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Enantioselective Synthesis of Substituted Piperidines by Addition of Aryl Grignard Reagents to Pyridine *N*-Oxides

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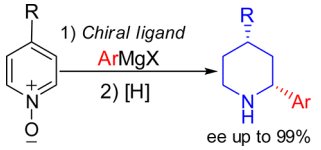
ABSTRACT



The synthesis of optically active piperidines by enantioselective addition of aryl Grignard reagents to pyridine *N*-oxides and lithium binolate followed by reduction is reported for the first time. The reaction results in high yields (51−94%) in combination with good ee (54−80%). Some of these products were subsequently recrystallized, affording enhanced optical purities (>99% ee).

As a consequence of its prevalence in many materials, natural products, and therapeutic agents, the piperidine framework has continued to capture the interest of chemists worldwide.[1] Although 4-substituted piperidines are very common in many of the top-brand drugs in the world (e.g., Risperdal[2a] and Aricept[2b]), their 2,4-substituted analogues have not been as thoroughly investigated. One explanation for this is the lack of practical methods that give access to optically pure materials.[2]

Pyridine *N*-oxides and Grignard reagents are easily accessible in most flavors, either from vendors or by synthesis.[3] In our search for a cheap, general, and scaleup friendly method for the synthesis of six-membered *N*-heterocycles, we revisited the addition of Grignard reagents to pyridine *N*-oxides in 2007.[4] A reaction previously studied by Kato and Kellogg in 1965 (Figure 1),[5] and that had been lying largely dormant since, as a consequence of inconclusive results. This reaction was developed into an efficient and high yielding synthesis of substituted pyridines, dihydropyridines, and dienal oximes.[4,6] However,

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due to the preferential isolation of the ring-opened products in the initial studies in mid-1960, pyridine *N*-oxides have not been viewed as starting materials for the synthesis of substituted piperidines.[7] Instead several methods were developed by using other activated pyridines, most notably by Comins,[2,8] Charette,[7,9a−9c] Shibasaki,[9d] Feringa,[9e] and Arndtsen.[9f−h] Challenged by this we developed the Grignard addition to pyridine *N*-oxides, into a productive methodology for the synthesis of substituted piperidines. Although, this reaction is efficient, e.g., high yielding and highly stereo- and regioselective, the products were racemic.[6]

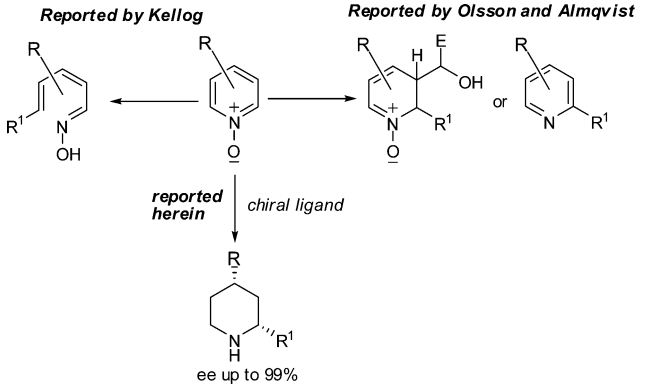

Figure 1. Grignard addition to pyridine *N*-oxides.

Herein we report the first enantioselective synthesis of substituted piperidines by the addition of Grignard reagents to pyridine *N*-oxides. The high reactivity between pyridine *N*-oxides and Mg reagents enables mild reaction conditions that increase the functional group tolerance and scope of the reaction. However the high reactivity makes stereoselective additions difficult. As a consequence of this, there are few examples reported on the use of reactive Grignard reagents in enantioselective additions. Initially, we were inspired by Fu and Shintani;[10] however using Grignard reagents in combination with (−)-sparteine gave no enantiomeric excess on addition to pyridine *N*-oxides. Notably, in our hands (−)-sparteine afforded optically active piperazines in the reaction between Mg reagents and pyrazine *N*-oxides.[11] Other sources of inspiration were the work from the groups of Seebach (TADDOL),[12a] Tejero (BINOL),[12b] and Frejd (BODOL)[12c] employing diols as chiral ligands.[12] In our evaluation of different reaction conditions BINOL stood out as the most promising chiral ligand for this reaction.[13]

4-Phenyl pyridine *N*-oxide (**1a**) was used in the initial studies of the reaction. The substrate selection was based on the rationale that control of additional stereocenters in the reaction is necessary to allow development of more complex substitution patterns. It is also important that the 4-substitution is not masking a substrate limitation, as is the case with additions to *N*-acyl activated pyridines, where additions to the 4-position have been seen.[1d]

The initial results emphasized the importance of the addition order of the reagents. A significant increase in yields and enantiomeric excess was observed when pyridine-*N*-oxide **1a** and the BINOL-ate complex was formed prior to the addition of the Grignard reagent. As it is likely that the first 2 equiv of the Grignard reagent resulted in magnesium binolates, we decided to investigate if the counterion was important

Hence, BINOL was deprotonated using *n*-BuLi (2.0 equiv) in THF prior to the addition of the Grignard reagent, which resulted in a trend toward an increase in both yield and enantiomeric purities.[13] However, the results were not reproducible and switching the counterion to sodium or potassium by deprotonating with NaH or KH, respectively, gave no significant effect.[13] In addition to being a strong base, *n*-BuLi is also a potential nucleophile, and the crude LC-MS spectrum of the *n*-BuLi generated Li-binolate complex showed a byproduct with *m*/*z* 343 (20−30%) corresponding to BINOL+butyl. Additional organolithium bases were therefore screened. In contrast to LDA, which gave no improvements, phenyl lithium in THF gave a significant increase in both yields, 51−94% (from 22 to 75%), and % enantiomeric excess, 46−80% (from 48 to 68%).[13] More importantly the robustness of the protocol improved considerably, resulting in reproducible results and cleaner reactions. The subsequent reduction was performed at low temperature to avoid ring opened byproducts as previously observed.[6,14] Reaction at a larger scale gave better yields (Table 1). The chiral ligand BINOL was both easily removed and recovered from the crude reaction mixture by extraction.[15]

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(14) General procedure for the synthesis of **2a**−**j** using PhLi (Table 1): In a 25 mL round-bottom flask *R* (+) BINOL (1.2 equiv) was dried under vacuum for 30 min and dissolved in THF (10 mL). The mixture was cooled to −78 °C, and PhLi (2.4 equiv) was added dropwise under inert atmosphere. Then the mixture was warmed to ambient temperature and stirred for 30 min. The colorless reaction mixture was cooled again to −78 °C, and 4-phenyl-pyridine-*N*-oxide (**1a**) or pyridine-*N*-oxide (**1b**) (1.0 equiv) was added. The mixture was allowed to reach room temperature, where it was stirred for another 60 min. A yellow mixture was obtained and cooled to −78 °C. To this cooled mixture, ArMgBr (3.0 equiv) in THF was added dropwise and stirred for 40 min (followed by LC-MS). A fresh $NaBH_4$ (3.0 equiv) suspension in MeOH (2 mL) was added to the mixture, which thereafter was allowed to reach room temperature. CH_2Cl_2 (20 mL) and H_2O (10 mL) were added to the reaction mixture, and the organic layer was shaken with NaOH 10% (3 × 10 mL) and then washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude reaction mixture was purified by flash silica column chromatography (AcOEt/heptane).
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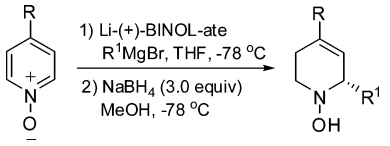
Table 1. Enantioselective Grignard Addition to Pyridine *N*-Oxides



entry	*N*-oxide[a]	R	R^1	yield (%)[c]	ee(%)[c]
1	**1a**	Ph	Ph	**2a** (86)	70
2	**1a**	Ph	4-MePh	**2b** (76)	62
3	**1a**	Ph	3,5(Me)$_2$Ph	**2c** (76)	46
4	**1a**	Ph	4-biphenyl	**2d** (68)	70
5	**1a**[b]	Ph	4-biphenyl	**2d** (70)	76(99)[d]
6	**1a**	Ph	4-(MeO)Ph	**2e** (94)	64
7	**1a**[b]	Ph	4-(MeO)Ph	**2e** (94)	74(98)[d]
8	**1a**	Ph	2-MePh	**2f** (51)	56
9	**1a**	Ph	4-ClPh	**2g** (71)	80
10	**1b**	H	4-biphenyl	**2h** (62)	72
11	**1b**[b]	H	4-biphenyl	**2h** (94)	80
12	**1b**	H	4-(MeO)Ph	**2i** (68)	51
13	**1b**[b]	H	4-(MeO)Ph	**2i** (71)	55
14	**1a**	Ph	Me	**2j** (trace)	–
15	**1a**	Ph	PhCC	**2k** (00)	–
16	**1a**	Ph	vinyl	**2l** (30)	33

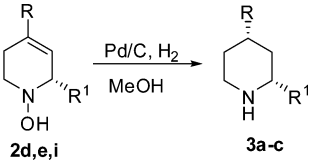
[a] 0.17 mmol scale. [b] 2.0 mmol scale. [c] Yields and ee when PhLi was used as base. [d] % ee after enantiomeric enrichment by recrystallization from ethanol.

Thereafter a set of different aryl Grignard reagents were used as nucleophiles (Table 1). This resulted in most cases in yields and ee's above 70% and 60% respectively, with the best example giving 80% ee (entry 9). However, the more sterically demanding aryl Grignard reagents (i.e., 2-methyl-phenylmagnesium bromide) and the 3,5-disubstituted phenyl Grignard gave lower yields, % ee, or both (entries 3 and 8). Notably scaling up of the reaction demonstrated a significant increase of yields and enantiomeric excesses (entries 4−7 and 10−13). When the Grignard reagent was added to a mixture of lithium BINOL-ate and the unsubstituted pyridine-*N*-oxide (**1b**), the products **2h** and **2i** were obtained in good yields (94% and 71%, respectively). In addition, comparable enantioselectivities as seen for the 4-phenyl substituted pyridine-*N*-oxide were obtained (entries 11 and 13). Further enantiomeric enrichment via crystallization from ethanol of the optically active *N*-hydroxyl tetrahydropyridines **2d** and **2e** resulted in >98% ee in both cases (entries 5 and 7).

Next alkyl, alkenyl, and alkynyl Grignard reagents were studied. As for the addition of alkyl Grignards to pyridine-*N*-oxide without binolate complexation,[4e] the result was deprotonation instead of nucleophilic attack resulting in unconsumed starting material after workup (Table 1, entry 14). The same result was seen when the phenylacetylene Grignard reagent was used (Table 1, entry 15). However, when a vinyl Grignard was used as the nucleophile the desired product **2l** was formed, albeit in low yield and modest enantiomeric purity (30% and 33%, respectively) (Table 1, entry 16).

Optically active *N*-hydroxyl tetrahydropyridines are generally interesting intermediates for further synthesis, but our main goal was to develop a robust method to obtain optically active substituted piperidines. The remaining reduction to the desired piperidines had to be stereospecific in the case of the 4-substituted analogues, since a new stereocenter would be formed. In the absence of a substituent in the 4-position we envisioned a high chance for double bond migration to the conjugated derivative, which would destroy the previously formed stereocenter. Indeed, although palladium on charcoal and hydrogen gas gave complete reduction of both the double bond and the *N*-hydroxyl functionality, these conditions proved detrimental to optical purity. For the 4-substituted derivatives **2d** and **2e** the enantiomeric excess dropped from >98% to 90% of both the resulting disubstituted piperidines **3a** and **3b** (Table 2, entries 1 and 2). However, the reduction was stereospecific, yielding the cis-diastereomer as the sole product. As suspected, the reduction of *N*-hydroxyl tetrahydropyridine **2i** with this method gave 2-substituted piperidine **3c** as a racemate (entry 3).

Table 2. One-Step Reduction to Optically Active Piperidines



entry	R[a]	R^1	yield (%)	ee (%)
1	Ph	4-biphenyl	**3a** (82)	90
2	Ph	4-(MeO)Ph	**3b** (88)	90
3	H	4-(MeO)Ph	**3c** (94)	Rac

[a] Starting with ee (**2d**) 99%, (**2e**) 98%, and (**2i**) 55%.

A solution to this problem could be a milder stepwise reduction, which besides solving the racemization issue also would result in new interesting optically active intermediates for further synthesis. Indeed, reduction of **2e** with PtO_2/EtOH/H_2 provided *N*-hydroxyl intermediate **4a** (84%), and subsequent reduction of the hydroxyl amine to the corresponding amine with In/Zn in sat. aq. NH_4Cl/EtOH[16] afforded the cis-2,4-disubstituted piperidine **3b** in 94% yield and with a retained ee of 98% (Table 3, entry 1). Fortunately, this stepwise approach was also mild enough to be applied for the reduction of analogues **3c** and **3d**, which racemized under the previous conditions. As a bonus, the intermediate 2-substituted hydroxyl amines **4b** and **4c** obtained after reduction (PtO_2/EtOH/H_2) were easy to purify via crystallization from ethanol resulting in enantiomeric enrichment (from 80% ee to 98% ee for **4c** and from 55% ee to 90% ee for **4b** (entries 2 and 3)). Subsequent reduction of the hydroxyl amines was

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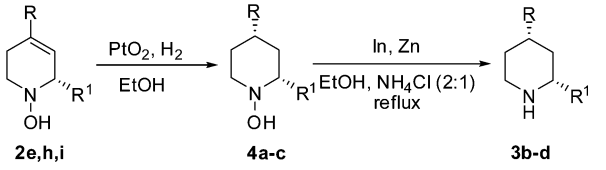
Table 3. Two-Step Reduction to Optically Active Piperidines



entry	R^a	R^1	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	4-(MeO)Ph	**4a** (84)	–[b]	**3b** (94)	98
2	H	4-(MeO)Ph	**4b** (94)	55, 90[c]	**3c** (71)	90
3	H	4-biphenyl	**4c** (96)	80, 98[c]	**3d** (94)	98

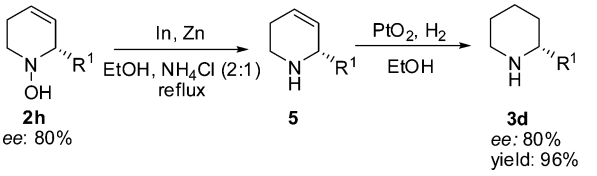
[a] Starting with ee (**2e**) 98%, (**2h**) 80%, and (**2i**) 55%. [b] At this stage ee was not measurable due to poor baseline separation. [c] ee after enantiomeric enrichment by crystallization in ethanol.

straightforward, and the piperidines **3c** and **3d** were synthesized with retained optical purities (entries 2 and 3).

If desired, the reduction sequence could be reversed without affecting the optical purity. Piperidine **3d** was successfully obtained from **2h** via tetrahydropiperidine **5** in a 96% overall yield (Scheme 1) with the same ee as obtained previously (80% ee) (Table 1, entry 11).

In conclusion, we have reported an efficient synthesis of optically active 2- and 2,4-disubstituted piperidines, *N*-hydroxyltetrahydropyridines, *N*-hydroxylpiperidines, and tetrahydropyridines. Enantioselective addition of Grignard

Scheme 1. Two-Step Reduction in Reverse Order



reagents to pyridine *N*-oxides gave *N*-hydroxyltetrahydropyridines in good optical purities, 54–80% ee. Crystallization, stepwise reduction, or both gave optically active piperidines with an enantiomeric purity up to 99% in high yields. The enantioselectivity was obtained simply by adding recycable chiral lithium binolate ligands; no chiral auxiliary that would require eventual removal is needed in the process.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.