

Cyclization of Allenyne-1,6-diols Catalyzed by Gold and Silver Salts: An Efficient Selective Synthesis of Dihydrofuran and Furan Derivatives

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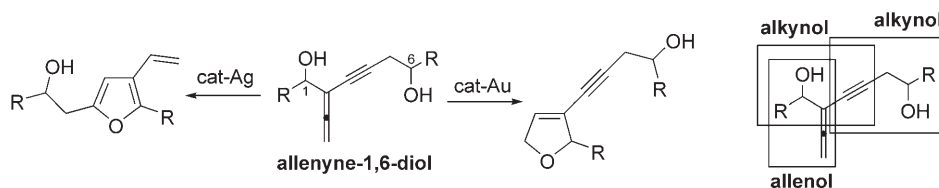
Abstract: Treatment of allenyne-1,6-diols with gold and silver catalysts selectively produced 2,5-dihydrofuran and furan derivatives, respectively, in good to excellent yields through the selective activation and differentiation of the double and triple bonds in allenyne-1,6-diols. It is noteworthy that the chemoselectivity is clearly switched by simply changing the metal from gold to silver.

Keywords: cyclization; dihydrofuran; furan; gold; silver

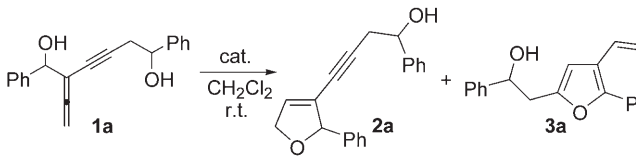
Dihydrofuran and furan derivatives widely occur as important structural units in a variety of natural products that can be applied as pharmaceuticals and flavor and fragrance compounds.^[1] Because they are useful and versatile synthetic intermediates for heterocyclic compounds, the development of methodologies for the synthesis of such compounds are of significant interest.^[2] To date various transition metal-, acid-, and base-catalyzed synthetic methods for dihydrofurans and furans have been reported.^[3] Recently, it has been demonstrated that cationic gold species show efficient catalytic activity for the cyclization of alkynyl ketones, allenyl ketones, alkynyl epoxides and enyne alcohols under mild conditions.^[4] In this respect, Hashmi et al. found that a gold catalyst was efficient

in the cyclization of 2-methylpent-2-en-4-yn-1-ol to furans^[5a] and the cyclization of allenyl carbinols to dihydrofurans^[5b] and Krause et al. described that gold-(III) chloride catalyzed the cyclization of allenols to polysubstituted 2,5-dihydrofurans.^[6] Although many examples of the synthesis of dihydrofurans and furans *via* the cyclization of alcohols bearing one alkynyl or allenyl group have been described,^[4b,5a,6a,7] the development of efficient methods for the synthesis of dihydrofuran and furan derivatives having diverse functional groups under mild conditions remains an important objective. Moreover, as far as we are aware, no selective synthesis of dihydrofurans and furans from compounds possessing both one allenol and two alkynols as a function of catalyst has been reported. Herein, we report selective synthetic routes to dihydrofurans and furans from allenyne-1,6-diols through the selective activation and differentiation of double and triple bonds catalyzed by gold and silver, respectively (Scheme 1).

Our initial study focused on the cyclization of 1,6-diphenyl-2-vinylidenehex-3-yne-1,6-diol (**1a**, *dr* = 1:1) with a variety of gold and silver catalysts. The results are summarized in Table 1. Treatment of **1a** with 3 mol % AuCl₃ gave 3-(4-hydroxy-4-phenyl-1-butyne-1-yl)-2-phenyl-2,5-dihydrofuran (**2a**) and 5-(2-hydroxy-2-phenylethyl)-2-phenyl-3-vinylfuran (**3a**) in 38 % and 31 % yields (25 °C, 10 min), respectively (entry 1). Increasing the catalytic amount of AuCl₃ gave a better selectivity (entries 1–3). The use of 15 mol % AuCl₃



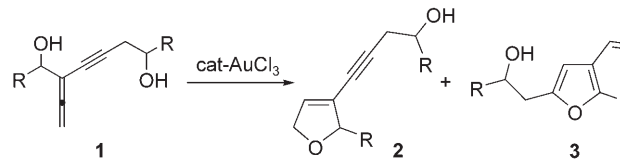
Scheme 1. Selective cyclization of allenyne-1,6-diols catalyzed by gold and silver salts.

Table 1. Optimization for selective cyclization of allenyne-1,6-diol catalyzed by Au and Ag salts.^[a]


Entry	Cat.	Time [h]	Yield [%] ^[b]	(2a:3a)
1	3 mol% AuCl ₃	0.17	69(23) ^[c]	1.2:1
2	10 mol% AuCl ₃	0.17	72	2.2:1
3	15 mol% AuCl ₃	0.17	78	3.3:1
4	5 mol% AuCl ₃	0.5	95 ^[d]	1.3:1
5	5 mol% AuCl ₃	0.5	78 ^[e]	1.2:1
6	5 mol% AuCl	0.5	81	1.1:1
7	5 mol% AuCl ₃ 5 mol% AgOTf	0.5	84	1.9:1
8	5 mol% AuCl ₃ 15 mol% AgOTf	0.5	51	0:100
9	5 mol% Ph ₃ PAuCl	24	21 ^[f] (60) ^[c]	0:100
10	5 mol% Ph ₃ PAuCl 5 mol% AgOTf	3	48	0:100
11	5 mol% AgOTf	12	80	1:3.4
12	10 mol% AgOTf	3	87	1:4.1
13	15 mol% AgOTf	1.5	80	0:100

^[a] Diastereomeric ratio of **1a** = 1:1.^[b] Isolated yield. Diastereomeric ratio of **2a** = 1:1.^[c] Recovery yield of **1a**.^[d] Reaction was carried out at 0 °C.^[e] MeCN was used as the solvent.^[f] Reaction was carried out in 1,2-DCE at 75 °C.

afforded **2a** as a major compound in 60% yield together with **3a** in 18% yield (entry 3), indicating that the gold catalyst preferentially activated the terminal double bond in the allenyl group of the allenyne-1,6-diol. The cyclic compounds were obtained in 95% yield (**2a:3a** = 1.3:1) at 0 °C (entry 4). Five mol% AuCl₃-5 mol% AgOTf gave **2a** and **3a** (1.9:1) in 84% yield (entry 7). However, exposure of **1a** to 5 mol% Ph₃PAuCl in DCE selectively produced **3a** in 21% yield despite recovery of **1a** in 60% yield (entry 9). Moreover, 5 mol% AuCl₃-15 mol% AgOTf and 5 mol% Ph₃PAuCl-5 mol% AgOTf selectively furnished **3a** in 51% and 48% yields, respectively (entries 8 and 10). With these results, the use of silver salts (AgOTf, AgBF₄, AgSbF₆, and AgAsF₆) as a co-catalyst in combination with cat-gold was applied to the cyclization of **1a**, producing selectively the cyclic compound (**3a**), however in low yields. Therefore, a variety of silver catalysts were used alone for the cyclization of **1a**. Cyclization of **1a** with 5 mol% silver triflate gave **2a** and **3a** in 80% yield (1:3.4) (entry 11). Increasing the catalytic amount of silver triflate (5, 7 and 10 mol%) resulted in better selectivity. Surpris-

Table 2. Synthesis of dihydrofurans from allenyne-1,6-diols catalyzed by AuCl₃.^[a]


Entry	R	Time [h]	Yield [%] ^[b]	(2:3)
1	<i>n</i> -Propyl	b 0.08	64	4.3:1
2	<i>c</i> -C ₆ H ₁₁	c 0.16	71	2.9:1
3	Ph	a 0.16	78	3.3 ^[c] :1
4	4-Cl-C ₆ H ₄	d 0.25	88	2.7:1
5	3-MeO-C ₆ H ₄	e 0.16	89	2.2:1
6	4-MeO-C ₆ H ₄	f 0.16	68	7.5:1
7	4-Ac-C ₆ H ₄	g 0.16	85	4.0:1
8	2-Furyl	h 0.16	70	5.4:1

^[a] Reactions were carried out with 15 mol% AuCl₃ in CH₂Cl₂ (0.20 M) at 25 °C.^[b] Isolated yield.^[c] Diastereomeric ratio = 1:1.

ingly, subjecting **1a** to 15 mol% silver triflate exclusively gave **3a** in 80% yield (entry 13), indicating that silver triflate selectively activated the alkynyl group in allenyne-1,6-diol. It is noteworthy that the chemoselectivity is clearly switched by simply changing the metal from gold to silver. Other silver catalysts such as AgBF₄, AgSbF₆, and AgAsF₆ failed to produce the cyclized products. It is noteworthy that no 2-[1-(1-hydroxyphenylmethyl)propan-1,2-dienyl-1-yl]-4,5-dihydrofuran (**4a**) formed in these reactions. Dichloromethane was the best solvent among several reaction media (CH₃CN, CH₂Cl₂ and ClCH₂CH₂Cl) that were examined.

Encouraged by above results, the selective cyclization of a variety of allenyne-1,6-diols catalyzed by gold was examined and the results are summarized in Table 2. Treatment of **1b** with 15 mol% AuCl₃ gave **2b** and **3b** in 64% yield (**2b:3b** = 4.3:1) (entry 1). Compound **1c**, obtained from cyclohexanecarbaldehyde, indium, and 1,6-dibromo-2,4-hexadiyne, was transformed to dihydrofuran **2c** and furan **3c** in 71% yield (**2c:3c** = 2.9:1) under the optimum conditions (entry 2). In the case of various allenyne-1,6-diols, electronic variation of substituents such as 4-chloro, 3-methoxy, 4-methoxy, and 4-acetyl groups on the aromatic ring did not affect the efficiency and selectivity of the reactions (entries 4–7). Subjecting **1f** to 15 mol% AuCl₃ gave rise to the cyclized product **2f** as the major compound (**2f:3f** = 7.5:1) (entry 6). Allenyne-1,6-diol **1g** bearing the electron-withdrawing acetyl group produced dihydrofuran **2g** and furan **3g** in 85% yield (**2g:3g** = 4.0:1) in the presence of 15 mol% AuCl₃ (entry 7). Under the optimum condi-

Table 3. Synthesis of furans from allenyne-1,6-diols catalyzed by AgOTf.^[a]

Entry	R		Time [h]	Yield [%] ^[b]
1	<i>n</i> -Propyl	b	2.5	68
2	<i>c</i> -C ₆ H ₁₁	c	1.5	86
3	Ph	a	1.5	80
4	4-Cl-C ₆ H ₄	d	3	79
5	3-MeO-C ₆ H ₄	e	5	81 (5) ^[c]
6	4-Ac-C ₆ H ₄	g	4.5	85

^[a] Reactions were carried out with 15 mol% AgOTf in CH₂Cl₂ (0.20 M) at 25 °C.

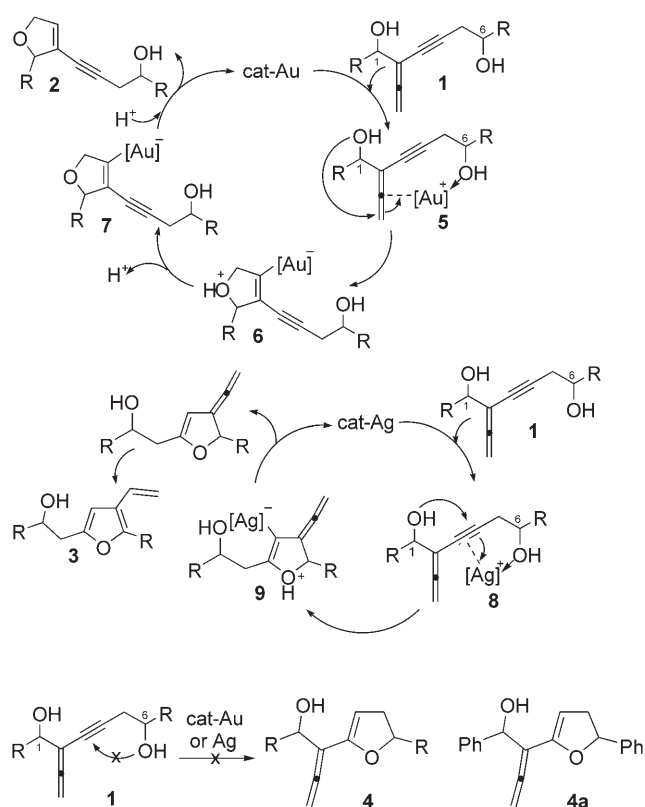
^[b] Isolated yield.

^[c] Compound **2e**.

tions, the selective cyclization of compound **1h** derived from 2-furaldehyde provided the dihydrofuran **2h** as the major compound (**2h**:**3h** = 5.4:1) (entry 8).

Next, the selective cyclization of various allenyne-1,6-diols catalyzed by silver was examined (Table 3). Exposure of **1b** to 15 mol% AgOTf selectively gave **3b** in 68% yield (entry 1). That indicates an initial activation of the alkynyl moiety, followed by the nucleophilic addition of the homoallenyl alcohol onto the resulting silver alkynyl complex. The method worked equally well with compound **1c**, producing selectively furan **3c** in 86% yield (entry 2). Varying the electron demand of the substituents (4-Cl, 3-MeO, and 4-Ac) on the aromatic ring did not diminish the efficiency and selectivity of the cyclization reactions (entries 4–6). Treatment of compound **1e** and **1g** with 15 mol% AgOTf selectively gave furans **3e** and **3g** in 81% and 85% yields, respectively (entries 5 and 6).

Although the mechanism of the cyclization reaction has not been established, a plausible reaction pathway is described in Scheme 2. The gold catalyst selectively activates the allenyl group in **1** and subsequent cyclization affords **6** to give the vinyl gold intermediate **7**. Subsequent protonation of the transient vinyl gold species **7** produces **2** and regenerates the gold catalyst to continue the catalytic cycle. However, when a catalytic amount of silver triflate is used, the alkynyl group in **1** is selectively activated and subsequent cyclization followed by isomerization provides **3** and silver catalyst to continue the catalytic cycle. As described in Table 1, Au(III) has a higher preference in the activation of allene over alkyne, while Au(I) and Ag(I) exhibited the opposite selectivity. It seems that the difference in selectivity could also originate from the charge difference of the catalysts rather than the identity of the metal itself. There is no dihydrofur-

**Scheme 2.** Mechanism of selective cyclization of allenyne-1,6-diol catalyzed by gold and silver salts.

an (**4**) formed in these reactions, indicating that the hydroxy group at the C1-position in allenyne-1,6-diol is more nucleophilic than the one at the C6-position because the hydroxy group at the C6-position might be coordinated to the gold and silver salts. More detailed mechanistic studies about the selective formation of dihydrofurans and furans are now in progress.

In summary, we have shown that treatment of allenyne-1,6-diols with gold and silver catalysts gave 2,5-dihydrofuran and furan derivatives, respectively, in good to excellent yields through the selective activation and differentiation of the double and triple bonds in the allenyne-1,6-diol. It is noteworthy that the chemoselectivity is switched by simply changing the metal from gold to silver. These results should immediately provide more opportunities for the selective synthesis of dihydrofurans or furans from the same starting materials as a function of catalyst.

Experimental Section

Typical Experimental Procedures for Intramolecular Cyclization Catalyzed by AuCl₃

AuCl₃ (9.8 mg, 0.032 mmol) was added to a solution of 1,6-diphenyl-2-vinylidenehex-3-yne-1,6-diol (63.0 mg,

0.217 mmol) in dichloromethane (1.5 mL). After the reaction mixture had been stirred for 10 min, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to give 3-(4-hydroxy-4-phenyl-1-butyn-1-yl)-2-phenyl-2,5-dihydrofuran (**2a**) (yield: 38.0 mg, 60%) using EtOAc/hexane = 1/3 (R_f = 0.3) and 5-(2-hydroxy-2-phenylethyl)-2-phenyl-3-vinylfuran (**3a**) (yield: 11.4 mg, 18%) using EtOAc/hexane = 1/5 (R_f = 0.3).

3-(4-Hydroxy-4-phenyl-1-butyn-1-yl)-2-phenyl-2,5-dihydrofuran (2a): ^1H NMR (400 MHz, CDCl_3): δ = 7.39–7.21 (m, 10H), 6.18 (s, 1H), 5.61 (s, 1H), 4.94 (dd, J = 5.99, 5.99 Hz, 1H), 4.83 (d, J = 14.4 Hz, 1H), 4.74–4.68 (m, 1H), 2.73–2.60 (m, 2H), 2.12 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): **Isomer A** δ = 142.34, 140.65, 130.80, 128.44, 128.40, 128.21, 127.89, 126.67, 125.61, 125.11, 91.17, 89.09, 75.97, 75.77, 72.30, 30.47; **Isomer B** δ = 142.30, 140.69, 130.80, 128.44, 128.40, 128.24, 127.85, 126.67, 125.68, 125.61, 91.11, 89.12, 76.08, 75.77, 72.13, 30.54; IR (film): ν = 3433, 3062, 3028, 2921, 1972, 1884, 1817, 1601, 1491 cm^{-1} ; HR-MS (EI): m/z = 290.1309, calcd. for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{M}^+$: 290.1307.

5-(2-Hydroxy-2-phenylethyl)-2-phenyl-3-vinylfuran (3a): ^1H NMR (400 MHz, CDCl_3): δ = 7.55 (d, J = 8.58 Hz, 2H), 7.43–7.34 (m, 6H), 7.32–7.27 (m, 2H), 6.84 (dd, J = 17.3, 10.8 Hz, 1H), 6.39 (s, 1H), 5.50 (d, J = 17.3 Hz, 1H), 5.20 (d, J = 10.8 Hz, 1H), 5.05 (t, J = 6.50 Hz, 1H), 3.07 (d, J = 6.5 Hz, 2H), 2.29 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 151.73, 149.39, 143.30, 131.05, 128.57, 128.52, 127.79, 127.65, 127.52, 126.54, 125.78, 121.09, 114.50, 107.35, 72.74, 38.42; IR (film): ν = 3419, 3061, 3029, 2923, 1954, 1668, 1598, 1491, 1261 cm^{-1} ; HR-MS (EI): m/z = 290.1308, calcd. for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{M}^+$: 290.1307.

Typical Experimental Procedures for Intramolecular Cyclization Catalyzed by AgOTf

AgOTf (8.4 mg, 0.032 mmol) was added to a solution of 1,6-diphenyl-2-vinylidenehex-3-yne-1,6-diol (63.0 mg, 0.217 mmol) in dichloromethane (1.5 mL). After the reaction mixture had been stirred for 1.5 h, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane = 1/5, R_f = 0.3) to give 5-(2-hydroxy-2-phenylethyl)-2-phenyl-3-vinylfuran (**3a**); yield: 51.0 mg (80%).

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