Au(III)-catalyzed ring opening reaction of 1-cyclopropyl-2-yn-1-ols with nucleophiles: highly efficient approach to (*Z*)-conjugated enynes†

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A highly efficient approach to (*Z*)-conjugated enynes has been developed by utilizing an Au(III)-catalyzed ring opening reaction of 1-cyclopropyl-2-yn-1-ols with nucleophiles under mild conditions; the method is valuable due to the excellent yield and high regio- and stereoselectivity.

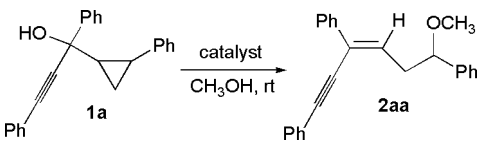
Conjugated enynes are one of the most versatile intermediates in organic synthesis.[1] Among a variety of approaches for their preparation, highly selective preparation of conjugated enynes is quite limited due to the competitive formation of undesired regio- and stereoisomers.[2] So a novel and efficient method for selective preparation of conjugated enynes should be developed from a synthetic viewpoint.

Recently, gold has emerged as a powerful homogeneous catalyst for the electrophilic activation of alkynes, alkenes and many other groups to afford a variety of C–C and C–X bonds.[3] However, little attention as been paid so far to gold-catalyzed reactions with three-membered rings and, in particular, cyclopropane.[4] Examples of gold-catalyzed ring opening reactions through nucleophilic attack on a cyclopropane ring are scarce.[4c] Consequently, the use of gold catalysts in the area of cyclopropanes remains largely unexplored. We envisioned that cyclopropanes with a hydroxy group at the α-position might undergo ring opening reaction after being activated by a gold catalyst in the presence of a nucleophile. Herein, we disclose the first results on the corresponding Au(III)-catalyzed nucleophilic attack reaction of 1-cyclopropyl-2-yn-1-ols with nucleophiles to afford (*Z*)-conjugated enynes with complete regio- and stereoselectivity.

We began our investigation with 1-cyclopropyl-2-yn-1-ol **1a**[5] (0.3 mmol) and MeOH (1.0 mL) using a variety of catalysts at room temperature without exclusion of moisture or air (Table 1). In the presence of 1 mol% of $HAuCl_4 \cdot 4H_2O$, the reaction proceeded efficiently to afford (*Z*)-enyne **2aa**[6] in 60% yield after 3 h (entry 1). On increasing the amount of catalyst to 3 mol%, an excellent yield (up to 90%) of **2aa** was obtained after 1 h (entry 2). With other gold catalysts, such as $Bu_4N[AuCl_4]$,[7] $AuCl_3$ and AuCl, no superior results were obtained (entries 3–5). When TsOH was used as the catalyst, only 58% yield was obtained (entry 6). $PtCl_2$ and $AgSbF_6$ were also applied to the reaction, however little or no trace of the product **2aa** was observed (entries 7 and 8). Thus, the use of $HAuCl_4 \cdot 4H_2O$ (3 mol%) at room temperature was found to be the most efficient and used as the standard conditions.

To probe the scope of the reaction, the relative reactivities of propargylic alcohols with different R^1, R^2 and R^3 groups were examined under optimal conditions, as shown in Table 2. Various aryl substituents on the three-membered ring, including phenyl, electron-rich, and electron-poor aryls, were compatible with this reaction, and generally good yields of the corresponding enynes were obtained (entries 1–3). Cyclopropane with heteroaromatic groups such as 2-furanyl also proceeded smoothly (entry 4). Substitution on the α-position of cyclopropyl carbinols was also tolerated (entries 5–7). Alkynes with different aryl groups as well as heteroaromatic groups such as 2-thienyl all afforded good yields of desired products (entries 8–10). When aliphatic and terminal alkynes were used, the reaction proceeded faster, furnishing the corresponding products in high yields within 0.5 h (entries 11 and 12). Although both electron-rich and electron-deficient

Table 1 Effect of catalysts on the reaction of **1a** to **2aa**[a]



Entry	Catalyst (mol%)	Time/h	Yield (%)[b]
1	$HAuCl_4 \cdot 4H_2O$ (1)	3	60
2	$HAuCl_4 \cdot 4H_2O$ (3)	1	90
3	$Bu_4N[AuCl_4]$ (3)	6	50
4	AuCl (3)	1	80
5	$AuCl_3$ (3)	1	75
6	TsOH (10)	4	58
7	$PtCl_2$ (3)	24	0
8	$AgSbF_6$ (3)	12	Trace

[a] Unless noted, all reactions were carried out using **1a** (0.3 mmol) with 3 mol% of catalyst in MeOH (1.0 mL) at room temperature. [b] Isolated yield.

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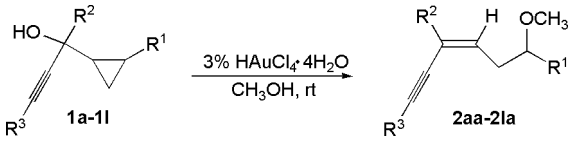
Table 2 $HAuCl_4 \cdot 4H_2O$-catalyzed synthesis of substituted conjugated enynes by treatment of 1-cyclopropyl-2-propyn-1-ols with methanol[a]



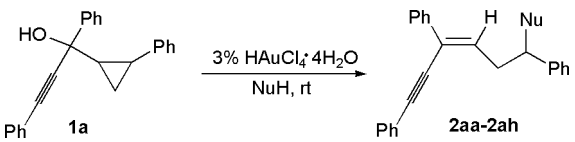
Entry	1	R^1	R^2	R^3	Time/h	2 (Yield %)[b]
1	**1a**	Ph	Ph	Ph	1	**2aa** (90)
2	**1b**	*p*-CH_3O–C_6H_4	Ph	Ph	0.5	**2ba** (89)
3	**1c**	*p*-Cl–C_6H_4	Ph	Ph	1	**2ca** (92)
4	**1d**	2-Furanyl	Ph	Ph	1	**2da** (85)
5	**1e**	Ph	*p*-Br–C_6H_4	Ph	1	**2ea** (82)
6	**1f**	Ph	*p*-CH_3O–C_6H_4	Ph	0.5	**2fa** (85)
7	**1g**	Ph	CH_3	Ph	0.5	**2ga** (92)
8	**1h**	Ph	Ph	*p*-CH_3–C_6H_4	1	**2ha** (92)
9	**1i**	Ph	Ph	*p*-Cl–C_6H_4	1	**2ia** (90)
10	**1j**	Ph	Ph	2-Thienyl	1	**2ja** (89)
11	**1k**[c]	Ph	Ph	*n*-C_5H_{11}	0.5	**2ka** (90)
12	**1l**	Ph	Ph	H	0.5	**2la** (75)

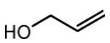
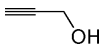
[a] Unless noted, all reactions were carried out using **1** (0.3 mmol) with 3 mol% of $HAuCl_4 \cdot 4H_2O$ in MeOH (1.0 mL) at room temperature. [b] Isolated yield. [c] *cis* substrate of **1k** was explored.

aryl groups were well accommodated in the reaction, the former reacted much faster, which might be due to the electronic activation of cyclopropane ring (entries 2 *vs.* 3, 5 *vs.* 6).

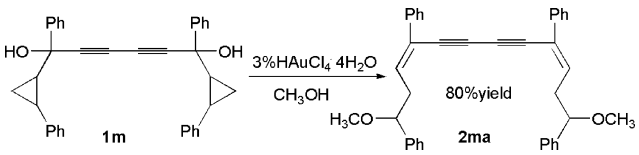
Then, we examined the scope of different nucleophiles in the ring opening reactions under the optimal conditions. It was found that, in addition to methanol, a variety of alcohols could be used as effective nucleophiles (Table 3), and the corresponding enynes were obtained in good yields with a complete regioselectivity. Treatment of **1a** with ethanol resulted in the formation of **2ab** in 82% yield (entry 2). More sterically hindered alcohols such as *i*-PrOH, and *t*-BuOH also proceeded smoothly to afford the corresponding products in 88% and 80% yields, respectively (entries 3 and 4). Functional alcohols, such as 2-chloroethanol, allylic alcohol and propargylic alcohol, were effective nucleophiles (entries 5–7). In addition, benzylic alcohol could also be readily reacted in good yield (entry 8).

Table 3 Synthesis of (*Z*)-conjugated enynes using different nucleophiles[a]



Entry	Nucleophile	Time/h	Yield (%)[b]
1	CH_3OH	0.5	**2aa** (90)
2	C_2H_5OH	1	**2ab** (82)
3	*i*-PrOH	1.5	**2ac** (88)
4	*t*-BuOH	3	**2ad** (80)[c]
5	$ClCH_2CH_2OH$	1	**2ae** (85)
6		1	**2af** (82)
7		1	**2ag** (78)
8	$PhCH_2OH$	2	**2ah** (80)

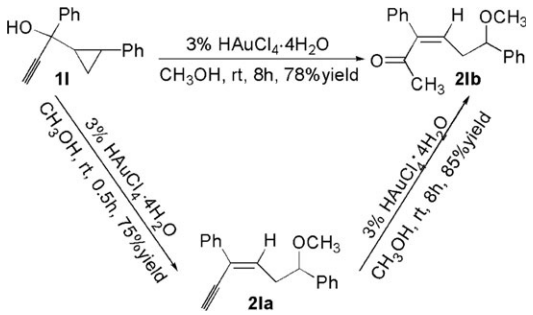
[a] Unless noted, all reactions of were carried out by using 0.3 mmol of **1a** in 1 mL of alcohols in the presence of 3 mol% of $HAuCl_4 \cdot 4H_2O$ at room temperature. [b] Isolated yield. [c] At 60 °C.



Scheme 1 Synthesis of enediyne compound **2ma** from **1m**.

Furthermore, we examined the reaction of compound **1m** with methanol under the same conditions. The reaction proceeded efficiently to afford the corresponding enediyne **2ma** in 80% yield after 4 h with complete regio- and stereoselectivity (Scheme 1). Enediyne compounds can be used not only to study their mechanism of function in antitumor antibiotics[8] such as dynemicin, neocarzinostatin, and esperamicin, but also are utilized in the synthesis of oligoenynes and oligoenediynes as well as *p*-conjugated polymers for electronic and photonic applications.[9]

Very interestingly, when terminal alkyne **1l** was employed, carbonyl compound **2lb** could be obtained in 78% yield after 8 h in the presence of 3 mol% of $HAuCl_4 \cdot 4H_2O$ at room temperature (Scheme 2). In this two-step one-pot reaction, cyclopropane **1l** undergoes a facile ring opening reaction to afford enyne **2la**, which further undergoes a hydration reaction of alkynes[10] to provide the corresponding product **2lb**. This mechanism was also confirmed by our experiment. Conjugated enyne **2la** could be obtained in 75% isolated yield by using cyclopropane **1l** in the presence of 3 mol% of $HAuCl_4 \cdot 4H_2O$ at room temperature for 0.5 h. Then compound **2la** was employed at the same condition for 8 h to afford the desired product **2lb** in 85% yield.



Scheme 2 Transformation of **1l** to **2la** and **2lb**.

In summary, we have successfully developed an efficient approach to (*Z*)-conjugated enynes through the gold-catalyzed ring opening reaction of cyclopropanes with various nucleophiles. The first example of a nucleophilic attack reaction of cyclopropane induced by gold activated propargylic alcohols was disclosed. The reaction proceeded under very mild conditions with complete regio- and stereoselectivity.

Experimental

General experimental procedure for the synthesis of 1-cyclopropyl-2-propyn-1-ols (1a–1l) from the corresponding ketones

To a stirring solution of the appropriate terminal alkyne (1.2 equiv.) in THF (1.0 M) was added ethylmagnesium bromide (1.0 M in THF, 1.1 equiv.) at room temperature. The resulting solution was stirred for 1 h at 50 °C. Then the corresponding ketone (1.0 equiv.) in THF (0.35 M) was added slowly by syringe to the resulting solution at room temperature and stirred for 3 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (40 mL) and extracted with diethyl ether (2 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel to obtain the pure 1-cyclopropyl-2-propyn-1-ol **1** as a mixture of diastereoisomers in 82% yield (petroleum ether–ethyl acetate, 20 : 1).

General experimental procedure for the preparation of (*Z*)-conjugated enynes

To a solution of a *cis*/*trans* mixtures of 1-cyclopropyl-2-propyn-1-ols **1**[5] (0.3 mmol) in alcohols (1 mL) was added 3 mol% of $HAuCl_4 \cdot 4H_2O$ under air at room temperature. When the reaction was considered complete as determined by TLC analysis, 30 mL of diethyl ether was added and the mixture was washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding conjugated enynes (petroleum ether–ethyl acetate, 40 : 1).

Acknowledgements

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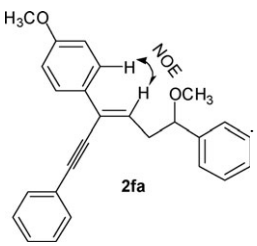
5 In the reaction, the *cis*/*trans* mixture of 1-cyclopropyl-2-propyn-1-ol (**1a**) was used. All of the propargylic alcohols (**1a**–**1j**) used in the reaction were *cis*/*trans* mixtures.
6 Only (*Z*)-enyne was obtained, and the structure of **2fa** was determined by an NOE study. (The NOE spectrum of **2fa** can be seen in the ESI†)



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