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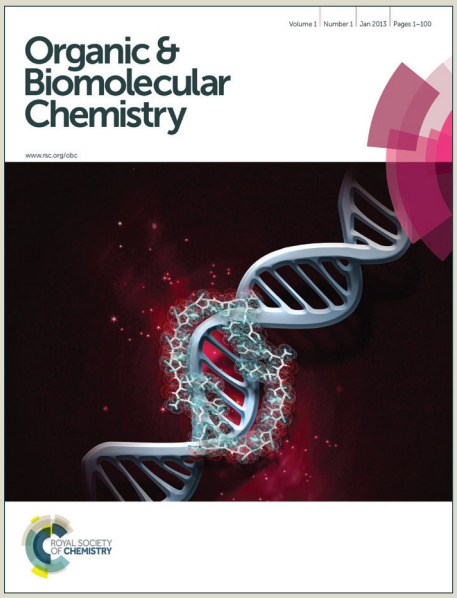


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PAPER

# Synthesis of 1,4-Amino Alcohols by Grignard Reagent Addition to THF and *N*-Tosyliminobenzyliodinane†

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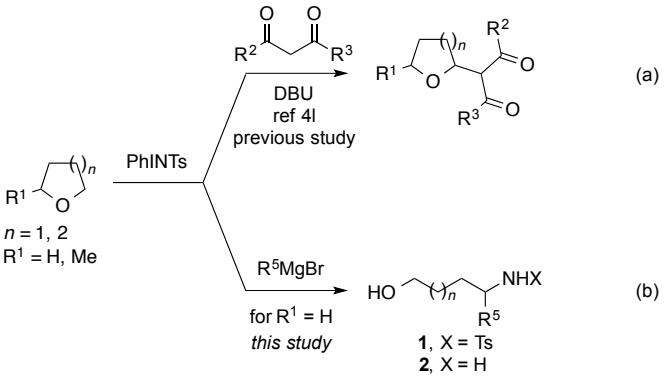
Ciputra Tejo,[c] Yang Feng Anders See,[c] Mitch Mathiew,[a] and Philip Wai Hong Chan[a,b]

The synthesis of 1,4-amino alcohols from THF treated with *N*-tosyliminobenzyliodinane (PhINTs) followed by a Grignard reagent under mild reaction conditions at room temperature is described herein. Various Grignard reagents were shown to be compatible, furnishing the corresponding 4-substituted-*N*-1,4-tosylamino alcohols in good to excellent yields. A partial or full detosylation of the *N*-tosyl-1,4-amino alcohol was observed in instances involving a sterically bulky Grignard reagent, leading to the deprotected 1,4-amino alcohol product in moderate to good yields. The synthetic utility of this protocol was demonstrated by the synthesis of a 5-substituted-*N*-tosyl-1,5-amino alcohol from THP and the conversion of two examples to their corresponding γ-lactam and pyrrolidine adducts.

## Introduction

The development of synthetic methodology to access 1,4-amino alcohols from low cost and readily accessible substrates is an important pursuit in organic chemistry.[1] This is due to their presence in many natural products and pharmaceutically interesting compounds as well as functional materials. The compound class is also a useful building block in organic synthesis and a versatile ligand for numerous types of metal complexes.

Recently, iminoiodane-based reagents have been demonstrated to possess an intriguing array of reactivities in a number of transition metal- and transition metal-free-mediated organic transformations.[2-5] In the case of the latter, for example, we reported the preparation of 2-tetrahydrofuran and -pyran substituted 1,3-dicarbonyl compounds from iminoiodane- and Brønsted base-mediated cross dehydrative coupling of the corresponding cyclic ethers with 1,3-dicarbonyl compounds (Scheme 1a).[4l] Building on this initial work and the well-documented reaction chemistry of cyclic ethers toward organometallic reagents, we envisaged a synthetic approach to 1,4-amino alcohols by Grignard reagent addition to THF in the presence of PhINTs might be achievable (Scheme 1b).[6,7] It was reasoned that 2-tosylaminotetrahydrofuran, generated in situ from the reaction of THF with PhINTs, might be susceptible to a path-




**Scheme 1.** Reactivities of cyclic ethers in the presence of PhINTs

way involving ring-opening under the basic conditions offered by a Grignard reagent.[4f,i,l] Subsequent addition of a second molecule of the Grignard reagent to the ensuing 4-tosyliminobutan-1-ol would then be expected to give the *N*-tosyl-1,4-amino alcohol product. Herein, we report the details of this chemistry that provides an expedient synthetic route to 4-substituted-4-tosyl-aminobutan-1-ols, and one example of a *N*-tosyl-1,5-amino alcohol analogue from THP, in moderate to excellent yields under mild conditions at room temperature. A concomitant detosylation in reactions involving a sterically bulky Grignard reagent to afford the 4-substituted-4-aminobutan-1-ol adduct and synthetic utility of the method by converting two examples to their corresponding γ-lactam and pyrrolidine derivatives is also presented.

## Results and Discussion

In an initial study, the treatment of THF (2 mL) with PhINTs (0.5 mmol) at room temperature for 50 min followed by 3

[a] School of Chemistry, Monash University, Clayton, Victoria 3800, Australia; Email: phil.chan@monash.edu
[b] Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK; Email: P.W.H.Chan@warwick.ac.uk
[c] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

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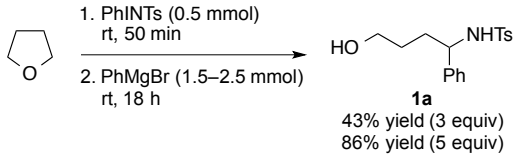
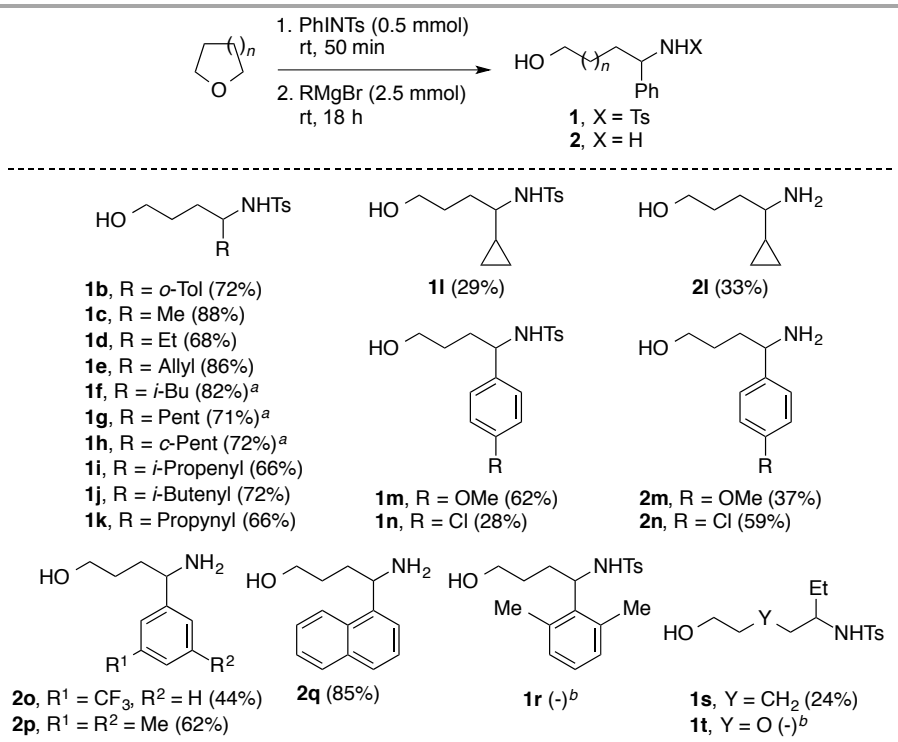
equiv of phenylmagnesium bromide furnished the *N*-tosylamino-1,4-amino alcohol product **1a** in 43% yield (Scheme 2). Increasing the amount of the Grignard reagent from 3 to 5 equiv was found to give the desired product in 86% yield.




**Scheme 2.** Reactions of THF with PhINTs and PhMgBr

With these conditions in hand, the present method was next assessed with a series of Grignard reagents (Scheme 3). When the reaction was repeated with *o*-tolylmagnesium bromide in place of phenylmagnesium bromide, the anticipated *o*-tolyl substituted *N*-tosyl-1,4-amino alcohol **1b** was obtained in 72% yield. Likewise, the analogous reactions with alkyl Grignard reagents such as methyl-, ethyl-, and allylmagnesium bromide were found to be well tolerated and afforded the corresponding 4-substituted-1,4-amino alcohols **1c–e** in good to excellent yields of 68–88%. The use of the Grignard reagent isobutylmagnesium bromide bearing a $\beta$-hydrogen on the alkyl group, was found to give **1f** in 42% yield. Based on $^1$H NMR analysis of the crude mixture, this could be due to a possible competitive reduction of the putative ring-opening adduct of 2-tosylaminotetrahydrofuran before addition of a second molecule of the Grignard reagent could take place.[8] Suppression of this competing side-reaction by the introduction of 5 mol % of copper(I) triflate to the reaction conditions gave the desired *N*-tosyl-1,4-amino alcohol product in an improved yield of 82%. Similarly, the respective transformations with *n*-pentyl- and cyclopentylmagnesium bromide were found to require the copper(I) salt so that **1g** and **1h** could be obtained in yields of 71% and 72%. Several alkenyl and alkynyl Grignard reagents were also tested and found to give the corresponding *N*-tosyl-1,4-amino alcohol products **1i-k** in 66–72% yield.

In our hands, the addition of cyclopropylmagnesium bromide to THF and PHI=NTs was found to result in the formation of *N*-tosyl protected 1,4-amino alcohol **1l** and 4-amino-4-cyclopropylbutan-1-ol **2l** in 29 and 33% yield, respectively. A similar outcome was observed for reactions with the Grignard reagents *p*-methoxyphenyl- and *p*-chlorophenylmagnesium bromide. In these experiments, the corresponding *N*-tosyl protected and secondary amino alcohols were obtained in respective yields of 62 and 37% for **1m** and **2m**, and 29 and 59% for **1n** and **2n**. On the other hand, the analogous transformations with the *meta*-substituted aryl Grignard reagents *m*-trifluoromethylphenyl- and 3,5-dimethylphenylmagnesium bromide gave the corresponding 1,4-amino alcohols **2o** and **2p** as the only product in 44 and 62% yield, respectively. Likewise, repeating the reaction with 1-naphthylmagnesium bromide gave 4-amino-4(naphta-1-yl)butan-1-ol as the only adduct in 85% yield. Replacing THF with THP and subjecting the hexacyclic ether to PhINTs




**Scheme 3.** Reactions of THF and PhINTs with a variety of Grignard reagents. All reactions were carried out under $N_2$ atmosphere with 0.5 mmol of PhINTs and THF (2 mL). Values in parentheses represent isolated product yield. [a]Reaction performed in the presence of CuOTf (5 mol %) as catalyst. [b]No reaction based on TLC and $^1$H NMR analysis of the crude mixture.

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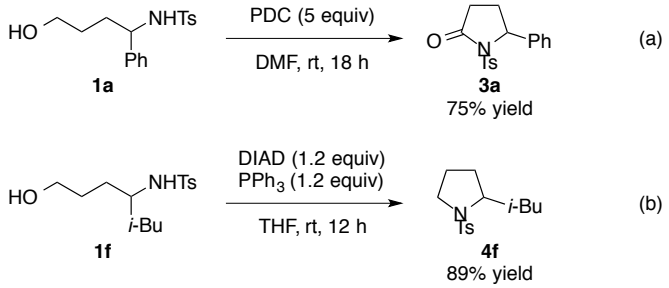
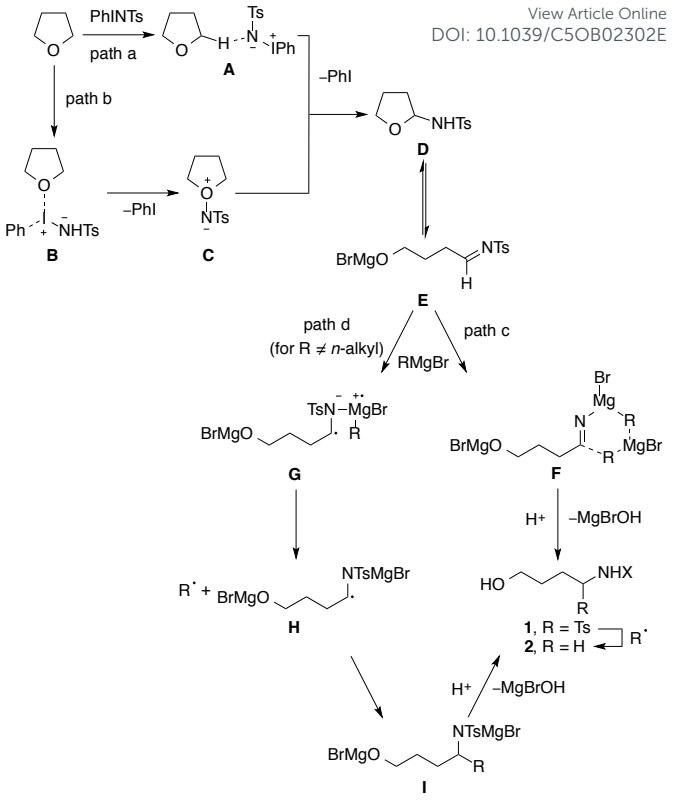
followed by ethylmagnesium bromide gave the corresponding *N*-tosyl-1,5-amino alcohol **1s** in 24% yield. The treatment of THF and PhINTs with 2,6-dimethylphenylmagnesium bromide, and 1,4-dioxane and PhINTs with ethylmagnesium bromide were the only instances in which no reaction was observed based on TLC and $^1$H NMR analysis of the crude reaction mixtures.

Next, the synthetic utility of the 1,4-amino alcohols obtained by the present procedure was examined (Scheme 4). First, oxidative cyclization of *N*-tosyl-1,4-amino alcohol **1a** in the presence of 5 equiv of pyridinium dichromate (PDC) in dimethylformamide at room temperature was demonstrated to give the $\gamma$-lactam **3a** in 75% yield (Scheme 4a). The synthesis of the *N*-tosylpyrrolidine **4f** was realized in 89% yield by subjecting *N*-tosyl-1,4-amino alcohol **1f** to the Mitsunobu reaction conditions of 1.2 equiv of diisopropyl azodicarboxylate and triphenylphosphine (Scheme 4b).



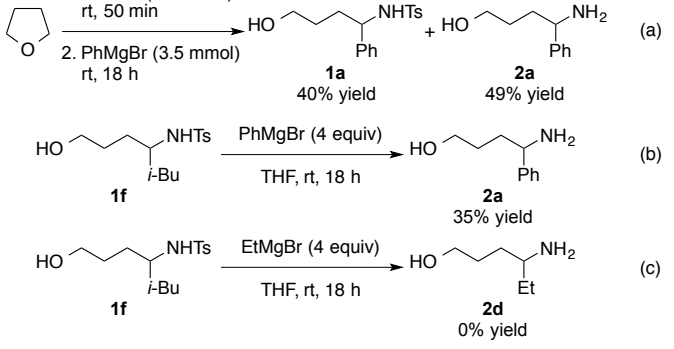

**Scheme 4.** Selective transformations of *N*-tosyl-1,4-amino alcohols **1a** and **1f**

A plausible mechanism for the present *N*-tosyl-1,4-amino alcohol forming reaction is illustrated in Scheme 5. This could involve the direct insertion of the putative nitrenoid group in PhINTs into the C–H bond of the cyclic ether via the concerted asynchronous transition state **A** (Scheme 5, path a).[4f,i] Alternatively, the direct C–H insertion of THF with PhINTs might occur in a stepwise manner through the sequential oxonium ylide intermediacies **B** and **C** (Scheme 5, path b). In both instances, the elimination of iodobenzene might afford 2-tosylaminotetrahydrofuran **D**. Under the basic conditions provided by the Grignard reagent, deprotonation of the sulfonamide moiety of the in situ formed aminated cyclic adduct might result in its ring-opening to give the 1,4-imino alcohol **E**. Subsequent addition of a second molecule of the Grignard reagent to the imine moiety of this newly formed putative intermediate via the Mg-coordinated species **F** and its aqueous work-up would provide the 4-substituted-4-tosylamino-1-ol product (Scheme 5, path c). For reactions leading to the formation of the 1,4-amino alcohol **2**, this could be due to a competing pathway involving single electron transfer on exposing the Grignard reagent to intermediate **E** (Scheme 5, path d).[9,10] Collapse of the ensuing radical-amine-radical cation pair **G** could give the radical species **H** and R·, which on recombination would provide the substituted adduct **I**; on aqueous work-up, this intermediate would then deliver the product **1**. The presence of an excess amount of the radical species **E** might result in the 4-substituted-4-tosylamino-1-ol to undergo a single electron triggered N–S bond cleavage to




**Scheme 5.** Proposed mechanism for the synthesis of 1,4- and 1,5-amino alcohols from THF or THP, respectively, PhINTs and RMgBr

deliver the 1,4-amino alcohol **2**. The proposed involvement of the radical source generated from the Grignard reagent initiating detosylation was further corroborated by our findings for the control reactions depicted in Scheme 6. Firstly, subjecting THF and PhINTs to 7 equiv of phenylmagnesium bromide at room temperature for 18 h gave the *N*-tosyl product **1** and 1,4-amino alcohol **2** in 40 and 49% yield, respectively (Scheme 6a). In a second set of experiments, treatment of **1f** to 4 equiv of phenylmagnesium bromide in THF at room temperature for 18 h afforded **1a** in 35% yield (Scheme 6b).[11] In marked contrast, repeating the reaction of **1f** with ethylmagnesium bromide was found to lead to the recovery of the *N*-tosyl-1,4-amino alcohol in near quantitative yield (Scheme 6c).




**Scheme 6.** Control experiments with THF and **1f**

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## Conclusions

In summary, we have developed a protocol to prepare *N*-tosyl-1,4-amino alcohols from THF, PhINTs and a Grignard reagent. Accomplished in good to excellent product yields, the synthetic method was shown to be applicable to a wide variety of Grignard reagents and the synthesis of 1,5-amino alcohols from THP. The formation of the detosylated 1,4-amino alcohol adduct also provided experimental evidence of a competing electron transfer pathway in reactions involving the addition of a sterically bulky Grignard reagent. Further exploration on the synthetic utility of the present transformation is currently underway and will be reported in due course.

## Acknowledgements

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