

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

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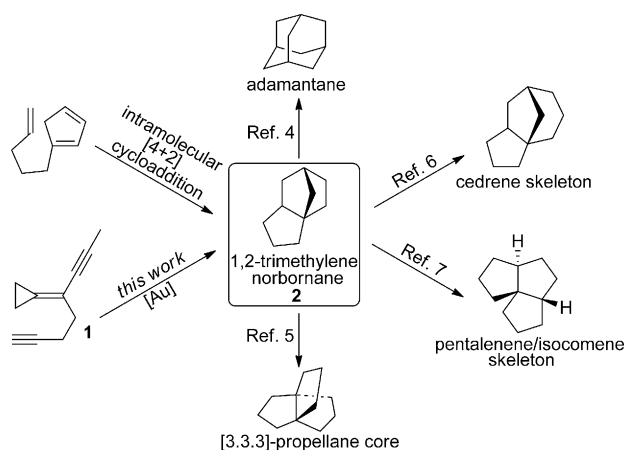
Abstract: An unprecedented gold-catalyzed diastereoselective cycloisomerization of 1,6-diynes bearing an alkylidene cyclopropane moiety has been developed. This methodology enables rapid access to a variety of 1,2-trimethylenenorbornanes, which are important building blocks in the preparations of abiotic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

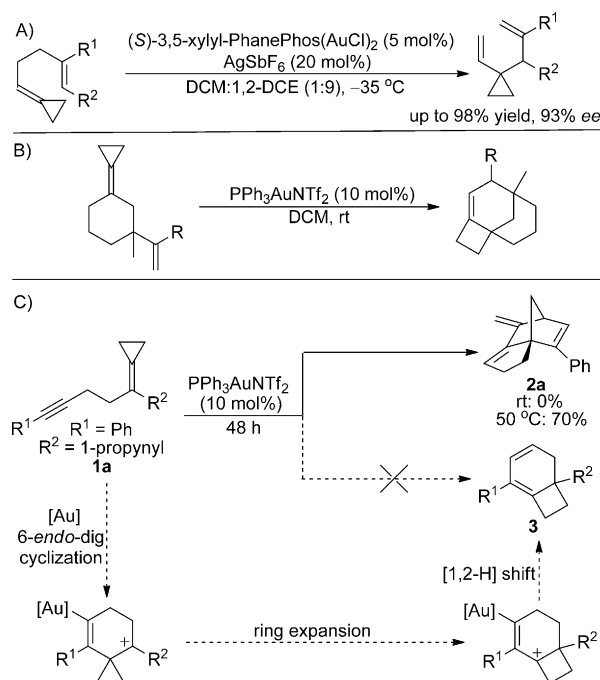
Illustrative of this point is 1,2-trimethylenenorbornane **2**, a structural motif that occurs in numerous synthetic precursors to abiotic adamantanes^[4] and [3.3.3]-propellanes,^[5] in addition to numerous classes of sesquiterpene natural products, including the cedrenes,^[6] and the pentalene/isocomenes (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) (≈ 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**.

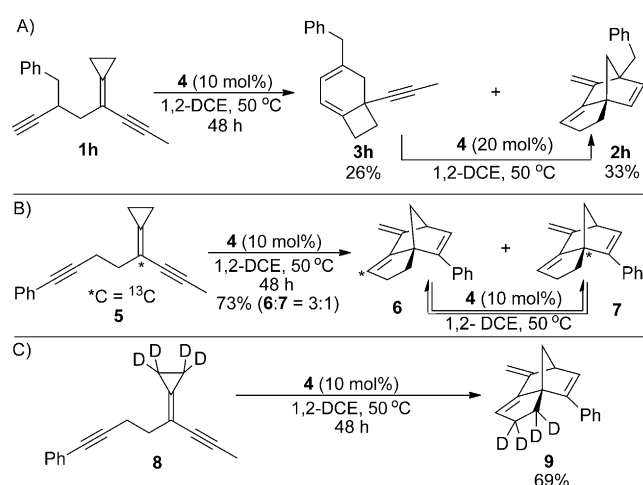
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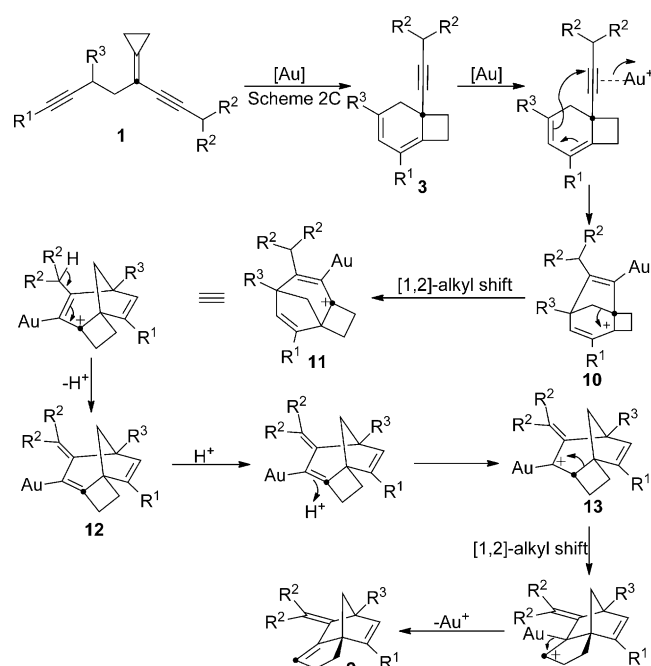
use of an aliphatic substituent in place of the aryl moiety at R^1 afforded the desired tricyclic compound, **2g**, but in a slightly lower yield (entries 1–5 versus entry 7). While a substrate bearing a terminal alkynyl group successfully rearranged to the tricyclic compound, the product was too volatile 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)₃PAuNTf₂ **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): δ = 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 $\text{C}_{17}\text{H}_{16}$: calcd. 220.1252, found 220.1253. **2a–2j** were similarly prepared and fully characterized (see the Supporting Information).

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- [15] See the Supporting Information for more details.