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Gold(I)-Catalyzed Domino Ring-Opening Ring-Closing Hydroamination of Methylenecyclopropanes (MCPs) with Sulfonamides: Facile Preparation of Pyrrolidine Derivatives

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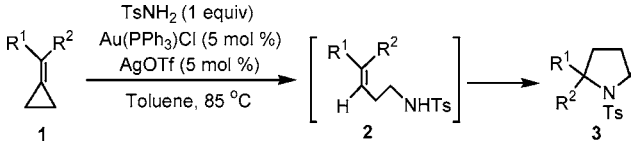
ABSTRACT



Reaction of methylenecyclopropanes 1 with sulfonamides produces the corresponding pyrrolidine derivatives 3 in moderate to good yields under the catalysis of Au(I) via a domino ring-opening ring-closing hydroamination process.

Nitrogen-containing saturated heterocyclic systems are important core structures in organic chemistry because of their presence in many natural products.[1] One of the most appealing approaches to pyrrolidines is intramolecular hydroamination, which is mainly developed by Hartwig and co-workers, under the catalysis of transition metals or Brønsted acids.[2] During our initial studies on the Lewis acids such as $Sn(OTf)_2$ promoted ring-opening reactions of methylenecyclopropanes[3] (MCPs) **1** with sulfonamides, we found that pyrrolidine derivatives could be formed for some substrates in moderate yields (27−51%).[4] Recently, He reported that gold(I)-mediated hydroamination of inert olefins with *p*-toluenesulfonamide ($TsNH_2$) can produce the corresponding acyclic or cyclic nitrogen-containing compounds in good to excellent yields under mild conditions.[5] Therefore,

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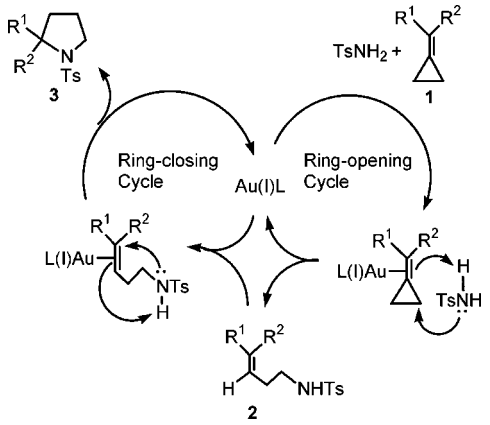
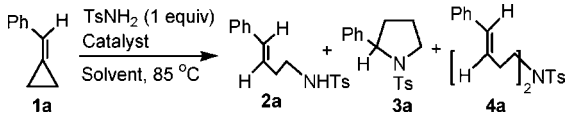
we envisioned that pyrrolidine derivatives would be obtained in better yields from methylenecyclopropanes and $TsNH_2$ under the catalysis of gold(I) salt, a powerful soft Lewis acid.[6] Herein, we wish to report gold(I)-catalyzed domino ring-opening ring-closing hydroamination of methylenecyclopropanes with sulfonamides, a facile synthetic route to pyrrolidine derivatives **3** (Scheme 1).

Scheme 1. Envisioned Reaction Pathway of Au(I)-Catalyzed Hydroamination of MCPs with $TsNH_2$



In our initial experiment using $Au(PPh_3)OTf$, prepared from equal equivalents of $Au(PPh_3)Cl$ and AgOTf, as the catalyst, we investigated the hydroamination of methylenecyclopropane **1a** with $TsNH_2$ (1.0 equiv). As we expected, the corresponding pyrrolidine derivative **3a** was obtained in good yield (70%) after 12 h in toluene at 85 °C (Table 1, entry 1). Though a trace of ring-opening product **2a** was detected by TLC analysis, none of the dialkylated product **4a** was formed. Meanwhile, the Brønsted acid trifluoromethanesulfonic acid (TfOH) and various other Lewis acids including $Au(PPh_3)Cl$ and $Au(PPh_3)Cl$ with $AgSbF_6$ were tested in this reaction under identical conditions. As can be seen from Table 1, TfOH could also catalyze the reaction but led to **3a** in lower yield (Table 1, entry 2). When 2 mol % of TfOH was used as the catalyst for a control experiment, product **3a** was isolated in only 10% yield along with the recovery of 54% of the starting materials (Table 1, entry 3). Other Lewis acids, such as $Sn(OTf)_2$, $In(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, and $BF_3{\cdot}Et_2O$, could promote the ring-opening reaction of **1a** with $TsNH_2$ to give the corresponding product **2a** as the major one along with the formation of product **4a** in low yields in most cases. However, these Lewis acids were not as efficient as gold(I) catalyst in the subsequent intramolecular ring-closing hydroamination of **2a** to afford pyrrolidine derivative **3a** under identical conditions (Table 1, entries 4−8). If $Au(PPh_3)Cl$ was used as a sole catalyst, no reaction occurred (Table 1, entry 9). On the other hand, AgOTf could only promote the ring-opening reaction of **1a** to give **2a** in 72% yield (Table 1, entry 10). When $AgSbF_6$ was used as the dechlorinating reagent instead of AgOTf, **3a** was obtained in 51% yield under identical conditions (Table 1, entry 11). $Au(PPh_3)NTf_2$, an air-stable gold(I) complex,[7] was also applied to the reaction as the catalyst

Table 1. Hydroamination of MCP **1a** (0.5 mmol) with $TsNH_2$ (0.5 mmol) in Toluene (2.0 mL)



			yield (%)		
entry	catalyst (mol %)	solvent	**2a**	**3a**	**4a**
1	$Au(PPh_3)Cl$ (5), AgOTf (5)	toluene	trace	70	
2	TfOH (10)	toluene	trace	48	trace
3	TfOH (2)[b]	toluene	trace	10	
4	$Sn(OTf)_2$ (10)	toluene	11	36	20
5	$In(OTf)_3$ (10)	toluene	24	22	15
6	$Yb(OTf)_3$ (10)	toluene	56		6
7	$Sc(OTf)_3$ (10)	toluene	34	18	8
8	$BF_3{\cdot}OEt_2$ (10)	toluene	47	16	trace
9	$Au(PPh_3)Cl$ (5)	toluene			
10	AgOTf (5)	toluene	72		
11	$Au(PPh_3)Cl$ (5), $AgSbF_6$ (5)	toluene	trace	51	
12	$Au(PPh_3)(NTf_2$ (5)	toluene			
13	$Au(PPh_3)Cl$ (5), AgOTf (5)	DCE	trace	61	
14	$Au(PPh_3)Cl$ (5), AgOTf (5)	CH_3CN			
15	$Au(PPh_3)Cl$ (5), AgOTf (5)	THF			

[a] Isolated yields. [b] 54% of **1a** was recovered.

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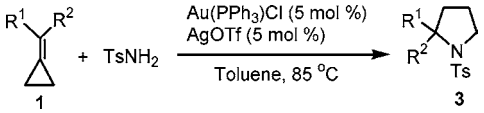
under identical conditions, but no reaction occurred (Table 1, entry 12). Solvent effects were examined with use of Au(PPh$_3$)OTf as the catalyst. The results are summarized in Table 1 as entries 13−15. Pyrrolidine derivative **3a** was also obtained in 1,2-dichloroethane (DCE) in 61% yield, but no reaction occurred in acetonitrile (CH_3CN) or tetrahydrofuran (THF) under the standard conditions. It should be noted that no reaction occurred at room temperature (20 °C) and product **2a** was obtained in 36% yield at 50 °C after 12 h without the formation of product **3a** under the standard conditions.

Next, we carried out the gold(I)-catalyzed domino ring-opening ring-closing hydroamination of methylenecyclopropanes **1b**−**o** with $TsNH_2$ under these optimal conditions. We found that the corresponding pyrrolidine derivatives **3b**−**o** were obtained in moderate to good yields (Table 2).

Table 2. Gold(I)-Catalyzed Hydroamination of MCPs **1** (0.5 mmol) with $TsNH_2$ (0.5 mmol)



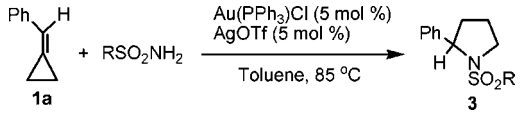
entry	R^1, R^2	time (h)	yield of **3** (%)[a]
1	*o*-MeC_6H_4, H (**1b**)	8	**3b**, 68
2	*m*-MeC_6H_4, H (**1c**)	8	**3c**,76
3	*p*-MeC_6H_4, H (**1d**)	8	**3d**, 70
4	*o*-$MeOC_6H_4$, H (**1e**)	4	**3e**, 34 (46[b])
5	1-naphthyl, H (**1f**)	12	**3f**, 54
6	C_6H_5, Me (**1g**)	12	**3g**, 68
7	*p*-MeC_6H_4, Me (**1h**)	8	**3h**, 72
8	*p*-$EtOC_6H_4$, Me (**1i**)	8	**3i**, 71
9	*p*-ClC_6H_4, Me (**1j**)	24	**3j**, 43
10	*m*-BrC_6H_4, Me (**1k**)	24	**3k**, 47
11	*n*-C_4H_9, *n*-C_4H_9 (**1*l***)	8	**3*l***, 70
12	*n*-C_7H_{15}, Me (**1m**)	8	**3m**, 64
13	cyclohexylene (**1n**)	8	**3n**, 63
14	4-phenylcyclohexylene (**1o**)	8	**3o**, 75

[a] Isolated yields. [b] TfOH (2 mol %) was used as the catalyst and the reaction time was prolonged to 12 h.

For methylenecyclopropanes **1b**−**f** substituted by a single aromatic group, the reactions proceeded smoothly to give the corresponding pyrrolidine derivatives **3b**−**f** in 34−76% yields (Table 2, entries 1−5). For methylenecyclopropanes **1b**−**d** having a methyl group on the aromatic ring, the corresponding pyrrolidine derivatives **3b**−**d** were obtained in good yields even for sterically hindered methylenecyclopropane **1b** (Table 2, entries 1−3). For methylenecyclopropane **1e** having a methoxy group on the aromatic ring as substrate, the corresponding pyrrolidine derivative **3e** was obtained in 34% yield. In addition, the yield of **3e** increased slightly to 46% when 2 mol % of TfOH was used as the catalyst (Table 2, entry 4). This may be due to the unstability of **1e** under the reaction conditions. MCP **1f**, having a 1-naphthyl group rather than a phenyl group, was also subjected to the reaction and the corresponding pyrrolidine derivative **3f** was obtained in 54% yield (Table 2, entry 5). For an aromatic group and a methyl group substituted methylenecyclopropanes **1g**−**k**, the reaction also proceeded smoothly to give the expected products **3g**−**k** in moderate to good yields. The electron-donating groups on the aromatic ring could accelerate the reaction and the corresponding pyrrolidine derivatives **3h**−**i** were obtained in higher yields within shorter reaction time (Table 2, entries 7 and 8). Conversely, electron-withdrawing groups on the aromatic ring could hold back the reaction rates (Table 2, entries 9 and 10). For double aliphatic groups substituted acyclic or cyclic methylenecyclopropanes **1*l***−**o**, the corresponding pyrrolidine derivatives **3*l***−**o** were obtained in good yields (Table 2, entries 11−14).

Afterward, using methylenecyclopropane **1a** as substrate, we investigated the hydroamination with other sulfonamides, amides, and amines under these optimized conditions. We found that when phenylsulfonamide and *m*- and *p*-nitrophenylsulfonamides were used, the corresponding pyrrolidine derivatives **3p**−**r** were obtained in good yields (Table 3, entries 1−3). *o*-Nitrophenylsulfonamide was also employed in the reaction but led to the corresponding product **3s** in 12% yield along with the formation of **2s** in 36% yield under the standard conditions (Table 3, entry 4, also see the Supporting Information). This may be due to that the *o*-nitro group sterically retarding the hydroamination process. Nevertheless, amides such as benzamide and acetamide, and amines such as aniline and benzylamine, did not react with MCPs at all to give the corresponding pyrrolidine derivative, as reported by Hartwig's group[2f] and He's group.[6a]

Table 3. Gold(I)-Catalyzed Hydroamination of MCP **1a** (0.5 mmol) with Sulfonamides (0.5 mmol)



entry	R	yield of **3** (%)[a]
1	C_6H_5	**3p**, 79
2	*m*-$NO_2C_6H_4$	**3q**, 69
3	*p*-$NO_2C_6H_4$	**3r**, 74
4	*o*-$NO_2C_6H_4$	**3s**, 12 (**2s**, 36

[a] Isolated yields.

In conclusion, we have developed a gold(I)-catalyzed domino ring-opening ring-closing hydroamination of methylenecyclopropanes with sulfonamides to give the corresponding pyrrolidine derivatives under mild conditions. In this synthetic protocol, various pyrrolidine derivatives **3** were easily obtained in moderate to good yields in a cascade process, substantially enriching gold chemistry. Efforts are underway to further explore more effective gold(I) catalyst and to understand the scope and limitations of this process.

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Supporting Information Available: The spectroscopic data (^{1}H, ^{13}C spectroscopic data), MS, HRMS and analytic data of the compounds shown in Tables 1−3 and the detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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