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Synthesis of 2-Cyclohexenone Derivatives via Gold(I)-Catalyzed Hydrative Cyclization of 1,6-Diynes

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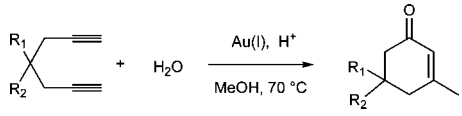
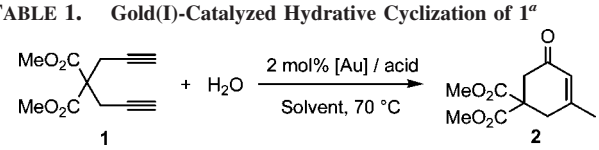


The gold(I) complex ($MeAuPPh_3$) was found to be a highly effective catalyst for the hydrative cyclization of 1,6-diynes to form the corresponding 3-methyl hex-2-enone derivatives with good to excellent yield. The proposed mechanism is described.

During the past 10 years, several research groups have developed gold-catalyzed homogeneous catalytic reactions.[1] A variety of organic transformations have been shown to be mediated by gold(I) or gold(III) complexes in solution.[2] In addition to its ability to activate alkynes and related substrates, the catalysis of nucleophilic addition by gold complexes for the formation of carbon−carbon and carbon−heteroatom bonds has been one of the most investigated reactions in modern organometallic catalysis.[3] Herein, we first report a new process of gold(I) complex in conjunction with acidic cocatalysts efficiently catalyzed hydrative cyclization of 1,6-diynes to form highly substituted cyclohexenones;[4] the latter are commonly found in natural products and biologically active molecules.[5]

TABLE 1. Gold(I)-Catalyzed Hydrative Cyclization of 1[a]



1 2

entry	cat. (2 mol %)	H_2O (mol %)	acid (mol %)	solvent	yield of **2** (%)[b]
1	***MeAuPPh₃***	***100***	***CF₃SO₃H (50)***	***MeOH***	***94 (84)***
2	$MeAuPPh_3$	50	CF_3SO_3H (50)	MeOH	42
3	$MeAuPPh_3$	—	CF_3SO_3H (50)	MeOH	0
4	$MeAuPPh_3$	200	CF_3SO_3H (50)	MeOH	25
5	$MeAuPPh_3$	100	CF_3SO_3H (20)	MeOH	76
6	$MeAuPPh_3$	100	CF_3SO_3H (50)	EtOH	60
7	$MeAuPPh_3$	100	CF_3SO_3H (50)	toluene	0
8	$MeAuPPh_3$	100	$H_3PW_{12}O_{40}$ (4)	MeOH	21
9	$MeAuPPh_3$	100	$H_3PMo_{12}O_{40}$ (4)	MeOH	5
10	$MeAuPPh_3$	100	$H_4SiW_{12}O_{40}$ (4)	MeOH	29
11	***MeAuPPh₃***	***100***	***CH₃SO₃H (50)***	***MeOH***	***96 (89)***
12	$MeAuPPh_3$	100	H_2SO_4 (50)	MeOH	44
13	$AuClPPh_3$	100	CF_3SO_3H (50)	MeOH	15
14	$NaAuCl_4$	100	CF_3SO_3H (50)	MeOH	42
15	$HAuCl_4$	100	CF_3SO_3H (50)	MeOH	23
16	$AuCl_3$	100	CF_3SO_3H (50)	MeOH	trace
17	$MeAuPPh_3$	100	—	MeOH	0
18	—	100	CH_3SO_3H (50)	MeOH	0

[a] Reactions were conducted with 0.5 mmol of **1**, 0.5 mmol of H_2O, 50 mol % of acidic additives, and 2 mol % of gold catalyst in 2.0 mL of solvent for 1 h. [b] GC yield using dodecane as an internal standard. Isolated yields are shown in parentheses.

Our initial studies focused on testing the feasibilities for the hydrative cyclization of 4-substituted 1,6-diyne, catalyzed by gold(I) salts (Table 1). In a preliminary experiment, a mixture of 4,4-(dimethoxycarbonyl)hepta-1,6-diyne (**1**, 0.5 mmol), [$(Ph_3P)AuCH_3$] (0.01 mmol, 2 mol %), trifluoromethanesulfonic acid (TfOH) (0.25 mmol, 50 mol %), and H_2O (0.5 mmol) in methanol (2 mL) was heated for 1 h at 70 °C, affording the corresponding hydrative cyclization product cyclohexenone (**2**) in 94% GC yield (entry 1), without possible hydration product diketone or methanol addition.[6,7] Structure of **2** was determined on ^1H, ^{13}C NMR, GC−mass spectrum, and elemental analysis.

We observed that formation of **2** was closely related with the amount of H_2O: when the amount of H_2O was reduced to 50 mol % or increased to 200 mol %, the yield of cyclohexenone derivative **2** became considerably lower (entries 2 and 4). Importantly, no reaction takes place in the absence of H_2O (entry 3). Different solvents were screened, and methanol was found to be the best one (entries 6 and 7). A useful yield of **2** (76%)

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(1) For recent reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (c) Arcadi, A.; Di, Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795.

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(3) (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (b) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (c) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

(4) Zhang, C.; Yao, L. Y.; Wang, B. S. ZL 2006 1 0050316.7.

(5) For examples, see: (a) Antioxidant: Braca, A.; Tommasi, N. D.; Bari, L.-D.; Pizza, C.; Politi, M.; Morelli, I. *J. Nat. Prod.* **2001**, *64*, 892. (b) Facilitate neurite outgrowth: Girlanda-Junges, C.; Keyling-Bilger, F.; Schmitt, G.; Luu, B. *Tetrahedron* **1998**, *54*, 7735.

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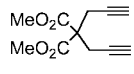
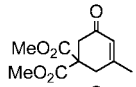
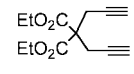
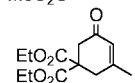
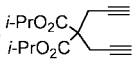
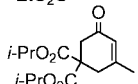
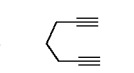
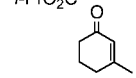
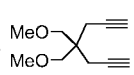
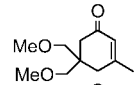
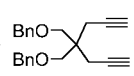
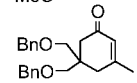
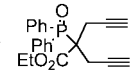
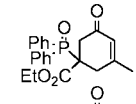
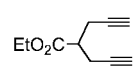
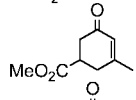
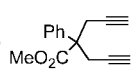
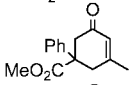
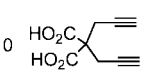
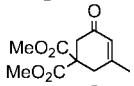
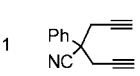
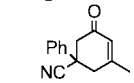
TABLE 2. Gold-Catalyzed Hydrative Cyclization Reaction of 1,6-Heptadiynes[a]

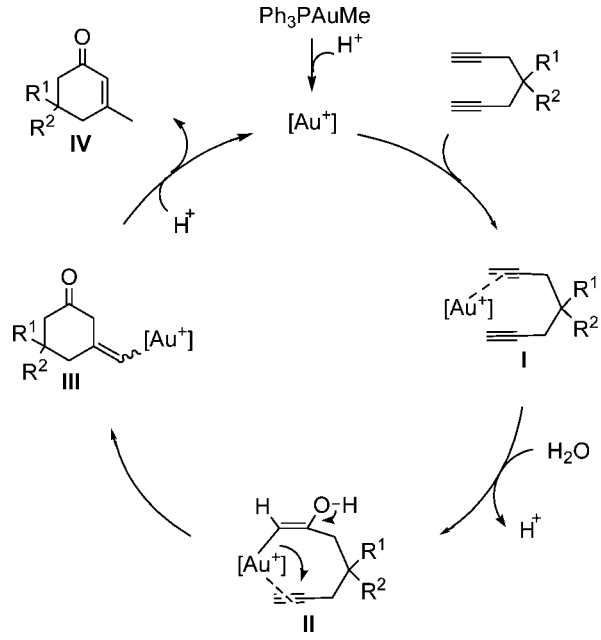
entry	1,6-diynes		product		time (h)	yield (%) [b]
1		**1**		**2**	1	89
2		**3**		**4**	1	87
3		**5**		**6**	3	87
4		**7**		**8**	10(min)	71
5		**9**		**10**	3	71
6		**11**		**12**	3	91
7		**13**		**14**	3	77
8		**15**		**16**	3	90
9		**17**		**18**	3	69
10		**19**		**2**	3	40
11		**20**		**21 + 18**	3	47 [c]

[a] All reations were performed with 0.5 mmol of substrate and H_2O, 50 μL of methanesulfonic acid, and 2 mol % of gold catalyst in 2.0 mL of MeOH at 70 °C. [b] Isolated yield. [c] **18**:**21** = 1:1.

was also obtained with 20 mol % of TfOH (entry 5). Other acid catalysts, such as heteropolyacids ($H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$) were utilized to afford **2** with lower yields (entries 8−10). Methanesulfonic acid can also play the same role as an excellent cocatalyst (entry 11). Indeed, the inorganic acid H_2SO_4, which was effective for Au(I)-catalyzed hydration of alkynes,[6,7] was used in this reaction, and the cyclic compound **2** could be observed only with 44% yield (entry 12). However, superior efficiency of $(Ph_3P)AuCH_3$ was demonstrated through a comparison with $AuClPPh_3$, $NaAuCl_4$, $HAuCl_4$, and $AuCl_3$ under the same conditions (entries 13−16). The reaction did not proceed in the absence of either the Au catalyst or proton acid (entries 17 and 18).

The scope of this hydrative cyclization process was studied, and the results are shown in Table 2. Various 4-substituted 1,6-diynes were investigated, and the hydrative cyclization proceeded in mostly good to excellent efficiencies. The 5,5-di(alkoxycarbonyl)-substituted cyclohex-2-enones (**2**, **4**, and **6**) or 5-ethoxycarbonyl cyclohex-2-enone (**16**) were isolated with high yields (entries 1−3 and 8). Alkyloxymethyl-substituted cyclohex-2-enones (**10** and **12**) were also isolated with excellent yields (entries 5 and 6). The cyclic products with different substituent group pairs, such as diphenylphosphoryl and ethoxycarbonyl (**14**), or phenyl and methoxy carbonyl (**18**), were

SCHEME 1. Proposed Catalytic Cycle for Hydrative Cyclization



obtained in good yields. The hydrative cyclization reaction of 1,6-heptadiyne (**7**) occurred rapidly under the same conditions, and 3-methyl cyclohex-2-enone (**8**) was obtained with useful yield (71%, entry 4). Only esterified product **2** was isolated from reaction of diacid 1,6-diyne **19** with 40% yield (entry 10). The possible product of intramolecular addition of carboxylic acid to alkyne was not observed.[3a] Reaction of 5-cyano-5-phenyl 1,6-diyne (**20**) with H_2O produced the corresponding cyclic product (**21**) and its esterified product (**18**) (1:1) with 47% total yield (entry 11).

The proposed catalytic cycle for hydrative cyclization is shown in Scheme 1. The gold cation coordinates with diynes to form complex **I**, H_2O attacks the gold cation chelated C≡OC band to form the intermediator **II**, and it soon isomerizes to the gold cyclohexenone complex **III** by intramolecular nucleophilic attack of the enolic ion of **II** to the Au^+-binding triple bond.[8] Then the cyclic product **IV** was released from active intermediate **III** via the metal elimination and tandem double-bond isomerization processes.

We have described a useful process of ionic gold-catalyzed hydrative cyclization of 1,6-heptadiyne to provide 3-methyl 5-substituted hex-2-enone derivatives. Efforts to explore further applications are currently in progress in our laboratory.

Experimental Section

General Process for the Cyclization Reaction: The substrate (0.5 mmol), gold catalyst (0.01 mmol, 2 mol %), MeOH (2.0 mL), methanesulfonic acid (50 μL), and H_2O (10 μL) were added to the sealed tube subsequently. The mixture was stirred at 70 °C for 0.5−3.0 h. After that, saturated aqueous $NaHCO_3$ was added to the mixture to neutralize methanesulfonic acid. The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. Solvent was evaporated under reduced pressure. Purification by the flash chromatography (petroleum/ethyl acetate) gave the expected products.

(8) For insertion of alkynes into a carbon−Au bond, see: Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 11372.

Dimethyl 3-methyl-5-oxocyclohex-3-ene-1,1-dicarboxylate (2): A colorless oil; bp 120 °C/5 mmHg; R_f 0.35 (petroleum/ethyl acetate = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (br, 1 H), 3.75 (s, 6 H), 2.90 (s, 2 H), 2.87 (s, 2 H), 2.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 170.2, 158.7, 126.2, 55.5, 53.3, 41.7, 36.3, 24.3: IR (neat, cm^{-1}) 2957, 1735, 1675, 1436, 1380, 1300, 1249, 1075, 1054; GC−MS (M^+) 226. Anal. Calcd for $C_{13}H_{18}O_5$: C, 58.40; H, 6.24. Found: C, 58.43; H, 6.25.

Diethyl 3-methyl-5-oxocyclohex-3-ene-1,1-dicarboxylate (4): A colorless oil; bp 130 °C/4 mmHg; R_f 0.5 (petroleum/ethyl acetate = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (q, J = 1.2 Hz, 1 H), 4.20 (q, J = 7.0 Hz, 4 H), 2.89 (s, 2 H), 2.86 (s, 2 H), 2.01 (d, J = 1.2 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 169.8, 158.7, 126.2, 62.2, 55.5, 41.7, 36.2, 24.3, 13.9; IR (neat, cm^{-1}) 2983, 1733, 1678, 1300, 1244, 1188, 1073, 1053, 855; GC−MS (M^+) 254. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.32; H, 7.30.

Diisopropyl 3-methyl-5-oxocyclohex-3-ene-1,1-dicarboxylate (6): A colorless oil; R_f 0.4 (petroleum/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.875 (m, 1 H), 5.04 (hept, J = 6.4 Hz, 2 H), 2.85 (s, 2 H), 2.83 (s, 2 H), 2.0 (s, 3 H), 1.23 (d, J = 6.0 Hz, 6 H), 1.21 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 169.1, 158.5, 125.9, 69.5, 55.3, 41.6, 35.9, 24.1, 21.3, 21.2; IR (neat, cm^{-1}) 2982, 2937, 1730, 1678, 1636, 1377, 1297, 1245, 1193, 1147. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.06; H, 7.89.

3-Methyl cyclohex-2-enone (8): A colorless oil; R_f 0.75 (petroleum−ethyl acetate = 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (d, J = 1.2 Hz, 1 H), 2.58−2.40 (m, 2 H), 2.36−2.28 (m 2 H), 2.09−1.98 (m, 2 H), 1.96 (d, J = 0.65 Hz, 1 H).

5,5-Bis(methoxymethyl)-3-methylcyclohex-2-enone (10): A buff oil; R_f 0.6 (petroleum/ethyl acetate = 15:1); ^{1}H NMR (400 MHz) δ 5.86 (s, 1 H), 3.30 (s, 6 H), 3.23 (s, 4 H), 2.34 (s, 2 H), 2.32 (s, 2 H), 1.94 (s, 3 H); ^{13}C NMR (100 MHz) δ 198.9, 159.8, 125.4, 77.2, 76.9, 76.6, 75.4, 59.2, 53.3, 41.6, 41.3, 34.8, 24.3; IR (neat, cm^{-1}) 2925, 1669, 1438, 1379, 1248, 1105; HRMS (ESI) calcd for $C_{11}H_{18}O_3$ 198.1256, found 221.1149.

5,5-Bis(benzyloxymethyl)-3-methylcyclohex-2-enone (12): A buff oil; R_f 0.45 (petroleum/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (m, 10 H), 5.82 (d, J = 1.2 Hz, 1 H), 4.45 (dd, J = 12.4, 4.8 Hz, 4 H), 3.36 (s, 4 H), 2.41 (s, 2 H), 2.36 (s, 2 H), 1.88 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 159.7, 138.1, 128.1, 127.4, 127.2, 125.3, 73.0, 72.7, 41.7, 41.4, 34.9, 24.2; IR ($CHCl_3$, cm^{-1}) 3030, 2858, 1666, 1496, 1453, 1363, 1249, 1206, 1093, 1027, 905. Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.33; H, 7.48.

Ethyl 1-(diphenylphosphoryl)-3-methyl-5-oxocyclohex-3-enecarboxylate (14): White solid; mp 122.3−125.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.02 (m, 2 H), 7.90−7.85 (m, 2 H), 7.69−7.47 (m, 6 H), 5.84 (s, 1 H), 3.93−3.79 (m, 2 H), 3.03−2.83 (m, 4 H), 1.92 (s, 3 H), 0.91−0.86 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4 (d, $J_{c\text{-}p}$ = 11.3 Hz), 170.8 (d, $J_{c\text{-}p}$ = 20.2 Hz), 159.2 (d, $J_{c\text{-}p}$ = 12.4 Hz), 132.2 (q, $J_{c\text{-}p}$ = 2.8 Hz), 131.9 (d, $J_{c\text{-}p}$ = 8.9 Hz), 131.6 (d, $J_{c\text{-}p}$ = 8.9 Hz), 129.0 (d, $J_{c\text{-}p}$ = 10.6 Hz), 128.3 (d, $J_{c\text{-}p}$ = 2.0 Hz), 128.2 (d, $J_{c\text{-}p}$ = 2.0 Hz), 128.0 (d, $J_{c\text{-}p}$ = 11.0 Hz), 125.6, 61.7, 60.0, 53.0 (d, $J_{c\text{-}p}$ = 57.0 Hz), 39.1, 33.9, 24.1, 20.6 (d, $J_{c\text{-}p}$ = 4.1 Hz), 13.1; ^{31}P NMR (201.7 MHz, $CDCl_3$) 30.02 (s); IR ($CHCl_3$, cm^{-1}) 2982, 1717, 1672, 1632, 1438, 1377, 1290, 1252, 1191, 1113, 1065; HRMS (ESI) calcd for $C_{22}H_{23}O_4P$ 382.1334, found 405.1219.

Methyl 3-methyl-5-oxocyclohex-3-enecarboxylate (16): A colorless oil; R_f 0.65 (petroleum/ethyl acetate = 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1 H), 3.72 (s, 3 H), 3.10−3.04 (m, 1 H), 2.67−2.51 (m, 4 H), 2.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 173.5, 160.2, 126.5, 52.1, 39.6, 38.6, 33.0, 24.2; IR ($CHCl_3$, cm^{-1}) 3018, 2954, 2848, 1735, 1668, 1437, 1380, 1344, 1246, 1197, 1047, 1025; HRMS (ESI) calcd for $C_9H_{12}O_3$ 168.0786, found 191.0682.

Methyl 3-methyl-5-oxo-1-phenylcyclohex-3-enecarboxylate (18): White solid; mp 83.0−84.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5 H), 5.93 (d, J = 1.6 Hz, 1 H), 3.64 (s, 3 H), 3.29−3.21 (m, 2 H), 2.81−2.73 (m, 2 H), 2.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 174.0, 160.4, 140.0, 128.9, 127.7, 126.5, 125.5, 52.8, 51.8, 45.1, 40.1, 24.6; IR (neat, cm^{-1}) 2977, 1725, 1666, 1499, 1431, 1380, 1327, 1287, 1260, 1191, 1072. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.58; H, 6.58.

3-Methyl-5-oxo-1-phenylcyclohex-3-enecarbonitrile (21): White solid; mp 76.5−78.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.39 (m, 5 H), 6.12 (s, 1 H), 3.01−2.90 (m, 4 H), 2.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 157.5, 137.4, 129.3,128.8.126.9, 125.5, 121.6, 46.1, 43.1, 42.1, 24.1; IR ($CHCl_3$, cm^{-1}) 2924, 2237, 1668, 1600, 1497, 1379, 1250, 1066. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.70; H, 6.22; N, 6.52.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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