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Metal-free synthesis of 1,2-amino alcohols by one-pot olefin aziridination and acid ring-opening

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ABSTRACT

A one-pot, two-step reaction comprising olefin aziridination and ring-opening of an aziridine intermediate to synthesize 1,2-amino alcohols has been developed. This reaction is suitable for several types of olefin. This methodology allows an efficient and highly stereoselective approach to various 1,2-amino alcohols, readily providing an alternative route to conventional vicinal amino alcohols.

1. Introduction

1,2-Amino alcohols are important structural features[1] and are ubiquitous in natural products and therapeutic agents possessing a wide variety of biological activities, as well as in chiral ligands and auxiliaries for asymmetric synthesis.[2-4] The hormones epinephrine and norepinephrine[5] are well known amino alcohols (Fig. 1). The α-glucosidase inhibitor miglitol is an approved oral anti-diabetic drug.[6] Metoprolol is a β1 receptor blocker used for the treatment of a number of cardiovascular conditions.[7] Jaspine B, also known as pachastrissamine, is a naturally-occurring novel anhydrosphingosine derivative that was isolated from a marine sponge, and is cytotoxic against P388, A549, HT29, and Mell 28 cell lines at an IC_{50} level of 0.01 μg/mL.[8,9] For this reason, much effort has been devoted to the development of new effective methods for the enantioselective synthesis of β-amino alcohols.[1] A variety of powerful procedures has been reported,[10-14] including the ring opening of aziridines.[15-19]

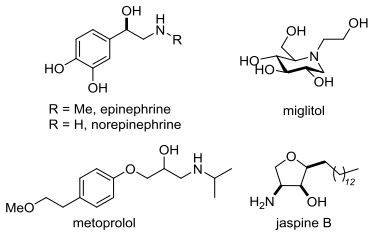
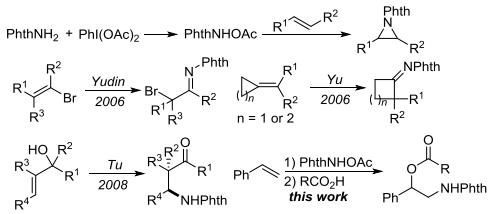


Figure 1. Molecules with 1,2-amino alcohol substructures

Aziridines[20] are present in a wide range of biologically active molecules and natural products,[21,22] and represent one of the most valuable three-membered ring systems in modern synthetic chemistry. Aziridines are widely recognized as important versatile building blocks for chemical bond elaborations and functional group transformations.[23-28] Numerous olefin aziridination methods involve the use of metal salts or complexes as catalysts.[29-34] From both environmental and economical viewpoints, electrochemical aziridination has been reported, and *N*-aminophthalimide has been used for synthesis of aziridine.[35-37] Moreover, $PhI(OAc)_2$- and aryl iodide-mediated aziridination of alkenes has been described for metal-free catalyzed C–N bond forming reactions.[38-40] Nitrene equivalent-mediated reactions of alkenyl bromides, alkylidenecyclopropanes, and allylic alcohols are shown in Scheme 1.[41-43] To the best of our knowledge, there has been no reports on the ring-opening reaction of N-phthalimide aziridines with acid as a one-pot reaction (Scheme 1).

Scheme 1. Nitrene equivalent-mediated reactions of alkenes



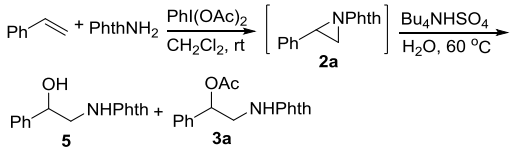
Multicomponent reactions (MCRs) are an effective strategy to improve the efficiency of a chemical reaction by avoiding lengthy separation processes and purification of intermediates.[44,45] Many powerful MCRs have been developed and applied to the synthesis of active pharmaceutical ingredients.[46]

We wish to highlight our results on an MCR involving olefin aziridination and ring-opening of N-phthalimide aziridines with various carboxylic acids from our continued efforts to establish novel 1,2-amino alcohol derivatives with good biological activity[47-49] and tandem reaction with olefins.[43] This work is an extension of Che's work (Scheme 1). Different types of olefins and carboxylic acids gave the desired products using this method.

2. Results and discussion

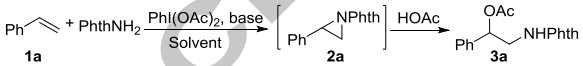
Our investigations began with a one-pot olefin aziridination, followed by ring-opening with H_2O.[16] In the process, the expected 1,2 amino alcohol **5** and a small amount of unexpected product **3a** were isolated (Scheme 2). Different reaction conditions were screened to improve the yield of **3a**.

Scheme 2. One-pot reaction of olefin aziridination followed by ring-opening with H_2O



Styrene was used as the model substrate, and initial studies revealed that without any base, the reaction yield increased with increasing amounts of N-aminophthalimide ($PhthNH_2$) and $PhI(OAc)_2$ (Table 1, entries 1–4). When using a larger dosage of $PhthNH_2$ and $PhI(OAc)_2$, a base was used to improve the reaction yield. K_2CO_3 was selected as the base giving a decrease of both PhthNH2 and $PhI(OAc)_2$ (Table 1, entries 5–7). Treatment of styrene (1 equiv) with 1.4 equiv of $PhthNH_2$, 1.5 equiv of $PhI(OAc)_2$, and 2.8 equiv of K_2CO_3 produced the β-amino ester 3a in 65% yield (Table 1, entry 8). When the reaction was conducted at −20 °C, a lower yield was obtained (Table 1, entry 9). Compared with toluene, dichloromethane was a better solvent for this reaction (Table 1, entry 10).

Table 1. Optimization of the reaction conditions

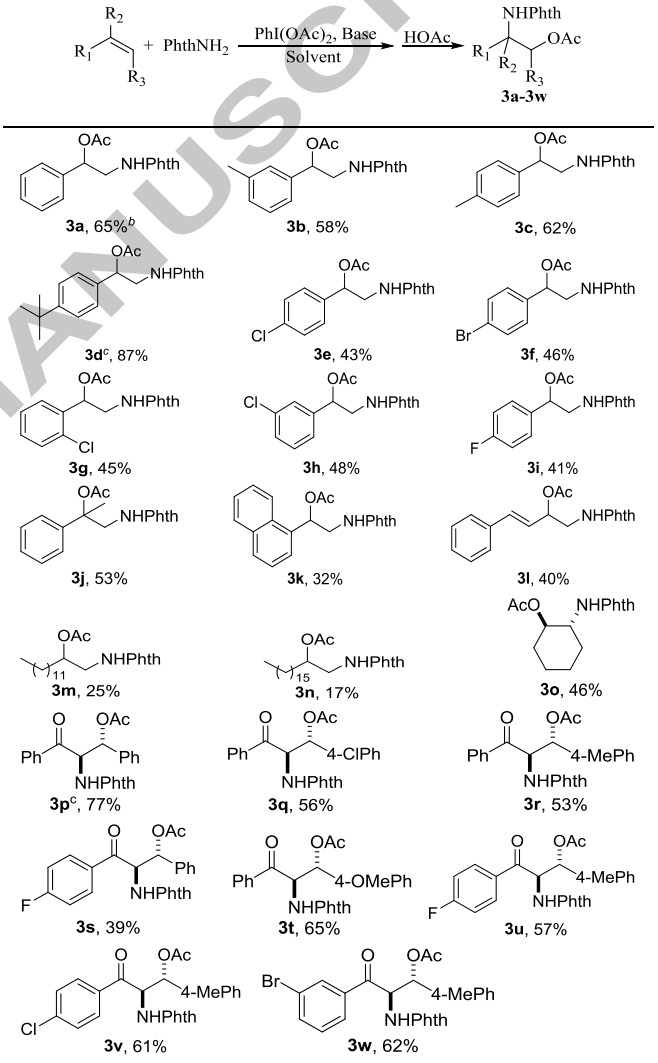


Entry	Solvent	Base	Equiv.[a]	Yield (%)[b]
1	CH_2Cl_2	—	1/1.4/1.5	50
2	CH_2Cl_2	—	1/2/1.5	50
3	CH_2Cl_2	—	1/2/2.2	59
4	CH_2Cl_2	—	1/2.5/2.5	67
5	CH_2Cl_2	K_2CO_3	1/2/1.5/2.8	54
6	CH_2Cl_2	K_2CO_3	1/2/2/4	55
7	CH_2Cl_2	K_2CO_3	1/2.5/2.5/5	65
8	CH_2Cl_2	K_2CO_3	1/1.4/1.5/2.8	65
9[c]	CH_2Cl_2	K_2CO_3	1/1.4/1.5/2.8	57
10	Toluene	K_2CO_3	1/1.4/1.5/2.8	60

[a] All reactions were performed at room temperature for 12 h with styrene (1 mmol)/$PhI(OAc)_2$/N-aminophthalimide/base molar ratio.
[b] Isolated yield;
[c] Reaction was performed at -20°C

A series of terminal and internal alkenes were then examined to explore the generality of the present procedure (Table 2). Styrenes with electron-donating substituents at different positions of the phenyl ring afforded the desired products in good yields (Table 2, products **3b–3d**). In contrast, styrenes with halogen substituents gave inferior yields (**3e–3i**). This reaction also gave good yields of 1,1-disubstituted styrenes (**3j**). The reaction gave moderate yields with 1-vinylnaphthalene and its conjugate alkene (**3k** and **3l**). Reactions of 1-octodecene and 1-tetradecene under these conditions afforded the corresponding 1,2-amino esters in lower yield (**3m–3n**). In a cycloalkene reaction, the product was obtained in a moderate yield (**3o**). To our delight, chalcones were also good substrates for this one-pot reaction. All expected products were produced from differently-substituted chalcones in moderate to good yield in this reaction.

Table 2. Investigation of the scope of olefins **1**[a]

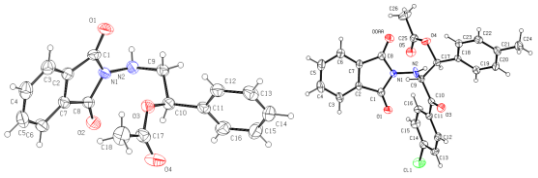


[a] Similar conditions as for Table 1, entry 8. All reactions were performed for 12 h for the first step, then CH_3CO_2H was added. [b] **1** (10 mmol) at room temperature for 12 h. [c] First step as entry 8 of Table 1, second step at 40 °C for 8 h.

In general, this reaction was suitable for several types of olefin and gave expected products in moderate to good yields. For the purpose of examining the synthetic potential of the present approach, a gram-scale synthesis of ring-opened product was performed for this system. The final product (3.3 g, 13.5mmol, Table 2, product **3d**) was obtained in a total yield of 87% under the same reaction conditions.

To probe the regioselectivity and diastereoselectivity of the present MCR reaction, X-ray diffraction analysis of **3a** and **3v** was carried out (Figure 2).[50] The regioselectivity and diastereoselectivity of this one-pot reaction was confirmed. These

results were in accordance with a previously reported olefin aziridination and acid ring-opening.[51]



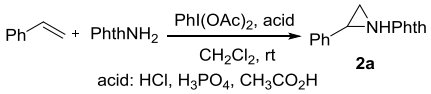
3a **3v**

Figure 2. X-ray structures of **3a** and **3v**

To confirm the reaction mechanism of the one-pot reaction, we obtained intermediate **2a** from the first step of the one-pot reaction and proved its structure by NMR. After acetic acid was used for the nucleophile attack on intermediate **2a**, compound **3a** was obtained successfully in 90% yield.

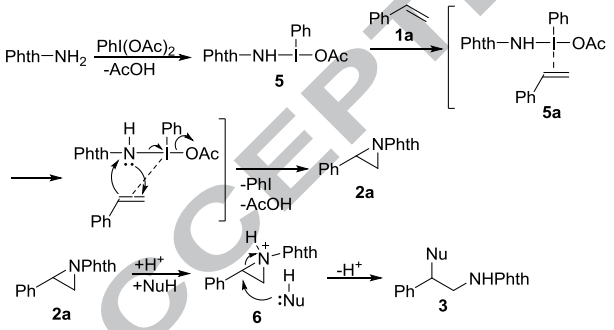
To verify whether a nitrenium ion[52] or a nitrene was the reactive species, another experiment was carried out (Scheme 3). In this experiment, hydrochloric acid, phosphoric acid or acetic acid (2 mmol) was added instead of base to afford only aziridine **2a** after 24 h. This proved that a nitrenium ion is probably not the reactive species in this reaction**.** The amount of acid (35 mmol) is crucial for the ring-opening reaction.

Scheme 3. Mechanism verification experiment



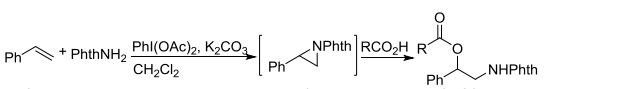
The reaction mechanism of the one-pot reaction is shown in Scheme 4. NH_2-Phth reacts with $PhI(OAc)_2$ to form aminoiodane intermediate **5**, then aminoiodane **5** reacts with styrene **1a** to form aziridine **2a**.[37] The nucleophile reacts with the aziridine under acidic conditions to initiate the ring-opening reaction of the aziridine to obtain the final product **3**.[53]

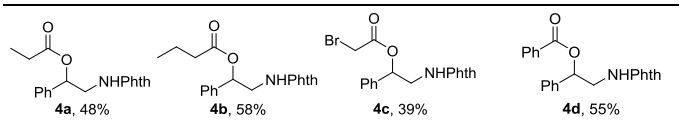
Scheme 4. Proposed reaction mechanism for the one-pot reaction



To further explore the scope of the acids in this MCR reaction, a series of carboxylic acids including propionic acid, butyric acid, bromoacetic acid, and benzoic acid were examined. The results are summarized in Table 3. Other alkyl acid-related products were successfully obtained from the representative propionic acid (Table 3, **4a**) and butyric acid (**4b**) in comparable yields. The bromoacetic acid ring-opened product (**4c**) was also obtained, but the yield was relatively low (39%). The benzoic acid ring-opened product (**4d**) was obtained in 55% yield, which confirmed that aromatic acids are also good substrates.

Table 3. Investigation of the scope of the acids[a]





[a] Similar conditions as Table 1, entry 8. All reactions were performed for 12 h for the first step, then the different carboxylic acids were added.

3. Conclusions

In conclusion, we have discovered a new one-pot olefin aziridination and ring-opening reaction with carboxylic acids under metal-free conditions. Furthermore, various functionalized 1,2-amino alcohols were obtained with high regioselectivity and diastereoselectivity from olefins without purification of the aziridine intermediates using this efficient method. Given the advantages of this effective protocol, we expect this method to become widely applicable in organic synthesis and drug development.

Acknowledgments

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Highlights

1) A new method for ring opening of aziridines by acid has been developed.

2) This method completes an one-pot conversion of olefins to 1,2-aminoalcohols.

3) This new reaction is applicable to a wide range of olefins and acid.

Graphical Abstract

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