Gold Catalysis

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Gold-Catalyzed Diastereoselective Cycloisomerization of Alkylidene-Cyclopropane-Bearing 1,6-Diynes**

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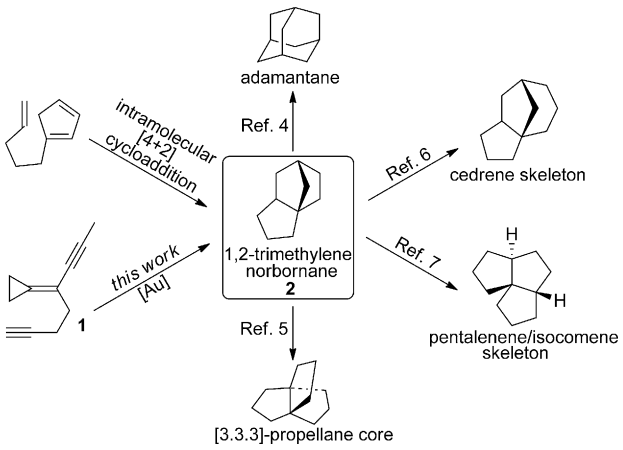
Abstract: *An unprecedented gold-catalyzed diastereoselective cycloisomerization of 1,6-diynes bearing an alkylidene cyclopropane moiety has been developed. This methodology enables rapid access to a variety of 1,2-trimethylenenorbornanes, which are important building blocks in the preparations of abiotic and sesquiterpene core structures.*

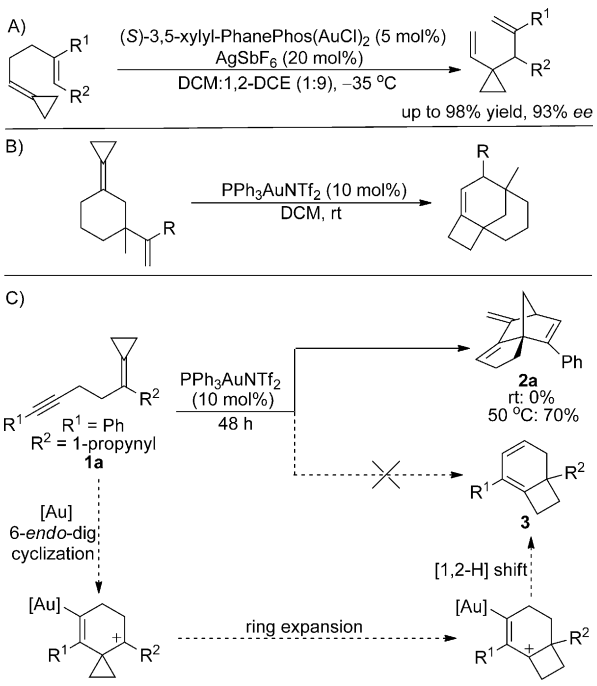
Increasing pressure on our natural resources has made sustainability a key theme in many research areas, which in turn has led to a premium being applied to methods able to generate complex target molecules in a step- and atom-economical manner.[1] Since catalysis provides the wherewithal to improve efficiency, selectivity, complexity, and rate,[2] it provides a powerful tool for the efficient construction of complex chemical architectures that would be difficult to achieve using traditional reaction schemes.[3]

Illustrative of this point is 1,2-trimethylenenorbornane **2**, a structural motif that occurs in numerous synthetic precursors to abiotic adamantanes[4] and [3.3.3]-propellanes,[5] in addition to numerous classes of sesquiterpene natural products, including the cedrenes,[6] and the pentalenene/isocomenes (Scheme 1).[7] The traditional approaches to **2** have relied on intramolecular [4+2] cycloaddition reactions,[4–7] but the laborious process for preparing the needed starting materials has limited the applicability of **2** in complex molecule synthesis. Efficient methods for the construction of the tricyclic ring system of **2** under catalyst control are thus desirable and would enable their application in synthesis. To this end, we report a gold-catalyzed, remarkably complex cycloisomerization of readily synthesized 1,6-diynes **1** to a collection of products containing the 1,2-trimethylenenorbornane core (Scheme 1).

The inherently high ring strain of alkylidene cyclopropanes (ACPs) ($\approx$40 kcal mol^{-1}) make them an especially useful and reactive class of synthetic intermediates.[8] When this strain can be released under the careful guidance of a catalyst, it is possible for this potent thermodynamic driving force to be harnessed for otherwise unfavorable reactions.[9] Taking advantage of the ring strain relief strategy, our group recently reported the first enantioselective Cope rearrangement (gold-catalyzed) from achiral 1,5-dienes (Scheme 2 A).[9b] This success led us to investigate ACP-containing cyclic 1,5-dienes and to the discovery of a ring-expanding



Scheme 1. 1,2-Trimethylenenorbornane **2** as synthetic intermediate.



Scheme 2. Gold-catalyzed: A) Enantioselective Cope rearrangement of achiral 1,5-dienes. B) Ring-expanding cycloisomerization of 1,5-dienes. C) Cycloisomerization of cyclopropylidene-bearing 1,6-diyne **1a**.

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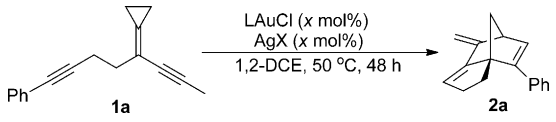
cycloisomerization that yields tricyclic compounds incorporating the bicyclo[4.2.0]oct-1-ene core (Scheme 2B).[9c] Based on this result, we reasoned that gold catalysis of ACP-bearing 1,5-enynes such as **1a**, would yield bicyclo[4.2.0] dienes (**3**) through a sequential 6-*endo*-dig-cyclization/ring expansion/net 1,2-hydrogen shift process (Scheme 2C).[10] However, when **1a** (R^2 = 1-propynyl) was treated with 10 mol% PPh_3AuNTf_2 in 1,2-dichloroethane at 50°C, the expected bicyclo product **3** was not formed. Instead, the tricyclic compound **2a** was obtained as a single diastereomer in 70% yield (48 h, Scheme 2C). DFT calculations indicated that the conversion of **1a** to **2a** was exothermic by approximately 63 kcal mol^{-1}, making the high selectivity and yield even more remarkable.[11] The structure of **2a** was elucidated by a 2D-INADEQUATE experiment (see the Supporting Information).

In the first optimization round, a number of gold catalysts were evaluated for their ability to accelerate the cycloisomerization of **1a** (entries 1–9, Table 1). The simple Lewis acid $AuCl_3$ and the common cationic gold precursor PPh_3AuCl showed almost no catalytic activity for this rearrangement (entries 1–2, Table 1). In addition, the data indicated that the ligand has a significant impact on the catalytic activity, with triaryl phosphines (entries 3, 6, and 7, Table 1) exhibiting better catalytic efficiency than trialkyl (entry 4, Table 1) and mixed aryl–alkyl phosphine ligands (entry 5, Table 1). Other ligands, including dialkyl sulfide (entry 8), and an N-heterocyclic carbene (entry 9) showed no improvements. Electron-rich triaryl phosphine ligands (entry 7) were superior to electron-poor variants (entry 6). The catalyst $(p\text{-Tol})_3PAuNTf_2$ **4**, derived from the activation of $(p\text{-Tol})_3PAuCl$ with $AgNTf_2$ provided the highest yield (entry 7, Table 1). A subsequent screen of silver salts (entries 7 and 10–12) confirmed that $AgNTf_2$ and $AgSbF_6$ provided optimal yields (entries 7 and 11). Since **4** is an air-stable white solid, this catalyst was chosen for additional optimization.

A solvent optimization study using 10 mol% **4** showed a preference for halogenated solvents (see the Supporting Information). The need for slightly elevated temperatures led to 1,2-dichloroethane (DCE) being chosen (entry 7). A screen of catalyst loadings showed that 10 mol% was preferable (entries 7, 13, and 14). Increasing the concentration of the reaction mixture had little impact on the reaction yield (entries 7 and 15). Finally, a control run in the absence of **4** led to no product formation (entry 16).

With these optimized conditions (10 mol% **4** in DCE at 50°C), the scope of substrates was explored. As shown in Table 2, a variety of aryl substitutions at R^1 were tolerated, with electron-rich through electron-poor substituents (entries 1–5, Table 2) successfully generating the expected tricyclic compounds **2a**–**2e** in good yield. Worth noting is the tolerance of the cyano group in **1f** (entry 6), which has the potential for side reactions through nitrile activation.[12] The

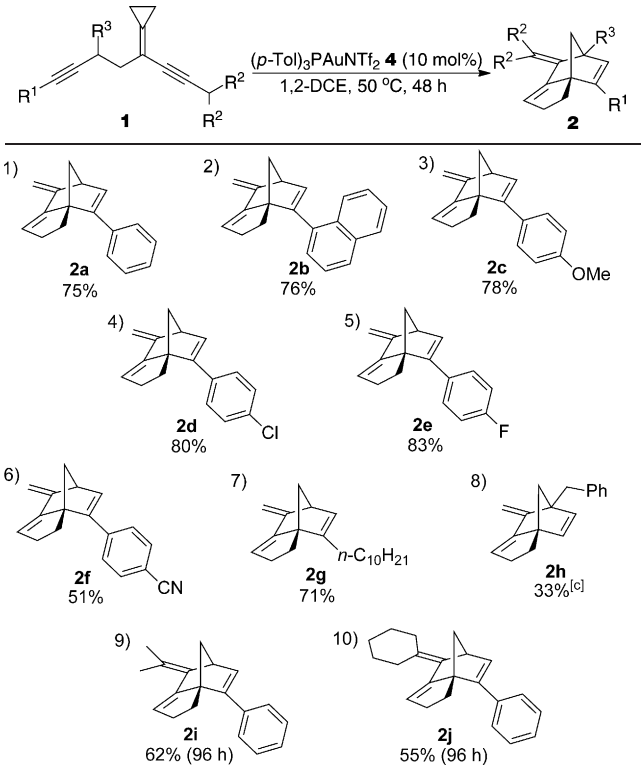
Table 1: Optimization of reaction conditions for the Au-catalyzed cycloisomerization of **1a**.[a]



Entry	LAuCl	AgX	Loading (mol%)	Yield [%][b]
1	$AuCl_3$	–	10	trace
2	Ph_3PAuCl	–	10	0
3	Ph_3PAuCl	$AgNTf_2$	10	70
4	Me_3PAuCl	$AgNTf_2$	10	17
5	(*t*BuXPhos)AuCl	$AgNTf_2$	10	52
6	$(F_5C_6)_3PAuCl$	$AgNTf_2$	10	36
7	**$(p\text{-Tol})_3PAuCl$**	**$AgNTf_2$**	**10**	**75**
8	Me_2SAuCl	$AgNTf_2$	10	complex mixture
9	(IPr)AuCl	$AgNTf_2$	10	trace
10	$(p\text{-Tol})_3PAuCl$	$AgBF_4$	10	65
11	$(p\text{-Tol})_3PAuCl$	$AgSbF_6$	10	71
12	$(p\text{-Tol})_3PAuCl$	$AgPF_6$	10	61
13	$(p\text{-Tol})_3PAuNTf_2$ (**4**)		20	74
14	$(p\text{-Tol})_3PAuNTf_2$ (**4**)		5	32[c]
15[d]	$(p\text{-Tol})_3PAuNTf_2$ (**4**)		10	72
16[e]	–		–	0

[a] Reaction conditions: LAuCl (0.01 mmol) was added to a solution of AgX (0.01 mmol) in DCE (1.0 mL) at RT. The solution was stirred at RT for 15 min and the precipitate was filtered over Celite. To the filtrate was added **1a** (22 mg, 0.1 mmol) and the resulting mixture was warmed to 50°C and stirred for 48 h. [b] Yields of **2a** purified by column chromatography. [c] The yield was not increased even if a prolonged reaction time (96 h) was employed. [d] A more concentrated reaction mixture (0.4 M) was employed. [e] Control: no gold catalyst added. IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazolidene, Tf = trifluoromethane-sulfonyl, *p*-Tol = *para*-toluenyl. XPhos = 2-dicyclohexyl-phosphino-2′,4′,6′-triisopropylbiphenyl.

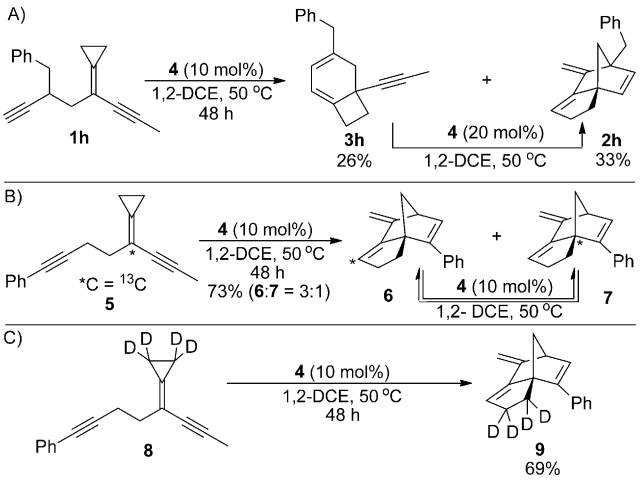
Table 2: Gold-catalyzed cycloisomerizations of 1,6-diynes **1**.[a,b]



[a] See the Experimental Section for the typical procedure. [b] Yields of isolated **2** purified by column chromatography on silica gel. [c] A yield of 28% of bicyclo[4.2.0]diene **3h** was isolated (see Scheme 1).

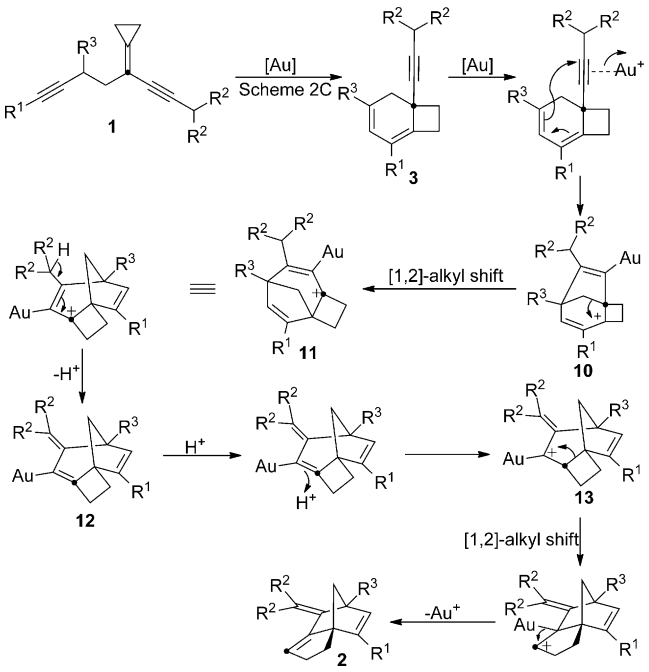
use of an aliphatic substituent in place of the aryl moiety at R^1 afforded the desired tricyclic compound, **2g**, but in a slightly lower yield (entries 1–5 versus entry 7). While a substrate bearing a terminal alkynyl group successfully rearranged to the tricyclic compound, the product was too volatile to isolate from the reaction mixture. The introduction of a benzyl group at R^3 led to the desired product, **2h**, and enabled its isolation in a synthetically useful yield (entry 8). 1,6-Diynes with sterically hindered substituents at the R^2 position were also suitable, provided a longer reaction time was employed (entries 9 and 10). In all cases, the desired tricyclic products were obtained as a single diastereomer (Table 2).

The mechanism of this cycloisomerization is undoubtedly complex, but some preliminary observations are included here.[13] When **1h**, which bears a terminal alkyne, was subjected to the optimal reaction conditions, it afforded **2h** together with the bicyclo compound **3h** (Scheme 3A). As



Scheme 3. Mechanistic investigation of the cycloisomerization of alkylidene-cyclopropane-bearing 1,6-diynes using isotopic labeling experiments.

discussed above, **3h** is reasonably generated through a sequential 6-*endo*-dig cyclization/ring expansion/net 1,2-hydrogen shift sequence from **1h** (Scheme 2C).[10] When **3h** was treated with 20 mol% **4** in DCE at 50 °C, it slowly converted into **2h** (Scheme 3A),[14] suggesting that **3h** might be an intermediate in the conversion of **1h** to **2h**. The cycloisomerization of isotopically labeled substrates, **5** and **8**, also provided beneficial mechanistic information.[15] As shown in Scheme 3B, when ^{13}C-labeled substrate **5** was treated with 10 mol% **4** in 1,2-dichloroethane at 50 °C, two isotopomers were obtained, **6** and **7**, in a 3:1 ratio. Resubjecting these purified products to the reaction conditions (10 mol% **4**, DCE, 50 °C) converged the mixture to a 1:1 ratio of **6** and **7**. Those experiments suggest that gold catalysis of **5** initially affords **6** as the kinetic product, but that a secondary process acts to interconvert these two positions in the product. Although the mechanism for interconversion of **6** and **7** is not known, this ^{13}C-labeling experiment together with the conversion of **8** to **9** (Scheme 3C) suggests a mechanism for the



Scheme 4. Proposed mechanism; the black dot denotes the movement of the ^{13}C label in **5**.

kinetically controlled phase of the cycloisomerization (Scheme 4).[13]

As mentioned in Scheme 2C, the bicyclic diene **3** is reasonably generated through a sequential 6-*endo*-dig cyclization/ring expansion/net 1,2-hydrogen shift sequence from **1**.[10] Alkyne activation of **3** by the gold complex triggers the cyclogeneration of allylic carbocation **10**, which then undergoes a 1,2-alkyl shift to afford a second allylic carbocation **11**, followed by elimination to **12**. Reactivation of **12** by H^+ generates yet another allyl cation **13**, which experiences a 1,2-alkyl shift to furnish the final product. Although alternative sequences are possible,[14] this mechanism correctly predicts the kinetic preference for **6** and the conversion of **8** to **9**.

In summary, we have developed a novel gold-catalyzed high yielding, highly diastereoselective cycloisomerization of ACP-containing 1,6-diynes leading to tricyclic compounds containing the 1,2-trimethylenenorbornane core. The reaction is highly exothermic, and yet the catalyst exercises near perfect control over the product identity and selectivity. The now straightforward synthesis of the useful 1,2-trimethylenenorbornane core should enable its applicability in complex molecule synthesis.

Experimental Section

Typical procedure for the gold-catalyzed formation of 7-methylene-4-phenyl-2,3,6,7-tetrahydro-3a,6-methanoindene (**2a**, Table 2): To a solution of **1a** (22 mg, 0.1 mmol) in DCE (1.0 mL) at RT was added (p-Tol)$_3$PAuNTf$_2$ **4** (7.8 mg, 0.01 mmol). The resulting solution was stirred at 50 °C for 48 h. Upon evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (100% hexanes) to afford **2a** (16.5 mg, 75% yield) in pure form. ^1H NMR (600 MHz, CD_2Cl_2): $\delta = 7.36$ (t, $J = 7.6$ Hz,

2H), 7.28 (t, $J=7.4$ Hz, 1H), 7.22 (d, $J=7.7$ Hz, 2H), 6.02 (d, $J=3.2$ Hz, 1H), 5.70 (t, $J=2.4$ Hz, 1H), 5.22 (s, 1H), 5.08 (s, 1H), 3.52–3.48 (m, 1H), 3.10–3.00 (m, 1H), 2.97–2.90 (m, 1H), 2.37 (ddd, $J=14.1$, 8.5, 1.9 Hz, 1H), 2.12 (d, $J=7.4$ Hz, 1H), 1.98–1.90 (m, 1H), 1.65 ppm (d, $J=7.7$ Hz, 1H). ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=$ 153.2, 150.8, 146.1, 137.2, 132.2, 128.2, 126.8, 126.2, 114.9, 103.9, 70.1, 58.8, 54.3, 38.4, 24.3 ppm. HRMS (EI) for $C_{17}H_{16}$: calcd. 220.1252, found 220.1253. **2a–2j** were similarly prepared and fully characterized (see the Supporting Information).

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[14] In practice, the conversion of **3h** to **2h** occurs considerably more slowly than the direct transformation in situ and requires 20 mol% **4**.

[15] See the Supporting Information for more details.

