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Gold(I)-Catalyzed Ring Expansions of Unactivated Alkynylcyclopropanes to (*E*)-2-Alkylidenecyclobutanamines in the Presence of Sulfonamides

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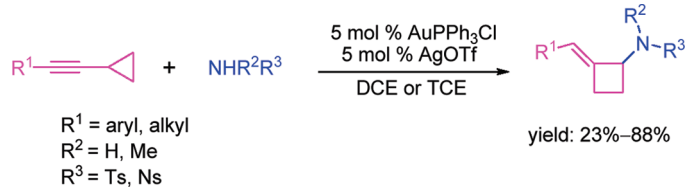
ABSTRACT



The ring expansion of cyclopropane derivatives provides a powerful method to construct synthetically useful four-membered carbocycles. Herein, a new type of gold(I)-catalyzed ring expansion of an unactivated alkynylcyclopropane/sulfonamide trapping strategy to (*E*)-2-alkylidenecyclobutanamines was described. The reaction tolerates a range of aryl and alkyl substituents with moderate to good yields.

Four-membered carbocycles are found in many natural products of significant biological activities.[1] Also, four-membered carbocycles are very useful building blocks that can be further transformed to various ring skeletons in organic synthesis.[2] However, methods for synthesis of four-membered carbocycles are limited compared to the synthesis of five- and six-membered carbocycles. This is mainly due to the following reasons. Thermal [2 + 2] cycloaddition[3] of two π components with or without catalysts is limited to special substrates. Photochemical [2 + 2] cycloaddition[4] is another approach to achieve four-membered carbocycles, in which the intramolecular type is usually efficient, but the intermolecular type has not been well developed.[5] Due to this, synthesis of four-membered carbocycles has to be accomplished via either a ring expansion or a ring contraction strategy. Ring expansion[6] is a powerful method to realize this dream because cyclopropanes can be easily prepared by many known methods, such as Simmons−Smith,[7] Kulinkovich,[8] de Meijere−Kulinkovich,[9] and others. Asymmetric

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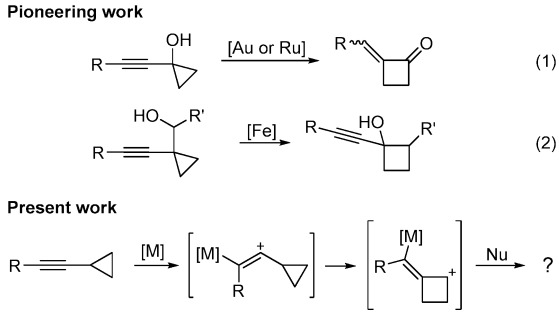
synthesis of cyclopropanes[10] has also been well developed, and therefore ring expansion from chiral cyclopropanes to chiral cyclobutane skeletons can be fulfilled potentially.

One such ring expansion strategy is to use alkynylcyclopropanes as substrates. For example, Toste's group[11] and Trost's group[12] reported intramolecular ring expansions of alkynylcyclopropanols[13] to alkylidenecyclobutanones under Au and Ru catalysts, respectively. In Au catalysis, it was proposed that cationic species were generated by coordination of transition metals to the carbon−carbon triple bonds of the alkynylcyclopropanes. Then a cation-triggered ring expansion gave the four-membered carbocyclic cations, which underwent further reactions to furnish the final alkylidenecyclobutanones. It must be pointed out that the hydroxyl group in the cyclopropane rings is required for the success of Toste's and Trost's reactions. Recently, Jiao's group[14] also reported Fe-catalyzed ring expansions of alkynylcyclopropyl alkanols to cyclobutanols (eq 2, Scheme 1). Here, a cation was generated from the secondary alcohol

Scheme 1

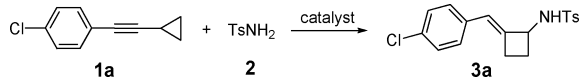


of the substrate. Then, a similar ring expansion occurred to give a cationic four-membered carbocycle, which was then trapped by the hydroxyl group to give the final product.

Inspired by these seminal studies, we envisioned that alkynylcyclopropanes without activating groups in the cyclopropane ring could also undergo cation-triggered expansion to give four-membered carbocycles if an appropriate nucleophile could trap the in situ generated cation (Scheme 1).[15] If this can be realized, multifunctional four-membered carbocycles can be readily synthesized from simple alkynylcyclopropanes.

We quickly synthesized alkynylcyclopropane **1a** by Sonogashira cross-coupling from commercially available 1-chloro-4-iodobenzene and cyclopropylacetylene. Treatment of substrate **1a** with various nucleophiles (water, phenol, indole, aniline, $BocNH_2$, and $TsNH_2$, in a stoichiometric amount)[16] under 10 mol % $(PPh_3)AuOTf$ suggested that only $TsNH_2$ was efficient. The reaction produced alkylidenecyclobutanamine **3a** in 65% yield as a single olefin isomer (entry 1, Table 1).[17] We then concentrated on screening the optimal conditions for this reaction. When only AgOTf was employed as the catalyst, a trace amount of **3a** was observed, indicating that the effective component should be the cationic gold(I) (entry 2, Table 1). N-Heterocyclic carbene ligand (*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) turned out to be less efficient in this ring expansion (entry 3, Table 1). Other common Lewis acids, which may have good affinity toward the alkynes, such as $AuCl_3$, $PtCl_2$, and $Sc(OTf)_3$, were also tested, but the yields were far from ideal (entries 4−7, Table 1). Strong Brönsted acid TfOH could accelerate the consumption of substrate **1a** but did not improve the yield. In contrast, weaker Brönsted acid, such as CF_3COOH, was not effective to catalyze this transformation (entries 8 and 9, Table 1). The solvent effect was quite strong because the ring expansion deteriorated in dioxane and toluene (entries 10 and 11, Table 1). When the catalyst loading was reduced from 10 mol % to 5 mol %, the reaction became slower (entry 12, Table 1). By raising the temperature to 80 °C, the reaction gave the highest efficiency with a 76% yield and a complete conversion of the substrate (entry 13, Table 1).

Table 1. Optimization Studies on the Ring Expansion[a]

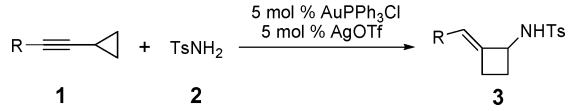


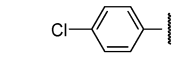
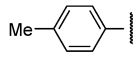
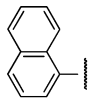
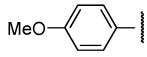
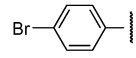
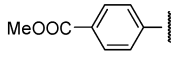
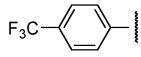
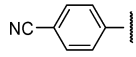
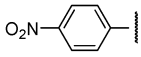
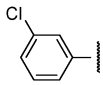
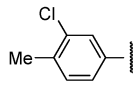
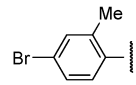
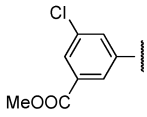
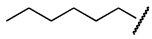
1a **2** **3a**

entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]	conversion (%)
1	10 mol % $AuPPh_3Cl$, 10 mol % AgOTf	DCE	60	24	65	>99
2	10 mol % AgOTf	DCE	60	24	trace[c]	
3	10 mol % AuIPrCl, 10 mol % AgOTf	DCE	60	24	21	85
4	10 mol % $AuCl_3$, 10 mol % AgOTf	DCE	60	24	15	>99
5	10 mol % $AuCl_3$	DCE	60	24	trace[c]	
6	10 mol % $PtCl_2$	DCE	60	24	NR[d]	
7	10 mol % $Sc(OTf)_3$	DCE	60	24	20	44
8	10 mol % TfOH	DCE	60	7	28	>99
9	10 mol % CF_3COOH	DCE	60	24	NR[d]	
10	10 mol % $AuPPh_3Cl$, 10 mol % AgOTf	dioxane	60	24	ND[e]	88
11	10 mol % $AuPPh_3Cl$, 10 mol % AgOTf	toluene	60	24	20	52
12	5 mol % $AuPPh_3Cl$, 5 mol % AgOTf	DCE	60	24	74	90
13	5 mol % $AuPPh_3Cl$, 5 mol % AgOTf	DCE	80	14	76	>99

[a] Reaction condition: **1a** (0.5 mmol), $TsNH_2$ (0.6 mmol), catalyst (0.05 or 0.025 mmol), solvent (5 mL). [b] Isolated yields without considering the recovered **1a**. [c] Most of **1a** remained unchanged. [d] NR = no reaction. [e] ND = product not detected. DCE = 1,2-dichloroethane. IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Table 2. Ring Expansions of Alkylnylcyclopropanes[a]



entry	R		condition[a]	time (h)	yield (%)[b]	
1		(**1a**)	A	14	76	(**3a**)
2		(**1b**)	A	6	63	(**3b**)
3		(**1c**)	A	20	46	(**3c**)
4		(**1d**)	A	42	23[c]	(**3d**)
5		(**1d**)	B	14	14	(**3d**)
6		(**1e**)	C	24	ND[d,e]	
7		(**1e**)	B	14	ND[d,f]	
8		(**1f**)	B	7	66	(**3f**)
9		(**1g**)	B	7	77	(**3g**)
10		(**1h**)	B	13	84	(**3h**)
11		(**1i**)	B	13	70	(**3i**)
12		(**1j**)	B	13	54	(**3j**)
13		(**1k**)	B	7	75	(**3k**)
14		(**1l**)	B	7	88	(**3l**)
15		(**1m**)	A	36	87	(**3m**)
16		(**1n**)	B	13	59	(**3n**)
17		(**1o**)	B	13	85	(**3o**)
18		(**1p**)	C	20	45	(**3p**)

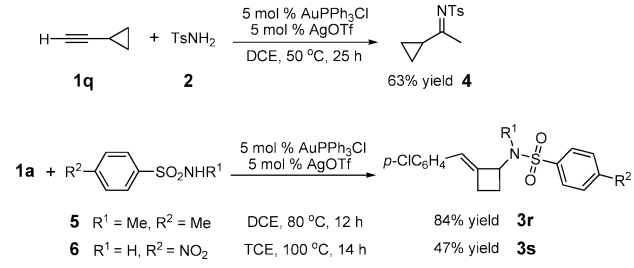
[a] Condition A: DCE as solvent, heated at 80 °C. Condition B: TCE as solvent, heated at 100 °C. Condition C: DCE as solvent, heated at 50 °C. [b] Isolated yields without considering the recovered substrates. [c] 33% of **1d** was recovered. [d] ND = product not detected. [e] A considerable amount of **1e** remained. [f] **1e** was totally consumed. DCE = 1,2-dichloroethane. TCE = 1,1,2,2-tetrachloroethane.

We then studied the scope and limitation of this reaction. Because the *p*-chloro phenyl group was demonstrated as a suitable substituent in the substrate, we speculated that electron-rich aryl groups in substrates would increase the nucleophilicity of the carbon−carbon triple bond through conjugation toward cationic gold catalyst, making these substrates more reactive. However, we found that the more electron-donating the aryl group in the substrate was, the worse the result was. For example, the phenyl-substituted substrate **1b** afforded a slightly diminished yield (entry 2, Table 2), while the yield dropped to 46% when the *p*-tolyl group was introduced (entry 3, Table 2). The electron-rich 1-napthyl group turned out to be less suitable. When substrate **1d** was heated at higher temperature (100 °C) to reach full conversion, the yield became poorer (entries 4 and 5, Table 2). Unfortunately, the strong electron-donating *p*-methoxy group did not fit this reaction, as demonstrated by the fact that substrate **1e** failed to furnish the desired product (entries 6 and 7, Table 2).

However, electron-withdrawing groups were well compatible with this ring expansion. From the weak electron-withdrawing bromo group to the strong ones, such as ester, trifluoromethyl, cyano, and nitro groups, all of them afforded the expected alkylidenecyclobutanamines in moderate to good yields (entries 8−12, Table 2). We found that electron-withdrawing groups made the target reaction very slow. Consequently, the reaction temperatures for these substrates needed to be elevated (solvent changed from DCE to TCE) for the reaction completion in a reasonably short time. Besides *para*-substitution, *ortho*-, *meta*-, and even disubstituted phenyl alkynyl substrates could be well transformed into the expected products (entries 13−17, Table 2), suggesting that the steric effect on the benzene ring did not affect the reactivity significantly.

It is noteworthy that alkyl-substituted substrate **1p** underwent the ring expansion smoothly to give product **3p** in 45% yield (entry 18, Table 2). However, when the substituent was hydrogen, an imine product **4**[18] with the cyclopropyl moiety unchanged was obtained, indicating that cyclopropylacetylene **1q** underwent a hydroamination[19] instead of a ring expansion (Scheme 2). Furthermore, other sulfonamides, like TsNHMe

Scheme 2



(**5**) and $NsNH_2$ (**6**), were proved to be effective trapping reagents in the ring expansion (Scheme 2). In addition, the framework and the *E* olefin configuration of the products **3a**−**3s** were further confirmed by X-ray crystallographic analysis of **3h** (Figure 1). Finally, we examined the effect of certain substituents on the cyclopropane ring. Unfortunately, these reactions gave mixtures of unidentified products, and no target products were obtained (for details, see Supporting Information).

In summary, we have developed a new type of gold(I)-catalyzed ring expansion of unactivated alkynylcyclopropanes, which can be easily synthesized from simple and

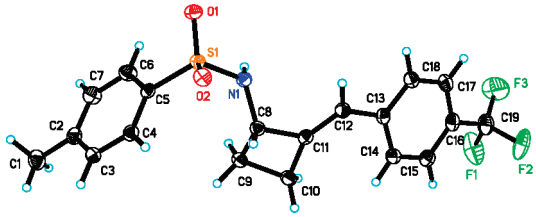


Figure 1. X-ray structure of product **3h**.

commercially available starting materials. The in situ generated cation from the ring expansion can be efficiently trapped by sulfonamides. This reaction provides an easy and efficient way to synthesize (*E*)-2-alkylidenecyclobutanamines that are architecturally interesting and useful in organic synthesis. The reaction tolerates a range of aryl and alkyl substituents, especially the electron-withdrawing ones. We believe this ring expansion/trapping reaction provides a general, easy, and quick approach to synthesize multifunctional cyclobutanes and will find application in organic synthesis.

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Supporting Information Available: Experimental procedures, spectral data of all new compounds, and crystal structure data of **3h** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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