

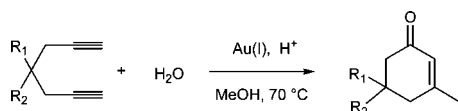
Synthesis of 2-Cyclohexenone Derivatives via Gold(I)-Catalyzed Hydrative Cyclization of 1,6-Diynes

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The gold(I) complex (MeAuPPh₃) 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

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TABLE 1. Gold(I)-Catalyzed Hydrative Cyclization of **1**^a

entry	cat. (2 mol %)	H ₂ O (mol %)	acid (mol %)	solvent	yield of 2 (%) ^b
1	MeAuPPh ₃	100	CF ₃ SO ₃ H (50)	MeOH	94 (84)
2	MeAuPPh ₃	50	CF ₃ SO ₃ H (50)	MeOH	42
3	MeAuPPh ₃	—	CF ₃ SO ₃ H (50)	MeOH	0
4	MeAuPPh ₃	200	CF ₃ SO ₃ H (50)	MeOH	25
5	MeAuPPh ₃	100	CF ₃ SO ₃ H (20)	MeOH	76
6	MeAuPPh ₃	100	CF ₃ SO ₃ H (50)	EtOH	60
7	MeAuPPh ₃	100	CF ₃ SO ₃ H (50)	toluene	0
8	MeAuPPh ₃	100	H ₃ PW ₁₂ O ₄₀ (4)	MeOH	21
9	MeAuPPh ₃	100	H ₃ PMo ₁₂ O ₄₀ (4)	MeOH	5
10	MeAuPPh ₃	100	H ₄ SiW ₁₂ O ₄₀ (4)	MeOH	29
11	MeAuPPh ₃	100	CH ₃ SO ₃ H (50)	MeOH	96 (89)
12	MeAuPPh ₃	100	H ₂ SO ₄ (50)	MeOH	44
13	AuCIPPh ₃	100	CF ₃ SO ₃ H (50)	MeOH	15
14	NaAuCl ₄	100	CF ₃ SO ₃ H (50)	MeOH	42
15	HAuCl ₄	100	CF ₃ SO ₃ H (50)	MeOH	23
16	AuCl ₃	100	CF ₃ SO ₃ H (50)	MeOH	trace
17	MeAuPPh ₃	100	—	MeOH	0
18	—	100	CH ₃ SO ₃ H (50)	MeOH	0

^a Reactions were conducted with 0.5 mmol of **1**, 0.5 mmol of H₂O, 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.

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

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), [(Ph₃P)AuCH₃] (0.01 mmol, 2 mol %), trifluoromethanesulfonic acid (TfOH) (0.25 mmol, 50 mol %), and H₂O (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, ¹³C NMR, GC–mass spectrum, and elemental analysis.

We observed that formation of **2** was closely related with the amount of H₂O: when the amount of H₂O 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 H₂O (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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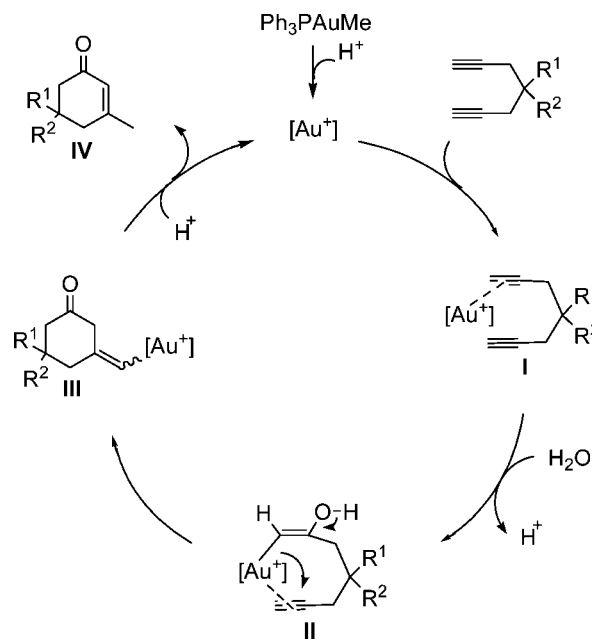
TABLE 2. Gold-Catalyzed Hydrative Cyclization Reaction of 1,6-Heptadiynes^a

entry	1,6-diynes	product	time (h)	yield (%) ^b
1			1	89
2			1	87
3			3	87
4			10(min)	71
5			3	71
6			3	91
7			3	77
8			3	90
9			3	69
10			3	40
11			3	47 ^c

^a All reactions were performed with 0.5 mmol of substrate and H₂O, 50 μ L 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 (H₃PW₁₂O₄₀, H₃PMo₁₂O₄₀, H₄SiW₁₂O₄₀) 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 H₂SO₄, 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 (Ph₃P)AuCH₃ was demonstrated through a comparison with AuClPPh₃, NaAuCl₄, HAuCl₄, and AuCl₃ 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). Alkylloxymethyl-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 H₂O 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**, H₂O attacks the gold cation chelated C≡OC band to form the intermediate **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 μ L), and H₂O (10 μ L) were added to the sealed tube subsequently. The mixture was stirred at 70 °C for 0.5–3.0 h. After that, saturated aqueous NaHCO₃ was added to the mixture to neutralize methanesulfonic acid. The mixture was extracted with ethyl acetate (3 \times 50 mL), and the combined organic layers were dried over Na₂SO₄. Solvent was evaporated under reduced pressure. Purification by the flash chromatography (petroleum/ethyl acetate) gave the expected products.

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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); ^1H 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 $\text{C}_{13}\text{H}_{18}\text{O}_5$: 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); ^1H 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 $\text{C}_{13}\text{H}_{18}\text{O}_5$: 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); ^1H 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 $\text{C}_{15}\text{H}_{22}\text{O}_5$: 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); ^1H 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); ^1H 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 $\text{C}_{11}\text{H}_{18}\text{O}_3$ 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); ^1H 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 $\text{C}_{23}\text{H}_{26}\text{O}_3$: 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; ^1H 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, $J_{\text{C-P}}$ = 11.3 Hz), 170.8 (d, $J_{\text{C-P}}$ = 20.2 Hz), 159.2 (d, $J_{\text{C-P}}$ = 12.4 Hz), 132.2 (q, $J_{\text{C-P}}$ = 2.8 Hz), 131.9 (d, $J_{\text{C-P}}$ = 8.9 Hz), 131.6 (d, $J_{\text{C-P}}$ = 8.9 Hz), 129.0 (d, $J_{\text{C-P}}$ = 10.6 Hz), 128.3 (d, $J_{\text{C-P}}$ = 2.0 Hz), 128.2 (d, $J_{\text{C-P}}$ = 2.0 Hz), 128.0 (d, $J_{\text{C-P}}$ = 11.0 Hz), 125.6, 61.7, 60.0, 53.0 (d, $J_{\text{C-P}}$ = 57.0 Hz), 39.1, 33.9, 24.1, 20.6 (d, $J_{\text{C-P}}$ = 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 $\text{C}_{22}\text{H}_{23}\text{O}_4\text{P}$ 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); ^1H 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 $\text{C}_9\text{H}_{12}\text{O}_3$ 168.0786, found 191.0682.

Methyl 3-methyl-5-oxo-1-phenylcyclohex-3-enecarboxylate (18): White solid; mp 83.0–84.0 °C; ^1H 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 $\text{C}_{15}\text{H}_{16}\text{O}_3$: 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; ^1H 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 $\text{C}_{14}\text{H}_{13}\text{NO}$: 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 ^1H 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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