of substituted piperazines.

Keywords
Grignard reagents, pyridine N-oxide, pyrazine N-oxide, dienal-oxime, pyridine, ortho-metalation, piperidine, piperazine, asymmetric
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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.*

I Reaction of pyridine N-oxides with Grignard reagents: a stereodefined synthesis of substituted dienal-oximes
Andersson, H.; Wang, X.; Björklund M.; Olsson, R.; Almqvist, F.

II Synthesis of 2-Substituted Pyridines via a Regiospecific Alkyla-
tion, Alkynylation, and Arylation of Pyridine N-Oxides
Andersson, H.; Almqvist, F.; Olsson R.

III Selective synthesis of 2-substituted pyridine N-oxides via directed
ortho-metalation using Grignard reagents
Andersson, H.; Gustafsson, M.; Olsson R.; Almqvist, F.
(Highlighted in _Synfacts, 2009_, 1)

IV The regio- and stereoselective synthesis of trans-2,3-
dihydropyridine N-oxides and piperidines
Andersson, H.; Gustafsson, M.; Olsson, R.; Almqvist, F.
(Highlighted in _Synfacts, 2009_, 7)

V Complete regioselective addition of Grignard reagents to pyrazine
N-oxides, towards an efficient enantioselective synthesis of substi-
tuted piperazines
Andersson H.; Thomas, S.L.; Das, S.; Gustafsson, M.; Olsson R.;
Almqvist F.
_Manuscript, 2009._

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*The author’s contributions to paper I-V have been: the formation of the projects and research problems, experimental work and contribution in writing the manuscripts.
Abbreviations

aacac  acetylacetonate
Boc   tert-butoxycarbonyl
DDQ   2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA diisopropylamine
DMD   dimethyldioxirane
DDQ   2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF   N,N-dimethylformamide
DMG   direct metatation group
DOM   directed ortho-metalation
DOS   diversity-oriented synthesis
dr    diastereomeric ratio
ee    enantiomeric excess
equiv. equivalent
HPLC  high performance liquid chromatography
hmbc  heteronuclear multiple bond coherence
i-Pr  iso-propyl
LC    liquid chromatography
LiDMAE lithium 2-(dimethylamino)ethoxide
mCPBA meta-chloroperoxybenzoic acid
Me    methyl
MeCN  acetonitrile
MeOH  methanol
MS    mass spectrometry
MW    microwave
n-Bu  normal-butyl
NMP   N-methyl-2-pyrrolidone
NMR   nuclear magnetic resonance
NOESY nuclear overhauser effect spectroscopy
OBn   benzyloxy
Ph    phenyl
rt.   room temperature
TCT   trichlorotriazine
TEA   triethylamine
THF   tetrahydrofuran
TLC   thin layer chromatography
TMEDA N,N,N',N'-tetramethylethyldiamine
UHP   urea hydrogen peroxide
Å     ångström
1

Introduction

In recent decades there have been exponential advances in organic chemistry that have resulted in the development of large numbers of new methods and improvement of already known. Nevertheless, the medical and materials sciences continue to require novel drugs and other products, hence there are continuing needs for the development of new methods, and the enhancement of current methods, for synthesizing organic compounds.

This thesis is based on studies in which new synthetic methodologies have been developed to synthesize molecules that have interesting bioactivities, such as pyridines, piperidines and piperazines. These structures are common fragments in both pharmaceuticals and natural products, and a number of synthetic methods for their preparation are known today. However, the focus in this thesis is on organometallic additions to an already existing, activated pyridine or pyrazine ring.

Direct attempts to react organometallic reagents with pyridines are often troublesome and require harsh conditions. To circumvent this problem, acyl-activated pyridines have commonly been used. This strategy has been well studied, but the reported methods often suffer from drawbacks such as the formation of regioisomers or the need for multi-step synthetic protocols. However, as an alternative to these starting materials, we have studied the reaction between pyridine N-oxides 2 and Grignard reagents. Pyridine N-oxide 2 is a cheap, commercially available and bench-stable starting material. Furthermore, differently substituted pyridine N-oxides 2 are easily obtained from the oxidation of pyridines 1, by one of several published methods (Scheme 1.1). Given the number of commercially available pyridines, these methods have the potential to generate a vast diversity of substituted pyridine N-oxides, which potentially could be used as starting materials for multitude of target molecules.

\[\text{Scheme 1.1}\]


Although the pyridine N-oxide 2 has structural resemblance to pyridine 1, the reactivity of the two compounds differs significantly. For example, pyridine 1a reacts inefficiently upon nitration, even at high temperatures, and only 6% of the corresponding 3-nitro pyridine is obtained (Scheme 1.2). In contrast, the nitration of pyridine N-oxide 2a proceeds smoothly and the corresponding 4-nitro pyridine N-oxide is obtained with a yield of 95% (Scheme 1.2). In addition to its lower reactivity, pyridine yields the 3-nitro isomer while the pyridine N-oxide gives the 4-substituted product (Scheme 1.2). Furthermore, the differences in reactivity are reflected in the results of reacting pyridine or pyridine N-oxides with nucleophilic reagents. While pyridine 1a reacts slowly, or requires harsh conditions to react with phenyl lithium (PhLi), phenylmagnesium chloride (PhMgCl) readily add to pyridine N-oxide 2a, even at -40 °C. Although the main product from the addition occurs at the same position, the 2-substituted pyridine 1c is obtained with PhLi, while the reaction between PhMgCl and pyridine N-oxide gives the ring-opened dienral-oxide 3a (Scheme 1.2).

Furthermore, the distinctive reactivity of pyridine N-oxides can be understood by looking at the different possible resonance structures (Figure 1.1). Because of the mesomeric electron release from the oxygen, pyridine N-oxides can easily be reacted with electrophiles, as illustrated in Scheme 1.2

1Joule, J. A. ; M. Heterocyclic Chemistry 4th Ed., 75-76.
(structures II and III, Figure 1.1). The situation is some subtle as the same positions are also activated towards nucleophilic additions, however, after coordination to the $N$-oxygen the electrophilicity of pyridine $N$-oxide is more pronounced (structures IV and V, Figure 1.1).

Figure 1.1. Different resonances of pyridine $N$-oxides.

Our interest in the reactivity of pyridine $N$-oxides and their potential as starting materials for the synthesis of a multitude of target molecules, led us to revisit the reaction between Grignard reagents and pyridine $N$-oxides. As a result from these studies we have been able to apply the same chemistry to include the synthesis of substituted piperazines, from pyrazine $N$-oxides and Grignard reagents. Figure 1.2 gives a general overview of the chemical transformations discussed in this thesis.

Figure 1.2. General overview of chemical transformations discussed in this thesis.
A stereodefined synthesis of substituted dienal-oximes

Paper I

2.1 Introduction

The first report on the reaction between Grignard reagents and pyridine $N$-oxide (2a) was published by Colonna and co-workers in 1936. They claimed the reaction to yield 2-phenyl pyridine (1c) when PhMgCl was reacted with pyridine $N$-oxide (2a) in diethyl ether (Scheme 2.1). The same reaction was later investigated by Kato et al. in 1965, who instead reported the isolation of 1,2-dihydropyridine 4 in a yield of 60-80% (Scheme 2.1). As a result Kellog et al. became interested in the structural aspects of the reaction and therefore reinvestigated the Grignard addition to pyridine $N$-oxides in 1971. Instead of 2-phenylpyridine (1c) or 1,2-dihydropyridine (4), they reported the isolation of ring-opened dienal-oxime (3a) in 45% yield (Scheme 2.1).

\[ \begin{align*}
&\text{PhMgX} \\
&\text{THF} \\
&\text{Reported by Kato} \\
&\text{X= Cl, Br} \\
\end{align*} \]

\[ \begin{align*}
&\text{PhMgX} \\
&\text{THF} \\
&\text{Reported by Colonna} \\
\end{align*} \]

\[ \begin{align*}
&\text{PhMgX} \\
&\text{THF} \\
&\text{Reported by Kellogg} \\
\end{align*} \]

Scheme 2.1. Reported reactions between pyridine $N$-oxides and Grignard reagents.

---

2.2 Rapid addition of Grignard reagents to pyridine N-oxides

In 2003, Almqvist and co-workers published a method for the synthesis of 4-substituted piperidines, based on copper-catalyzed organozinc addition to N-acyl pyridinium salts. During these studies, the potential utility of pyridine N-oxides for the synthesis of 2-substituted piperidines was investigated. The use of organozinc reagents or organolithium reagent in combination with pyridine N-oxides resulted in no reaction and in a complex mixture, respectively. However, when Grignard reagents were used, a ring-opened product was observed, and later the dienal-oxime 3a was confirmed by structural elucidation using NMR (Figure 2.1). Furthermore, it could be conducted that only one isomer was formed suggesting the reaction to be a concerted electrocyclic ring-opening reaction. (Figure 2.1).

![Figure 2.1. Electrocyclic ring-opening to dienal-oxime 3a.](image)

2.2.1 Synthesis of substituted dienal-oximes

The formation of dienal-oximes, with a defined diene-system and oxime functionality present in the structure, appeared as an attractive intermediate for further transformations. Therefore, the reaction between Grignard reagents and pyridine N-oxides was studied further. When PhMgCl was added slowly to pyridine N-oxide (2a) at -40 °C, only a moderate 38% yield of dienal-oxime 3a was isolated. However, if the addition rate was increased and the reaction performed at room temperature (rt.), the yield of dienal-oxime 3a increased to 85% (entry 1, Table 2.1). This protocol was therefore used to prepare a small set of dienal-oximes 3a-3l starting from differently substituted pyridine N-oxides 2a-2g (Table 2.1).

2-substituted and 4-substituted pyridine N-oxides 2b, 2d-2g reacted smoothly with aryl and alkynyl Grignard reagents to form dienal-oximes 3b, 3d-3l in yields between 66-95% (entries 2, 4-12, Table 2.1). However, when the reaction between PhMgCl and 3-picoline N-oxide (2c) was performed, dienal-oxime was not observed by crude-NMR or isolated (entry 2, Table 2.1). Instead, the 2,3-disubstituted pyridine was obtained in a 43% yield (see Chapter 3 for a more detailed discussion).

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Table 2.1. Synthesis of 3,5-substituted dienal-oximes.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>oxime</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>3b</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>3c</td>
<td>0b</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>3d</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>3e</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>2e</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>3e</td>
<td>77c</td>
</tr>
<tr>
<td>7</td>
<td>2e</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>2-Thiophene</td>
<td>3g</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>2f</td>
<td>H</td>
<td>H</td>
<td>OBn</td>
<td>Ph</td>
<td>3h</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>2f</td>
<td>H</td>
<td>H</td>
<td>OBn</td>
<td>Naphthyl</td>
<td>3i</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>2f</td>
<td>H</td>
<td>H</td>
<td>OBn</td>
<td>PhCC</td>
<td>3j</td>
<td>78c</td>
</tr>
<tr>
<td>11</td>
<td>2f</td>
<td>H</td>
<td>H</td>
<td>OBn</td>
<td>2-Thiophene</td>
<td>3k</td>
<td>76</td>
</tr>
<tr>
<td>12</td>
<td>2g</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>Ph</td>
<td>3l</td>
<td>86</td>
</tr>
</tbody>
</table>

Reactions conditions: pyridine N-oxide (1 equiv.) in THF, Grignard reagent 1.2 (equiv.) at rt. aIsolated yields. bNo dienal-oxime observed instead the corresponding 2,3-substituted pyridine was isolated. cTo consume starting material the reaction mixture was heated gently. PhCC = phenylethynyl.

2.2.2 Addition of alkyl Grignard reagents.

To broaden the scope for the synthesis of dienal-oximes, we studied the possibility of synthesizing 5-alkyl substituted dienal-oximes by using alkyl-Grignard reagents. Iso-propylmagnesium chloride (i-PrMgCl) and methyl-magnesium chloride (MeMgCl) were reacted with pyridine N-oxides 2a and 2e as previously described. Unfortunately only low yields (< 10%) were isolated after aqueous work-up and purification by column chromatography. This was surprising since LC-MS analysis indicated that a large amount of the product was present in the crude reaction mixture, together with only minor amounts of by-products. Although this could have been due to differences in the MS response factors of the products, it indicated that the alkylated dienal-oxime formed in the reaction is less stable than the previously isolated 5-aryl dienal-oximes (Table 2.1). Therefore, we set out to perform a transformation of the ring-opened dienal-oxime into a potentially more stable product before purification. A well-known transformation of oximes is the Beckmann rearrangement.10 Whereas ketoximes result in the corresponding amides, aldoxime normally gives the corresponding nitrile by the elimi-

nation of water. Since this is quite a straightforward transformation, and the corresponding nitrile is, potentially, a more stable product, we investigated the possibility of transforming the aldoximes into the corresponding nitriles before purification. Initially, the reaction was performed using trichlorotriazine (TCT) in dimethylformamide (DMF), followed by addition of dienaloxime 3e. The reaction was complete after 30 minutes at rt. and the nitrile 5a was isolated in a 59% yield. However, using the commercially available Vilsmeier salt 6 gave a more straightforward protocol and a cleaner reaction.

Salt 6 was dissolved in dichloromethane (DCM) and added to the crude mixture obtained after Grignard addition, which increased the yield of isolated nitrile 5a to 74% (entry 1, Table 2.2). The reaction was also performed on alkylated dienal-oximes, and the nitriles 5b and 5c from the addition of i-PrMgCl and MeMgCl to pyridine N-oxides 2a and 2e, were isolated with yields of 49% and 64%, respectively (entries 2 and 3, Table 2.2).

Table 2.2. Conversion to nitriles.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>R</th>
<th>R</th>
<th>nitrile</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>Ph</td>
<td>5a</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>H</td>
<td>CH(Me)₂</td>
<td>5b</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>2e</td>
<td>Ph</td>
<td>Me</td>
<td>5c</td>
<td>64</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, Grignard reagent (1.2 equiv.) at rt. Vilsmeier salt (2 equiv.) in DCM at rt. *Isolated yields.

2.2.3 Further transformations of dienal-oximes.

Having developed this efficient method for the preparation of dienal-oximes, we addressed the possibility that we might be able to transform the intermediate products further into other compounds. If possible, this could constitute a platform for diversity-oriented synthesis (DOS) – a strategy based on small molecules with potential for further transformations giving a range of diverse structures. Basically, there are two ways for planning DOS pathways, the reagent-based and the substrate-based approach. The substrate-based approach take advantage of different starting materials, whereas in the

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reagent-based approach the same starting material is treated with different reagents to generate a set of diverse compounds. In our case the reagent-based strategy would be the most suitable for planning DOS via dienal-oximes, starting from pyridine N-oxides (Figure 2.2).

Figure 2.2. Reagent-based approach towards DOS.

Perhaps the most straightforward transformation would be the synthesis of the corresponding saturated primary amine 9 (Scheme 2.2). Reduction of 3e, using the practical hydrogen transfer method, palladium on charcoal, Pd/C, with ammonium formate in methanol (MeOH), gave the secondary amine 7 in a 48% yield and not the expected primary amine 9 (Scheme 2.2). A higher yield (62%) of the secondary amine 7 was obtained when using t-BuNH2-BH3 and Pd/C; but again, the primary amine 9 was not observed (Scheme 2.2).

To synthesize the primary amine, a two-step protocol was tested: reduction of the oxime 3e followed by hydrogenation to give the saturated primary amine 9 (Scheme 2.2). Nucleophilic hydride reagents such as NaCNBH3 and LiAlH4 only returned the starting material; and the electrophilic hydride reagent BH3-SMe2 gave complex reaction mixtures. Our attention was therefore turned instead to zinc dust in acetic acid, a method often used to reduce nitroso functionalities to amines. Zn dust in acetic acid gave a rapid and clean conversion to amine 8 without reduction of the double bonds (Scheme 2.2). Although the E/Z isomers 8a and 8b were obtained in a 2:1 mixture, the subsequent reduction gave the primary saturated amine 9 in a 86% yield calculated over two steps (Scheme 2.2).

Reacting 4-benzyloxypyridine N-oxide (2f) with PhMgCl gave 3-benzyloxy substituted dienal-oxime 3h in a 95% yield (entry 8, Table 2.1). Compound 3h can be considered as a masked enamino one, hence debenzylation followed by reduction of the oxime functionality would render the enamino. Enaminones are versatile intermediates that combine the nucleophilic prop-

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erties of enamines and the electrophilic properties of enones, which makes them very important intermediates for the synthesis of various heterocyclic compounds. To our delight no dimerization – which had been seen in previous reductions, i.e. 3e (Scheme 2.2) – was observed when 3h was subjected to Pd/C and ammonium formate reduction, and the enaminone 10 was isolated in a 78% yield (Scheme 2.2). To demonstrate further transformations using this intermediate, enaminone 10 was reacted with hydrazine hydrate under microwave irradiation to yield pyrazole 11 in a yield of 71%.

![Scheme 2.2. Further transformation of dienal oxime 3e and 3h.](image)

### 2.3 Conclusion and outlook

In this chapter, the synthesis of dienal-oximes by the addition of Grignard reagents to pyridine N-oxides at rt. has been discussed. The addition of aryl and alkynyl Grignard reagents gave the dienal-oximes in good to excellent yields, whereas an in situ transformation of the resulting oxime to a more stable intermediate, its corresponding nitrile, was necessary after the reaction with alkyl Grignard reagents. In addition, these intermediates can potentially be converted into a diverse set of compounds e.g. nitriles, amines, enamines and pyrazoles. Thus, the generation of dienal-oximes from the reaction between Grignard reagents and pyridine N-oxides, affords an excellent platform for the design and synthesis of diversity-oriented synthesis (DOS).

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Complete regioselective synthesis of substituted pyridines

Paper II

3.1 Introduction

Due to the importance of pyridines in bioactive compounds and materials (Figure 3.1), a considerable number of methods have been developed for the synthesis of substituted pyridines. Typically, these methods are based on cyclization reactions, i.e. from an aldehyde, 1,5- or 1,3-dicarbonyls, and ammonia: also known as Hantzsch pyridine synthesis. However, the additional functionalization of already existing pyridines still poses a significant synthetic challenge. This chapter discusses the synthesis of substituted pyridines derived from pyridine N-oxides, a transformation that proceeds via the previously described dienal-oximes (Chapter 2).

Figure 3.1. Examples of important pyridines. 12 is a promising new sodium channel inhibitor. 13 acts as an allosteric antagonist at the metabotropic glutamate receptor mGlu and 14 a chiral catalyst used in asymmetric synthesis.

\[ \text{Figure 3.1. Examples of important pyridines.} \]

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\[ ^{21}\text{Joule, J. A.; K., M. Heterocyclic Chemistry 4th Ed., 103-110.} \]
\[ ^{25}\text{Usuda, H.; Kuramoto, A.; Kanai, M.; Shibasaki, M. Org. Lett. 2004, 6, 4387-4390.} \]
3.1.1 Organometallic addition to activated pyridines

Even though pyridine is much more electron-poor than benzene, nucleophilic additions to pyridines are slow and requires harsh reaction conditions in order to react with organometallic reagents with reasonable efficiency (Chapter 1, Scheme 1.2). One way to address this problem is to activate the pyridine prior to the nucleophilic attack. Consequently, Fraenkel and co-workers presented a method based on ready addition of Grignard reagents to pyridines in the presence of ethylchloroformate to yield the corresponding substituted dihydropyridine intermediates. These intermediates were easily oxidized, and the carbamate was hydrolyzed to yield the substituted pyridines. Comins and co-workers further developed this strategy into an efficient method for the synthesis of substituted pyridines, including activated acyl- and alkyl-pyridines and the use of other organometallic reagents (i.e. Li and Zn) (eq. 1, Scheme 3.1). However, the formation of a mixture of regioisomers, which results from addition at the 2- or 4-positions, has limited the applicability of this methodology (Scheme 3.1). To achieve selective addition at either position, protection of the unwanted addition site has been necessary, which limits the scope of the method.

Nevertheless, this strategy is attractive, and additional methods using activated pyridine derivatives with directing groups have been reported. For example, Charette and co-workers presented a method in 2001 for the synthesis of substituted pyridines and piperidines. Their method relies on the stereoselective formation of N-pyridinium imidate from the reaction between amide and pyridine. In this case, the nitrogen imidate lone pair is oriented so

\[ \text{Ph-N} \rightarrow \text{Ph-N} \]

Scheme 3.1. Examples of methods for synthesis of substituted pyridines.

as to direct the addition of an organometallic reagent at the 2-position (eq. 2, Scheme 3.1). In general, the regioselectivity is good, favoring the formation of 1,2-dihydropyridine, which can then be oxidized with 2,3-dichloro-5,6-dicyanobezoquinone (DDQ) to the corresponding 2-substituted pyridine.

Despite the large number of reports on the preparation of substituted pyridines from organometallic reagents and N-activated pyridines, previously described methods often result in the formation of isomeric mixtures of 2- and 4-substituted products. With this in mind, and the knowledge of the excellent regiocontrolled synthesis of dienal-oximes described in Chapter 2, we focused on the use of these intermediates in the synthesis of substituted pyridines.

### 3.2 Regiospecific synthesis of substituted pyridines

The formation of dienal-oximes from the reactions between Grignard reagents and pyridine N-oxides, and their subsequent transformations into a range of different compounds was discussed in Chapter 2. Now, we wanted to explore these compounds further, to also include the synthesis of substituted pyridines. Kellogg et al. have earlier reported a ring closure of dienal-oximes in presence of acetic anhydride to yield the substituted pyridine, (exemplified with two reactions). However, as a result from the low isolated yields of dienal-oximes, the pyridines were only obtained in 17 and 24% yields calculated from the pyridine N-oxides (Scheme 3.2).

![Scheme 3.2](image)

**Scheme 3.2.** Synthesis of pyridines from dienal-oximes.

The transformation is probable to proceed via the formation of intermediate I, upon reaction with acetic anhydride. The reaction is suggested to be an electrocyclic ring-closure reaction forming one new σ-bond (intermediate II, Scheme 3.2). Subsequent elimination of acetic acid provides the substituted pyridine 1 (Scheme 3.2).

---

3.2.1 Synthesis of 2-substituted and 2,4-disubstituted pyridines

In initial studies, the isolated dienal-oxime 3e (Chapter 2, entry 5, Table 2.1) was dissolved in acetic anhydride, and then subjected to microwave irradiation at 100 °C for 2 minutes. According to LC-MS analysis of the crude reaction mixture, the corresponding pyridine 1g was the major product with considerable amount of starting material still present in the reaction mixture. To consume the starting material, both the reaction temperature and reaction time were increased to 120 °C and 4 minutes. These adjustments of the reaction conditions gave the corresponding pyridine 1g in an isolated yield of 92% calculated from the dienal-oxime. However, to increase the practicality of the method, without isolating the dienal-oxime, the unsubstituted pyridine N-oxide 2a was reacted with PhMgCl, quenched, worked-up using extraction, and concentrated. The crude residue was then dissolved in acetic anhydride and heated under microwave irradiation at 120 °C for 4 minutes. After work-up and purification, 2-phenyl pyridine (1c) was isolated in a 63% yield (entry 1, Table 3.1). As expected, when studying the crude mixture by NMR, the 4-substituted regioisomer was not observed. The scope of the reaction was further studied by reacting p-Me- and p-OMe phenylmagnesium chloride to yield corresponding 2-substituted pyridines 1d and 1e, both in 83% yield (entries 2 and 3, Table 3.1). In addition, 2,4-disubstituted pyridines were prepared by starting from 4-substituted pyridine N-oxides 2e-2g (Table 3.1). Aryl, alkynyl and heteroaryl Grignard reagents reacted well with 4-phenyl and 4-benzyloxy substituted pyridine N-oxides, 2e and 2f to form the corresponding 2,4-disubstituted pyridines 1g-1m in yield of 73-86% (entries 5-11, Table 3.1). To challenge the regioselectivity in the reaction further, and enable use of starting materials that are predisposed for further transformations, the 4-chloropyridine N-oxide (2g) was reacted with PhMgCl (entry 14, Table 3.1). In this case no 4-substitution was observed and pyridine 1p was isolated in a yield of 74%. This is a higher yield than reported in previous studies in which phenoxy-carbonyl activated 4-chloropyridines have been reacted with Grignard reagents to yield 55% of the corresponding 2-substituted pyridine.\(^\text{29}\)

As can be seen in Table 3.1, the low yields obtained when alkyl Grignard reagents were used to synthesize dienal-oximes are also reflected in attempts to synthesize alkyl substituted pyridines (entries 4, 12 and 13, Table 3.1). Thus, alkyl Grignard reagents such as benzyl magnesium chloridre, i-PrMgCl and MeMgCl chloride resulted in low yields (37-45%), when reacted with pyridine N-oxides 2a and 2f (For a more detailed discussion of alkyl Grignard reagents and N-oxides see Chapter 4).

Table 3.1. Synthesis of 2-substituted and 2,4-disubstituted pyridines.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>R</th>
<th>R'</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>Ph</td>
<td>1c</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>H</td>
<td>p-MePh</td>
<td>1d</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>H</td>
<td>p-OMePh</td>
<td>1e</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>H</td>
<td>Bn</td>
<td>1f</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>Ph</td>
<td>Ph</td>
<td>1g</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>2e</td>
<td>Ph</td>
<td>2-naphthyl</td>
<td>1h</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>2e</td>
<td>Ph</td>
<td>PhCC</td>
<td>1i</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>2e</td>
<td>Ph</td>
<td>Cy-propylCC</td>
<td>1j</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>2e</td>
<td>Ph</td>
<td>2-thienyl</td>
<td>1k</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>2f</td>
<td>OBn</td>
<td>Ph</td>
<td>1l</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>2f</td>
<td>OBn</td>
<td>2-naphthyl</td>
<td>1m</td>
<td>79</td>
</tr>
<tr>
<td>12</td>
<td>2f</td>
<td>OBn</td>
<td>Iso-propyl</td>
<td>1n</td>
<td>45</td>
</tr>
<tr>
<td>13</td>
<td>2f</td>
<td>OBn</td>
<td>Me</td>
<td>1o</td>
<td>37</td>
</tr>
<tr>
<td>14</td>
<td>2g</td>
<td>Cl</td>
<td>Ph</td>
<td>1p</td>
<td>74</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, Grignard reagent 1.2 (equiv.) at rt. Crude residue was dissolved in acetic anhydride and heated in microwave for 4 minutes at 120 °C. Isolated yields.

3.2.2 Reaction with 2- and 3-substituted N-oxides

The pyridine N-oxides used in the reaction described as yet have either been unsubstituted, or substituted at the 4-position. To extend the usefulness of the reaction further, the scope for using 2- and 3-substituted pyridine N-oxides was explored. In the case of 2-picoline N-oxide (2b), one α-position is blocked which could promote the formation of 4-addition products. Furthermore, pyridine N-oxide 2b has the potential of deprotonation of the methyl in the 2-position upon addition of the Grignard reagent. Despite this, pyridine 1q was isolated in an excellent yield of 87% and the 4-substituted regioisomer was not observed (Scheme 3.3).

In the first addition of PhMgCl to 3-picoline N-oxide (2c), attempts were made to isolate the corresponding dienal-oxime (Chapter 2, entry 2, Table 2.1). Surprisingly, no dienal-oxime was observed; instead the 2,3-disubstituted pyridine 1r was formed directly, and was isolated in a moderate yield of 43% (Scheme 3.3.). However, the regioselectivity was excellent and only trace amounts of the 2,5-addition product were observed. This regioselectivity was somewhat unexpected, since the steric hindrance caused by the methyl group at the ortho-position would be expected to give a domi-
nance of a 2,5-disubstituted product if any regioselectivity at all. However, similar results have been previously reported, in studies that have shown the ortho-positions to be more susceptible towards nucleophilic addition than the para-position (with respect to the methyl group).\textsuperscript{30} Furthermore, the addition of acetic anhydride to the reaction mixture was not necessary. Elimination of magnesium chloride occurred instantaneously, which allowed the corresponding pyridine Ir to form directly (Scheme 3.3). Corresponding results were also observed when 3,5-picoline N-oxide (2h) was reacted, and the trisubstituted pyridine 1s was isolated in an excellent yield of 91% (Scheme 3.3).

![Scheme 3.3. Synthesis of substituted pyridines.](image)

3.2.3 Synthesis of unsymmetrical 2,6-disubstituted pyridines

Oxidation of the ring-cycled intermediate 15, instead of reduction, should open up for a second addition of Grignard reagents (Scheme 3.4). If possible this would serve as an attractive method for the synthesis of 2,6-disubstituted pyridines (Scheme 3.5).

![Scheme 3.4. Oxidation of dienal oximes](image)

To oxidize dihydropyridines, reagents such as DDQ, potassium permanganate (KMnO\textsubscript{4}) or Pd/C are typically used. However, both DDQ and KMnO\textsubscript{4},

in combination with heating, gave sluggish reaction mixtures that produced only traces of the oxidized product. The use of Pd/C and microwave irradiation gave slightly better, but still unsatisfactory results. Our attention was therefore turned to heating the reaction mixture in DMF in the presence of air. By refluxing the crude intermediate dienal-oxime, from reacting pyridine N-oxide 2f with PhMgCl, dissolved in DMF in the presence of oxygen, the corresponding 2-phenylpyridine N-oxide (2i) was obtained in 86% yield. The addition of PhMgCl or p-tolyl magnesium chloride, followed by treatment with acetic anhydride and microwave irradiation, produced the corresponding pyridines 1t and 1u with yields of 73% and 63%, respectively (Scheme 3.5).

![Scheme 3.5. Synthesis of 2,6-disubstituted pyridines.](image)

### 3.2.4 One-pot synthesis of 4,2-disubstituted pyridines

In the method described above, the Grignard reagent was added to the pyridine N-oxide at rt., but to obtain good yields of the substituted pyridines, liquid-liquid extractive work-up, followed by the addition of acetic anhydride and microwave irradiation, was essential. However, to get a more robust and straightforward synthesis of substituted pyridines we set-out to improve this method. To avoid the work-up and the need to transfer products to another reaction flask, the Grignard addition was performed in the microwave vial, and the pH was adjusted to 6-8 using aqueous NaHCO₃ after consumption of the pyridine N-oxide. After addition of 10 equivalents of acetic anhydride, the resulting slurry was irradiated at 120 °C for 4 minutes. Upon completion of the reaction, the product was purified using solid phase extraction, which makes the method amenable for parallel synthesis. Using this protocol, pyridine 1l was isolated in a yield of 69% compared to an 82% yield (entry 10, Table 3.1) when using the liquid-liquid extraction between dienal-oxime and pyridine formation (entry 1, Table 3.2). The lower yield can be explained by the use of solid-phase extraction, in which the focus is on the purity of the products rather than their yield. This procedure gave similarly good yields when used to synthesize additional 4 examples of disubstituted pyridines, 1v–1y (entries 2-5, Table 3.2).
Table 3.2. One-pot procedure for synthesis of substituted pyridines.

![Reaction mechanism](image)

| entry | R   | R'     | pyridine  (yield %) 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>I1 (69)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>4-Cl-Ph</td>
<td>I1v (73)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>N-Me-indole</td>
<td>Iw (72)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2-thienyl</td>
<td>Ix (69)</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>4-OMe-Ph</td>
<td>Iy (76)</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, Grignard reagent 1.2 (equiv.) at rt, pH 6-8, Ac2O (10 equiv.) 4 minutes at 120 °C. *Isolated yields.

3.3 Synthesis of 4-pyridones
(Appendix I)

In investigations outlined here we extended the scope of 4-benzyloxypyridine N-oxide to the synthesis of substituted 4-pyridones and 4-aminopyridinium salts. Both of these compound classes are frequently used in pharmaceuticals and are therefore of considerable interest. 31

The previous chapter described a one-pot synthesis of substituted pyridines from 4-benzyloxypyridine N-oxides. We postulated that this method, with removal of the benzyl group (e.g. via application of Pd/C in combination with hydrogen gas), could provide easy access to the corresponding substituted 4-pyridone. Indeed, thin layer chromatography (TLC) and LC-MS analysis indicated good results when pyridine I1 was hydrogenated under atmospheric pressure (eq 1, Scheme 3.6). However, during attempts to identify product 16 a brown insoluble solid was formed. The identity of this compound is still unclear, but one possibility is that the 4-pyridone is prone to aggregate, radically changing both its chemical reactivity and solvation (eq 1, Scheme 3.6). 32

Due to the difficulties in identifying product 16, we searched for other methods and found one recently reported by Dudley and co-workers. They re-


ported that the 2-benzylxy pyridinium salt 17 could be used as a benzyla-
tion reagent for alcohols providing the benzylated alcohol together with the
2-hydroxyl pyridinium salts 18 (eq. 2, Scheme 3.6).33

\[
\begin{align*}
\text{Scheme 3.6. (eq 1.) Attempt to synthesize 4-pyridone from Pd/C and H}_2\text{ gas. (eq 2.) Dudley’s benzyla-
tion of alcohols from 2-benzylxy pyridinium salts.}
\end{align*}
\]

Hence, this approach could potentially serve as a method for the synthesis of
2-pyridones (eq 2, Scheme 3.6). Inspired by this method for debenzylation,
we started to investigate possible quartenization methods for pyridines. The
addition of methyl iodine to pyridine 11 dissolved in acetone yielded the
Corresponding iodopyridinium salt. However this reaction was slow (requi-
ring stirring overnight); but higher yields were obtained, more quickly, using
methyl triflate as the alkylating agent in the reaction with pyridine 11. In the
next step, a 2M aqueous sodium hydroxide solution was added to the gene-
rated pyridinium salt 19a, and the corresponding 4-pyridone 20a was isolated
in a 81% yield (entry 1, Table 3.3).

Table 3.3. Synthesis of 4-pyridones.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'</th>
<th>pyridone (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>20a (81)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>1-naphthyl</td>
<td>20b (74)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>4-OMe-Ph</td>
<td>20c (79)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2-thienyl</td>
<td>20d (82)</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>4-OMe-Ph</td>
<td>20e (70)</td>
</tr>
</tbody>
</table>

Reaction conditions: MeOTf (1.05 equiv.) in toluene at 0 °C to rt. 30 min, then crude residue treated with 2M
NaOH at rt. *Isolated yields.

Using the method described above, a small set of substituted 4-pyridones 20a - 20e was synthesized (Table 3.3). As can be seen, the corresponding 4-pyridones was all obtained in isolated yields between 70% and 82% (entries 1 to 5, Table 3.3).

3.3.2. Synthesis of 4 aminopyridines

During the debenzylation investigation, we also studied the use of ammonia-saturated THF solution. The aim was to generate the 4-pyridone by adding a pre-saturated ammonia-THF solution to the crude pyridinium salt, followed by removal of reagents and solvent by concentration under reduced pressure. However, when ammonia was allowed to react with the 2-phenylpyridinium salt 19a, no 4-pyridone was observed. Instead the 4-aminopyridinium salt 21a was obtained. Therefore, in parallel with the synthesis of the 4-pyridone, the same set of pyridinium salts were reacted with amines to generate the 4-amino-pyridinium salts 21a-21e (Scheme 3.7).

The pattern seen in Table 3.3 can also be observed in scheme 3.7 and corresponding pyridinium salts were isolated in similar yields as the pyridones (Scheme 3.7). In addition to ammonia, the potential use of other amines were also investigated, and the simple addition of either morpholine or piperidine to the pyridinium salt 19a gave the corresponding 4-amino substituted pyridinium salts 22a and 22b with reasonable yields of 50 and 60%, respectively (Scheme 3.7).

3.4 Conclusion and outlook

In this chapter, the synthesis of substituted pyridines via an electrocyclic ring-closure reaction of dienal-oximes has been presented. The method provides a complete regioselective synthesis of substituted pyridines starting
from the reaction between Grignard reagents and pyridine N-oxides. The method is robust, allowing use of alkyl, alkynyl, aryl and heteroaryl Grignard reagents to synthesize diverse pyridines. In addition, we have demonstrated ring-closure followed by oxidation to the corresponding 2-substituted pyridine N-oxide, which allows the synthesis of unsymmetrical 2,6-disubstituted pyridines. Furthermore, a one-pot procedure of substituted pyridines has been demonstrated, which is more suitable for library synthesis. Finally, if the 4-benzyloxy substituted N-oxide is used as the starting material, both 4-pyridones and 4-amino pyridinium salts can be obtained in a fast and simple manner.
4

Synthesis of 2-substituted pyridine \(N\)-oxides via directed ortho-metalation (DOM)

Paper III

4.1 Introduction

In the reactions between Grignard reagents and pyridine \(N\)-oxides, discussed in Chapter 2 and 3, alkyl Grignard reagents mainly resulted in low to moderate yields. This chapter presents the optimization of a side-reaction – a metalation reaction that competes with the nucleophilic addition – as one reason for the low yields observed earlier for the alkylations.

4.1.1 Directed ortho-metalation reaction

In about 1940, Henry Gilman and Georg Wittig reported the first directed ortho-metalation (DOM) reaction between anisole and \(n\)-BuLi. This discovery has since been developed into what is now a fundamental method for the construction of substituted aromatic and heteroaromatic compounds. The general principle for DOM is the chelation of an organometallic reagent (II, Scheme 4.1) to a direct metalation group (DMG), followed by a proton abstraction ortho to the DMG. The metalated species so created (III, Scheme 4.1) is then reacted with an electrophile to form a new carbon-carbon- or carbon-heteroatom bond (IV, Scheme 4.1).

\[ \text{DMG} \quad \text{II} \quad \text{DMG}^{M-R} \quad \text{III} \quad E \rightarrow \text{IV} \]

\( R-M = \text{Organometallic, } R-Li, R-MgX \text{ etc.} \)

Scheme 4.1. Principle of directed ortho-metalation (DOM).

\(^{34}\)For reviews see: (a) Snieckus, V. Chem. Rev. 1990, 90, 879-933. (b) Schlosser, M.; Mongin, F. Chem. Soc. Rev. 2007, 36, 1161-1172.
Despite intensive studies of *ortho*-metalation reactions, problems frequently arise when the method is applied to heterocyclic compounds, e.g. pyridines. In these cases one of the greatest challenges is to circumvent the formation of regioisomers. To this end a number of papers have reported successful outcomes when symmetrical pyridines have been used in the reaction (eq. 1, Scheme 4.2). However, similar successes have not been achieved when unsymmetrical pyridines have been used (eq. 1, Scheme 4.2). To obtain regioselectivity with these compounds, the starting material often needs to contain a directing substituent, or to have a halogen substituent that undergoes metal–halogen exchange when reacted with organometallic reagents (eqs. 2 and 3, Scheme 4.2). However, the limited availability of such suitable starting materials makes these procedures impractical for the synthesis of substituted pyridines.

Scheme 4.2. Different DOM reactions of pyridines.

### 4.2 Metalation of pyridine *N*-oxides

Pyridine *N*-oxides are more prone to undergo C-2 metalation than pyridines. This can be explained by the presence of the electron withdrawing N-O functionality, which not only activates the ring towards deprotonation but also allows chelation of the organometallic reagent. The deprotonation of pyridine *N*-oxides using *n*-BuLi as the reagent (eq. 1, Scheme 4.3) has been thoroughly studied. However, only low to moderate yields of between 14% and 44% have been reported, with the disubstituted products being among the most abundant by-products observed. An alternative method to deprotonation of pyridine *N*-oxide was developed by Fagnou and co-workers. They took advantage of the reactivity of pyridine *N*-oxides for the

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took advantage of the reactivity of pyridine N-oxides for the synthesis of substituted pyridines via C-H activation using Pd as the metal. Although their synthetic procedure is elegant, it is restricted to arylation, and requires an excess of up to 4 equivalents of the pyridine N-oxide (eq. 2, Scheme 4.3).

\[
\text{Scheme 4.3. DOM and C-H activation of pyridine N-oxides.}
\]

Our studies of the synthesis of alkyl substituted pyridines, suggested that the low yields of dienal-oxime 3 (Chapter 2) resulted from a competing deprotonation of the pyridine N-oxide. Given the previous problems encountered with n-BuLi for deprotonation, we became interested in investigating the possibility of using Grignard reagents to synthesize substituted pyridine N-oxide via a deprotonation reaction.

4.2.1 Directed ortho-metallation using Grignard reagents

In our preliminary investigations n-BuMgCl was added drop-wise to pyridine N-oxide 2f dissolved in THF at -78 °C. After 60 minutes the reaction was quenched by the addition of MeOD. NMR studies of the crude reaction mixture indicated that more than 90% had achieved a regioselective incorporation of deuterium at the 2-position (Scheme 4.4).

\[
\text{Scheme 4.4. DOM using n-BuMgCl followed by addition of MeOD.}
\]

Inspired by this result, we changed the electrophile to benzaldehyde but, disappointingly, this resulted in a significant decrease of the isolated yield to 45% of pyridine N-oxide 24d (entry 3, Table 4.1). However, if n-BuMgCl was exchanged to i-PrMgCl an improvement of the yield to 65% of 24d was accomplished (entry 3, Table 4.1). A set of five different pyridine N-oxides were therefore reacted with i-PrMgCl followed by quenching with benaldehyde or iodine. These initial results are summarized in Table 4.1.
Table 4.1. Deprotonation of pyridine N-oxides followed by addition of benzaldehyde or iodine.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>E</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2c</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>PhCHOH</td>
<td>24b</td>
<td>61b</td>
</tr>
<tr>
<td>2</td>
<td>2e</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>PhCHOH</td>
<td>24c</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>2f</td>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>PhCHOH</td>
<td>24d</td>
<td>65e</td>
</tr>
<tr>
<td>4</td>
<td>2f</td>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>I</td>
<td>24e</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>2h</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>I</td>
<td>24f</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>2j</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>PhCHOH</td>
<td>24g</td>
<td>86</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, Grignard reagent (1.7 equiv.) at -78 °C stirred for 60 minutes. Benzaldehyde (2.0 equiv.) added at -78 °C and allowed to attain rt and stirred for additional 30 minutes. *Isolated yields. Isomeric mixture of 2,3 and 2,5 disubstituted N-oxide obtained in 1:1.5 ratio respectively. *A lower yield 45% was obtained when n-BuMgCl was used.

The isolated yields varied between 38% and 92% depending on the pyridine N-oxide used in the reaction (Table 4.1). Generally, high yields were obtained when the pyridine N-oxide was substituted with electron donating groups Me, OBn and OMe (Table 4.1) When deprotonated and reacted with benzaldehyde, both 3-picoline N-oxide (2c) and 3-methoxy pyridine N-oxide (2j) resulted in good yields of 61% and 86% of the disubstituted pyridine N-oxides 24b and 24g, respectively (entries 1 and 6, Table 4.1). As expected, the reaction with 3-picoline N-oxide (2c) gave a mixture of isomers (24b), comprising 2,3- and 2,5-disubstituted pyridine N-oxides in a 1:1:5 ratio, whereas the 3-methoxy N-oxide (2j) resulted in 2,3-disubstituted pyridine N-oxide 24g as the sole product (entries 1 and 6, Table 4.1). The 3,5-picoline N-oxide (2h) was also reacted to give the corresponding trisubstituted pyridine N-oxide 24f (entry 5, Table 4.1) in an excellent yield of 92%. Furthermore, pyridine N-oxide (2f) gave approximately the same results whether iodine or benzaldehyde were used as the electrophile (entries 3 and 4, Table 4.1). The 4-phenylpyridine N-oxide (2e) formed the expected 2,4-disubstituted pyridine N-oxide 24c (entry 2, Table 4.1), but the product was isolated in only a low yield of 38%. The major product isolated in a 56% yield was 2-iso-propyl substituted N-oxide, as a result from the addition of i-PrMgCl followed by oxidation (entry 2, Table 4.1).

4.2.2 DOM comparison between Grignard and lithium reagents

In the protocol described above, 1.7 equivalents of Grignard reagents were used with 2.0 equivalents of the electrophile. To further improve and explore
the directed ortho-metalation of pyridine N-oxides, we aimed to reduce the number of equivalents and use more demanding electrophiles. We also wanted to be able to compare our results with previously reported using n-BuLi.\(^{39}\) Cyclohexanone was therefore chosen as the electrophile, which potentially impact the reaction in two ways, increased bulkiness and the presence of acidic \(\alpha\)-protons. The results are summarized in table 4.2.

Table 4.2. DOM followed by trapping with cyclohexanone.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(R^4)</th>
<th>product</th>
<th>yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24h</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24i</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>24j</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>2f</td>
<td>H</td>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>24k</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>2g</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>24l</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>2h</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>24m</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>2k</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24n</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2j</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>24o</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>2l</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>24p</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>2m</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24q</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, Grignard reagent (1.2 equiv.) at -78 °C stirred for 60 minutes. Cyclohexanone (1.5 equiv.) was added at -78 °C and allowed to attain rt and stirred for additional 30 minutes. *Isolated yields.

A regioselective incorporation of cyclohexanone was achieved with pyridine N-oxide (2a) to give the substituted pyridine N-oxide 24h in a 38% yield (entry 1, Table 4.2). Although the isolated yield is rather low, compared with the previously reported 7% yield using n-BuLi, this is still a marked improvement.\(^{39}\) As a by-product, the corresponding 2-substituted iso-propyl pyridine N-oxide was isolated in a 15% yield. Similar results were obtained with 2- and 4-picoline N-oxide (2b and 2d), which gave yields of 32% and 36% of 29i and 29j, respectively (entries 2 and 3, Table 4.2), compared with yields of 0% and 21% when \(n\)-BuLi was used.\(^{39}\) Furthermore, with 2-chloro and 2-methoxy pyridine N-oxide 2k and 2m, no products were observed after LC-MS or crude-NMR analysis (entries 7 and 10, Table 4.2). However, by switching to 4-chloro- and 4-methoxypyridine N-oxides (2g and 2l), the yields were improved to 20% and 22% respectively (entries 5 and 9, Table 4.2). Finally, pyridine N-oxides 2f, 2h, and 2j were deprotonated, followed by the

addition of cyclohexanone, to yield the corresponding tertiary alcohols 24k (62%), 24m (81%) and 24o (90%), respectively, (entries 4, 6 and 8, Table 4.2).

In conclusion, Table 4.2 indicates that the best results are achieved when the pyridine N-oxides are substituted with an electron-donating group in the 3- or the 3- and 5-positions. We therefore decided to explore further the incorporation of different electrophiles by reacting 3-methoxy-pyridine N-oxide (2j) with the three different electrophiles, piperidinone 25, iodine, and phenylisocyanate, each of which has different useful properties. The reactions were carried out in the same manner as previously described (Scheme 4.5).

![Scheme 4.5. Direct trapping of intermediate 23b with piperidinone, iodine or phenylisocyanate.](image)

The direct trapping of the intermediate 23b using commercially available N-methyl piperidinone, was performed first. After the addition of N-methyl piperidinone to the solution of 23b, a white precipitation was formed and the reaction congested resulting in only a 36% yield of isolated product. However, this yield was improved to an excellent 93% when N-Boc-protected piperidinone 25 was used instead (Scheme 4.3). Furthermore, the addition of iodine to the intermediate 23b gave the corresponding 2-ido pyridine N-oxide 24s in a 96% yield. This compound, being predisposed to be used in further transformations such as Suzuki-Miyaura (see Chapter 4.3), Heck40 and Stille41 couplings. Finally, reacting phenylisocyanate with intermediate 23b gave 2-phenylcarbamoyl pyridine N-oxide 24t in 81% yield (Scheme 4.5).

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4.3 Suzuki–Miyaura coupling of 2-iodo pyridine N-oxides (Appendix II)

The Suzuki-Miyaura cross-coupling reaction was first reported in 1979 and has since developed into one of the most popular methods for carbon-carbon bond formation.\(^{42}\) Although tremendous progress has been made such that couplings can now be performed with more challenging substrates,\(^{43}\) only a few reports can be found in the literature concerning Suzuki–Miyaura coupling of halo-pyridine N-oxides.\(^{44}\) We therefore decided to investigate the possibility of coupling N-oxide 24s (Scheme 4.5) in a Suzuki–Miyaura coupling reaction.

We started to investigate the reaction using conditions, previously reported successful on similar substrates. A mixture of 24s, phenyl boronic acid, tetrakis (triphenylphosphine) palladium (Pd(PPh\(_3\))\(_4\)) and potassium carbonate (K\(_2\)CO\(_3\)) in DMF/water was irradiated with microwaves for 10 minutes at 100 °C to give the corresponding 2,3-substituted N-oxide 26a in an excellent 99% yield (entry 1, Table 4.3). When phenyl boronic acid was changed for 3-methyl- or 3-nitrophenyl boronic acids, the corresponding pyridine N-oxides 26b and 26c were isolated in yields of 97% and 90%, respectively (entries 2, 3, Table 4.3).

![Suzuki–Miyaura coupling reaction](image)

**Table 4.3.** Suzuki–Miyaura coupling of 2-iodo pyridine N-oxide 24s.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>26a</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>3-Me-Ph</td>
<td>26b</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>3-NO(_2)-Ph</td>
<td>26c</td>
<td>90</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in DMF:water 4:1, boronic acid (3 equiv.), Pd(PPh\(_3\))\(_4\) (10 mol%), K\(_2\)CO\(_3\) (3 equiv). Irradiated 10 minutes at 100 °C. \(^*\)Isolated yields.

During attempts to improve the reaction, it was found that when MeOH was used as the solvent, the reaction time could be reduced from 10 to 2 minutes, and the temperature could be decreased slightly from 100 °C to 80 °C.


addition, to further ease the work-up, the amount of catalyst was reduced from 10 mol% to 1 mol% by using a solid supported palladium catalyst: VersaCat™ Pd. Eight different substituted pyridine N-oxides were synthesized in parallel using these changes to the method. Thus, the two pyridine N-oxides 24e and 24s, were reacted with four boronic acids i.e. phenyl, 4-methoxy, 3-tolyl, and 3-nitro phenyl boronic acids. After irradiation the catalyst was filtered off and the solvent removed under reduced pressure. The eight crude mixtures were then purified by parallel column chromatography to give the corresponding pyridine N-oxides 26a–26h in 80% to 92% isolated yields (entries 1–8, Table 4.4).

Table 4.4. Parallel synthesis of pyridine N-oxides using Suzuki–Miyaura coupling.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>R</th>
<th>R'</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24s</td>
<td>3-OMe</td>
<td>Ph</td>
<td>26a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>24s</td>
<td>3-OMe</td>
<td>3-Me-Ph</td>
<td>26b</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>24s</td>
<td>3-OMe</td>
<td>3-NO₂-Ph</td>
<td>26c</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>24s</td>
<td>3-OMe</td>
<td>4-OMe-Ph</td>
<td>26d</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>24e</td>
<td>4-OBn</td>
<td>Ph</td>
<td>26e</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>24e</td>
<td>4-OBn</td>
<td>3-Me-Ph</td>
<td>26f</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>24e</td>
<td>4-OBn</td>
<td>3-NO₂-Ph</td>
<td>26g</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>24e</td>
<td>4-OBn</td>
<td>4-OMe-Ph</td>
<td>26h</td>
<td>92</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in MeOH, boronic acid (3 equiv.), VersaCat (1 mol%), K₂CO₃ (3 equiv). Irradiated 2 min at 80 °C. *Isolated yields.

In summary we were able to isolate eight new pyridine N-oxides in high yields in only 7 hours, including reactions and the final purification.

4.4 The direct coupling of the metalated pyridine N-oxides

The direct cross-coupling of Grignard reagents and halides has recently been the focus of much attention. Several different methods have been reported, including the use of an iron catalyst as an economical and green alternative to palladium and nickel in cross-coupling reactions. The arylation, vinylation and alkynylation of Grignard reagents with different aryl and alkyl magnesium halides using iron as catalyst. In 2004, Fürstner and co-workers reported a cross-coupling of alkyl halides with aryl Grignard reagents, that was catalyzed by low-valency iron complexes such as FeCl₃, Fe(acac)₂ or

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Fe(acac)₃ (where acac = acetylacetonate). Interested in this method, we
decided to investigate the use of metallated pyridine N-oxides, with an iron
catalyst, as a method for the direct coupling of Grignard reagents with vari-
ous halides (Scheme 4.6). Unfortunately neither 1-bromopentane nor bromo-
cyclohexane, in combination with FeCl₃ or Fe(acac)₃ in THF or a THF:NMP
(9:1) mixture, reacted successfully: only the starting material was recovered
(Scheme 4.6). Other reports have shown that the addition of N,N,N′,N′-
tetramethylethylidyldiamine (TMEDA) facilitates the coupling. However,
equimolar amounts of Grignard reagent and TMEDA, in the presence of 5
mol% FeCl₃ again returned only the starting material. Cahiez et al. reported
that the addition of 1.5 equivalents of TMEDA to a solution of FeCl₃ gen-
erates a [{FeCl₃}(tmeda)₃] complex that can be efficiently used for cross-
coupling reactions. Unfortunately, also with this additive only the starting
material 2j was isolated (Scheme 4.6).

Because of the unsuccessful results using iron as catalyst, our attention was
turned to copper instead. Pyridine N-oxide 2j was therefore first depro-
nated, and then transferred to a solution of 1-bromopentane with catalytic
amounts of either Cul or CuCN (5% in both cases) (Scheme 4.6). Again,
these attempts failed to cross-couple and only the starting material 2j was
recovered.

The failure of both iron and copper in the cross-coupling reactions, led us to
study palladium as the catalyst. Therefore the palladium-catalyzed direct-
coupling of Grignard, known as the Kumada coupling was investigated. Since
coupling with alkyl, vinyl or aryl has been reported, the metallated
pyridine N-oxide 23b was reacted with either iodobenzene in the presence of
Pd(PPh₃)₄, or with benzyl chloride in the presence of palladium acetate

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50 Terao, J.; Todo, H.; Begum, S. A.; Kumiyasu, H.; Kambe, N. Angew. Chem. Int. Ed. 2007, 46, 2086-
  Shaikh, N.; Zapf, A.; Beller, M. Angew. Chem. Int. Ed. 2002, 41, 4056-4059. for review see (c) Corbet,
(Pd(OAc$_2$)). Unfortunately, in both cases no product was observed and only
the starting material 2$j$ was recovered (Scheme 4.7).

![Scheme 4.7. Kumadacoupling of pyridine N-oxide 2$j$.](image)

Next our attention was turned to diaryliodonium salts 28. These salts have
proven to be excellent alternatives to aryl halides for the introduction of aryl
substitutents.\(^{52}\) The diaryliodonium salt 28 was prepared in a 79% yield
according to a published method (Scheme 4.8).\(^{53}\) However, the uncatalyzed
reaction between Grignard reagents and diaryliodonium salts has been re-
ported to be troublesome.\(^{54}\) Also in our case the arylated pyridine N-oxide
was not observed when iodinium salt 28 was added directly to intermediate
23$c$. However, repeating the reaction in presence of catalytic amount of zinc
chloride (ZnCl$_2$) and Pd(PPh$_3$)$_4$ gave trisubstituted pyridine N-oxide 26$i$
in 10% yield. This yield was increased to 51% when the reaction was irradiated
for 10 minutes at 70 °C in a microwave reactor (Scheme 4.8).\(^{55}\)

![Scheme 4.8. Double metal catalyzed arylation of metalated N-oxide 6$h$.](image)

### 4.4 Conclusion and outlook

In this chapter, a complete regioselective deprotonation of pyridine N-oxides
using i-PrMgCl has been described. Previously reported deprotonations,
using lithium reagents, have suffered from drawbacks such as low yields and
the formation of the disubstituted product as the major product. This prob-

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\(^{55}\) Further optimization of the reaction was not performed.
lem was not encountered when Grignard reagents were used. Although electron-donating groups in the third position of the ring were crucial in order to obtain good yields, the reaction allowed incorporation of a range of different electrophiles. We also demonstrated the efficacy of 2-iodo-pyridine N-oxides in a Suzuki–Miyaura coupling. This method was used to synthesize eight different aryl substituted pyridine N-oxides in a parallel manner. Finally, we demonstrated a direct cross-coupling reaction between metalated pyridine N-oxide and diaryliodonium salt under zinc and palladium catalysis.
Synthesis of trans-2,3-dihydropyridine N-oxides and piperidines

Paper IV

5.1 Introduction

The main focus in Chapter 5, is the synthesis of substituted piperidines, a frequently occurring motif in pharmaceuticals and natural products (Figure 5.1). For example, Paroxetine 29, which is used in the treatment of depression, contains a 3,4-disubstituted piperidine (Figure 5.1). Another interesting compound is the naturally occurring alkaloid conine 30, which, despite its simple structure, is very toxic, and due to its stereochemistry, is a great challenge to synthesize. As a final example, compound 31 is the analgesic morphine, which is a multi-ring fused compound with piperidine embedded in its structure.

![Figure 5.1. Structures of pharmaceuticals and natural products containing piperidine.](image)

The importance of piperidines has stimulated intense research into the development of new methods for their preparation. One recently reported method included a reductive cross-coupling between homoallylic alcohols and imines followed by a cyclisation to the substituted piperidines. (eq. 1, Scheme 5.1). This method resulted in good regio- and stereocontrol of the reaction (dr 95:5). An alternative method, to cyclisation, that has proven

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useful is the asymmetric hydrogenation of activated pyridines (eq. 2, Scheme 5.1). For example, Charette and co-workers developed an iridium-catalyzed asymmetric hydrogenation of N-iminopyridinium ylides for the synthesis of enantiomerically enriched piperidines (Scheme 5.1).\(^{59}\)

\[
\begin{align*}
\text{(eq 1)} & \quad \text{Scheme 5.1. Examples of stereoselective synthesis of piperidines.} \\
\text{(eq 2)} & \quad \text{Chiral N-acyl activated pyridinium salts 32 have also been used for the asymmetric synthesis of substituted piperidines (Scheme 5.2). In the synthesis of a range of different piperidine containing alkaloids, Comins and coworkers used 4-dihydropyridones 33 as common intermediates formed from the addition of Grignard reagents to N-acyl-4-methoxypyridinium salts.}^{60}
\end{align*}
\]

\[
\begin{align*}
\text{Pyridine N-oxides 2, on the other hand, have earlier been shown to undergo ring-opening when reacted with Grignard reagents (Chapter 2 and 3) and have not been used as precursors to piperidines. However, since our previous results indicated that ring-opening can be avoided by modifying the reaction conditions, we were interested to see whether this approach could be used for the synthesis of substituted piperidines (Scheme 5.2).}
\end{align*}
\]


5.2 Synthesis of trans-2,3-dihydropyridine N-oxide

During our studies of the previously discussed metatation reaction (Chapter 4), PhMgCl was reacted with pyridine N-oxide (2a) at -78 °C, followed by the addition of MeOD. The expected incorporation of deuterium at the 2-position was not observed. Instead, the 2-phenyldihydropyridine N-oxide 34 was observed as the major product according to LC-MS analysis (Scheme 5.3). However, attempts to isolate this compound by silica column chromatography only resulted in its decomposition. To circumvent this, the reaction was repeated at -40 °C; but immediately after the addition of MeOD, a slurry of NaBH₄ in MeOH was added (Scheme 5.3). This time, after work-up and purification, the reaction resulted in N-hydroxyl 2-phenyl tetrahydropyridine 35, which was isolated in a quantitative yield. NMR studies revealed that the deuterium was assigned to the 5-position; not the 2-position as had been expected. The experiment was then repeated using MeOH instead of MeOD and the corresponding tetrahydropyridine 36 was isolated in a 94% yield (Scheme 5.3).

To study the reaction further, benzaldehyde was used instead of MeOH. Thus, after the addition of PhMgCl to pyridine N-oxide (2a), benzaldehyde was added at -78 °C. The reaction mixture was stirred at -78 °C for 30 min, and, according to LC-MS, a disubstituted product was formed. Repeating the experiment at -40 °C gave a total conversion of the starting material and the disubstituted dihydropyridine N-oxide 37a was isolated in a 79% yield (Scheme 5.4). Data from ¹H-NMR and ¹³C-NMR analysis confirmed the 2,3-disubstitution pattern, and not the expected 2,5-disubstituted product that was obtained when MeOD or MeOH was used as the electrophiles (Scheme 5.3). This finding was further confirmed by 2D-NMR, noesy and hmbc experiments, and the elucidation of a crystal structure. Furthermore, H-NMR analysis of the crude reaction mixture confirmed that the 2,3-trans isomer
was formed exclusively, with the *cis* isomer not being detected at all. The diastereomeric mixture formed in the reaction results from the benzylic alcohol substituted in the third position. Although an isomeric mixture is obtained, the diastereomeric ratio (dr) of 82/18, is rather impressive, especially considering that three stereocentres are formed in one reaction step.

![Scheme 5.4 Synthesis of trans 2,3-dihydropyridine N-oxide.](image)

To further support the diene-structure, dimethyl acetylene-dicarboxylate was reacted with the *trans*-2,3-dihydropyridine N-oxide in a Diels–Alder reaction. Thus, heating 37a and dimethyl acetylenedicarboxylate in toluene for 30 min gave the aza-bicyclo compound 38 in an 86% yield (Scheme 5.5).

![Scheme 5.5 Diels–Alder reaction and structures of aza-bicyclo compound 38.](image)

The structure of the Diels–Alder product 38 was determined by a noesy experiment, which showed a strong cross-coupling-peak between the proton in the 3-position and the bridged proton. Two energy minimized structures of the product, using molecular mechanics (MM2) are shown in Scheme 5.5. Based on these calculations, the distance between the two protons in each structure should be 3.2 Å and 4.3 Å, respectively. However, because 4.3 Å is not likely to give a strong coupling in the noesy spectra (Scheme 5.5), the diasteromer 38 shown in Scheme 5.5 is supported by the results of the analysis.

Further investigation of the scope for the reaction was performed with different pyridine *N*-oxides and PhMgCl followed by sequential addition of
benzaldehyde, butyraldehyde or cyclohexanone. These results are summarized in Table 5.1.

Table 5.1. Synthesis of 2,3-dihydropyridine N-oxides.

<table>
<thead>
<tr>
<th>entry</th>
<th>N-oxide</th>
<th>E'</th>
<th>product</th>
<th>dr° yield (%)</th>
<th>entry</th>
<th>N-oxide</th>
<th>E'</th>
<th>product</th>
<th>dr° yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>2a</td>
<td>37b</td>
<td>82/18 59</td>
<td>6</td>
<td>39</td>
<td>2b</td>
<td>37d</td>
<td>78/22 98</td>
</tr>
<tr>
<td>2</td>
<td>2e</td>
<td>2e</td>
<td>37f</td>
<td>89/11 81</td>
<td>7</td>
<td>39</td>
<td>2n</td>
<td>39</td>
<td>90/10 96</td>
</tr>
<tr>
<td>3</td>
<td>2e</td>
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<td>37g</td>
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<td>8</td>
<td>40</td>
<td>2n</td>
<td>37h</td>
<td>50/50 56°</td>
</tr>
<tr>
<td>4</td>
<td>2f</td>
<td>2f</td>
<td>37i</td>
<td>88/12 86</td>
<td>9</td>
<td>39</td>
<td>2o</td>
<td>37i</td>
<td>60/40 71°</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>2f</td>
<td>37k</td>
<td>72/28 71</td>
<td>10</td>
<td>39</td>
<td>2e</td>
<td>41</td>
<td>- 50°</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, PhMgCl (1.2 equiv.), electrophile (1.5 equiv.).

*Diastereomeric mixture (dr) reported as major/minor with respect to the alcohol. Estimated from crude NMR analysis. *Isolated yields. *Reaction performed at -20°C. *Reaction performed in toluene.

Pyridine N-oxide (2a) and the substituted 4-phenyl and 4-benzyloxy pyridine N-oxides (2e and 2f) gave the corresponding trans-2,3-dihydropyridine N-oxides 37b-37f using either benzaldehyde or butyraldehyde as electrophiles (entries 2-5, Table 5.1). 2-Phenylpyridine N-oxide (2n) gave excellent yields of the 2,3-substituted products 37g and 37h, of 98% and 96%, respectively, (entries 6 and 7, Table 5.1). Pyridine N-oxide 2o, which is already substituted in both the 2- and 3-positions, was also examined. In this case the nucleophilic addition, and thus the consumption of the pyridine N-oxide, was slower. The reaction was therefore conducted at -20 °C instead of -40 °C. Using this procedure, benzaldehyde gave product 37i, which was isolated in a 56% yield (entry 8, Table 5.1), whereas the corresponding reaction with butyraldehyde gave the product 37j in a 71% yield (entry 9, Table 5.1). It

*°A series of temperature experiments at -78, -40, -20, 0 °C proved that -20 °C was the upper limit. At temperatures above -20 °C a substantial amount of dienal-oxime was observed.
was also observed that the diastereomeric mixture ratios differed, depending on the temperature. The low drs. of 50/50 for 37i and 60/40 for 37j could be due to the fact that they were reacted at -20 °C (entries 8 and 9, Table 5.1). This tendency was also observed in the preparation of compounds 37c and 37h. Changing temperatures from -40 °C to -78 °C improved the dr. from 89/11 to 98/2 and from 78/22 to 92/8, for 37c and 37h respectively.

The incorporation of other functionalities was also investigated. Unfortunately, using cyclohexanone, iodine, or phenylisocyanate as electrophiles only resulted in complex product mixtures. However, these electrophiles are less reactive than aldehydes, and to address this, the temperature was increased, but unfortunately without success. However, changing THF to toluene gave a better result when cyclohexanone was used, and the corresponding tertiary alcohol 37k was obtained in a 50% yield (entry 10, Table 5.1). The rationale for this could be a tighter coordination of the reactive species to the carbonyl group, thereby increasing the reactivity of the carbonyl, i.e. ketone. However, these changes in the method was not successful when either iodine or phenylisocyanate were used as electrophiles, which might indicate that the strong coordination to the oxyphilic magnesium is necessary.

Table 5.2. Synthesis of 2,3-dihydropyridine N-oxides.

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgX</th>
<th>product</th>
<th>dr</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClMg</td>
<td>37l</td>
<td>81/19</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>ClMg</td>
<td>37m</td>
<td>79/21</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>BrMg</td>
<td>37l</td>
<td>81/19</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>BrMg</td>
<td>37o</td>
<td>81/19</td>
<td>60</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in THF, PhMgCl (1.2 equiv.), electrophile (1.5 equiv.). *Diastereomeric mixture (dr) reported as major/minor with respect to the alcohol. Estimated from crude NMR analysis. †Isolated yields.
The reactivity of different Grignard reagents in combination with benzaldehyde was studied next. Both electron rich and electron poor arylmagnesium chloride reacted in a similar manner to PhMgCl to give the corresponding products 37l and 37m in yields of 72% and 76% respectively (entries 1 and 2, Table 5.2).

As might be expected, reacting the alkyl Grignard reagent n-BuMgCl with pyridine N-oxide (2a) gave 37n in only a 28% yield. This further confirms the previous results obtained when pyridine N-oxides were reacted with alkyl Grignard reagents at low temperature (see section 4.2.1). The addition of vinyl magnesium chloride to 2a followed by benzaldehyde, gave product 37o in 60% yield (entry 4, Table 5.2).

5.3 Synthesis of piperidines

From the synthesis of substituted tetrahydropyridine N-hydroxyls 36 and 2,3-dihydropyridine N-oxides 37 described above, we now wanted to use these intermediates in the preparation of substituted piperidines.

5.3.1 Synthesis of 2-substituted piperidines

Performing atmospheric hydrogenation using catalytic amounts of Pd/C (10 mol%) in MeOH gave the desired piperidine, but a long reaction time (up to three days) was necessary unless the amount of Pd/C was greatly increased. The reaction time could be reduced by the addition of catalytic amounts of acetic acid, but 48 hours or more were still necessary for all the starting material to be consumed. Increasing the pressure of hydrogen gas to 35-50 psi reduced the reaction time further, but still, more than 24 hours were required and from a practical point of view this is not optimal. From these experiments, we observed that the double bond was easily reduced, but that the removal of the N-hydroxyl was more troublesome. In order to address this, we applied a double reduction strategy. First the tetrahydropyridine N-hydroxyl 36 was reacted with Zn dust in acetic acid and MeOH (1:1). Only after complete removal of the hydroxyl group, which took 4 hours at rt., was Pd/C (10 mol%) added and the mixture subjected to hydrogen gas. To facilitate the purification of the amine, a N-Boc protection was performed and the 2-phenyl piperidine 42 was isolated in a 79% yield (Scheme 5.6).

![Scheme 5.6. Synthesis of 2-substituted piperidine.](image-url)
This is the first reported synthesis of piperidines derived from pyridine $N$-oxide. The method is complete regioselective and provides an easy access to 2-substituted piperidines.

### 5.3.2 Synthesis of trans-2,3 disubstituted piperidines

In addition to 2-substituted piperidines, we also wanted to synthesize 2,3-disubstituted piperidines from the previously described 2,3-dihydropyridine $N$-oxides. With the stereochemistry of the 2- and 3-position already defined, a reduction of the diene system, followed by removal of the hydroxyl group, would render a diastereoselective synthesis of 2,3-disubstituted piperidines. Being interested in a recently reported hydrogenation, using Pd/C and 1,4-cyclohexadiene as the hydrogen source in combination with microwave irradiation, we decided to try the same procedure.\(^2\) After optimization of the reaction time and temperature, dihydropyridine $N$-oxide 37a was irradiated for 40 min at 145 °C in the presence of 10 equivalents of 1,4-cyclohexadiene, which resulted in a complete conversion to the secondary amine. After Boc protection, the corresponding piperidine 43 was isolated in an excellent 90\% yield (Scheme 5.7). Surprisingly, this method only gave trace amounts of piperidine 44 when dihydropyridine $N$-oxide 37o was reacted in the same manner. However, this transformation was performed instead, by using Raney-Nickel as the catalyst. Thus, Raney-Nickel was added to 37o dissolved in MeOH and the resulting slurry was subjected to atmospheric pressure of hydrogen gas for 45 minutes at rt. to give piperidine 44 in a 71\% yield (Scheme 5.7).

![Scheme 5.7. Synthesis of trans-2,3-disubstituted piperidines.](image)

### 5.4 Conclusion and outlook

In this chapter we have shown that readily available pyridine $N$-oxides can be used with advantage for the complete regio- and stereoselective synthesis of substituted piperidines. We have proven that, if the reaction is kept cold during the addition of Grignard reagents to pyridine $N$-oxides, the ring re-

mains intact. The method can be used for the synthesis of both 2-substituted piperidines and 2,3-substituted piperidines. The latter compounds are formed via a sequential addition of Grignard reagents and aldehydes or ketones, to pyridine N-oxides at -40 °C, yielding the trans-2,3-dihydropyridine N-oxide addition. Furthermore, we have shown that these novel intermediates formed in the reaction, can be used for further transformations, such as a Diels–Alder reaction, to give a substituted aza-bicyclo scaffold.
Grignard addition to pyrazine N-oxides: towards an efficient enantioselective synthesis of substituted piperazines

Paper V

6.1 Introduction

Substituted piperazines are motifs often found in bioactive compounds. The scaffold is considered to be a privileged structure, and a recent survey showed that 60 out of 1000 orally administrated drugs contained a piperazine fragment.

Synthetic strategies for substituted piperazines often rely on cyclisation procedures. Madsen and co-workers recently reported an iridium catalyzed synthesis of piperazines from diamines and diols (eq. 1, Scheme 6.1). Another efficient strategy is the hydrogenation of pyrazines. This procedure can allow asymmetric control of the reaction, although few examples have been reported to date, and most of these report only modest enantiomeric excess e.g. 78% ee (eq. 2, Scheme 6.1).

Scheme 6.1. Different methods to prepare substituted piperazines.

The organometallic additions to activated pyrazines for the synthesis of piperazines, in analogues to activated pyridines, have not been reported. This is surprising since activated pyrazines could potentially constitute an excellent precursor for the preparation of substituted piperazines. In this chapter we discuss discoveries regarding Grignard reagent addition to pyrazine N-oxides for the synthesis of substituted piperazines.

6.1.2 Pyrazine N-oxide compared to pyridine N-oxide

In contrast to pyridine N-oxide 2a the pyrazine N-oxide 45 contains two nitrogens (Figure 6.1). As a result, the ring is more π-electron deficient and is therefore more susceptible to nucleophiles. When pyridine N-oxide is reacted with nucleophiles, we have shown excellent regioselectivity towards the 2- and 6-positions. However, the nucleophilic reaction with pyrazine N-oxide could potentially result in addition at either the 2- and 6-positions, or at the 3- and 5-positions.

Figure 6.1. Comparison between pyridine and pyrazine N-oxide.

As with pyridine N-oxides, the pyrazine N-oxides are commercially available, or can be prepared by the oxidation of the corresponding pyrazine.

6.2 One-pot synthesis of 2-substituted piperazines

Assuming that the pyrazine N-oxide reacts in a similar manner to the pyridine N-oxide, the rationale was that after the addition of the Grignard reagent, a sequential addition of a hydride source would generate the saturated hydroxyl piperazine 46 (Scheme 6.2). Protection of this intermediate would then result in a short and efficient route to substituted piperazines 47, which are protected so that the nitrogens can be orthogonally deprotected and thus selectively functionalized (Scheme 6.2).

Scheme 6.2. Overview of the synthetic route to orthogonally protected piperazine.
Initially, different reaction temperatures were investigated. Bearing in mind the fact that the reaction between Grignard reagents and pyridine N-oxides is fast, even at -78 °C (30-60 minutes, see chapter 5), the reaction with pyrazine N-oxide might be expected to be even faster. We therefore reacted PhMgCl with pyrazine N-oxide at -78 °C, -40 °C, -17 °C and 0 °C. Immediately (1 minute) after the addition of the Grignard reagent, the reaction mixtures were analyzed by TLC. In all cases total consumption of the starting material was observed. However, when the reaction was performed at temperatures above -40 °C, a black insoluble solid was seen to form almost directly after the addition of PhMgCl. It was also noticed that DCM was a more suitable solvent due to its solvation properties being better than THF.

In a second reaction, PhMgCl was added to pyrazine N-oxide at -78 °C followed by a reduction using NaBH₄ in MeOH and subsequent protection of the secondary amine using di-tert-butyl dicarbonate (Boc₂O) in a one-pot sequence (Scheme 6.3). This gave the corresponding piperazine 47a in an overall yield of 42%. LC-MS analysis indicated that the low yield was mainly due to the formation of the possible dimer 48 as a by-product (Scheme 6.3).

![Scheme 6.3. Synthesis of N,N-diprotected substituted piperazines.](image)

We hypothesized that the dimer 48 (Scheme 6.3) had been formed by the reaction between the intermediate and the unconsumed pyrazine N-oxide, in analogy with the results discussed in Chapter 5. To overcome this problem the addition was reversed. Instead of adding the Grignard reagent to pyrazine N-oxide, pyrazine N-oxide was added drop-wise, to 2.5 equivalents of PhMgCl at -78 °C. Furthermore, the reaction of the reduction and protection time was prolonged to 25 and 60 minutes, respectively. By using this protocol a better result was obtained and to our delight piperazine 47a was isolated in 91% overall yield (entry 1, Table 6.1).
We then followed this protocol in further investigations of reactions between different Grignard reagents and pyrazine N-oxide 45. These results are summarized in Table 6.1.

Table 6.1. Synthesis of N-Boc, N-hydroxy 3-substituted piperazines.

<table>
<thead>
<tr>
<th>entry</th>
<th>RMgX</th>
<th>product</th>
<th>yield (%)</th>
<th>entry</th>
<th>RMgX</th>
<th>product</th>
<th>yield (%)</th>
</tr>
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<tbody>
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<td>91b</td>
<td>8</td>
<td>MgCl</td>
<td><img src="https://example.com/structure8.png" alt="" /></td>
<td>67</td>
</tr>
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<td>9</td>
<td>MgCl</td>
<td><img src="https://example.com/structure9.png" alt="" /></td>
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<td>MgBr</td>
<td><img src="https://example.com/structure4.png" alt="" /></td>
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<td>MgBr</td>
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</tr>
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<td>MgCl</td>
<td><img src="https://example.com/structure7.png" alt="" /></td>
<td>53</td>
<td>14</td>
<td>MgCl</td>
<td><img src="https://example.com/structure14.png" alt="" /></td>
<td>54</td>
</tr>
</tbody>
</table>

Reaction conditions: pyridine N-oxide (1 equiv.) in DCM, Grignard reagent (2.5 equiv.), NaBH₄ (1.1 equiv.) in 2 mL MeOH, Boc₂O (3.0 equiv.). aYields of isolated products. bAlso performed in gram-scale resulting in piperazine 47a in a isolated yield of 76%.

Electron rich and electron poor aryls (entries 2-6, Table 6.1) gave similar good isolated yields of the the protected piperazines 47b-47f. Also a TMS protected alkyne was successfully incorporated, and yielded corresponding piperazine 47g in a 53% yield. A sterical influence could be observed when 4-biphenyl, 2-biphenyl and naphthyl magnesium chloride was reacted resulting in 67%, 33% and 76% yields, respectively (entries 8, 9 and 10, Table 6.1). The heteroaromatic, thiienyl and indole Grignard reagents were also
successfully reacted resulting in 55% and 52% isolated yields (entries 11 and 12, Table 6.1). Furthermore, the formation of an ortho-metalated derivative was not observed after pyrazine N-oxide was reacted with n-BuMgCl followed by trapping experiments with benzaldehyde. Instead, the corresponding n-butyl substituted piperazine 47m was isolated in a 40% yield. We also reacted propenyl magnesium chloride that gave the corresponding piperazine 47n in 54% yield. Finally, we performed the reaction between pyrazine N-oxide 45 and PhMgCl in gram-scale (10 mmol). This time the corresponding piperazine was isolated in a 76% yield.

### 6.3 Orthogonal deprotection

Having developed a good method for the synthesis of N-Boc protected 3-substituted hydroxyl piperazines, we went on to investigate the possibility of selectively removing the N-hydroxyl or the N-Boc-group, thus making the corresponding amine accessible for further transformation. This can be important since the incorporation of piperazine fragments in pharmaceuticals often requires selective transformations on either one of the two nitrogens (e.g. Scheme 6.4).

![Scheme 6.4](image)

Scheme 6.4. Orthogonally protection and deprotection included in the synthesis of indinavir.\(^{67}\)

As discussed previously, the N-hydroxyl can be reduced to the corresponding amine when treated with zinc dust in acetic acid (Chapter 5, Scheme 5.4). However, to circumvent the possible removal of the acid-labile N-Boc-group at the same time as the hydroxyl, we used MeOH as the solvent, together with a few drops of acetic acid and zinc dust. In this way, the loss of the Boc group was avoided and the deprotection was completed after 4 hours at rt. Performing this reaction in the microwave at 80 °C reduced the reac-

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tion time to only 6 minutes. The dehydroxylated piperazine was reacted, without further purification, with benzylbromide to give piperazine 50 in a 92% yield over two steps (Scheme 6.5). The selective N-Boc deprotection was accomplished by dissolving piperazine 47a in a 4M HCl saturated dioxane solution, and stirring for 30 minutes at rt. After evaporation of the solvent, the crude residue was reacted with benzylbromide resulting in piperazine 51 in an 89% yield (Scheme 6.5). The selective N-deprotection was accomplished by dissolving piperazine 47a in a 4M HCl saturated dioxane solution, and stirring for 30 minutes at rt. After evaporation of the solvent, the crude residue was reacted with benzylbromide resulting in piperazine 51 in an 89% yield (Scheme 6.5). The deprotection of both the N-hydroxyl and the N-Boc protecting groups was then investigated further. The most straightforward reaction of zinc dust in 4M HCl saturated dioxane, did not yield the diamine. Instead, diamine 52 was obtained by first reacting piperazine 47a with zinc dust at pH 4, followed by adjusting the pH to 1 with a 4M HCl saturated solution of dioxane, which resulted in the isolation of piperazine 52 in a 90% yield (Scheme 6.5).

Scheme 6.5. Orthogonal deprotection of piperazine 47a.

6.4 Enantioselective synthesis of substituted piperazines

In an attempt to synthesize enantioenriched monosubstituted piperazines, our attention turned next to the asymmetric reaction between Grignard reagents and pyrazine N-oxides. Principally, there are two concrete alternatives to achieve this: first, by using a chiral auxiliary attached to the starting material, which then directs the Grignard reagent; or second, by using a combination of a chiral ligand together with the Grignard reagent. We decided to investigate the latter alternative.

6.4.1 Chiral induction with ligand in combination with Grignard

While enantioselective addition using chiral ligands in combination with zinc and/or lithium reagents, has been reported, far fewer publications ad-
dress the reaction with organomagnesium reagents.\textsuperscript{68} This limited success is mainly due to the high reactivity of Grignard reagents, combined with decreased reactivity upon forming the complex with chiral ligands. Nevertheless, a few successes have been reported concerning this topic. For example, Harada and co-workers presented a method for the asymmetric alkylaion and arylation of aldehydes using a combination of Grignard, titanium tetraisopropoxide and the chiral ligand 3-(3,5-diphenylphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (DPP-binol) (eq. 1, Scheme 6.5).\textsuperscript{69} In 2002, Chong and co-workers reported an enantioselective alkylaion of aldehydes using chiral organomagnesium amides (eq. 2 Scheme 6.5).\textsuperscript{70} They took advantage of the Schlenk equilibrium to form a dialkyl magnesium species that was used in combination with chiral secondary amines. As a final example, Fu and co-workers reported a de-symmetrization of anhydrides by using Grignard reagents and (−)-sparteine 53 (eq. 3, Scheme 6.5).\textsuperscript{71}

\[ \text{Scheme 6.5. Different successful enantioselective reactions using Grignard reagents and a chiral ligand.} \]

(−)-Sparteine 53 appeared as suitable ligand, commercially available and cheap ligand (1 g cost approximately 7 EUR) to start the investigation for synthesis of enantioenriched phenyl substituted piperazines.


6.4.2 Enantioselective synthesis of substituted piperazines

PhMgCl and (-)-sparteine 53 were stirred together in DCM at rt. for 30 minutes before cooling to -78 °C. To this mixture, pyrazine N-oxide 45 was added drop-wise. After further stirring for 10 minutes, NaBH₄ in MeOH was added, followed by protection with Boc₂O. This protocol gave a very promising result as chiral HPLC analysis showed an 82% ee. However, due to unconsumed pyrazine N-oxide 45, piperazine 54 was isolated in a low yield of only 21% (entry 1, Table 6.2). Although low yields, the ee for the reaction prompted us to investigate further different reaction conditions. The results are summarized in Table 6.2.

Table 6.2 Enantioselective synthesis of orthogonally protected 3-substituted piperazine

<table>
<thead>
<tr>
<th>entry</th>
<th>Grignard/sparteine</th>
<th>solvent</th>
<th>temperature °C</th>
<th>time hr</th>
<th>ee %</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2/1.2</td>
<td>DCM</td>
<td>-78</td>
<td>2.5</td>
<td>82</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>1.2/1.2</td>
<td>DCM</td>
<td>-78</td>
<td>2.5</td>
<td>83</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>1.5/1.5</td>
<td>DCM</td>
<td>-78</td>
<td>16</td>
<td>78</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>1.5/1.5</td>
<td>DCM</td>
<td>-78</td>
<td>2.5</td>
<td>rac</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>1.5/1.5</td>
<td>DCM</td>
<td>-78 to rt</td>
<td>2.5</td>
<td>nd</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1.5/1.5</td>
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<td>24</td>
</tr>
<tr>
<td>7</td>
<td>1.5/1.5</td>
<td>THF</td>
<td>-78</td>
<td>2.5</td>
<td>rac</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
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<td>DCM</td>
<td>-78</td>
<td>2.5</td>
<td>62</td>
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<td>9</td>
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<td>rac</td>
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<tr>
<td>12</td>
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<td>DCM/THF</td>
<td>-78</td>
<td>2.5</td>
<td>rac</td>
<td>54</td>
</tr>
</tbody>
</table>

General procedure exemplified with entry 1: PhMgCl (1.2 equiv.) and (-)-sparteine (1.2 equiv.) was diluted with 4 mL DCM and stirred at rt. After 30 minutes the mixture was cooled to -78 °C and stirred additional 15 minutes at -78 °C, whereupon pyrazine N-oxide (1 equiv.) was added dropwise. NaBH₄ (1.1 equiv.) in 2 mL MeOH was added and stirred 25 min before Boc₂O (3 equiv) was added and stirred for 60 minutes. Isolated yields.

Increasing the reaction time did not improve the isolated yield, and the percentage ee remained unchanged (entry 2, Table 6.2). A slightly better yield was obtained when the Grignard/sparteine complex equivalent was increased to 1.5, but still not satisfactory (entry 3, Table 6.2). However, when pyrazine N-oxide was pre-treated with (-)-sparteine, followed by addition to PhMgCl at -78 °C, a 37% yield was obtained, but unfortunately only as a racemic mixture (entry 4, Table 6.2). When the temperature was allowed to reach rt., a complex reaction mixture was obtained (entry 5, Table 6.2), and by changing the solvent to toluene, similar results were obtained to those when DCM was used as the solvent (entry 6, Table 6.2). However, this was not the case when using THF, which resulted in the isolation of the racemate in a 24%
yield (entry 7, Table 6.2). We also studied the effect of increasing the Grignard/sparteine equivalents by reacting 3 and 4 equivalents, but this decreased enantioselectivity and did not change the yields (entries 8 and 9, Table 6.2). We then tried to force the consumption of the pyrazine N-oxide by a sequential addition of another 1.5 equivalents of Grignard and/or the Grignard/sparteine complex. By doing so, we managed to increase the yields slightly but, to our surprise, we obtained the racemate (entries 10 and 11, Table 6.2). This finding suggests that the intermediate so formed, epimerizes upon the sequential addition of more Grignard or Grignard/sparteine complexes. Finally, we decided to use a combination of sparteine and PhMgCl*LiCl, the latter generated from the addition of LiCl to PhMgCl. In this instance, the total consumption of the starting material was achieved, but again, only the racemate was obtained (entry 12, Table 6.2).

The results reported here are only representative of some initial studies from an on-going project in our laboratory. There are still many things that can be tested in an effort to improve the ee and the isolated yield of the reaction.

6.5 Conclusion and outlook

In this chapter, we have described the first synthesis of 2-substituted piperazines by reacting Grignard reagents and pyrazine N-oxides. In fact, this is, to our knowledge, the first reported reaction between Grignard reagents and pyrazine N-oxides giving piperazines. The reaction is a scalable one-pot strategy that includes the addition of pyrazine N-oxide to a Grignard reagent at -78 °C followed by reduction with NaBH₄ and then protection of the secondary amine with Boc-anhydride. The use of aryl, vinyl and alkyl Grignard reagents in the reaction, resulted in differentially protected, 3-substituted piperazines. Furthermore, this compound could be orthogonally de-protected, which allowed further derivatisation on either of its two nitrogens. Finally, we presented some initial studies of the enantioselective synthesis of these orthogonally protected substituted piperazines. While the initial results regarding the enantiomeric excess are promising, the isolated yields are unfortunately still too low.
Concluding Remarks

This study of compounds derived from reactions between Grignard reagents and pyridine and pyrazine N-oxides, that has formed the basis of this thesis, has clearly demonstrated these reactions to have been underestimated since reports in the 1970's established them to be simply low yielders of dienal-oximes. Initial confirmation of these previously reported results was followed by our improvements of the method that enabled us to establish high yielding synthesis of a diverse range of substituted dienal-oximes. Further studies of these compounds confirmed them to be excellent intermediates in the preparation of other interesting compounds such as saturated amines, nitriles or enaminoones. During the development of our method of synthesizing dienal-oximes, we observed them to be prone to ring-closure upon heating. This led us to explore further the usefulness of dienal-oximes in the synthesis of substituted pyridines. We found that if dienal-oximes were treated with acetic anhydride and irradiated with microwaves, the corresponding substituted pyridines could be obtained. Furthermore, the abundance of commercially available pyridine N-oxides allowed us to use 4-benzoyloxy pyridine N-oxide, which meant that the scope for the reaction could be expanded even further to include the synthesis of substituted 4-pyridones and 4-aminopyridinium salts.

Aryl Grignard reagents consistently performed better than alkylmagnesium halides in the reactions. The reason for this proved to be a competitive metatation reaction. Earlier problems encountered in the deprotonation of pyridine N-oxides using n-BuLi led us to investigate the possibility of executing this proton abstraction with alkylmagnesium chlorides. However, it appeared that good yields were only obtainable when the pyridine N-oxide was substituted with an electron-donating group in the third position, although, the reaction tolerated several different electrophiles e.g. aldehydes, ketones, isocyanates or halogens. Furthermore, the usefulness of incorporating iodine was realized in a Suzuki-Miyaura coupling reaction when eight different arylsubstituted N-oxides were synthesized. We made our most noteworthy discovery during the investigation of metatation. We found that attempts to metatate pyridine N-oxide with PhMgCl, followed by the addition of deuterated methanol, did not result in the expected 2-deuterated pyridine N-oxide. Instead, the reaction yielded an incorporation of deuterium in the 5-position. We discovered that this reaction could be used to synthesize 2-substituted piperidines after reduction of the obtained tetrahydropyridine. Further stud-
ies of this reaction showed that, if the electrophile was changed to an aldehyde or ketone, a regio- and stereoselective synthesis of trans-2,3-dihydropyridine N-oxides could be obtained. This novel heterocycle that, with an additional reduction gave the corresponding piperidine, could also be reacted in a Diels-Alder reaction to yield the aza-bicyclo system.

In chapter 6, we showed that the method developed for the synthesis of substituted pyridines and piperidines, could also be used for the synthesis of substituted piperazines. In that chapter we reported how pyrazine N-oxides were reacted with different Grignard reagents at -78 °C, followed by reduction and N-Boc protection, to yield the N,N-diprotected piperazines. This differentially protected piperazine could be orthogonally de-protected, giving opportunities for synthetic modifications at either nitrogen. Finally, we have shown promising results for the enantioselective synthesis of substituted piperazines using a combination of PhMgCl and (-)-sparteine.
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Det är många som ska tackas, här är några:

Fredrik Almqvist, för att du trodde på mig och vågade låta mig driva detta projekt. Din idéri-kedom och inspirerande teorier har ständigt drivit mig framåt. Du har till och med lyckats inspirera mig till att heja på Skellefteå AIK.

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