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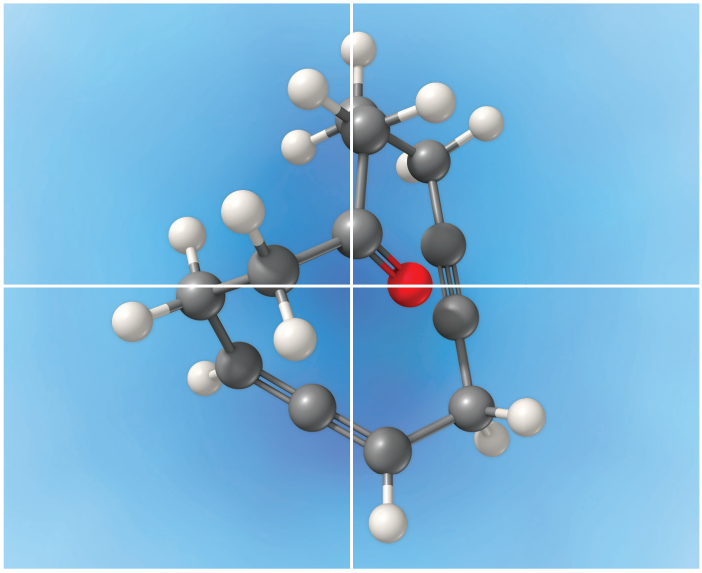

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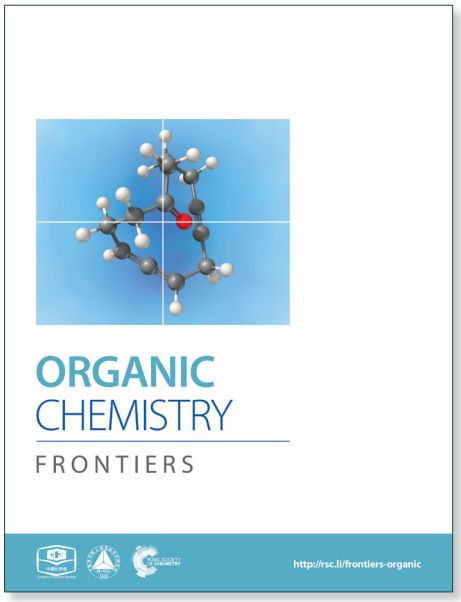

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ARTICLE

Synthesis of Morpholine or Piperazine Derivatives Through Gold-Catalyzed Cyclization Reactions of Alkynylamines or Alkynylalcohols

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A convenient and efficient synthetic method for the construction of morpholine and piperazine derivatives in moderate to good yields was established. The reaction proceeds smoothly with 1.0 mol% gold catalyst loading. A plausible mechanism involving the cascade cyclization and isomerizations to produce the six-membered ring was proposed and supported by deuterium labeling experiments.

Introduction

Morpholine and Piperazine derivatives have attracted considerable attention owing to their occurrence in biologically active natural products[1] and pharmaceuticals, such as antivertigo/antiemetic agent Buclizine,[2] antibacterial agent Grepafloxacin hydrochloride.[3] gyrase and topoisomerase IV inhibitor Gatifloxacin,[4] and antidepressant drug Reboxetine.[5] They also serve as versatile building blocks in organic synthesis. While various methodologies have been established on the synthesis of morpholine[6] and piperazine[7] derivatives, there are still several challenges to overcome, including of limitation of starting materials, harsh reaction conditions, low efficiency, poor selectivity, *etc*. Only very few literature reports exist to provide a mild and highly regioselective access to functionalized-morpholine and piperazine derivatives.[8] Alkynylamines and alkynylalcohols can be used to assemble various heterocyclic compounds and can serve as precursors for morpholine and piperazine derivatives. They typically undergo two different pathways to afford endo- or exo-cyclization products (Scheme 1).[9] Recent reports have demonstrated that endo-cylization of alkynylamines can be catalyzed by transition metal complexes, such as Pd[10], Ru,[11] and W,[12] as the catalysts. On the other hand, exo-cyclization of alkynylamines has been achieved in the presence of I_2[13] or ^{t}BuOK.[14] Analogous cyclization reactions of alkynylalcohols have also been developed with a range of catalysts, such as $Pd(OAc)_2$,[15] Bu_4NF,[16] Ag_2CO_3,[17] AuCl,[18] $AuCl(PPh_3)/AgSbF_6$,[19] $Cu(OTf)_2$,[20] NaH,[21] $PtCl_2$,[22] and AgOTf.[23] To our best knowledge, there is, however, no existing methodology to allow the preparation of morpholine and piperazine derivatives under the same reaction conditions. With this in mind, it is highly desired to develop a simple and facile method to prepare these molecules. Herein, we demonstrate a simple gold(I)-catalyzed reaction to afford morpholine and piperazine derivatives in moderate to good yields. These reactions can be conducted with only 1 mol% of the gold catalyst.

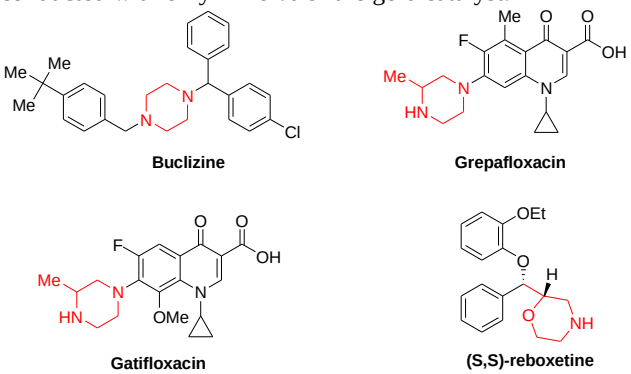
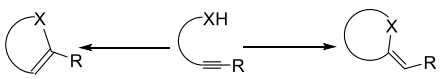


Figure 1. Representative drugs containing morpholine or piperazine derivatives.



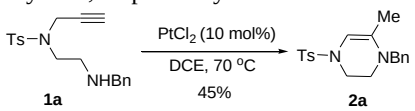
(XH = nucleophilic group, such as NH_2 or OH)

Scheme 1. Cyclization of alkynylamines and alkynylalcohols.

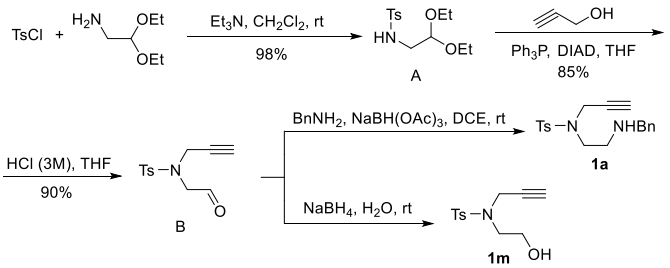
Results and discussion

The Takemoto group has recently reported that the Lewis acid-catalyzed intramolecular hydroamination of *N*-Ns alkynylamide (Ns = *o*-nitrobenzenesulfonyl) in 1,2-dichloroethane proceed smoothly to furnish the cyclization products.[24] This work was done exclusively on phenyl alkynes and no mechanistic discussion was provided. On the basis of these results, we started to examine the reaction of the alkynylamines in the presence of carbophilic Lewis acids (Scheme 2).[25] Suitable substrates were conveniently

synthesized through the four steps shown in Scheme 3. Fragment **A** was prepared from toluenesulfonyl chloride and aminoacetaldehyde diethyl acetal in the presence of Et_3N in 98 % yield. Subsequent treatment of **A** under the Mitsunobu reaction condition followed by hydrolysis with 3M HCl aqueous solution gave alkynylaldehyde **B** in 77% yield over two steps. Reductive amination of **B** and reduction of **B** with $NaBH_4$ afforded alkynylamine **1a** and alkynylalcohol **1m** in 75% and 95% yields, respectively.



Scheme 2. The $PtCl_2$-catalyzed 6-Exo hydroamination of alkynylamine **1a**

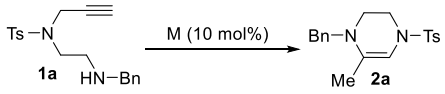


Scheme 3. Synthesis of substrates **1a** and **1m**.

The reactivity of these substrates was examined in the presence of $PtCl_2$. To our delight, the reaction proceeded smoothly and generated a 6-exo-cyclized product (**2a**) as a single product in 45% yield. In contrast to the earlier work, the C=C bond was formed inside the ring. The reaction conditions were then optimized (Table 1). The temperature effect screening revealed that different temperatures gave similar results when $PtCl_2$ (10 mol%) was used as the catalyst (Entries 1-3). When different combinations of $AuCl(PPh_3)/AgX$ were examined, **2a** was obtained in improved yields (entries 4-6). Among these silver salts screened, $AgNTf_2$ was identified to offer the best result (entry 6). Using Lewis acid $Bi(OTf)_3$ as a catalyst only delivered **2a** in 35% yield (entry 7). This reaction did not occur without the catalyst in DCE even at 80 ℃ for overnight (entry 8). When the loading of gold catalyst was reduced from 10 mol% to 1 mol%, the outcome of this reaction was not affected significantly and gave the corresponding product **2a** in 82% yield (entry 9). When slightly elevating the temperature to 40 ℃, **2a** can be produced in 92% yield (entry 10).

With the optimized reaction condition, our attention was directed toward the exploration of the substrate scope. Screening results are shown in Table 2. We first tested various substituents at the terminal amino group. The benzyl substituted substrates **1b** and **1c** can be smoothly converted into corresponding products **2b** and **2c** in high yields of 85% and 77%, respectively. When using phenyl groups in place of benzyl groups, **2d** can be formed in 88% yield. In addition, the steric bulkiness of the substituent was also examined (**1e**), and to our delight, the reaction was not affected significantly and product **2e** could also be furnished in 75% yield. Treatment with substrates containing a strong electron-withdrawing group at the *meta* position on the phenyl ring under the optimized condition gave product **2f** in 86% yield. Heteroatom containing substrate **1g**, however, did not give the desired product **2g**

Table 1. Optimized reaction condition



Entry	catalysts	conditions	yield(%)
1	$PtCl_2$	DCE, 70 °C	45
2	$PtCl_2$	DCE, 40 °C	65
3	$PtCl_2$	DCE, rt	63
4	$AuCl(PPh_3)/AgOTf$	DCE, rt	75
5	$AuCl(PPh_3)/AgNTf_2$	DCE, rt	85
6	$AuCl(PPh_3)/AgBF_4$	DCE, rt	78
7	$Bi(OTf)_3$	DCE, 70 °C	35
8	-	DCE, 80 °C	-
9	$AuCl(PPh_3)/AgNTf_2$	DCE, rt	82[a]
10	***$AuCl(PPh_3)/AgNTf_2$***	***DCE, 40 °C***	92

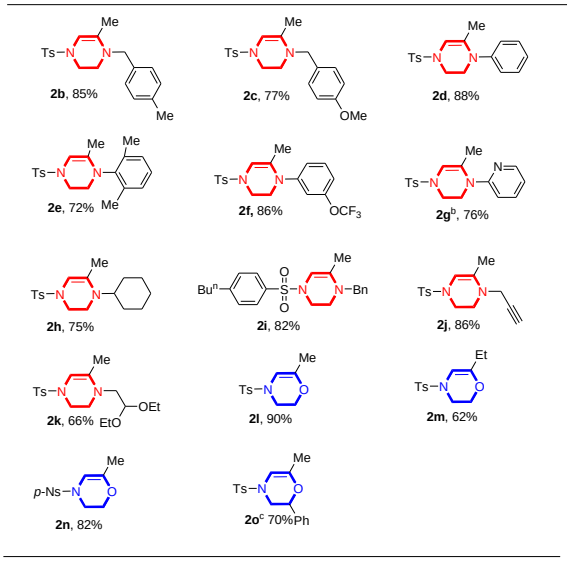
[a] 1 mol% catalyst was used.

under the standard condition, but 76% yield was achieved when the reaction temperature was elevated to 80 ℃ for 24 hrs. Various alphatic substituents were also explored, including cyclohexyl (**1h**) and propargyl (**1j**), and the desired products **2h** and **2j** could be produced in 75% and 86% yield, respectively. It should be noted that the acid sensitive substrate **1k** was also tolerated, giving the expected product **2k** in 66% yield. Other alkynyl alcohol substrates **1l-1o** were investigated as well, revealing that substrate **1l** produced the corresponding morpholine derivative **2l** in 90% yield under the otherwise identical condition. A methyl group could be incorporated at the alkyne end, but furnishing product **2m** in a lower yield of 62%. When a different sulfonyl group (**1n**) was involved, a similar result was obtained compared with that of **1l**. Interestingly, a secondary alcohol substrate (**1o**) was also found suitable for this process, and the desired product **2o** was obtained in 70% yield at a slightly higher temperature.

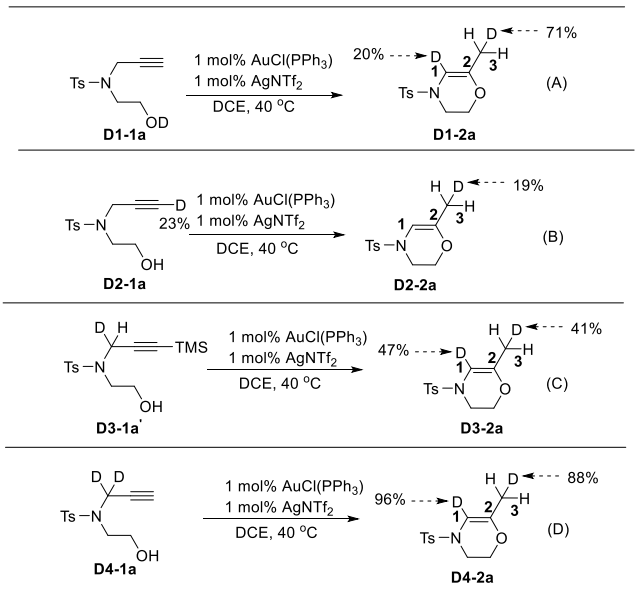
To shed light on the mechanism of the above-mentioned reaction, deuterium labeling studies have been performed. The results are summarized in Scheme 4. Accordingly, incorporations of the D-label at C1 and C3 positions in product **D1-2a** were achieved at 20% and 71%, respectively. The scrambling of the D label suggests the deprotonation and protonation events at C1 and protonation at C3 (Scheme 4, A). When substrate **1a** (with a D-label at the C3 position) was involved, almost no loss of the D-label at the C3 position in product **D2-2a** was observed, indicating that the formation of a gold acetylide intermediate was unlikely (Scheme 4, B). In both cases of substrates **D3-1a'** (mono-D-labeled at the C1 position) and **D4-1a** (di-D-labeled at the C1 position) under the optimized reaction condition, the D labels were distributed at C1 and C3 almost equally, suggesting a reversible deprotonation/protonation process at the C1 position before the irreversible formation of the final product (Scheme 4, C and D).

Scheme 5 depicts a plausible mechanism for the present cyclization reaction. Initially, the π-activation of the triple bond by gold (I) takes place to furnish intermediate **A**, which triggers the 6-exo cyclization through a nucleophilic addition to the

Table 2. Reactions of substrates **1b-o**[a]



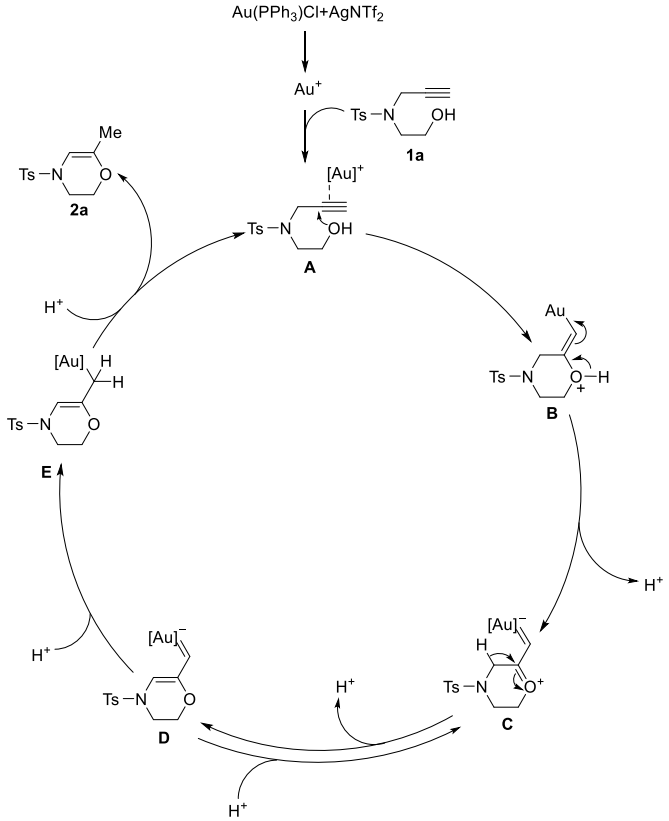
[a]Reaction Conditions: Substrates (0.2 mmol), $AuCl(PPh_3)$ (1 mol%), $AgNTf_2$ (1 mol%), 1,2-dichloroethane, 40 °C. [b]The reaction was carried out at 80 °C for 24 h. [c]The reaction was carried out at 60 °C for 3 h.



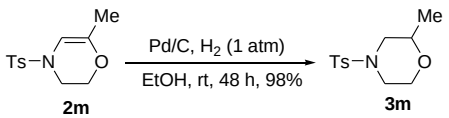
Scheme 4. Deuterium-Labeling Studies.

internal carbon- carbon triple bond to afford intermediate **B**[26]. Subsequent loss of a proton forms the gold carbenoid intermediate **C**[27]. Deprotonation of intermediate **C** results in the formation of intermediate **D**, a process which is rationalized to be reversible based on the D-labeling results. The protonation of the gold carbenoid intermediate **D** then commences, leading to intermediate **E**. Finally, protonation of intermediate **E** takes place to release the product (**2a**) and regenerate the active gold (I) specie to complete the catalytic cycle.

At last, it is important to note that the hydrogenation of the 6-exo cyclization product **2m** could be conveniently achieved according to literature procedures by using Pd/C as a catalyst to give morpholine derivative **3m** in high yield (Scheme 6).



Scheme 5. Plausible mechanism for the formation of **2a** from **1a**



Scheme 6. Hydrogenation of product **2m**

Conclusion

In conclusion, we have established a simple and efficient synthetic route to morpholine and piperazine derivatives through a gold(I)-catalyzed 6-exo cyclization reaction with only 1 mol% catalyst loading. This methodology therefore has considerable potential toward the preparation of heterocyclic motifs. Further studies to extend their applications are currently underway and will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental, characterization data (^1H, ^2H and ^{13}C spectroscopic data), HRMS of the compounds **1a-1o**, **2a-2o** and **3m**. See DOI: 10.1039/b000000x/

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