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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, important building blocks in the preparations of abiotic and sesquiterpene core structures.

Keywords

gold catalysis; cycloisomerization; 1, 6-diyne; cyclopropylidene; synthetic methods

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 by its nature, 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 paradigms.[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 (Figure 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 (Figure 1).

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The inherently high ring strain of alkylidene cyclopropanes (ACPs) (~40 kcal/mol) 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 unfavourable 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 (Figure 2A).[9b] This success led us to investigate ACP containing cyclic 1,5-dienes and the discovery of a ring expanding cycloisomerization that yields tricyclic compounds incorporating the bicyclo[4.2.0]oct-1-ene core (Figure 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**) *via* a sequential 6-endo-dig-cyclization/ring expansion/net 1,2-hydrogen shift process (Figure 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, Figure 2C). DFT calculations indicated that the conversion of **1a** to **2a** was exothermic by ~63 kcal/mol, making the high selectivity and yield even more remarkable.[11] The structure of **2a** was elucidated by a 2D-INADEQUATE experiment (see SI).

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 a common cationic gold precursor PPh_3AuCl showed almost no catalytic activity for this rearrangement (entries 1–2, Table 1). In addition, the data indicate that ligand has a significant impact on the catalytic activity, with triaryl phosphines (entries 3 and 6–7, 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 a *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 SI). 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 and 13–14). 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 8).

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 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 *vs* 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 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 9–10). 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 1A). As discussed above, **3h** is reasonably generated *via* a sequential 6-endo-dig cyclization/ring expansion/net 1,2-hydrogen shift sequence from **1h** (Figure 2C).[10] When **3h** was treated with 20 mol% **4** in DCE at 50 °C, it slowly converted into **2h** (Scheme 1A),[14] suggesting that **3h** might be an intermediate in the conversion of **1h** to **2h**. The cycloisomerization of isotopically labelled substrates, **5** and **8**, also provided beneficial mechanistic information.[15] As shown in Scheme 1B, 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 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 1C) suggests a mechanism for the kinetically controlled phase of the cycloisomerization (Scheme 2).[13]

As mentioned in Figure 2C, the bicyclic diene **3** is reasonably generated *via* 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 succumbs to 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 3): 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 hours. 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. ^{1}H 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): δ = 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 SI).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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14. Inpractice, the conversion of **3h** to **2h** occurs considerably more slowly than the direct transformation in situ, and requires 20 mol% **4**.
15. See SI for more details.

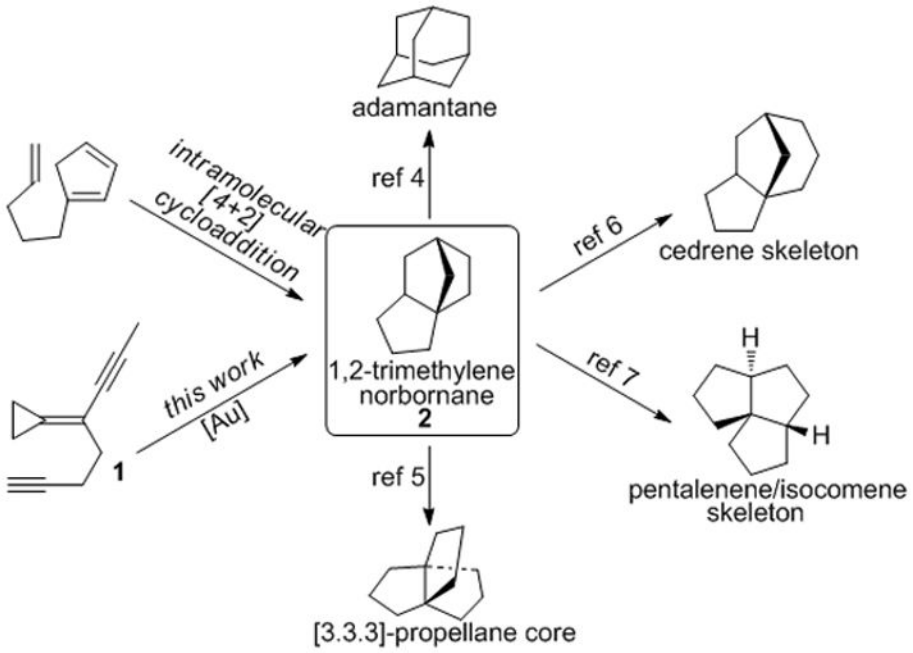


Figure 1.
1,2-Trimethylenenorbornane **2** as synthetic intermediates.

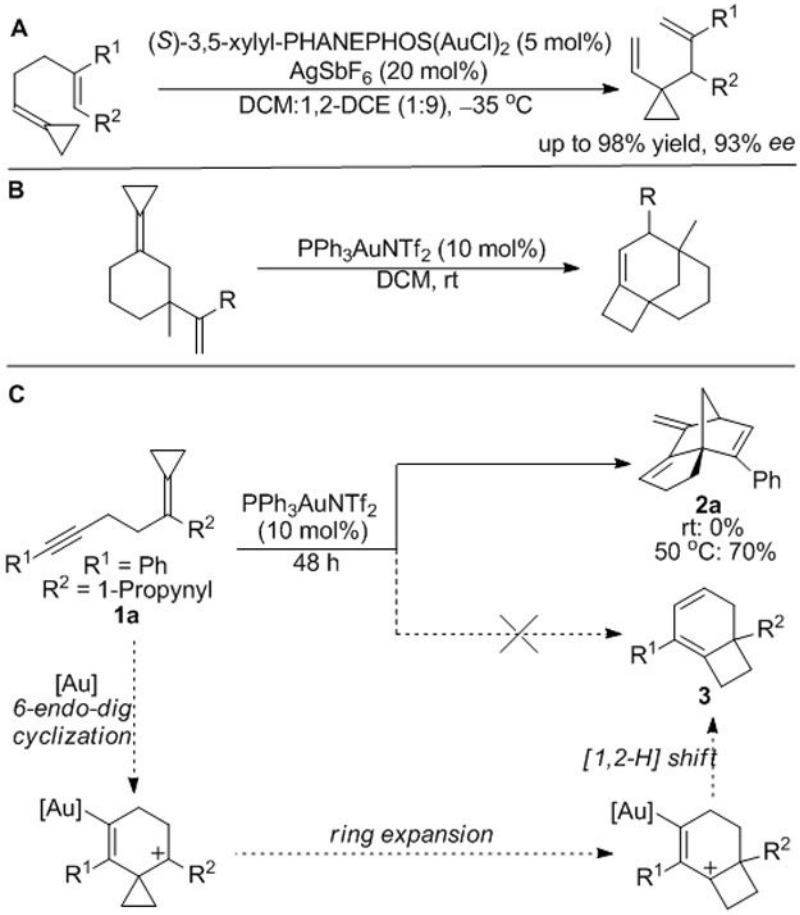
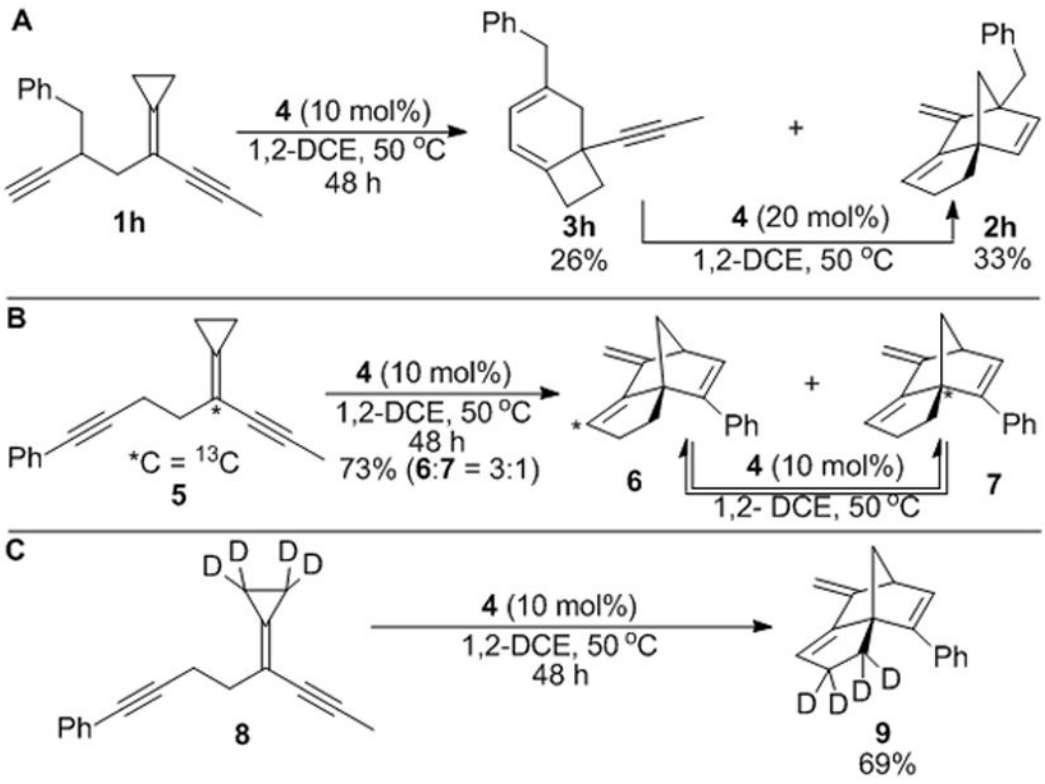


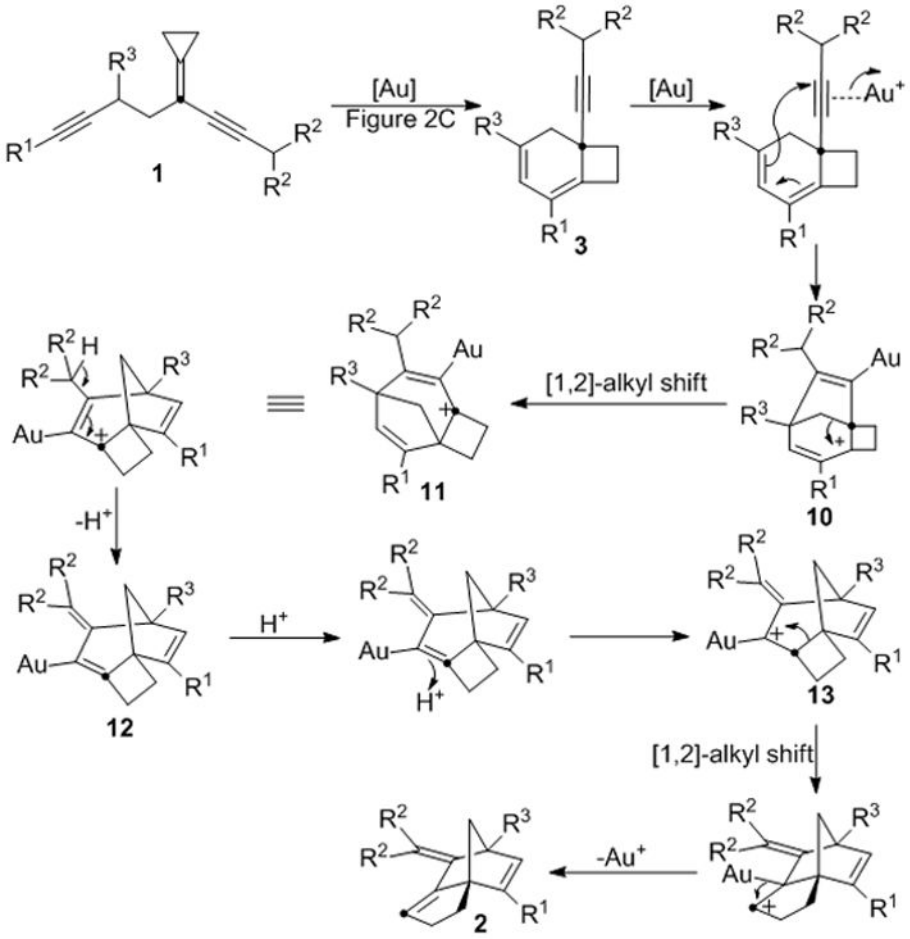
Figure 2.

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**.



Scheme 1.

Mechanistic investigation of cycloisomerization of alkylidene cyclopropane bearing 1,6-diynes using isotopic labelling experiments.

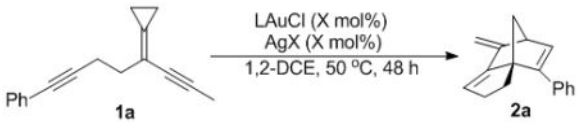


Scheme 2.

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

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*-Tol)$_3$PAuCl**	**$AgNTf_2$**	**10**	**75**
8	Me_2SAuCl	$AgNTf_2$	10	complex mixture
9	(IPr)AuCl	$AgNTf_2$	10	trace
10	(*p*-Tol)$_3$PAuCl	$AgBF_4$	10	65
11	(*p*-Tol)$_3$PAuCl	$AgSbF_6$	10	71
12	(*p*-Tol)$_3$PAuCl	$AgPF_6$	10	61
13	(*p*-Tol)$_3$PAuNTf$_2$ **4**		20	74
14	(*p*-Tol)$_3$PAuNTf$_2$ **4**		5	32[c]
15[d]	(*p*-Tol)$_3$PAuNTf$_2$ **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.

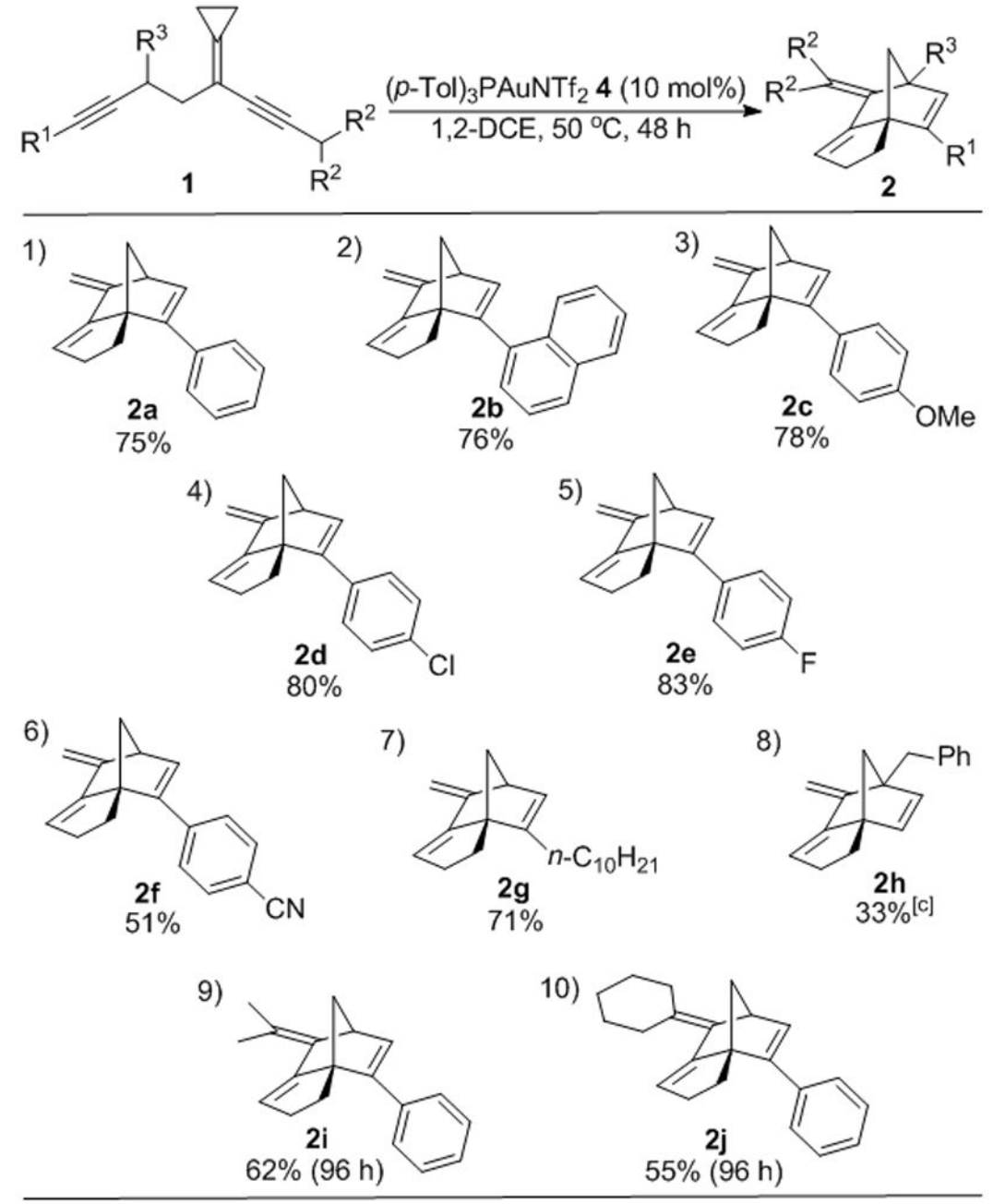
[d]A more concentrated reaction mixture (0.4 M) was employed.

[e]Control: no gold catalyst added.

IPr = 1,3-bis(2,6diisopropylphenyl)-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 experimental section for typical procedure.

[b] Yields of isolated **2** purified by column chromatography on silica gel.

[c] 28% of bicyclo[4.2.0]diene **3h** was isolated (see Scheme 1).