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Organocatalysis

One-Pot Synthesis of *O*-Allylhydroxylamines through the Organocatalytic Oxidation of Tertiary Allylic Amines Followed by a [2,3]-Meisenheimer Rearrangement

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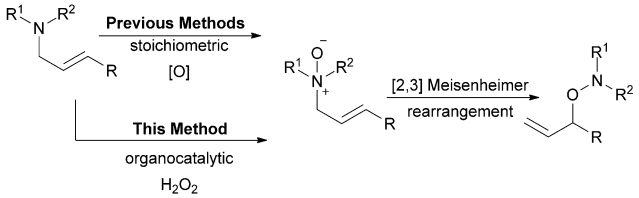
Abstract: A cheap, green, and highly efficient one-pot method for the synthesis of O-protected allylic alcohols is described. By utilizing 2,2,2-trifluoroacetophenone as the organocatalyst and H_2O_2 as the oxidant, a variety of allylic amine *N*-oxides were synthesized, which upon heating are converted to the final products through a [2,3]-Meisenheimer rearrangement.

Introduction

One of the most important methods for the synthesis of allylic alcohol products is the [2,3]-Meisenheimer rearrangement, first reported in 1919.[1] This consists of the rearrangement of an allylic amine *N*-oxide to the corresponding *O*-allylhydroxylamine. Significant efforts have been devoted to the rearrangement itself,[2] for the synthesis of natural products and potential antiviral agents.[3] The vast majority of literature reports involve the use of stoichiometric amounts of oxidants, mostly *meta*-chloroperbenzoic acid (*m*CBPA), for the first key step, that is, the oxidation of tertiary amines to the corresponding *N*-oxides.[4] Such methods may be inexpensive, but often generate large amounts of waste, thus making purification a difficult task. The asymmetric variant of this transformation has also been reported;[5,6] however, most reports involved the use of chiral auxiliaries or chiral substrates leading to lower selectivities.[5] There is a single report for the asymmetric catalytic reaction, in which the chiral induction occurs at the rearrangement step.[6]



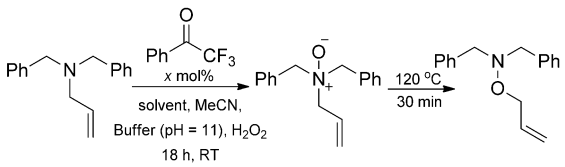
Scheme 1. Approaches for the synthesis of *O*-allylhydroxylamines.

Results and Discussion

The past two years, we have been involved in the development of a green, environmentally friendly, organocatalytic oxidation protocol and its application in various transformations.[7] Herein, we present the first organocatalytic one-pot approach for the synthesis of *O*-allylhydroxylamines, by utilizing hydrogen peroxide exclusively as the green oxidant (Scheme 1).

Previously, 2,2,2-trifluoacetophenone was proven to be the optimum catalyst, among a series of activated ketones, for the organocatalytic oxidation of silanes to silanols.[7a] Following our initial contribution, the same catalyst was found to promote both the oxidation of azines and tertiary amines to *N*-oxides[7b] and olefins to epoxides.[7c] Herein, optimization reactions were carried out to establish the optimum conditions for the model

Table 1. Optimization of the reaction conditions.



Entry	Catalyst [mol %]	MeCN [equiv]	H_2O_2 [equiv]	Solvent	Yield[a] [%]
1	10	2	2	CH_2Cl_2	27
2	10	2	2	THF	20
3	10	2	2	MeOH	21
4	10	2	2	EtOAc	44
5	10	2	2	*t*BuOH	99(92)[b]
6	5	2	2	*t*BuOH	85
7	10	1.2	1.1	*t*BuOH	84
8	10	2	2	*t*BuOH	43[c]
9	10	2	2	*t*BuOH	45[d]
10	10	2	2	*t*BuOH	7[e]

[a] Yield determined by GC–MS. [b] Yield of the product isolated after column chromatography. [c] A temperature of 100 °C was applied. [d] The reaction time was 15 min for the rearrangement step. [e] An initial temperature of 120 °C was applied.

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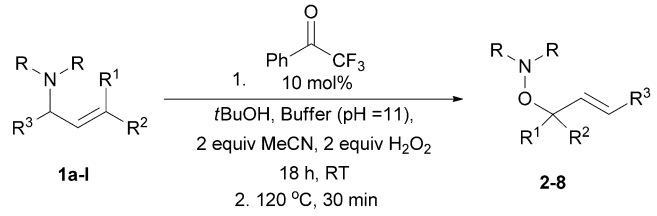
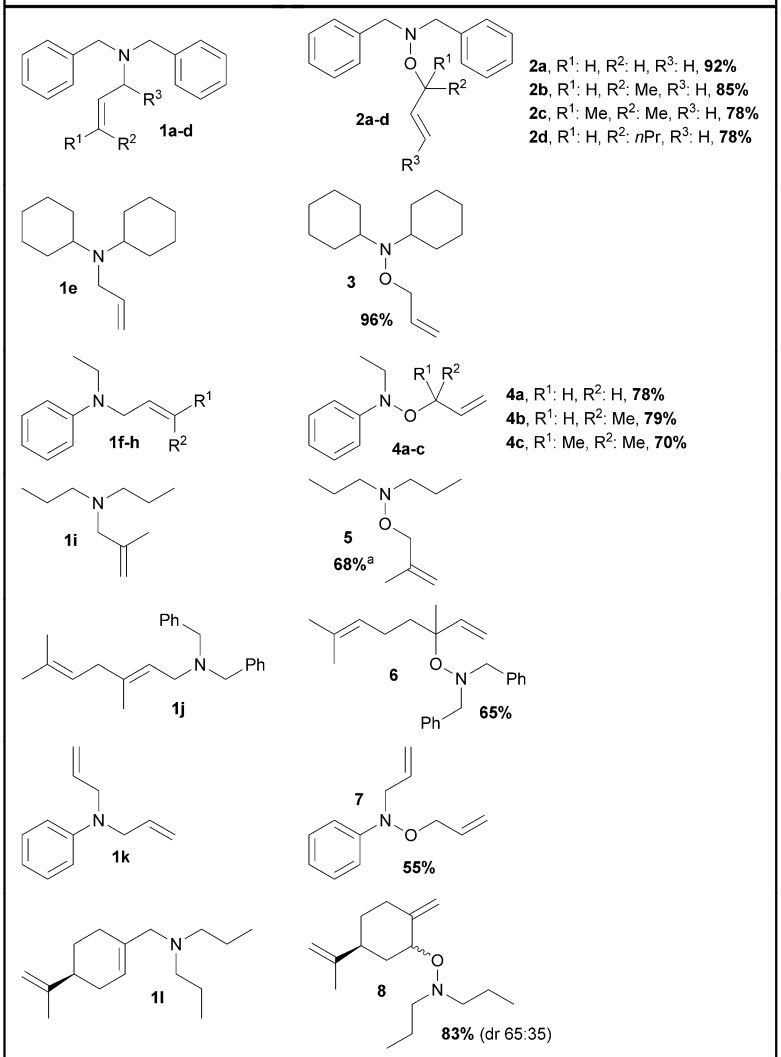
reaction of the synthesis of *O*-allyl-*N*,*N*-dibenzylhydroxylamine (Table 1).[8] Initially, the reaction conditions for the second step were kept constant (heating to 120 °C for 30 min) and the oxidation step was studied. Utilizing 10 mol% catalyst loading and 2 equiv of MeCN and H_2O_2, respectively, several solvents were tested; dichloromethane, THF, methanol, and ethyl acetate did not prove to be suitable solvents (Table 1, entries 1–4). *tert*-Butanol proved the best solvent, providing the desired product in excellent yield (Table 1, entry 5). Reducing the catalyst loading to 5 mol% led to a reduced yield (Table 1, entry 6). Similar results were observed when the amounts of MeCN and H_2O_2 were decreased to 1.2 and 1.1 equivalents, respectively (Table 1, entry 7). Next, the rearrangement conditions were investigated. Reducing the temperature from 120 to 100 °C or the heating time from 30 to 15 min led to significantly lower yields (Table 1, entries 8 and 9). Finally, when the temperature was set to 120 °C from the beginning of the reaction, only traces of the product were observed (Table 1, entry 10). It has to be highlighted that the rearrangement did not occur, even when the reaction mixture was left stirring at room temperature for additional reaction time (20 h).

Having in hand the ideal reaction conditions, we turned our focus to exploring the substrate scope of this method (Table 2). There is a literature report in which, depending on the oxidation system and the substrate utilized, a mixture of oxidation of amine (*N*-oxide) and alkene (epoxide) is obtained.[3i] Although our oxidation protocol can perform both the oxidation of tertiary amines[7b] and alkenes,[7c] in all substrates utilized in this study, no epoxide was detected, thus providing excellent selectivity for the oxidation of tertiary amines (see also the Supporting Information). Initially, a number of dibenzyl allylic amines (**1a**–**d**), bearing mono-, di-, or nonsubstituted short and long aliphatic chains[8] were tested, providing the corresponding products in very high yields (**2a**–**d**). The amine bearing the simple allyl moiety provided the product **2a** in the highest yield, whereas monosubstituted amines **1b** and **1d** produced—in slightly lower yields—the allylic alcohols **2b** and **2d**, respectively, which contain a stereogenic center. Furthermore, doubly substituted alkenes on the ω-position led to allylic alcohol **2c** having a quaternary carbon. Replacing the benzyl moiety with that of cyclohexyl had no effect on the reaction outcome, affording product **3** in almost quantitative yield. In addition, utilizing non-symmetrical amines, like amines having a phenyl substituent on the nitrogen atom, thus creating steric bulkiness, provided the corresponding *O*-allylhydroxylamines (**4a**–**c**) in slightly lower yields. As before, various substitution patterns on the allylic moiety were well-tolerated, leading to primary (**4a**), secondary (**4b**), and tertiary alcohols (**4c**). When the substitution on the double bond is not at the terminal position, like amine **1i**, then prolonged heating (2 h) is required for the rearrangement to occur, affording product **5** in high yield. Moreover, the long unsaturated chain of geraniol could be embedded on amine **1j** and, when subjected to the reaction conditions, provided tertiary alcohol **6** in good yield. Introducing two allylic groups on amine **1k** resulted in product **7** being isolated in a mediocre yield. Lastly, when allylic amine **1l**, based on (*S*)-(−)-perillyl alcohol, was utilized, product **8** was isolated in 83% yield as a mixture of diastereomers (65:35).

Table 2. Substrate scope of the oxidation.



Substrate Product

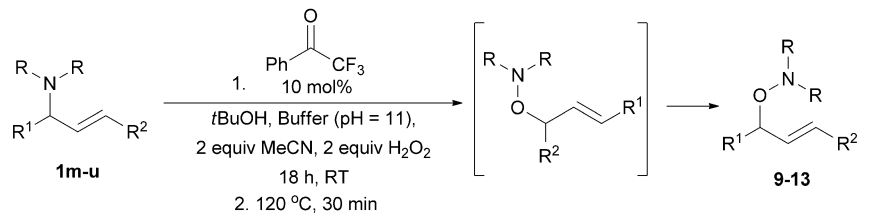


[a] A reaction temperature of 120 °C for 2 h was applied.

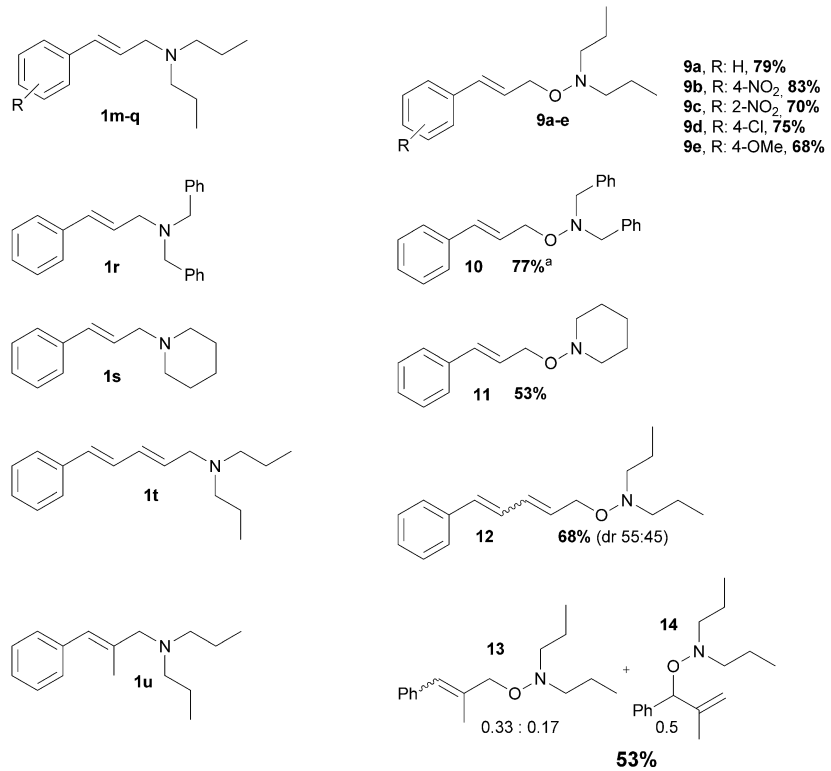
In an effort to test more classes of substrates, allylic amine **1m** was synthesized (Table 3). To our surprise, an additional rearrangement took place. Literature reports indicate such an additional rearrangement could occur only at extended heating and with a change of solvent.[9] However, in our case, this happened only when an aromatic or a conjugated aromatic moiety was utilized at the terminal substituent of the allylic amine (Table 3). Presumably, the reason for this additional [1,3]-shift lies with the stability of the extended conjugated aromatic system of the final products.

Although Majumdar and Jana reported that all kinds of allylic amines provide this additional shift at elevated temperatures for extended reaction times,[9] we only observed this shift on conjugated allylic systems (Table 3). Initially, various phenyl-substituted allylic amines (**1m**–**r**) were tested, leading to allylic alcohols **9a**–**e** and **10** in high yields. Electron-withdrawing substituents, such as 4-Cl or 4-NO_2, provided the desired products in slightly higher yields, with the exception of the sterically hindered 2-NO_2-phenyl moiety (**9b**–**d**). In contrast, ring-activating groups like 4-OMe led to a decreased yield (**9e**). Replacing the *n*-propyl moiety with benzyl resulted in a similar yield (product **10**). *O*-Cinnamyl-*N*,*N*-dipropylhydroxylamine (**1s**) provided the corresponding product **11** in mediocre yield, indicating that cyclic allylic amines can be employed successfully. When an extensive aromatic conjugated system (amine **1t**) was utilized, product **12** was obtained in good yield, but as a mixture of diastereomers. Finally, the presence of a methyl substituent at the β-position to the nitrogen (amine **1u**) proved problematic, because a mixture of products was obtained, seemingly indicating the steric difficulty of the second rearrangement to take place. However, this proved that the initial [2,3]-Meisenheimer is followed by a [1,3]-shift to afford products **9**–**14**, rather than a direct [1,2]-Meisenheimer rearrangement of the generated *N*-oxide. Further evidence for this was the fact that when the mixture of **13** and **14** was subjected to the same reaction conditions, product **13** was the only product observed in the crude reaction mixture (see the Supporting Information). Furthermore, when amine **1o** was subjected to the same reaction conditions, but heating occurred at 60 °C for 30 min, the [2,3]-rearrangement was the main reaction pathway (see the Supporting Information).

Table 3. Additional rearrangement products of aryl-substituted aryl amines.



Substrate Product



[a] A reaction temperature of 120 °C for 18 h was applied.

Conclusion

We have developed a green and efficient one-pot protocol for the synthesis of O-protected allylic alcohols starting from tertiary allylic amines. All literature reports utilize a stoichiometric oxidation, isolation of the intermediate *N*-oxide followed by the Meisenheimer rearrangement. In just one case a catalytic second step is reported. Our method constitutes the first organocatalytic methodology to provide access to these compounds, focusing on the initial oxidation step and followed by a thermal rearrangement. An extensive survey of substrate scope was successfully carried out, tolerating a variety of substituents on the amine and the allylic moiety and providing the products in moderate to high yields. In the case of stabilized allylic tertiary amines, an additional shift was observed leading to the conjugated products. To the best of our knowledge, this is the first one-pot method utilizing a cheap and commercially available metal-free molecule for such a transformation. Further investigation of the applications of this method is currently under way.

Experimental Section

General procedure

Organocatalytic oxidation of tertiary allyl amines followed by a Meisenheimer rearrangement: Allyl amine (1.00 mmol) was placed in a round-bottom flask and dissolved in *tert*-butanol (0.5 mL), followed by 2,2,2-trifluoro-1-phenylethanone (17.4 mg, 0.10 mmol). Aqueous buffer solution (0.5 mL, 0.6 M K_2CO_3/4×10^{-5} M ethylenediaminetetraacetic acid (EDTA) tetrasodium salt), acetonitrile (0.10 mL, 2.00 mmol), and 30% aqueous H_2O_2 (0.21 mL, 2.00 mmol) were added consecutively. The reaction mixture was left stirring for 18 h at room temperature and then a reflux condenser was added and the reaction mixture was stirred at 120 °C for 30 min. The crude product was purified using flash column chromatography (5% EtOAc in pet. ether) to afford the desired product.

Acknowledgements

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Keywords: alcohols · green chemistry · organocatalysis · oxidation · rearrangement

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[8] For extensive optimization studies, as well as allylic amine preparation procedures, see the Supporting Information.

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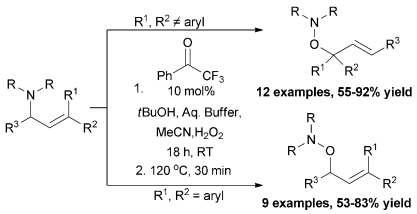
All in one pot: The organocatalytic oxidation of tertiary allylic amines followed by a Meisenheimer rearrangement leads to protected hydroxylamines (see scheme).



Organocatalysis

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One-Pot Synthesis of *O*-Allylhydroxylamines through the Organocatalytic Oxidation of Tertiary Allylic Amines Followed by a [2,3]-Meisenheimer Rearrangement