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Gold-Catalyzed Enantioselective Ring-Expanding Cycloisomerization of Cyclopropylidene Bearing 1,5-Enynes

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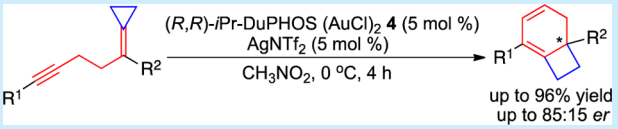
Supporting Information

ABSTRACT: An enantioselective ring-expanding cycloisomerization of 1,5-enynes bearing a cyclopropylidene moiety has been developed. This methodology provides a new approach to bicyclo[4.2.0]octanes, a structural motif present in many biologically active natural products.



Catalysis as a tool for increasing molecular complexity is crucial across the spectrum of chemical enterprises from pharmaceuticals to commodity chemicals.[1] Industry and academia alike seek organic transformations that not only produce important chemicals but do so efficiently and cost effectively.[2] In this regard, homogeneous gold catalysis is particularly powerful for the construction of complex target molecules.[3] The bicyclo[4.2.0]octane is a structural motif that occurs in a large number of natural products, e.g., Figure 1. Its

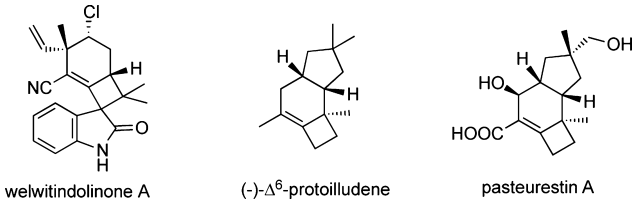


Figure 1. Natural products containing the bicyclo[4.2.0]octane core.

synthesis has therefore attracted much attention,[4] including two gold-catalyzed cycloisomerization approaches that generate a key cyclopropylmethyl carbocation intermediate:[5] one cyclo-generated from 1,6-enynes (Toste)[6] and a second from 1,7-allene-enes (Echevarren).[7] As part of a program aimed at utilizing strain relief in alkylidenecyclopropanes to drive the rearrangement of unsaturated hydrocarbons,[8] we hypothesized that easily synthesized 1,5-alkynylalkylidenecyclopropanes like **1** would efficiently yield the [4.2.0]-skeleton and further be amenable to asymmetric catalysis (Figure 2C). We now report a gold-catalyzed enantioselective ring-expanding cycloisomerization of 1,5-enynes **1** to chiral bicyclo[4.2.0]octadiene **2** (Figure 2C).

The high strain inherent in the cyclopropylidene moiety (~40 kcal/mol) underpins its utility as an important class of synthetic intermediates in organic chemistry.[9] The relief of its strain can provide a potent thermodynamic driving force for otherwise unfavorable reactions.[8,10] Taking advantage of the ring strain relief strategy, we recently reported the first gold-catalyzed enantioselective Cope rearrangement of achiral, acyclic 1,5-dienes (Figure 2A).[8a] The application of a similar

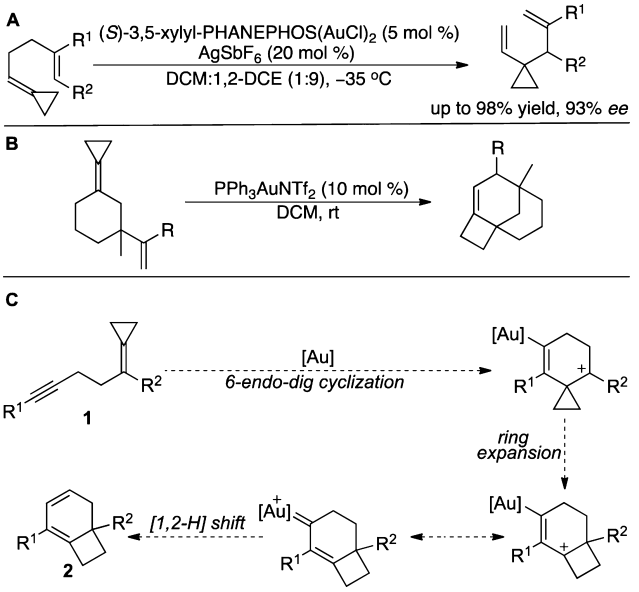


Figure 2. Gold-catalyzed (A) enantioselective Cope rearrangement of achiral 1,5-dienes; (B) ring-expanding cycloisomerization of 1,5-dienes; (C) proposed ring-expanding cycloisomerization of 1,5-enynes.

approach to cyclic 1,5-dienes led to an unexpected gold-catalyzed ring-expanding cycloisomerization and access to fused tricyclics containing the bicyclo[4.2.0]oct-1-ene core (Figure 2B).[8b] This result reasonably suggested that 1,5-enynes bearing a cyclopropylidene unit, **1**, could be coaxed to rearrange to bicyclo[4.2.0] diene **2** under gold catalysis via a sequential 6-*endo-dig* cyclization/ring expansion/net 1,2-hydrogen shift sequence (Figure 2C). DFT calculations indicated that the **1** to **2** conversion was exothermic by ~39 kcal/mol.[11]

To test the hypothesis outlined in Figure 2C, 1,5-enyne **1a** was treated with 10 mol % of $Ph_3PAuNTf_2$ in DCM. To our delight, the desired 6,4-bicyclo diene **2a** was obtained in 82% yield within 2 h (entry 1, Table 1). The versatility of this

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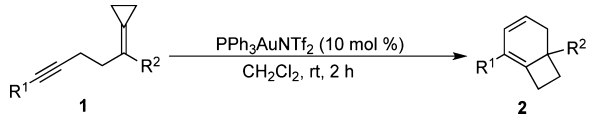
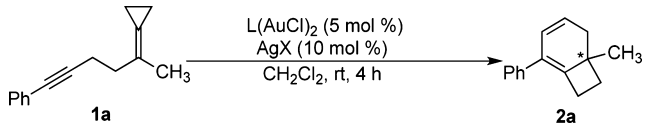
Table 1. Gold-Catalyzed Ring-Expanding Cycloisomerizations of 1,5-Enynes 1[a]



entry	enyne	R^1	R^2	product	yield[b] (%)
1	**1a**	Ph	CH_3	**2a**	82
2	**1b**	Ph	cyclopropyl	**2b**	82
3	**1c**	Ph	allyl	**2c**	87
4[c]	**1d**	Ph	vinyl	**2d**	83
5	**1e**	Ph	Ph	**2e**	90
6	**1f**	Ph	4-FC_6H_4	**2f**	81
7	**1g**	Ph	4-ClC_6H_4	**2g**	90
8	**1h**	Ph	4-$CH_3OC_6H_4$	**2h**	83
9	–[d]	Ph	H	–[d]	–[d]
10	**1i**	CH_3	Ph	**2i**	73
11[e]	**1j**	H	Ph	**2j**	50

[a]Reaction conditions: $Ph_3PAuNTf_2$ (0.01 mmol) was added to a solution of 1,5-enyne **1** (0.1 mmol) in CH_2Cl_2 (1.0 mL). The solution was stirred at rt for 2 h. [b]Yields of isolated **2** purified by column chromatography on silica gel. [c]20 mol % catalyst loading was used. [d]A complex mixture was obtained. [e]**2j** is unstable and decomposes quite rapidly at rt.

Table 2. Survey of Catalysts for the Au-Catalyzed Enantioselective Ring-Expanding Cycloisomerization of a Model 1,5-Enyne 1a[a]



entry	ligand	X^-	er[b]
1	(*S*)-xylyl-BINAP	NTf_2	57:43
2	(*R*)-C3-TUNEPHOS	NTf_2	64:36
3	(*R*)-xylyl-MeO-BIPHEP	NTf_2	65:35
4	(*R*)-DIFLUORPHOS	NTf_2	–[c]
5	(*R*)-xyl-SDP	NTf_2	56:44
6	(*R*)-DM-SEGPHOS	NTf_2	65:35
7	(*R*)-DTBM-SEGPHOS	NTf_2	61:39
8	(*R,R*)-Me-DuPHOS	NTf_2	73:27
9	**(*R,R*)-*i*-Pr-DuPHOS (4)**	**NTf_2**	**80:20[d]**
10	(*R*)-SYNPHOS	NTf_2	77:23
11	(*R*)-3,5-xylyl-PHANEPHOS	NTf_2	75:25
12	(*R,R*)-*i*-Pr-DuPHOS (4)	BF_4	–[e]
13	(*R,R*)-*i*-Pr-DuPHOS (4)	SbF_6	–[e]
14	(*R,R*)-*i*-Pr-DuPHOS (4)	PF_6	81:19[f]
15	(*R,R*)-*i*-Pr-DuPHOS (4)	OTf	–[f]

[a]Reaction conditions: $L(AuCl)_2$ (0.005 mmol) was added to a solution of AgX (0.01 mmol) in CH_2Cl_2 (1.0 mL) at rt. The solution was stirred at rt for 15 min before addition of **1a** (0.1 mmol). The resulting mixture was stirred at rt for 4 h. Unless otherwise mentioned, the reaction was complete and the GC yields of **2a** fell within the 70–85% range. [b]The er was determined by chiral stationary-phase GC, and the absolute configuration of the major enantiomer was not determined. [c]No reaction. [d]Enantioselectivity varied with the equivalents of Ag(I) salts used. Most reproducible results came with utilization of 5 mol % of $AgNTf_2$. [e]Catalyst decomposed during the reaction. [f]Significant acid-catalyzed side products were formed.

catalytic system for ring-expanding cycloisomerization was evaluated on a variety of 1,5-enynes. As shown in Table 1, variable substitution on the cyclopropylidene were tolerated, as cyclopropyl-, allyl-, vinyl-, and phenyl-substituted substrates all reacted smoothly, yielding bicyclo[4.2.0] dienes **2b–e** in excellent yields (entries 2–5, Table 1). Aryl substitution at R^2 also proceeded efficiently, with electron-poor (entries 6–7) and electron-rich substrates (entry 8) providing excellent yields of the corresponding dienes. However, when the 1,5-enyne bears a terminal cyclopropylidene, a complex mixture was obtained (entry 9, Table 1). A variety of substituents on the alkyne moiety were also tolerated (entries 10 and 11, Table 1). The use of an aliphatic substituent in place of the aryl moiety at R^1 afforded the desired bicyclo[4.2.0] diene, **2i**, but in a slightly lowered yield (entries 10 vs 5, Table 1). A substrate bearing a terminal alkynyl group also rearranged to the bicyclo[4.2.0] diene (**2j**) successfully, although **2j** was not stable and decomposed at room temperature after isolation (entry 11, Table 1). Unfortunately, 1,4-enynes were not suitable substrates, as indicated by the failure of **3** to rearrange.[12]

Given the chirality of the generated bicyclo[4.2.0]octadienes **2** and the general need for de novo methods to access all-carbon quaternary centers,[13] we embarked on the development of an enantioselective variant of this gold-catalyzed ring expanding cycloisomerization. In the first round of exploration, a number of chiral bis(gold) catalysts were evaluated for their ability to enantioselectively catalyze the ring-expanding cycloisomerization of **1a** (entries 1–11, Table 2). The catalyst derived from the activation of (*R,R*)-*i*-Pr-DuPHOS$(AuCl)_2$ **4** with $AgNTf_2$ provided the highest enantioselectivity (entry 9, Table 2). A subsequent screen of silver salts (entries 9 and 12–15) confirmed that $AgNTf_2$ was optimal in terms of yield and enantioselectivity (entry 9, Table 2). Further experimentation with the reaction in entry 9 revealed poor reproducibility, a phenomenon that was traced to the high sensitivity of the yield and enantioselectivity to the Au/Ag ratio, with the most robust conditions coming from a 1:1 ratio of **4** to $AgNTf_2$ (entry 1, Table 3). Although this silver effect is not yet understood, $AgNTf_2$ alone slowly converts **1a** to **2a**.[14]

Further optimization of reaction parameters confirmed that the use of catalyst **4** (5 mol %) and $AgNTf_2$ (5 mol %) in nitroalkane solvents provided the best reaction conditions (entries 1–4, Table 3). This catalytic system was still effective at 0 °C, affording the desired bicyclic diene **2a** in a slightly increased enantioselectivity, provided a longer reaction time was used (entries 5 and 6, Table 3). Although better enantioselectivity could be achieved at even lower reaction temperatures, the yield was sacrificed significantly due to undesired side reactions or incomplete reactions (entries 7 and 8, Table 3).

With an optimized set of reaction conditions in hand, the 1,5-enynes **1a–i** listed in Table 1 were investigated (Scheme 1). All substrates readily rearranged to the desired bicyclo dienes **2** in high yields within 4 h. Although the substituent on the cyclopropylidene moiety had only a small impact on the yield of **2**, it played an important role in the enantioselectivity of the rearrangement. As a result, the alkyl- (**2a,b**), allyl- (**2c**), and electron-rich aryl-substituted bicyclic dienes (**2h**) were obtained with good enantioselectivities; vinyl- (**2d**), phenyl- (**2e**), and electron-poor aryl-substituted bicyclic dienes (**2f,g**) gave only moderate enantioselectivities (Scheme 1).

From a mechanistic point of view,[15] the present Au(I)-catalyzed ring-expanding cycloisomerization can be rationalized as depicted in Scheme 2. π-Acid activation of the alkyne in **1a**

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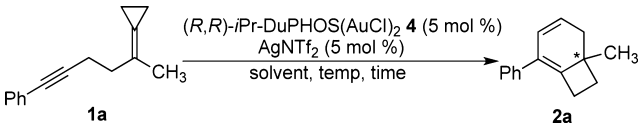
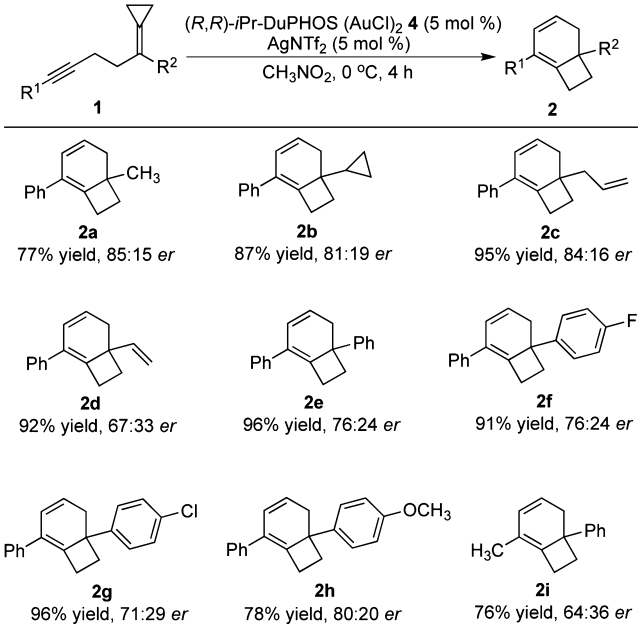
Table 3. Solvent and Temperature Optimization for the Au-Catalyzed Enantioselective Ring-Expanding Cycloisomerization of 1a[a]



entry	solvent	temp (°C)	time (h)	er[b]
1	CH_2Cl_2	rt	2	70.5:29.5
2	1,2-DCE	rt	2	79:21
3	CH_3NO_2	rt	2	83:17
4	$EtNO_2$	rt	2	81.5:18.5
5	**CH_3NO_2**	**0**	**2.5**	**85:15**
6	$EtNO_2$	0	2.5	84:16
7	$EtNO_2$	−20	6	86.5:13.5[c]
8	$EtNO_2$	−50	−[d]	91.5:8.5[c]

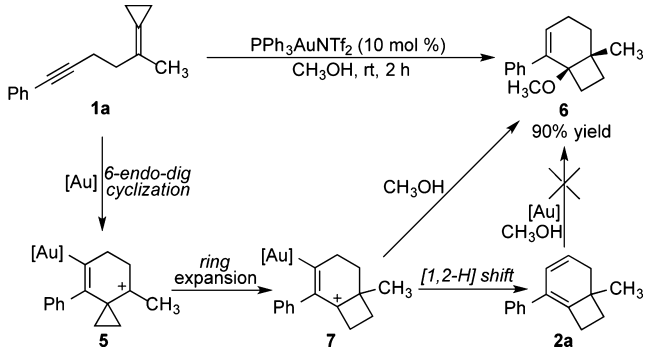
[a]Reaction conditions: **4** (0.005 mmol) was added to a solution of $AgNTf_2$ (0.005 mmol) in the indicated solvent (1.0 mL) at rt. The solution was stirred at rt for 15 min and then cooled to the indicated temperature. **1a** (0.1 mmol) was added to the above solution and the reaction stirred at the indicated temperature for the specified time. Unless otherwise mentioned, the reaction was complete and the GC yields of **2a** fell within the 70−85% range. [b]er values determined by chiral stationary-phase GC, and the absolute configuration of the major enantiomer was not determined. [c]Significant side products formed. [d]Reaction incomplete after 24 h.

Scheme 1. Gold-Catalyzed Enantioselective Ring-Expanding Cycloisomerizations of the 1,5-Enynes 1



by gold triggers a 6-*endo*-*dig*[16] cyclization that generates cyclopropylcarbinyl cation (**5**), which ring expands to the more stable allylic carbocation **7** and terminates by a net 1,2-hydrogen shift to form **2a**.[6] Consistent with this proposal, the addition of CH_3OH as an external nucleophile generates bicyclo ether **6** as a single diastereomer in 90% yield. Since **6** is not formed from a Au-catalyzed electrophilic addition of CH_3OH to **2a**, it most likely results from a trapping of **7**.[17] Compound **6** is similar in structure and stereochemistry to the russujaponol D family of natural products.[7] This mechanism

Scheme 2. Proposed Mechanism and Supporting Control Experiment for the Conversion of 1a to 2a



also suggests an explanation for the poor behavior of the unsubstituted enyne in entry 9 (Table 1), which would cyclogenerate a secondary cation in the initiating 6-*endo*-*dig* cyclization. These data point to the viability (and trapability) of allylic carbocation **7** as a reactive intermediate during the gold-catalyzed ring-expanding cycloisomerization of 1,5-enynes.

It is also intriguing to consider which elementary step in Scheme 2 is stereochemistry determining. Provided that no steps are reversible (a questionable hypothesis), good enantioselectivities suggests that the chiral catalyst may be controlling which enantiotopic cyclopropane C−C bond migrates to the adjacent carbenium ion (i.e., **5** to **7**).[18] This ring expansion sets the all-carbon quaternary center and the stereochemistry of the product.

In summary, we have developed a gold-catalyzed enantioselective ring-expanding cycloisomerization of 1,5-enynes, leading to enantioenriched bicyclo[4.2.0]octadienes in high yields and with moderate-to-good enantioselectivities. Although room remains for improvement in enantioselectivity, the present asymmetric gold catalysis represents an efficient approach to 6,4-bicyclo structures bearing a quaternary all-carbon stereocenter, a structural motif found in many biologically active natural products. Studies to apply this methodology to the total synthesis of biologically important molecules are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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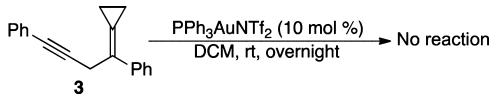
(12) The 1,4-enyne **3** was treated with PPh_3AuNTf_2 (10 mol %) in DCM, and no reaction was observed. As a result, all starting materials were recovered.



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