Gold-catalyzed cyclo-isomerization of 1,6-diyne-4-en-3-ols to form naphthyl ketone derivatives†

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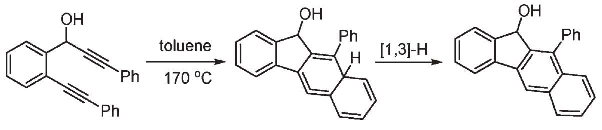
We report a new efficient gold-catalyzed cyclization of 1,6-diyne-4-en-3-ols to give naphthyl ketone derivatives under ambient conditions. The value of this cyclization is reflected by its applicability to a wide range of alcohol substrates.

Metal-catalyzed cyclo-isomerization of acyclic molecules to various cyclic frameworks is very useful in organic synthesis.[1–4] Despite intensive studies of the metal-catalyzed cyclo-isomerization of 1-en-6-ynes,[1–4] 3,5-dien-1-ynes[5,6] and endiynes[7,8] functionalities, little attention has been focused on other molecules. Saá reported that 1,6-diyne-3-ols undergo thermal intramolecular [4 + 2] cycloaddition to give benzo[*b*]fluorene derivatives;[9] this process involves initial formation of a 1,4-vinyl biradical, which then undergoes rapid intramolecular coupling to form strained cyclic allene intermediate (eqn 1). Toste and coworkers reported[10] the use of Au(I) catalysts to implement a tandem [3,3]-sigmatropic rearrangement[11]/formal Myers–Saito[12] cyclization of propargyl acetates to produce naphthyl ketones *via* generation of 2-allenyl-1-alkynylbenzene intermediates (eqn 2). We report here gold-catalyzed cyclization of 1,6-diyne-4-en-3-ols to give different naphthyl ketones *via* a new mechanism. In contrast with Toste's pathway,[10] this cyclization is presumably initiated by a OH-chelating Au(I)–π-alkyne species, which controls the regioselective hydration of the other alkyne group to complete the aromatization (eqn 3).



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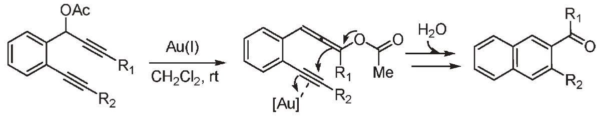

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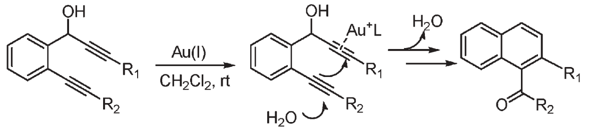
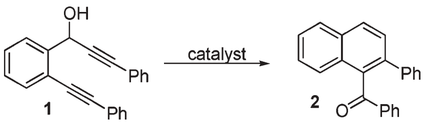


(3)

Table 1 shows a screening of the catalytic activity to cyclize 1,6-diyne-4-en-3-ol **1** using various π-alkyne activators; we observed no activity with catalysts such as AuCl, $AuCl_3$, $AuClPPh_3$, $AgSbF_6$ and $AuPPh_3SbF_6$ in CH_2Cl_2 (2%, 23 °C). In contrast, the use of $AuPPh_3OTf$ (2 mol%) in CH_2Cl_2 (23 °C) gave naphthyl ketone **2** with yield up to 85% (entry 6).‡ The presence of external water (2 equiv.) greatly decreased the yield of ketone **2** (21%). This result is expected as water can inhibit catalytic activity through coordination to the gold species. The structure of compound **2**§ was identified by X-ray diffraction.[13] $PtCl_2$ and $PtCl_2$/CO catalysts with a 2% loading are less efficient for this cyclization and gave ketone **2** in 45% and 56% yields respectively in hot toluene (100 °C, entries 8–9).

Table 1 Catalytic cycloaddition over various catalysts



Catalyst[a]	Solvent (conditions)	Yields[b]
(1) AuCl	CH_2Cl_2 (23 °C, 12 h)	N.R.[c]
(2) $AuCl_3$	CH_2Cl_2 (23 °C, 12 h)	N.R.[c]
(3) $AuClPPh_3$	CH_2Cl_2 (23 °C, 12 h)	N.R.[c]
(4) $AgSbF_6$	CH_2Cl_2 (23 °C, 12 h)	trace[d]
(5) $AuClPPh_3/AgSbF_6$	CH_2Cl_2 (23 °C, 12 h)	dec.[d]
(6) $AuClPPh_3$/AgOTf	CH_2Cl_2 (23 °C, 3 h)	85%
(7) $AuClPPh_3$/AgOTf	wet CH_2Cl_2 (23 °C, 3 h)	21%[e]
(8) $PtCl_2$	toluene (100 °C, 12 h)	45%
(9) $PtCl_2$/CO	toluene (100 °C, 12 h)	56%

[a] 2 mol% catalyst, [diyne] = 0.20 M. [b] Products were separated using a silica column. [c] Starting **1** was recovered in 90%, 89% and 93% respectively. [d] No starting substrates were recovered. [e] External water (2 equiv.) was added.

We prepared various 1,6-diyne-4-en-3-ols **3–17** to examine the generality and the scope of this cyclization; the results are depicted in Table 2. The catalytic reactions were performed using 2 mol% $AuPPh_3OTf$ in CH_2Cl_2 at 23 °C without external water. Entries 1–5 show the compatibility of this cyclization with variation of the alkynol groups of substrates **3–7** bearing R = *p*-tolyl, *p*-fluorophenyl, *p*-methoxyphenyl, methyl and butyl groups; the resulting naphthyl ketones **18–22** were obtained in 78–86% yields. The structures of compounds **19** and **20** were confirmed by ^{1}H-NOE effects.[13] A high efficiency was maintained for the gold-catalyzed cyclization of 1,6-diyne-4-en-3-ol derivatives **8–10** bearing a 4-methoxyphenyl group on their alkynes, giving expected phenyl naphthyl ketones **23A–25** in 73–81% yields with a small proportion of debenzylated products **23B** and **24B** (8–14%, entries 6–8). Furthermore, we obtained *p*-methoxybenzoic acid in 11% and 5% yields during the cyclization of alcohols **8–9** (entries 6–7). The gold-catalyzed cyclization of substrates **11–15** bearing a

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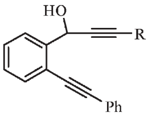
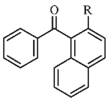
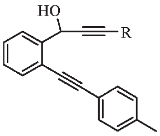
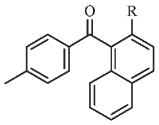
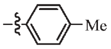
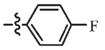
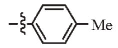
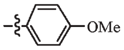
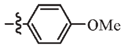
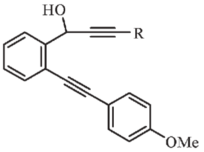
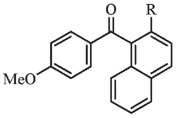
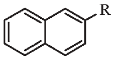
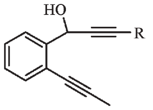
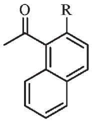
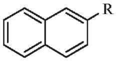
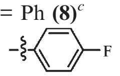
† Electronic supplementary information (ESI) available: NMR spectra, spectral data of compounds **1–32**, and X-ray structural data of compound **2**. See DOI: 10.1039/b618291g

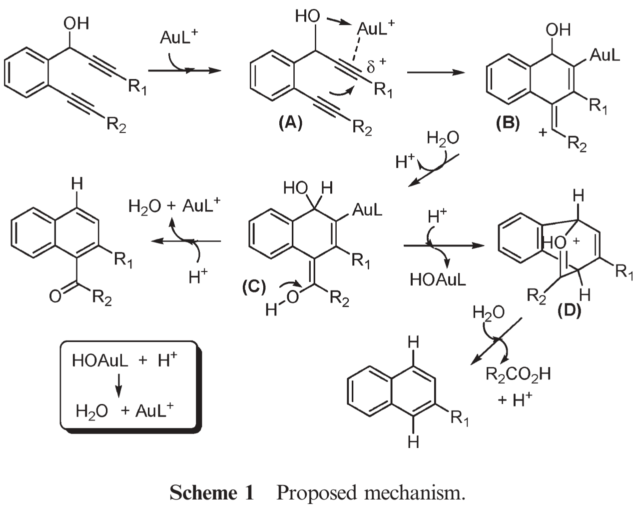
Table 2 Gold-catalyzed intramolecular cyclization of 1,6-diyne-4-en-3-ol derivatives

Substrates	Products (yields)[b]		Substrates		Products (yields)[b]
					
(1) R =  **(3)**	**18** (84%)		(9) R = Ph **(11)**		**26** (90%)
(2) R =  **(4)**	**19** (86%)		(10) R =  **(12)**		**27** (88%)
(3) R =  **(5)**	**20** (82%)		(11) R =  **(13)**		**28** (87%)
(4) R = CH_3 **(6)**	**21** (78%)		(12) R =  **(14)**		**29** (91%)
(5) R = n-Bu **(7)**	**22** (81%)		(13) R = CH_3 **(15)**		**30** (88%)
					
(6) R = Ph **(8)**[c]	**23 A** 73%	**23 B** (14%)	(14) R = CH_3 **(16)**	**31 A** (80%)	**31 B** (2%)
(7) R =  **(9)**[c]	**24 A** (80%)	**24 B** (8%)	(15) R = n-Bu **(17)**	**32** (85%)	
(8) R = CH_3 **(10)**	**25** (81%)				

[a] The reaction was performed using 1,6-diyne-4-en-3-ols **1** (1 equiv., 0.20 M) in the presence of $PPh_3AuCl/AgOTf$ (2 mol%) in dichloromethane at room temperature for 3 h. [b] Product yields are given after separation from a silica column. [c] *p*-Methoxybenzoic acid was obtained in 11% and 5% yields respectively in entries 6 and 7.

p-tolylalkynyl group produced only *p*-tolyl naphthyl ketones **26–30** without formation of by-products. This cyclo-isomerization works well with alcohol **16** bearing two propynyl groups, such that methyl naphthyl ketone **31A** was obtained with yield up to 80%. In a separate experiment, naphthyl ketone **23A** was treated with $AuPPh_3OTf$ in CH_2Cl_2 (23 °C, 120 h), from which we did not obtain its debenzylated product **23B** in the presence or absence of water. Formation of naphthalene **23B** is evidently not caused by debenzylation of species **23A**.

Scheme 1 shows our mechanistic speculation to rationalize the chemoselectivity of this gold-based catalysis. We envisage that the hydroxyl group of the alcohol substrate is to coordinate the cationic $AuPPh_3^+$ species to form π-alkyne species **A**, which preferably generates a cationic charge on the alkyne carbon adjacent to the phenyl group. This cationic charge induces a 6-*endo-dig* attack of the other alkyne group to generate highly electrophilic cationic vinylgold(I) intermediate **B**,[14] which was captured by water to form enol species **C**. An enol–ketone tautomerization of species **C**, followed by hydrodeauration and dehydroxylation, generates the observed naphthyl ketone products. According to this mechanism, a trace amount of water is sufficient for this catalytic sequence because a final step involves the release of one water. This allylic intermediate **C** enables us to propose the formation mechanism of naphthalene by-products. We envisage that this species will form oxonium species **D**, which is decomposed irreversibly by water to form naphthalene and organic acids. Yamamoto *et al.* demonstrate the feasibility of this step in a gold-catalyzed cyclization of 2-en-4-yn-1-als with alkynes.[15] Although formation of naphthalene products requires a stoichiometric amount of water, addition of excess water to this system fails to increase their yields because of its catalytic inhibition by water.



Scheme 1 Proposed mechanism.

In summary, we report an efficient gold-catalyzed cyclization of 1,6-diyne-4-en-3-ols to give naphthyl ketone derivatives under ambient conditions. The cyclization is proposed[16,17] to proceed *via* a OH-chelated Au(I)–π-alkyne species, which subsequently triggers the cyclization *via* a 6-*endo-dig* attack of the second alkyne group. The value of this cyclization is reflected by its applicability to diverse alcohol substrates. The application of this reaction mechanism to construct larger aromatic ketones is under investigation.

We wish to thank the National Science Council, Taiwan for supporting this work.

Notes and references

‡ Synthesis of phenyl(2-phenylnaphthalen-1-yl)methanone **(2)**: A solution of PPh_3AuOTf (2 mol%) was prepared by mixing PPh_3AuCl (3.2 mg, 0.006 mmol) and AgOTf (1.7 mg, 0.006 mmol) in dichloromethane (1.0 mL). To this solution was added compound **1** (100 mg, 0.32 mmol) at 25 °C, the mixture was stirred for 3 h. The resulting solution was filtered through a celite bed, and eluted through a silica gel column (ethyl acetate/hexane = 1/15) to give compound **2** (85.0 mg, 0.28 mmol, 85%) as yellow solid.

§ Crystallographic data for compound **2**: $C_{23}H_{16}O$ (M.W. = 308.36), triclinic, space group *P*-1, a = 9.3540(17) Å, b = 9.4771(18) Å, c = 10.2788(19) Å, α = 92.763(3), β = 116.301(3), γ = 91.150(3)°, V = 815.1(3) $Å^3$, Z = 2. Of the 9686 unique reflections, 4060 were considered observed with $I > 2\sigma(I)$. Final R = 0.0490 and Rw = 0.1121. The CIF file has been deposited at Cambridge Crystallographic Deposit Center with registry number CCDC 630914.

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13 ^{1}H NOE map of key compounds and X-ray data of compound **2** are provided in the Supporting Information†.

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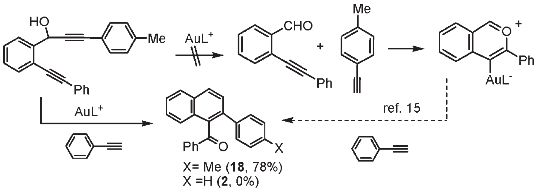
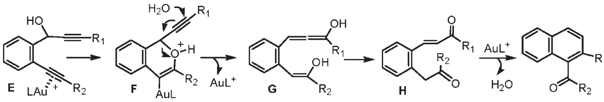
16 We have treated alcohol **3** with phenylacetylene (1.0 equiv.) in CH_2Cl_2 (25 °C) in the presence of $AuPPh_3OTf$ (3 mol%), and this condition gave only naphthyl ketone **18** in 78% yield without formation of ketone **2**. This observation suggests that the gold catalyst will not cause fragmentation of ethynyl alcohols into aldehydes and terminal alkynes, which may give the same products according



to the Yamamoto's mechanism[15].

17 As suggested by one reviewer, we cannot exclude an alternative mechanism as depicted below. In this mechanism, gold activates a 6-*endo-dig* addition of the alcohol of species **E** at its π-alkyne group to form oxacyclic species **F**, which undergoes cleavage of an ether ring to form enol **G**. A subsequent aldol-condensation of species **H** is expected to give the observed naphthyl ketones. For related references,



see: P. Dubé and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 12062.