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# Two complementary, diversity-driven asymmetric syntheses of a 2,2-disubstituted piperidine $NK_1$ antagonist

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**Abstract**—Two diversity-driven asymmetric syntheses of a potent $NK_1$ receptor antagonist **1** were achieved. These syntheses provided two complementary approaches that were well positioned for further modifications of several different sites of medicinal chemistry interests in the $NK_1$ structural motifs. The de novo piperidine ring construction approach delivered key intermediates that were best suited for piperidine C4 and C5 SAR investigations. The CNRS method fit well for modifications at C6 and the two exocyclic groups.
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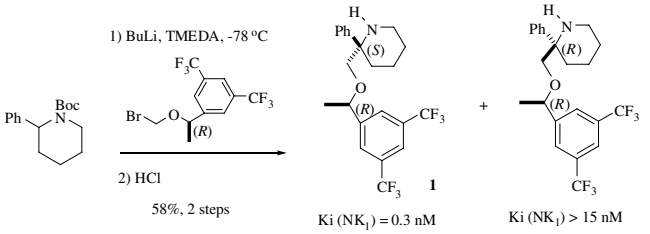
## 1. Introduction

We have recently described our work on the selective benzylic lithiation of *N*-Boc-2-phenylpiperidine and the application of this chemistry to a target-driven non-selective synthesis of a 2,2-disubstituted piperidine $NK_1$ antagonist **1**[1] (Scheme 1). Biological assay established **1** as a potent $NK_1$ antagonist ($K_i = 0.3$ nM) worthy of further exploration. Therefore, a stereoselective asymmetric synthesis of **1** was pursued. A literature search revealed several approaches towards these types of $NK_1$ compounds,[2,3] yet none were amenable to an asymmetric version. In general, asymmetric syntheses of piperidines are well known and had been the subject of many reviews;[4] however, the 2,2-disubstituted pattern[5] has received much less attention.




**Scheme 1.**

When this work was initiated in early 2000, general approaches were still in need.

Strategically, although **1** is the immediate target, the ultimate goal in pursuing synthesis in a medicinal chemistry context is to investigate the biological properties of the analogues of **1**. Unlike single target-driven synthesis, the goal of a medicinal chemistry approach is to increase the diversity of the products and to map out structure–activity relationships (SAR). Therefore, the most desirable synthesis would deliver a common intermediate, then introduce functional variations at the latest possible step. In order to modify different sites of medicinal chemistry interest, different synthetic approaches may be needed. Conceptually, **1** can be disconnected in two ways. First, the quaternary center can be set up followed by a de novo construction of the piperidine ring. Alternatively, the two C2 substituents can be installed onto a pre-existing chiral piperidine system. Although these two approaches may differ in their length and efficiency towards **1**, they would provide opportunities for modifications at complementary sites of the structure for further medicinal chemistry investigations.

## 2. Results and discussion

We set out to implement the first approach (Scheme 2) and decided to construct the piperidine quaternary center through an allylmetal addition to a chiral sulfinimine.[6] The synthesis started with the known chiral alcohol **2** (96%

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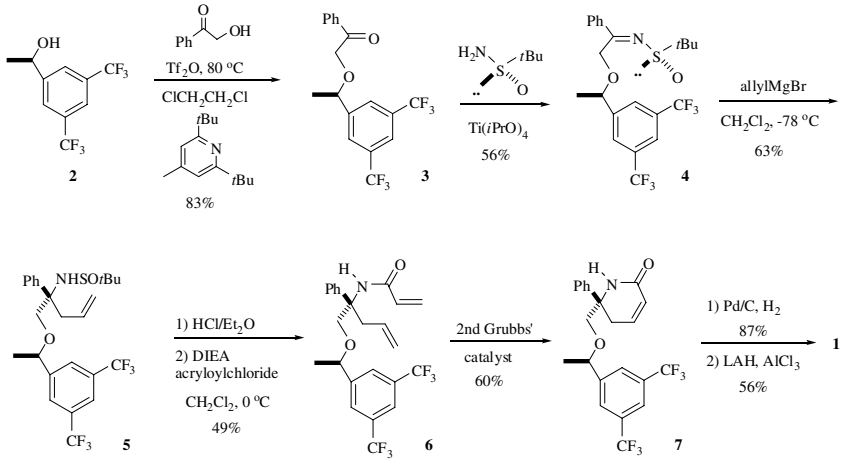
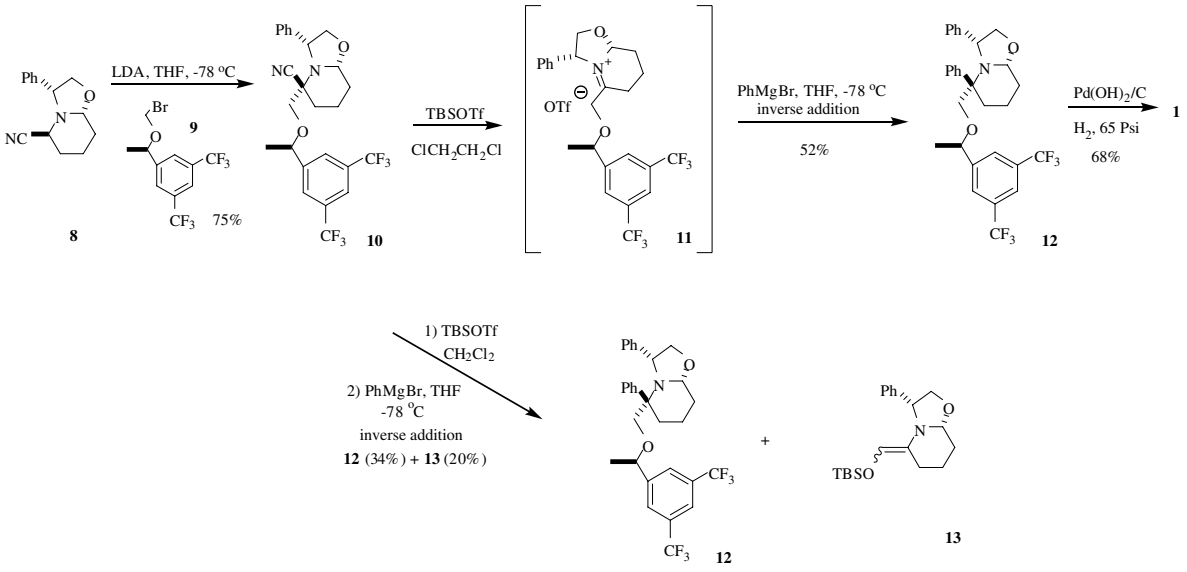


**Scheme 2.**

ee), which was converted to ketone **3** using a procedure published earlier.[7] The (*R*)-*t*-butylsulfinamide developed by Ellman et al. was used due to its superior ability to form imines with highly enolizable ketones, such as **3**.[8] Even with this reagent, the reaction conditions had to be modified in order to achieve acceptable yield. Thus, in the imine formation step, neat $Ti(iPrO)_4$ instead of $Ti(OEt)_4/EtOH$[8c] was used to circumvent the low reactivity of ketone **3** due to its steric hindrance. Imine **4** was obtained in 56% yield and as one, undetermined isomer by NMR at room temperature. The addition of allylmagnesium bromide to imine **4** at −78 °C gave the desired homoallylic sulfinamide **5** smoothly in 63% yield with 9:1 diastereoselectivity. The reaction can be run on a 10 g scale and the minor isomer can be separated using silica gel chromatography. After an efficient preparation of **5** was secured, we turned our attention to the piperidine ring construction. It has been reported that unsaturated lactams can be formed by ring closing olefin metathesis.[9] In this sequence, sulfinamide **5** was deprotected and the resulting amine acylated to give **6** in 49% yield, which set the stage for ring closing metathesis. This diene, upon exposure to the second generation Grubbs catalyst,[10] afforded the desired unsaturated piperidinone **7** in 60% yield. Further elaboration using hydrogenation to saturate the double bond and reduction of the amide delivered the final target **1**.

An alternative strategy for the synthesis of **1** (Scheme 3) utilized the CNRS method,[11] which provided the opportunity for the rapid installation of other $NK_1$ structural elements. Using our previously described procedure of alkylation with bromomethylether **9**,[7] we found that commercial oxazolidine **8** could be alkylated efficiently to afford **10** in 75% yield. The construction of the quaternary center, however, was not straightforward. Although the CNRS method has been used to set up quaternary centers in 2-piperidines,[11,12] there has been only one report describing the CN group used as a leaving group.[13] According to the published procedure, treatment of **10** with TBSOTf in $CH_2Cl_2$ produced iminium ion **11**.[13] However, the addition of PhMgBr in ether at −78 °C gave a very low yield (10%) of product **12** largely due to the insolubility of PhMgBr



**Scheme 3.**

in the reaction media. This problem was reduced by the inverse addition of an iminium ion solution **11** to a diluted solution of PhMgBr in THF pre-cooled to −78 °C, which afforded **12** with >20:1 stereoselectivity in 34% yield along with 20% of side product **13**. The ratio of **12**:**13** did not change when activated with TESOTf and TIPSOTf. The stereochemistry of **12** was assigned by extensive NMR study.[13] To further improve the reaction, additional NMR studies of the formation of the iminium ion were conducted. When **10** was treated with 4 equiv of TBSOTf (to ensure complete conversion) in $CD_2Cl_2$, the CN peak at 118.1 ppm in carbon NMR disappeared and the formation of an iminium ion peak at 190.1 ppm was observed, which was in agreement with the work of Husson et al.[14] We accidentally found that the activation in $CDCl_3$ afforded a complex mixture and no iminium ion formed. This finding prompted us to examine the reaction in other chlorinated solvent, such as $ClCH_2CH_2Cl$. When aminonitrile **10** was treated with 4 equiv of TBSOTf in $ClCH_2CH_2Cl$, followed by inverse addition to PhMgBr solution, formation of **13** was not observed and the yield of **12** increased to 52% as an 8:1 mixture at C6. To our surprise, the proton NMR spectra of TBSOTf activations in $CD_2Cl_2$ and $ClCD_2CD_2Cl$ were almost identical, suggesting that the different product profiles were a result of the addition of Grignard reagent to iminium ion **11** in different solvent mixtures. Although the nature of this solvent effect and the origin of **13** warranted further investigation, the useful yield of **12** allowed completion of the synthesis by hydrogenation of **12** at 65 psi for 48 h to deliver **1**. The salient feature of the CNRS approach is the introduction of both nucleophiles and electrophiles to the quaternary center, which would expand the availability of reagents and hence the diversity of products.

The $NK_1$ antagonist **1** synthesized by the above two methods was identical in all respects by spectroscopic characterization. It was also identical to the compound obtained through non-selective synthesis in our earlier work, in which an X-ray structure of the tosylate salt of **1** has been unequivocally determined.[1]

## 3. Conclusion

In conclusion, we have developed two general asymmetric syntheses of the 2,2-disubstituted piperidine $NK_1$ antagonist **1**. During this process, we discovered an interesting solvent effect on the Grignard addition to aminonitrile **10**. These conditions may be useful in expanding the general utility of the CNRS method. More importantly, the two syntheses described herein delivered two complementary approaches that were suitable for further SAR investigations of several different sites of medicinal chemistry interest of the $NK_1$ structural motif. The first approach delivered key intermediates such as **5** and **7**, which were best suited for C4 and C5 functionalizations. The CNRS method was well suited for modification at C6 and two exocyclic groups. Application of these syntheses towards the discovery of orally active $NK_1$ antagonists will be reported in the future.

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