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Tandem Aziridination/Rearrangement Reaction of Allylic Alcohols: An Efficient Approach to 2-Quaternary Mannich Bases

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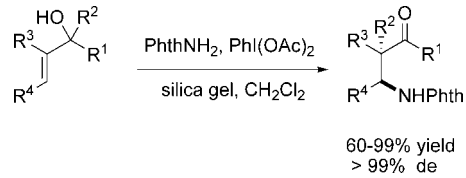
ABSTRACT



A novel tandem aziridination/rearrangement reaction of allylic alcohols has been discovered, in which the significant accelerating effect of silica gel has been identified. On the basis of this methodology, an efficient and highly stereoselective approach to various 2-quaternary Mannich bases has been put in place, readily providing an alternative route to the conventional vicinal amino-functionalization of alkenes.

3-Amino-aldehydes or ketones (Mannich bases) are regarded as crucial building blocks[1] for the synthesis of many nitrogen-containing biologically important organic molecules. In particular, Mannich bases bearing a quaternary carbon center (e.g., anhydrolycodoline, kopsonoline, and holstiine[2]) are of considerable synthetic importance. Generally, Mannich bases without a quaternary center can be readily accessed through aza-Michael addition,[3] Mannich reaction, and its modern variants.[1] However, efficient synthesis of Mannich bases with a quaternary stereocenter has proven to be challenging,[4] and the efficiency, regioselectivity, and stereoselectivity required for designing this structural unit still remains to be optimized.[5]

In recent years, aziridines have been distinguished as versatile synthetic intermediates and hence are well explored.[6] The strained three-membered ring can undergo a variety of reactions to give rise to amino-functionalized products.[6,7] In our previous investigation regarding construction of 2-quaternary-1,3-diheteroatom units,[8] a novel semi-pinacol rearrangement reaction of 2,3- aziridino alcohols was discovered, yielding 2-quaternary Mannich bases via a Lewis acid promoted ring-opening/rearrangement process with high efficiency and stereoselectivity.[8c] However, this protocol suffered from very low yields (20−30% yield) obtained for the preparation of the aziridino alcohols from tertiary or secondary allylic alcohols.[9] The procedure developed by the

(1) For reviews, see: (a) Blicke, F. F. *Org. React.* **1942**, *1*, 303–341. (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–2230. (c) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 893−951. (d) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 953−973. (e) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1007−1046. (f) Tramontini, M.; Angiolini, L. *Mannich-Bases, Chemistry and Uses*; CRC: Boca Raton, FL, 1994. (g) Arend, M.; Westermann, B.; Risch, N. *Angew.Chem., Int. Ed.* **1998**, *37*, 1044–1070. (h) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112. (i) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.

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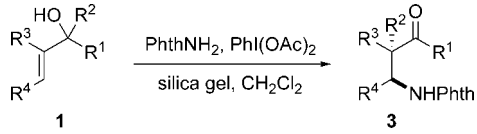
Sharpless group[10] was found to be inefficient due to a competitive bromonium-induced semipinacol rearrangement.[8e,9] Transition metal catalyzed aziridination[11] also proved to be inefficient, resulting in complicated reaction mixtures.[9] Hence, it has been our primary target to discover a tandem sequence, directly from allylic alcohols, to effectively construct synthetically valuable 2-quaternary Mannich bases.

Intrigued by a novel nitrene equivalent for aziridination of olefins described by Che and Yudin,[12] we recently developed an interesting tandem protocol based on the combination of *N*-aminophthalimide ($PhthNH_2$) and $PhI(OAc)_2$ in the presence of silica gel. Utilization of weakly acidic silica gel was employed for the first time in such a reaction system (Scheme 1).[12] This tandem reaction provides a

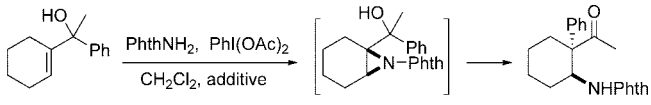
Scheme 1. Tandem Aziridination/Rearrangement of Allylic Alcohols



convenient stereoselective access to the important 2-quaternary Mannich bases directly from allylic alcohols. The synthetic utility of this reaction was highlighted by the effective amino-functionalization of allylic alcohols and the stereoselective incorporation of two adjacent stereocenters with one crucial quaternary carbon, providing an alternative to the conventional vicinal aminofunctionalization of alkenes.[7] Herein we report our progress toward the development and optimization of this synthetic route.

Allylic alcohol **1a** was used as a typical substrate to investigate the conventional aziridination conditions without any additive (entry 1, Table 1). Under these conditions,

Table 1. Optimization of Reaction Conditions



1a 2a 3a

entry	$PhI(OAc)_2/PhthNH_2$ (equiv)	additive	% yield[a]
1	2.5:2.5		0[b]
2	2.5:2.5	silica gel	70
3	3:3	silica gel	56
4	2:2	silica gel	65
5	1.5:1.5	silica gel	37

[a] Isolated yield. [b] Only aziridine intermediate **2a** was detected after 12 h.

however, the desired product **3a** could not be obtained. Aziridino alcohol **2a** was observed as an intermediate instead with, after 12 h, the disappearance of starting material **1a**. Although stoichiometric amounts of HOAc are theoretically formed in present reaction system, during the in situ generation of nitrene donor by the reaction of $PhthNH_2$ with $PhI(OAc)_2$,[12] no further semipinacol rearrangement of the above-mentioned intermediate **2a** occurred in this case, indicating that the protic acidity of HOAc cannot effectively promote the 1,2-rearrangement transformation. To realize the envisioned tandem aziridination/rearrangement sequence, we then investigated the role of other additives in the optimization of the existing reaction conditions. For the aziridination of alkenes, it has been established that some basic additives (e.g., K_2CO_3 and basic Al_2O_3) can improve the chemical yields.[12a] Among the additives that we screened, however, we found that the weakly acidic silica gel could significantly promote the tandem two-step transformation,[13] and the desired Mannich base **3a** could be isolated in 70% yield after 10 h (entry 2). Interestingly, the presence of silica gel not only promoted the semipinacol rearrangement, it also accelerated the initial aziridination significantly. In accordance, the allylic alcohol **1a** was observed to be consumed quickly

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(monitored by TLC) after the incorporation of silica gel in the current tandem protocol. In addition, the effect of other factors such as reagent ratios (entries 3−5) was also examined. It was found that increasing or lowering the ratio of $PhI(OAc)_2$/$PhthNH_2$ (e.g., 3:3, 2:2 or 1.5:1.5) did not have any effect, and the yields were lower than that obtained by using 2.5 equiv of both reagents.

To probe the stereochemistry in the present tandem reaction, X-ray diffraction analysis of **3a**[14] was carried out, as shown in Figure 1; this clearly demonstrated the relative

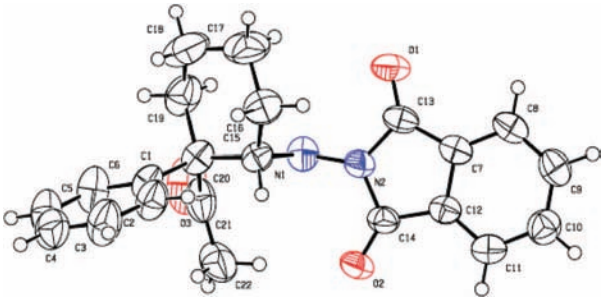


Figure 1. X-ray structure of **3a**.

anti configuration between PhthN and the migrating group R^2 (R^2 = Ph).

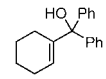
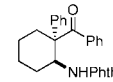
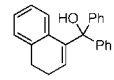
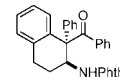
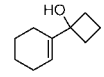
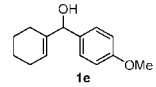
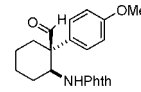
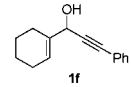
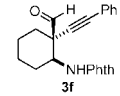
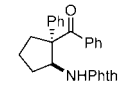
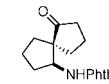
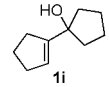
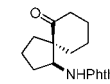
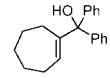
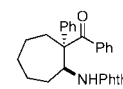
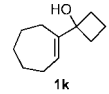
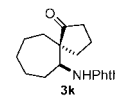
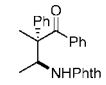
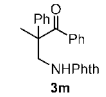
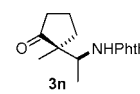
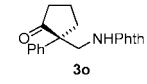
The generality of this tandem reaction was investigated for a series of tertiary and secondary allylic alcohols **1b**−**1o** (Table 2) using the optimized reaction conditions (entry 2, Table 1). The reaction was typically complete within 16 h with the corresponding products all being obtained in good to high yields (60−99%). From all of the examples investigated, except entries 13 and 15, only one diastereoisomer was isolated, indicating excellent stereoselectivity for this process. The structural diversity of 2-quaternary Mannich bases described in Table 2 shows its synthetic utility for accessing various nitrogen containing alkaloids.[8d]

For allylic alcohols involving a cyclohexene moiety (**1a**−**1f**, entries 1−6 from Table 2), the tandem aziridination/rearrangement provided a variety of 2-quaternary Mannich bases **3a**−**3f**, in which the migrating group was sp^2-aryl (entries 1−3 and 5), sp^3-alkyl (entry 4), or sp-alkynyl (entry 6) during the second process. For the secondary allylic alcohols (entries 5 and 6), longer reaction times (12−16 h) were generally required.

Analogously, some tertiary allylic alcohols consisting of cyclopentene or cycloheptene motifs were examined (entries 7−11 from Table 2), which afforded the desired 2-quaternary Mannich bases with high stereoselectivity. The interesting examples included several spirocyclic Mannich bases **3h**, **3i**,

(14) Crystallographic data for **3a** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-690341). Copies of these data can be obtained free of charge www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Tandem Aziridination/Rearrangement of Allylic Alcohols

entry	substrate	product	*t* (h)	yield[a] (%)
1	**1a**	**3a**	10	70
2	 **1b**	 **3b**	11	86
3	 **1c**	 **3c**	1	76[b]
4	 **1d**	 **3d**	2	99
5	 **1e**	 **3e**	12	60[b]
6	 **1f**	 **3f**	16	75[c]
7	 **1g**	 **3g**	12	98
8	 **1h**	 **3h**	0.5	77[b]
9	 **1i**	 **3i**	0.8	66[d]
10	 **1j**	 **3j**	3.5	72
11	 **1k**	 **3k**	1.5	66[e]
12	 **1l**	 **3l**	3	>99
13	 **1m**	 **3m**	5	99
14	 **1n**	 **3n**	1	70[e]
15	 **1o**	 **3o**	12	72

[a] Isolated yield. [b] Five equivalents of propylene oxide were added. [c] 1,2-Dichloroethane was used as solvent at 60 °C. [d] $PhthNH_2$ (2.0 equiv) and $PhI(OAc)_2$ (2.0 equiv) were used. [e] $PhthNH_2$ (1.1 equiv) and $PhI(OAc)_2$ (1.1 equiv) were used.

3k, as well as **3d**, which could be potentially used to synthesize a new category of ligands for asymmetric catalysis.[15]

Besides, some acyclic substrates consisting of trisubstituted and *gem*-substituted olefin moiety (**1l**−**1o**, entries 12−15 from Table 2) were found to be useful in this particular protocol. Indeed, the desired amino-functionalized products with the quaternary carbon were obtained smoothly, further demonstrating the broad scope of this protocol in choosing the substrates.

The reaction yields and the reaction times were found to be highly dependent upon the substrate structure and the migration capability of R^2 in **1**. For example, aziridino alcohol intermediates such as **2a** could be detected for substrates **1a**−**1 g** and **1j**−**1o**. However, **1h** and **1i** reacted at comparatively higher rates, and no corresponding intermediates could be observed. On the basis of the herein described experimental details and our previous report,[8c] this tandem protocol clearly consists of two chemical transformations, namely, aziridination and semipinacol rearrangement. Although the acidic nature and surface catalytic activity of silica gel might have a crucial effect on this tandem reaction, its exact role as a chemical promoter in the last rearrangement still remains unclear.[13]

In conclusion, we have successfully developed a new nitrene equivalent-mediated tandem aziridination/rearrangement of allylic alcohols, which provides a highly stereoselective approach toward synthesis of 2-quaternary Mannich bases under mild conditions. This tandem protocol not only is highly efficient compared to the previous two-step reaction starting from allylic alcohols but also provides an alternative methodology to the conventional vicinal aminofunctionalization of alkenes. Further investigations on its asymmetric version and synthetic applications of this methodology are currently in progress.

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Supporting Information Available: General experimental procedures, characterization data for all products, and X-ray crystallographic data for compounds **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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