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PERSPECTIVE

Reactions between Grignard reagents and heterocyclic *N*-oxides: Stereoselective synthesis of substituted pyridines, piperidines, and piperazines

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In this perspective we discuss the recent developments of stereoselective synthesis of substituted pyridines, piperidines, and piperazines from cheap and commercially readily available starting materials. Pyridine *N*-oxides and pyrazine *N*-oxides are reacted with alkyl, aryl, alkynyl and vinyl Grignard reagents to give a diverse set of heterocycles in high yields. Optically active substituted piperazines are obtained by an asymmetric reaction from pyrazine *N*-oxides using sparteine as chiral ligand. In addition, a stereoselective synthesis of dienal-oximes from the reaction between pyridine *N*-oxides and Grignard reagents is presented, which results in a useful intermediate for the synthesis of a diverse set of compounds.

Introduction

Six-membered nitrogen containing heterocycles (*e.g.*, pyridines, piperidines, and piperazines) are privileged structures that occupy a central role in bioorganic and medicinal chemistry.[1] Consequently, developing efficient regioselective and stereoselective methods to obtain these structures have attracted considerable attention during the past decades. These types of heterocycles have been successfully synthesized by using a range of cycloaddition reactions.[2] However, the obtained structural diversity is often limited as a result of the partial access of commercially available starting materials. Therefore, organometallic additions to activated pyridines, *e.g.*, *N*-acyl, *N*-alkyl, *N*-imidate, and *N*-benzoylimino ylides, have emerged as a complementary strategy to cycloaddition reactions.[3] Although there are major challenges associated with organometallic additions as well, *e.g.*, regio- and stereo- control, they do expand the possibilities of synthesizing heterocycles with a more diverse substitution pattern.

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Hans Andersson

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Roger Olsson

Roger Olsson, PhD is the Director of Medicinal Chemistry at ACADIA Pharmaceuticals and adjunct Professor in Medicinal Chemistry at the faculty of medicine, Lund University (from 2010) and at the faculty of science, University of Gothenburg (from 2008), Sweden. His research is focused on diseases of the CNS, e.g., *Parkinson's, Alzheimer's, schizophrenia and pain. Prior to joining ACADIA in 1999, he worked at ASTRA, Sweden discovering steroids targeting anti-inflammatory indications. Dr Olsson qualified as associate professor (Docent) in 2003 at Lund University, wherefrom he also earned his PhD in organic chemistry (1998) and a master of civil engineering (1993).*

In contrast to the *N*-activated pyridine derivatives mentioned above, pyridine *N*-oxides or pyrazine *N*-oxides have only been scarcely used as electrophiles in organometallic additions.[4] This is probably a result of reports in the early 1970s describing the reaction between Grignard reagents and pyridine *N*-oxides yielding ring-opened dienal-oximes in low yields.[4d] Hence, the intended products, substituted dihydropyridines, were not formed. Pyridine *N*-oxides have therefore not until recently been considered suitable starting materials for the synthesis of substituted pyridines and piperidines.[3g]

This perspective features the recent discoveries concerning reactions between Grignard reagents and pyridine *N*-oxides or pyrazine *N*-oxides. These heterocyclic *N*-oxides are either readily available through commercial sources or easily prepared and can serve as bench stable starting materials.[5] The scope and limitations for these reactions are compared between different methods in the ambition to evaluate the status-quo and as a guide to find the most efficient procedures for the synthesis of substituted pyridines, piperidines, piperazines and other accessible compounds (Fig. 1).

Dienal-Oximes

Colonna and co-workers published the first report on the reaction between Grignard reagents and pyridine *N*-oxide (**1**) in 1936.[4b] They claimed that the reaction yielded 2-phenyl pyridine (**2**) when PhMgCl was reacted with pyridine *N*-oxide (**1**) in diethyl ether (Fig. 2).

However, Kato *et al.* reinvestigated the reaction in 1965 where they, instead of the previous reported pyridine **2**, isolated 1,2-dihydropyridine **3** in 60–80% yield (Fig. 2).[4c] As a result, Kellogg *et al.* became interested in the structural aspects of the reaction in 1971,[4d] but in contrast to earlier reports, the reaction did neither yield 2-phenylpyridine (**2**) nor 1,2-dihydropyridine **3**. Instead they reported on the isolation of the ring-opened dienal-oxime **4** in a low 28% yield.[4d] This ring-opened product was confirmed by Schiess and co-workers the following year.[4e]

Fredrik Almqvist

Fredrik Almqvist received a PhD in Organic Chemistry in 1996 from Lund University under the guidance of Professor Torbjörn Frejd. From 1997–1998, Almqvist was a postdoctoral fellow in Professor Garland Marshall's laboratory at Washington University in St. Louis. In 1998 Almqvist joined Umeå University, Sweden, as an assistant professor. He was tenured the year after and in August 2007 he was appointed Professor in Organic Chemistry. His research interests are method developments in organic synthesis and design and synthesis of molecules that interact with macromolecules. Examples of the latter involve development of inhibitors of bacterial macromolecular assembly and amyloid formation.

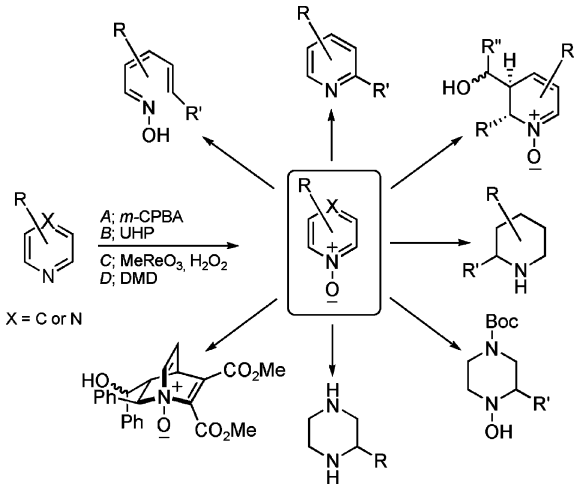


Fig. 1 A variety of structurally different nitrogen containing compounds are available *via* the reactions between pyridine- or pyrazine *N*-oxides and Grignard reagents. *m*-CPBA (3-chloroperoxybenzoic acid), UHP (urea hydrogen peroxide), DMD (dimethyldioxirane).

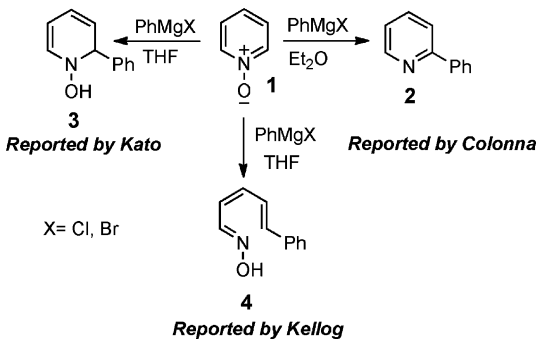
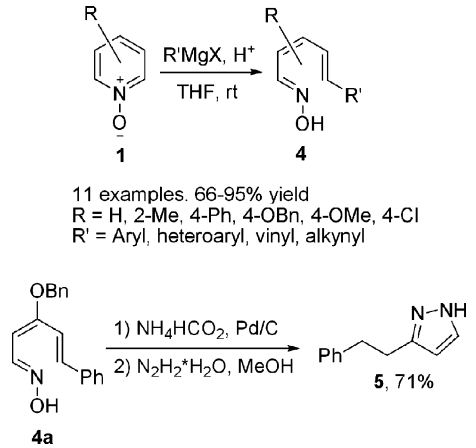


Fig. 2 Previous reports of Grignard additions to pyridine *N*-oxides.

In a collaborative effort, our laboratories recently started to look at the potential of using pyridine *N*-oxides as starting material for the synthesis of 2-substituted piperidines.[6] We confirmed previous results reported on dienal-oxime formation, and in addition found that a fast addition rate of the Grignard reagent to the pyridine *N*-oxide dissolved in THF was important for achieving high yields of the dienal-oximes.[7] Further studies showed that the reaction was compatible with a variety of differently substituted pyridine *N*-oxides and Grignard reagents (Scheme 1). Furthermore, the reaction gave complete regioselectivity, the sole formed product was from addition at the 2-position of the pyridine *N*-oxide. This outcome was also seen in the cases when the pyridine *N*-oxide was substituted with an activating group (*e.g.*, chlorine, methoxy, Scheme 1) in the 4-position. The reaction was evaluated by synthesizing a diverse set of functionalized dienal-oximes **4**, (Scheme 1)[8] which were used as starting materials in the synthesis of conjugated nitriles, aliphatic primary and secondary amines, enaminones, and the substituted pyrazole **5** (Scheme 1).

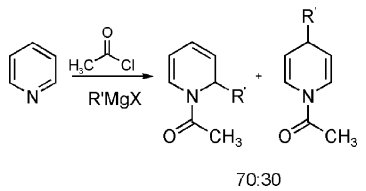
Synthesis of pyridines

The organometallic addition to activated pyridines, *i.e.*, acyl and alkyl pyridinium salts, is an attractive and widely used method to synthesize substituted pyridines.[3a–e] However, the formation of regioisomeric mixtures of 2- and 4-substituted products (eqn (1))



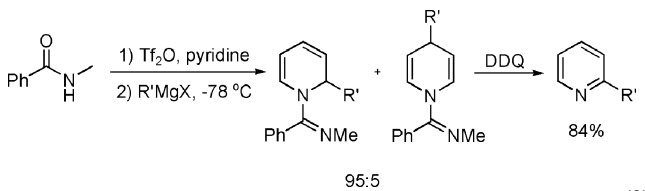
Scheme 1 Synthesis of different substituted dienal-oximes and further transformation, exemplified with the synthesis of pyrazole **5**.

are often limitations associated with these methods. One way to avoid regioisomeric mixtures is to block either position with a substituent. When 4-substituted products are desired, a practical solution is to remove the undesired conjugated 2-regioisomer by trapping it *via* a Diels–Alder reaction.[6]



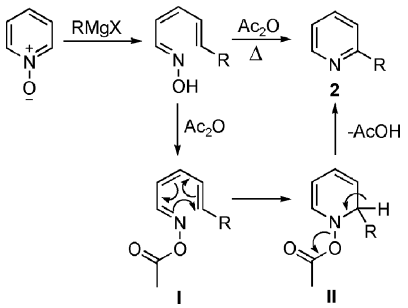
(1)

Nevertheless, the strategy of using activated pyridines is attractive, and additional methods using activated pyridine derivatives with directing groups have been reported. In 2001 Charette and co-workers presented a method for the synthesis of substituted pyridines and piperidines.[3f] *N*-pyridinium imidates, formed from the reaction between an amide and pyridine, direct the addition of the Grignard reagent to the 2-position (eqn (2)).



(2)

Kellogg *et al.* reported earlier a ring closure of dienal-oximes in the presence of acetic anhydride, to yield the corresponding substituted pyridine.[4d] However, as a result from the low isolated yields of the intermediate dienal-oximes, 2-phenylpyridine and 2-thienylpyridine were only synthesized in 12% and 24% yields, respectively; calculated from the pyridine *N*-oxides. This transformation was suggested to proceed *via* the formation of intermediate **I** (eqn (3)), upon reaction with acetic anhydride, followed by a ring-closure reaction which forms one new σ-bond (intermediate **II**). Subsequent elimination of acetic acid results in the substituted pyridine **2**.



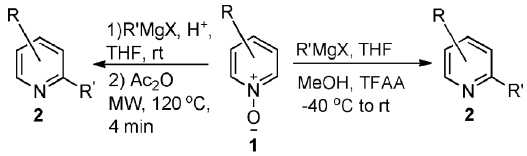
(3)

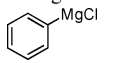
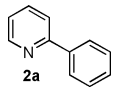
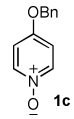
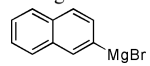
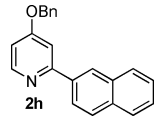
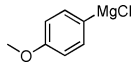
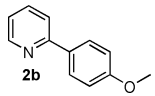
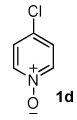
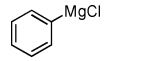
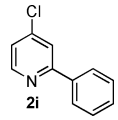
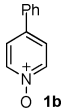
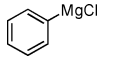
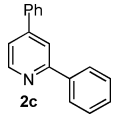
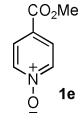
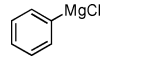
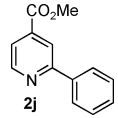
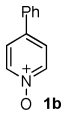
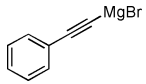
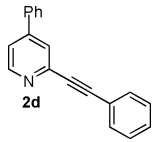
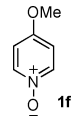
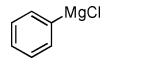
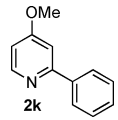
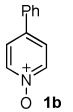
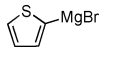
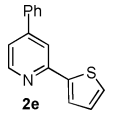
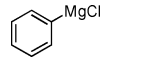
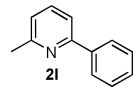
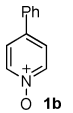
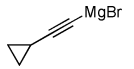
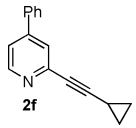
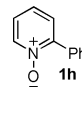
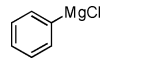
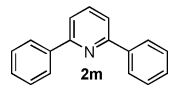
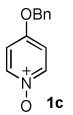
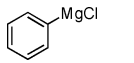
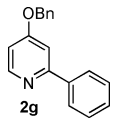
With the new reaction conditions in hand, which resulted in higher yields of dienal-oximes,[7] it appeared straight-forward to address the ring closure, which ultimately could result in a high yielding and regioselective synthesis of substituted pyridines (Method A, Table 1). The 2-substituents were introduced with complete regioselectivity and after a subsequent addition of acetic anhydride and heating, the corresponding pyridines were obtained in good to excellent yields when sp or sp^2-hybridized Grignard reagents were used (63–87%). However, sp^3-hybridized nucleophiles (*e.g.*, Me, Bn, and isopropyl) gave lower yields (37–45%) mainly due to a competing proton abstraction as discussed below.[9]

During our dienal-oxime studies we discovered that the ring was intact, as long as the temperature was below –20 °C. These findings gave inspiration to develop a complementary pyridine synthesis. In more detail, studies of different conditions proved the Grignard addition reaction to be efficient at temperatures ranging from –78 °C to –20 °C. At higher temperatures the ring-opened product started to form. Hence, by performing the reaction below –20 °C and directly aromatizing the dihydropyridine *in situ*, a mild and convenient one-pot procedure would be accessible. The rationale was to add an acylating agent to the initially formed dihydropyridine *N*-oxide, producing an acetoxy-dihydropyridine, which would eliminate acetic acid to form the substituted pyridine. From these studies, it became clear that quenching the dihydropyridine *N*-oxide magnesium intermediate with methanol, prior to the addition of the acylating agent, was important in order to get reproducible results. Among the acylating agents that were studied, trifluoro acetic anhydride (TFAA) gave the best result. By adding TFAA to the pre-quenched crude reaction mixture 2-phenyl pyridine **2c** was synthesized in an overall yield of 76% in one pot (Table 1, entry 3). Further examples and comparisons between these methods are shown in Table 1.[10]

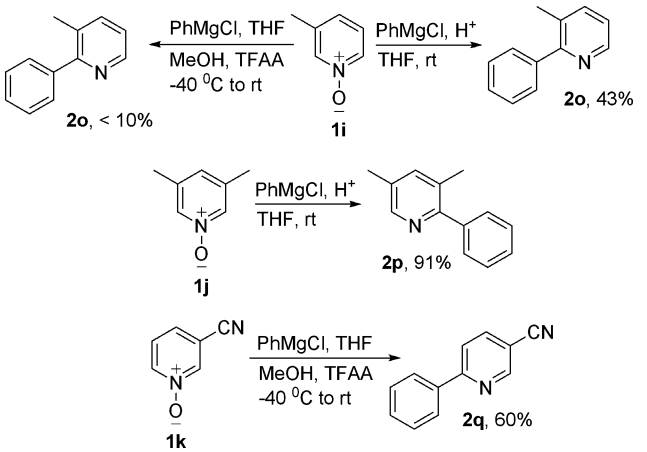
Although method **A** is a two-step transformation, this procedure generally results in slightly higher isolated yields of substituted pyridines. However, as can be seen in Table 1 the two methods complement each other. Method **A** requires room temperature to obtain the dienal-oxime in a high yield and this proved to be an advantage in terms of the incorporation of an alkyne functionality to the pyridine ring (Table 1, entries 4 & 6). These products were not possible to obtain at lower temperatures as required for method **B**, probably due to low nucleophilicity. Method **A** also proved to be more suitable for the incorporation of thienyls. Method **B** on the other hand was the only method of choice when pyridine *N*-oxides, carrying reactive functional groups such as carboxylic esters and nitriles, were used as starting materials; as exemplified with the syntheses of pyridines **2j** and **2q** in 63% and 60% yields, respectively (Table 1, entry 10 and Scheme 2).

Table 1 Selected examples using two independent methods for synthesis of substituted pyridines derived from pyridine *N*-oxides



Entry	*N*-oxide	R′MgX	Product	Method[a/b] **A/B**	Yield(%)[c]	Entry	*N*-oxide	R′MgX	Product	Method[a/b] **A/B**	Yield(%)[c]
1	 **1a**		 **2a**	**A**,**B**	63, 54	8	 **1c**		 **2h**	**A**	79
2	 **1a**		 **2b**	**A**	83	9	 **1d**		 **2i**	**A**,**B**	74, 68
3	 **1b**		 **2c**	**A**,**B**	86, 76	10	 **1e**		 **2j**	**B**	63
4	 **1b**		 **2d**	**A**	78	11	 **1f**		 **2k**	**B**	66
5	 **1b**		 **2e**	**A**,**B**	73, 54	12	 **1g**		 **2l**	**A**,**B**	87, 62
6	 **1b**		 **2f**	**A**	86	13	 **1h**		 **2m**	**B**	85
7	 **1c**		 **2g**	**A**,**B**	82, 68	14	**1h**		**2n**	**B**	77

[a] Reaction conditions: (method **A**) pyridine *N*-oxide (1 equiv.) in THF, Grignard reagent 1.2 (equiv.) at rt. The crude residue was dissolved in acetic anhydride and heated in microwave for 4 min at 120 °C. [b] (method **B**) pyridine *N*-oxide (1 equiv) in THF, PhMgCl (1.2 equiv), quenched with MeOH (1.3 equiv), followed by addition of trifluoroacetic anhydride (1.1 equiv). [c] Isolated yields.



Scheme 2 Synthesis of 2,3- and 2,5-substituted pyridines.

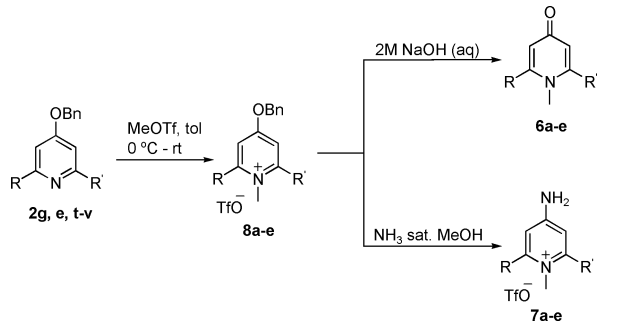
The possibility of using reactive functional groups in combination with Grignard reagents is an attractive feature of Method **B** and substantially increases its generality compared with method **A**. In addition to being more tolerant to various functional groups, method **B** is easily scalable as the synthesis is performed in one-pot, without the need of excessive heating.

When 3-substituted pyridine *N*-oxides, **1i–1k** (Scheme 2), were reacted with PhMgCl, a different reaction pattern was observed. Surprisingly, no dienal-oxime was detected. Instead the 2,3-disubstituted pyridine **2o** was formed directly, although it was isolated in a moderate yield of 43%. It is noteworthy that the regioselectivity was still excellent and only a trace amount of the 2,5-addition product was observed. This regioselectivity is interesting, the steric hindrance caused by the methyl group at the *ortho*-position would rather be expected to give a dominance of a 2,5-disubstituted product if any regioselectivity were expected at all. However, similar results have previously been reported.[11] Furthermore, the addition of acetic anhydride to the reaction mixture was not necessary, the corresponding pyridine **2p** was directly formed (Scheme 2).

In contrast to the regioselectivity obtained when 3-picoline was reacted, 3-cyanopyridine *N*-oxide (**1k**) gave the 2,5-disubstituted pyridine **2q** in 60% yield. The 2,3-substituted regioisomer was not observed when the synthesis was performed according to method **B** (Scheme 2).

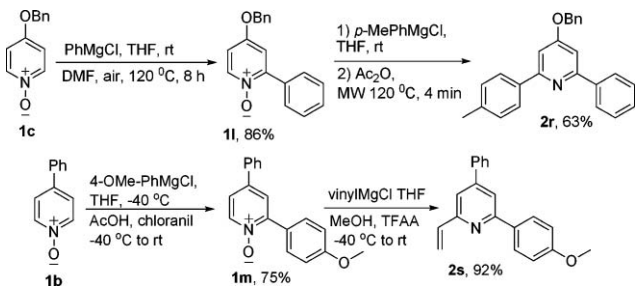
Efficient synthesis of 2,6-disubstituted pyridines from symmetrical ones have scarcely been reported and the few examples have so far mostly relied on 2,6-dihalo pyridines.[12] Pyridine *N*-oxides are easily synthesized by a number of methods,[4] enabling the use of 2-substituted pyridines as starting materials in the synthesis of 2,6-disubstituted pyridines. Alternatively, by changing the reaction conditions of ring closure it is possible to form the substituted pyridine *N*-oxide, which allows for a second Grignard addition. By slightly modifying Method **A** in the pyridine synthesis,[13] 2-substituted pyridine *N*-oxide **1l** was synthesized without first isolating the corresponding pyridine (Scheme 3). This was accomplished by dissolving the crude reaction mixture from the first Grignard addition in DMF, followed by conventional heating in the presence of air. In addition, Method **B** could also be modified to allow synthesis of 2-pyridine *N*-oxide **1m** tolerating the presence of heat sensitive or reactive functionalities in the starting material. Here a rearomatization, by using chloranil as oxidizing agent, was applied in order to get the substituted pyridine *N*-oxide ready for a second addition (Scheme 3).

Table 2 Synthesis of substituted 4-pyridones and 4-aminopyridinium salts



Entry	R	R′	4-Pyridone **6** yield (%)[a]	4-Amino pyridinium salt **7** yield (%)[a]
1	H	Ph	81	83
2	H	1-naphthyl	74	78
3	H	4-MeOC$_6$H$_4$	79	80
4	H	2-thienyl	82	81
5	Ph	4-MeOC$_6$H$_4$	70	75

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



Scheme 3 Synthesis of polysubstituted pyridines.

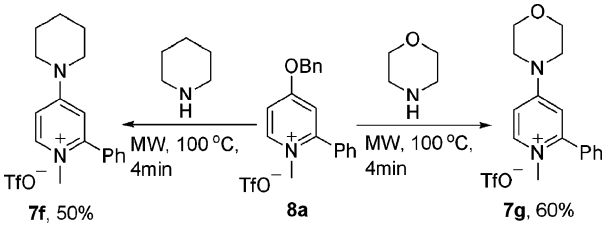
Synthesis of 4-pyridones and 4-aminopyridines

Substituted 4-pyridones **6** and 4-aminopyridinium salts **7** (Table 2) are classes of compounds that are commonly seen in pharmaceuticals.[14] Comins *et al.* reported on the formation of 2,3-dihydro-4-pyridones by the addition of Grignard reagents to acyl activated pyridinium salts,[3b] a procedure that was later used to synthesize 2,3-disubstituted 4-pyridones by Kitagawa *et al.* in their study to find an enoyl-ACP reductase FabI inhibitor.[14b] We postulated that by using 4-benzyloxy pyridine *N*-oxide (**1c**, Scheme 3) and a Grignard reagent in combination with a sequential removal of the benzyl group, a straight forward method to regioselectively synthesize 2-substituted 4-pyridones would be accessible.[15] In order to be able to perform the last transformation, the corresponding 4-benzyloxy-pyridinium salt **8** was prepared (Table 2).

While studying various debenzylation conditions, it was noted that the 4-pyridone was obtained after treatment with aqueous sodium hydroxide. While studying other alternatives for the cleavage, such as using an ammonia-saturated THF solution we instead obtained the corresponding 4-aminopyridnium salt **7**. Therefore in parallel with the synthesis of the 4-pyridones, the

same set of pyridinium salts was reacted with ammonia to generate a small library of 4-pyridones and 4-amino-pyridnium salts **6**, **7** (Table 2).

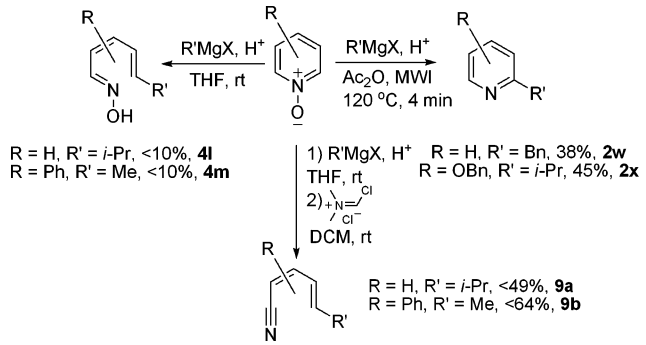
The scope of this strategy was further widened by using other amines in the debenzylation (*e.g.*, morpholine or piperidine) thus allowing synthesis of more diversely substituted 4-amino pyridinium salts with reasonable yields (50% and 60%, respectively of **7f** and **7g**, Scheme 4).



Scheme 4

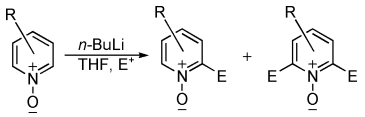
Directed *ortho*-metalation of pyridine *N*-oxides

As described in previous sections, the reaction between sp- or sp^2-hybridized Grignard reagents and different substituted pyridine *N*-oxides have been successfully applied yielding a variety of substituted heterocycles. However, an extended investigation of using sp^3-hybridized Grignard reagents has also been performed. When alkyl Grignard reagents reacted with pyridine *N*-oxides in room temperature, the previously described dienal-oximes **4** were only observed in small amounts and isolated in yields below 10%. Similar results were also observed in attempts to synthesize alkyl-substituted pyridines **2**, although the yields could be improved to 30–45%. This was probably because no isolation of the dienal-oxime was performed. Instead a direct transformation of the crude dienal-oxime to the substituted pyridine was carried out. With the same arguments, alkyl substituted conjugated nitriles **9a** (49%) and **9b** (64%) could also be synthesized (Scheme 5). The corresponding dienal-oximes were directly converted to nitriles *via* a mild *in situ* transformation of the oxime functionality by using a Vilsmeier–Haack salt.



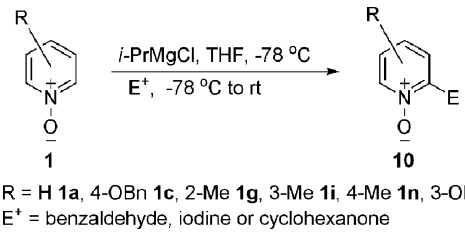
Scheme 5 Addition of alkyl magnesium halides to pyridine *N*-oxides.

During the reaction with alkyl Grignard reagents it was noticed that the starting pyridine *N*-oxide remained, even if up to 3 equivalents of the Grignard reagent were used. This indicated that instead of a nucleophilic addition, a competing deprotonation occurred. The metalation of pyridine *N*-oxides using *n*-BuLi as reagent has been previously studied. However, only low to moderate yields of alkylation products (between 14% and 44%, eqn (4)) have been reported, with disubstituted products being among the most abundant observed by-products.[16]



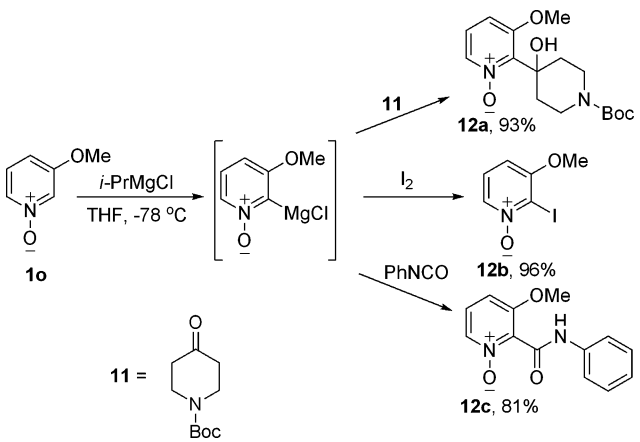
(4)

Given the problems associated with *n*-BuLi for deprotonation of pyridine *N*-oxides, we became interested in investigating the possibility of using Grignard reagents for *ortho* magnesiation. Therefore a set of differently substituted pyridine *N*-oxides (**1a,c,g,i,n,o**) were deprotonated at –78 °C with *iso*-propyl magnesium chloride followed by addition of benzaldehyde, iodine or cyclohexanone (Scheme 6).



Scheme 6 Deprotonation of pyridine *N*-oxides using isopropyl magnesium chloride.

By using the above protocol, no problems with disubstituted products were encountered. However, for the reactions to proceed with high yields, the pyridine *N*-oxide should preferably have a directing substituent in the 3- or the 3- and 5-positions. We therefore decided to explore further incorporation of different electrophiles by reacting 3-methoxy-pyridine *N*-oxide **1o** with *i*PrMgCl followed by three different electrophiles, piperidinone **11**, iodine, and phenylisocyanate, each of which has different useful properties. The reactions were carried out in the same manner as previously described (Scheme 7).[17]

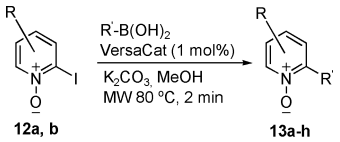


Scheme 7

Suzuki–Miuyara cross-coupling of 2-iodo pyridine *N*-oxides

Although tremendous progress has been made in reactions concerning palladium catalyzed Suzuki–Miyaura cross-couplings,[18]

Table 3 Suzuki–Miyaura arylations with iodo substituted pyridine *N*-oxides



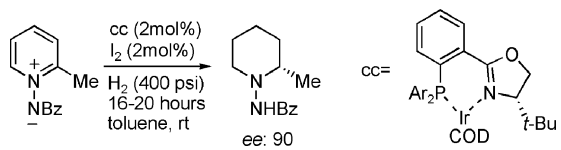
entry	R	R′	Yield (%)[a]
1	3-OMe	Ph	84
2	3-OMe	3-MeC_6H_4	86
3	3-OMe	3-$NO_2C_6H_4$	80
4	3-OMe	4-$MeOC_6H_4$	88
5	4-OBn	Ph	90
6	4-OBn	3-MeC_6H_4	93
7	4-OBn	3-$NO_2C_6H_4$	80
8	4-OBn	4-$MeOC_6H_4$	92

Reaction conditions: *N*-oxide (1 equiv.) in MeOH, boronic acid (3 equiv.), VersaCat (1 mol%), K_2CO_3 (3 equiv). Irradiated 2 min at 80 °C.[a] Isolated yields.

only a few reports can be found in the literature regarding Suzuki–Miyaura couplings of halo-pyridine *N*-oxides.[19] Since we were able to synthesize iodinated pyridine *N*-oxide **12b** in almost quantitative yields, we decided to test if the Suzuki–Miyaura coupling would be possible to use as a method to effectively arylate the *N*-oxide. To our delight the 2,3-substituted pyridine *N*-oxide could be synthesized in 99% isolated yield after small adjustments of reaction conditions previously reported successful on similar substrates.[20] During further reaction development, it was found that when MeOH was used as the solvent instead of DMF, the reaction time could be reduced from 10 to 2 min, and the temperature could be decreased slightly from 100 °C to 80 °C. In addition, to further ease the work-up and to potentially recover the catalyst for a second run, a solid supported palladium catalyst: VersaCat™ Pd[21] was tested in the reaction. This worked excellently and the amount of catalyst could even be reduced from 10 mol% to 1 mol%. Eight different substituted pyridine *N*-oxides were synthesized in parallel, using these changes to the method. Thus, the two pyridine *N*-oxides **12b** and **12c**, were reacted with four boronic acids *i.e.* phenyl, 4-methoxy, 3-tolyl, and 3-nitro phenyl boronic acids. After microwave irradiation the catalyst was filtered off and the solvent was removed under reduced pressure. The eight crude mixtures were then purified by parallel column chromatography to give the corresponding pyridine *N*-oxides **13a–13h** in 80% to 92% isolated yields (Table 3).

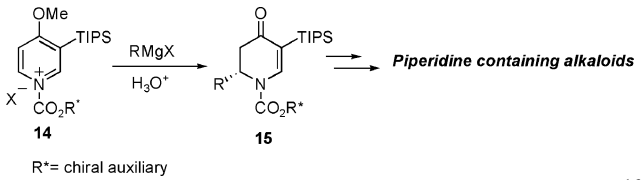
Synthesis of substituted piperidines

Charette and co-workers recently reported a method for the preparation of substituted piperidines from activated pyridines. The method is based on an iridium-catalyzed asymmetric hydrogenation of *N*-iminopyridinium ylides for the synthesis of enantiomerically enriched piperidines (eqn (5)).[22]



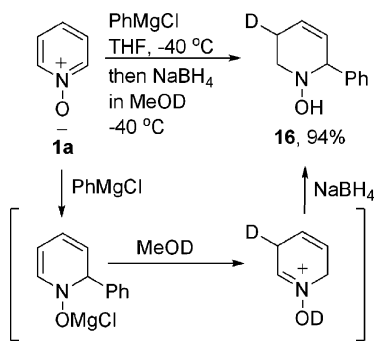
(5)

In spite of extensive research using a variety of *N*-activated pyridinium derivatives and nucleophiles, without blocking undesired electrophilic sites (*e.g.*, the 4-position) these reactions generally translate into the formation of regioisomeric mixtures. Chiral *N*-acyl activated pyridinium salts **14** have been used for the asymmetric synthesis of substituted piperidines (eqn (6)).[3b] In the synthesis of a range of different piperidine containing alkaloids, Comins and co-workers used 4-dihydropyridones **15** as common intermediates, formed from the addition of Grignard reagents to *N*-acyl-4-methoxypyridinium salts **14** (eqn (6)).



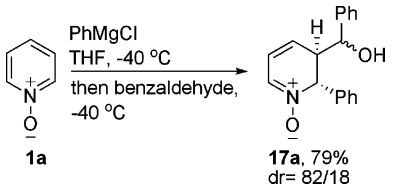
(6)

Probably because of the earlier reports that confirm that pyridine *N*-oxides **1** undergo ring-opening when reacted with Grignard reagents, pyridine *N*-oxides have never been used as precursors to piperidines. However, during our studies of the previously discussed *ortho* metalation reaction, PhMgCl was reacted with pyridine *N*-oxide (**1a**) at –40 °C, followed by the addition of MeOD. The expected incorporation of deuterium at the 2-position was not observed. Instead, after additional reduction with $NaBH_4$ the *N*-hydroxyl tetrahydropyridine **16** was isolated as the sole product in an excellent 94% yield with deuterium at the 5-position (Scheme 8). This result shows that when phenylmagnesium chloride is used, no deprotonation occurs and a reactive intermediate is formed that can further be reacted with an electrophile.



Scheme 8

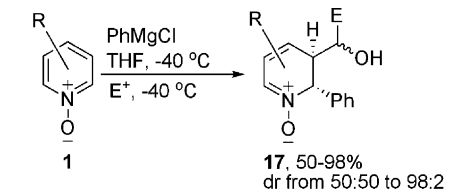
To study the reaction further, benzaldehyde was used instead of MeOD. Thus, after the addition of PhMgCl to pyridine *N*-oxide (**1a**), benzaldehyde was added at –40 °C. The reaction mixture was stirred for 30 min after which according to LC-MS a disubstituted product was formed. However, data from ^{1}H-NMR and ^{13}C-NMR analysis confirmed a 2,3-disubstitution pattern, and not the expected 2,5-disubstituted product that was obtained when MeOD was used as electrophile (Scheme 8 and 9). This finding was further confirmed by 2D-NMR, noesy and hmbc experiments, and the elucidation of a crystal structure.[23] Furthermore, H-NMR analysis of the crude reaction mixture confirmed that the 2,3-*trans* dihydropyridine *N*-oxide **17a** isomer was formed exclusively, with the *cis* isomer not being detected at all. The diastereomeric mixture formed in the reaction results from the third stereocentre created at the benzylic carbon. Although an isomeric mixture is obtained, the



Scheme 9

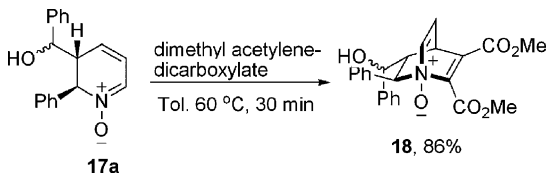
diastereomeric ratio (dr) of 82/18, is rather impressive, especially considering that three stereocentra are formed in one reaction step (Scheme 9).[23]

Further investigation of the scope of the reaction was performed with different pyridine *N*-oxides **1** and PhMgCl followed by sequential addition of benzaldehyde, butyraldehyde or cyclohexanone. These experiments demonstrated that the reaction is compatible with these electrophiles (Scheme 10). Furthermore, the dihydropyridine *N*-oxide was also accessible using electron poor and electron rich Grignard reagents, as well as vinyl Grignard reagents.



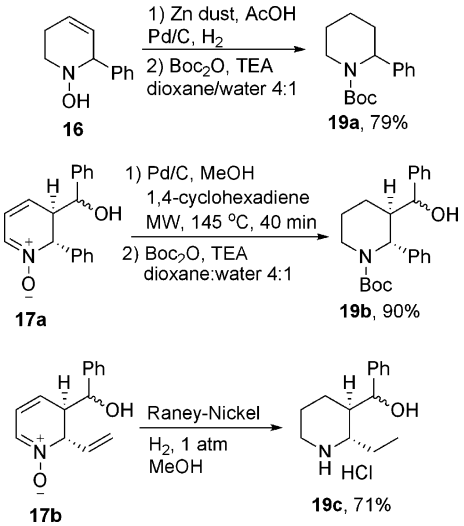
Scheme 10

The developed synthesis of dihydropyridine *N*-oxides **17** prompted us to further examine if these products could be transformed to other useful and interesting compounds. Therefore, compound **17a** was reacted in a Diels–Alder reaction using dimethyl acetylenedicarboxylate as dienophile in toluene. After being heated at 60 °C for 30 min, the aza-bicyclo compound **18** was isolated in an 86% yield (Scheme 11). Substituted aza-bicyclosystems with a bridged nitrogen, quinuclidines, are rigid molecules with very interesting properties. Besides occurring as key-fragments in natural products and drugs[24] (*e.g.*, quinine and the α7 selective AChR agonist TC1698) quinuclidine *N*-oxides have also been used in the development of strong non-nucleophilic bases and HMPA mimetics.[25]



Scheme 11

Furthermore, with the possibility to introduce both aryl and vinyl substituents with complete regioselectivity and high stereoselectivity, a procedure was also developed to further transform these intermediates to the corresponding substituted piperidines. A one-pot reduction and protection of **17** gave the corresponding Boc protected substituted piperidine **19a** in 79% yield (Scheme 12). An excellent 90% yield was obtained by using a one-pot microwave

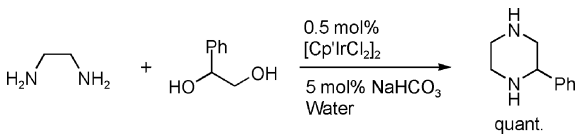


Scheme 12

accelerated reduction. The alkyl substituted analogue was also accessible from 2,3-dihydropyridine *N*-oxide, using RANEY® Nickel, to yield **19c** in 71% (Scheme 12).

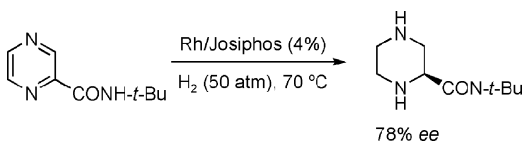
Synthesis of piperazines

Synthetic strategies for substituted piperazines often rely on cyclization procedures. Madsen and co-workers recently reported an iridium catalyzed synthesis of piperazines from diamines and diols (eqn (7)).[26]



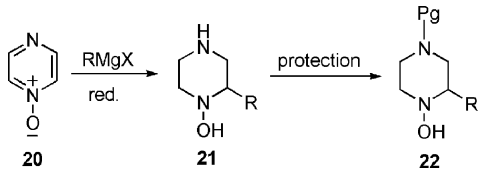
(7)

Another common 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 (eqn (8)).[27]



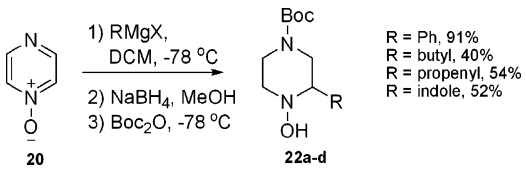
(8)

The organometallic additions to activated pyrazines for the synthesis of piperazines, in analogy to the reactions seen with activated pyridines and piperidines, have not gained as much attention. This is surprising since activated pyrazines could constitute an excellent precursor for the preparation of substituted piperazines. Assuming that pyrazine *N*-oxide **20** reacts in a similar manner to 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 *N*-hydroxyl piperazine **21** (eqn (9)). Protection of this intermediate would then result in a short and efficient route to orthogonally protected substituted piperazines **22** (eqn (9)).[28]



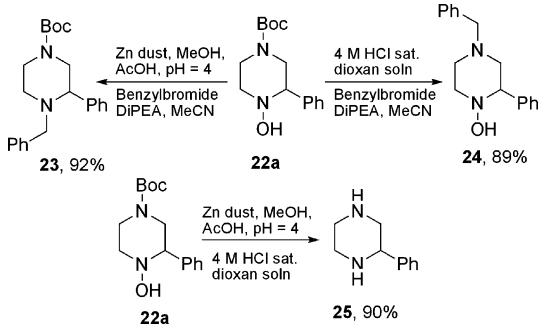
(9)

Bearing in mind the fact that the reaction between Grignard reagents and pyridine *N*-oxides is fast, even at –78 °C (30–60 min), the reaction with pyrazine *N*-oxide was 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 min) 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 observed to form almost directly after the addition of PhMgCl. It was also noticed that dichloromethane was a more suitable solvent than THF. In a second attempt, pyrazine *N*-oxide **20** in DCM was added to PhMgCl at –78 °C, followed by a reduction using $NaBH_4$ in MeOH. The resulting secondary amine was protected using di-*tert*-butyl dicarbonate (Boc_2O) in a one-pot sequence (Scheme 13). This gave the corresponding piperazine **22a** in an overall yield of 91%. Further investigations of the reaction proved the reaction to be compatible with electron rich and electron poor aryl, heteroaromatic, vinyl and alkyl Grignard reagents. Selected examples are shown in Scheme 13.



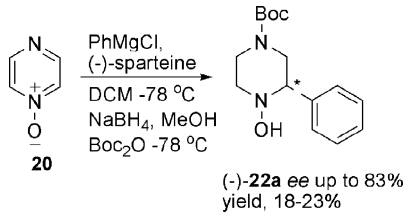
Scheme 13 Selected examples for synthesis of 2-substituted piperazines.

The incorporation of a piperazine fragment in pharmaceuticals often requires selective synthetic modifications at either nitrogen. Therefore an orthogonal deprotection of the *N*-Boc *N*-hydroxyl piperazine **22a**, was developed. Zinc dust in MeOH and acetic acid selectively removed the *N*-hydroxyl group, and a subsequent alkylation yielded piperazine **23** in 92% yield (Scheme 14). Furthermore, a selective *N*-Boc deprotection was accomplished by using a 4 M HCl saturated dioxane solution and piperazine **24** was isolated in 89% yield after the reaction with benzyl bromide. Deprotection of both nitrogens gave piperazine **25** in 90% yield.



Scheme 14 Deprotection of piperazines.

Since particular importance is constantly increasing for saturated *single enantiomer drugs* introduced on the market, the significance in developing enantioselective synthetic routes is highly interesting.[29] Although enantioselective methods have been developed using chiral ligands in combination with zinc and/or lithium reagents, far fewer publications address the reaction with organomagnesium reagents.[30] This limited success is mainly due to the high reactivity of Grignard reagents, combined with a decreased reactivity upon formation of the complex with chiral ligands. Nevertheless, a few successes have been reported concerning this topic. Fu and co-workers reported a de-symmetrization of anhydrides by using Grignard reagents and (–)-sparteine.[31] Inspired by this report, pyrazine *N*-oxide was added to phenylmagnesium chloride in the presence of (–)-sparteine. In addition, the reduction and Boc protection was also performed in one pot, which resulted in a promising *ee* of 62% for piperazine (–)-**22a** (Scheme 15).



Scheme 15 Enantioselective synthesis of protected piperazine.

However, the isolated yield (26%) was not satisfactory, mainly due to unconsumed starting material. Increasing the equivalents of Grignard reagents and (–)-sparteine resulted in a decrease in % *ee* (**22a**). Fortunately, decreasing the equivalents of PhMgCl and (–)-sparteine to 1.2 equiv with 1 equivalent of pyrazine *N*-oxide substantially increased the enantioselectivity and (–)-**22a** was obtained in a substantially improved enantiomeric excess of 83%. The reported results here regarding asymmetric synthesis are only representatives of some initial studies from an on-going project in our laboratory. There are still many parameters to study in order to improve the *ee's* and the isolated yields of the desired products.

Conclusion

There is a constant need for alternative methods to synthesize substituted nitrogen heterocycles to meet the need for fine tuning of substitution patterns *etc*. In this perspective we have shown the recent developments of how to use cheap and commercially available pyridine *N*-oxides and pyrazine *N*-oxides as reaction partners to Grignard reagents in order to regioselectively synthesize a variety of substituted heterocycles. Besides being an attractive alternative to earlier methods, these reactions can also lead to novel intermediates and new type of reactions and substitution patterns. Here a "smorgasbord" of reactions have been shown, which hopefully will inspire the development of new creative methods and innovative chemistry.

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