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Gold-Catalyzed Transannular [4+3] Cycloaddition Reactions

Benjamin W. Gung,*[a] Derek T. Craft,[a] Lauren N. Bailey,[a] and Kristin Kirschbaum[b]

Abstract: Macrocyclic propargyl acetates containing a furan ring were prepared by using a $CrCl_2$-promoted reaction. In the presence of either a Au^I or Au^{III} catalyst, a tandem 3,3-rearrangement/transannular [4+3] cycloaddition reaction occurred to give propargyl acetates that are regio- and diastereospecific. The regiochemistry of the product is controlled by the position of the acetoxy group in the starting material and the stereochemistry of the reaction depends on the ring size.

Keywords: cortistatin A · cycloaddition · fused-ring systems · gold · homogeneous catalysis

Introduction

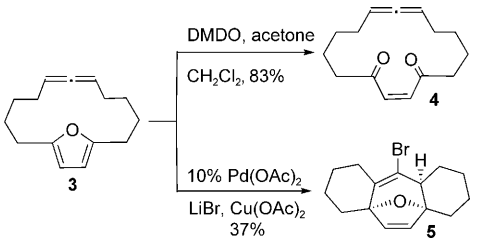
Transannular cycloaddition reactions are powerful synthetic tools for rapidly assembling multiple-ring systems in a single transformation.[1] Until recently, this methodology was limited to [4+2] cycloadditions, even though inter- and intramolecular [4+3] cycloadditions are well-established transformations.[2] Similarly, a single report of a $PtCl_2$-catalyzed transannular isomerization[3] stood in contrast to the huge number of intramolecular cycloisomerization reactions that have appeared in the last decade.[4,5]

Initially inspired by the pentacyclic structure of the potent antiangiogenesis natural product cortistatin A (**1**),[6] we were intrigued by the possibility of using a transannular [4+3] cycloaddition reaction to prepare the tetracyclic core structure (Scheme 1).

Several conditions must be met for the transannular [4+3] cycloaddition to succeed. These include the efficient preparation of the macrocyclic precursor molecule, a high yield in the transannular [4+3] cycloaddition step, and a diastereoselective bond formation process. Our initial plan was to prepare macrocyclic allenes, such as compound **3**, with a ring-closing metathesis (RCM) reaction.[7,8] The macrocyclic allene would then be selectively activated by a set of conditions to induce transannular [4+3] cycloaddition and form the central oxabicyclo[3.2.1]octene system with the simultaneous formation of two peripheral six-membered rings.

Scheme 1. Retrosynthetic analysis of the potent antiangiogenesis natural product cortistatin A (**1**).

Our initial exploratory studies led us to use the epoxidation reagent dimethyl dioxirane (DMDO) and the palladium catalyst complexes with macrocyclic allene **3** (Scheme 2).[9] The experiments were partially successful; DMDO oxidized the furan ring and afforded diketone **4** in 83% yield, but a tetracyclic product (**5**) was isolated in 37% yield when compound **3** was treated with a mixture of $[Pd(OAc)_2]$, LiBr, and $[Cu(OAc)_2]$, a catalytic system developed by Bäckvall et al.[10] The low yield of **5** prompted us to continue searching for a more efficient initiator for the transannular [4+3]



Scheme 2. Reactions of **3** with DMDO and the palladium catalyst system.

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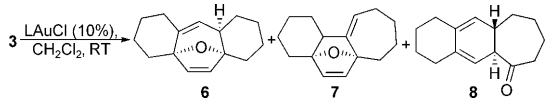
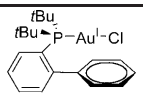
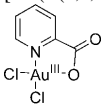
cycloaddition reaction. We provide herein the details of our investigation and the achievement of high-yield reactions.

Results and Discussion

Mascarenas et al. reported an intramolecular [4+3] cycloaddition reaction in which an allene functional group was selectively activated by a Pt or Au catalyst.[11] Their study was the first example to activate the allene function for an intramolecular [4+3] cycloaddition reaction. It was reasonable to apply this method to a transannular [4+3] cycloaddition reaction with macrocycle **3** (part of these results has appeared as a communication).[12] Therefore, we treated macrocycle **3** with several different gold salts and $PtCl_2$ and the results are shown in Table 1.

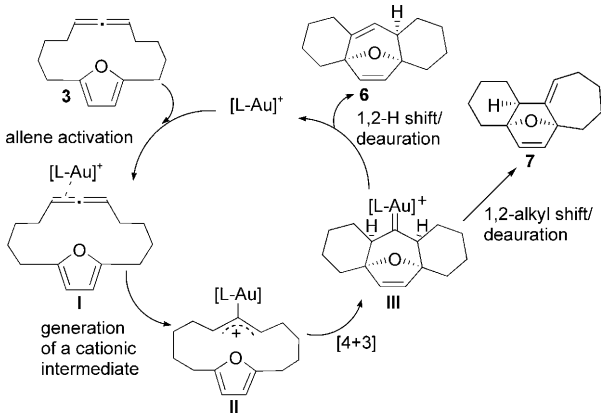
Table 1. Reactions of macrocyclic allene **3** under Au and Pt catalysis.[a]



Entry	Catalyst	*t* [d]	**6** [%]	**7** [%]	**8** [%]
1	 catalyst **9**[b]	0.3	**38**	34	0
2	$[Au(P(C_6F_5)_3)Cl]$[b]	0.1	0	0	96
3	$[Au(P(2,4,6\text{-}Ph(OMe)_3)_3)Cl]$[b]	3	no reaction		
4	 catalyst **10** (30% conversion)	5	13	16	0
5	$PtCl_2$	1	0	0	80[c]

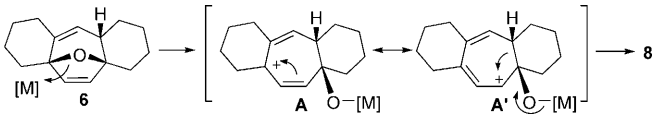
[a] Partial results have been published in reference [12]. [b] With 10% $AgSbF_6$. [c] See reference [12] for more examples.

After screening several gold and platinum complexes, Au^I catalyst **9** provided the best results in terms of promoting a transannular [4+3] cycloaddition reaction.[13] A combined yield of 72% for both the transannular [4+3] product (**6**) and a formal [4+2] cycloaddition product (**7**) were isolated.[12] Based on the latest studies of Mascarenas et al.,[14] [4+2] cycloaddition product **7** originates from a 1,2-alkyl migration of the carbenoid intermediate generated in the initial [4+3] cycloaddition. Our modified mechanism for the gold-catalyzed transannular [4+3] cycloaddition reaction of **3** is depicted in Scheme 3. The modification from our previous proposal is based on the new information reported by Mascarenas et al.[12,14] The initial activation of the allene function by the Au^I catalyst should generate cationic intermediate (**II**),[15] which undergoes a [4+3] cycloaddition reaction to give carbenoid intermediate **III**. A 1,2-hydride shift followed by elimination of the gold catalyst would produce transannular [4+3] cycloaddition product **6**. On the other hand, a 1,2-alkyl migration of the carbenoid intermediate would generate formal [4+2] cycloaddition product **7**. According to the reported DFT calculations, the transition-state energies for 1,2-alkyl and 1,2-hydride migration are similar.[14]



Scheme 3. Suggested mechanism for the Au^I-catalyzed transannular [4+3] cycloaddition reaction.

Tricyclic product **8** was isolated in high yields when either the electron-deficient Au^I complex $[AuCl\{(P(C_6F_5)_3\}]$ (Table 1, entry 2) or $PtCl_2$ was used as the catalyst. A suggested mechanism for its formation is depicted in Scheme 4.



Scheme 4. Suggested mechanism for the formation of **8**.

We believe that transannular [4+3] cycloaddition did initially occur to give product **6**. In the presence of the electron-deficient Au or Pt catalyst, tetracyclic ether **6** suffers from a C–O bond scission at the double allylic position to give tertiary allylic carbocation **A**. A 1,2-alkyl migration with concomitant ring expansion/contraction and ketone formation gives the thermodynamically more stable **8**.

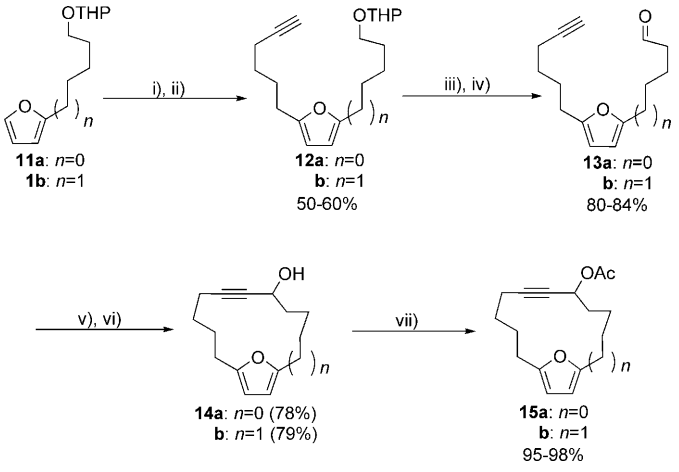
The Au^I catalyst $[AuCl\{P(2,4,6\text{-}PhOMe_3)_3\}]$ (Table 1, entry 3) with an electron-rich ligand failed to initiate any reaction. In the presence of Au^{III} catalyst **10**,[16] the reaction was sluggish and only 30% conversion of the starting material was observed after five days. Despite the encouraging results with catalyst **9**, we were dissatisfied with the competing transannular Diels–Alder reaction. Furthermore, the allene function would not provide any significant regioselectivity for a target molecule such as cortistatin A.

While our work was in progress, improved gold catalyst systems that initiate allene–diene intramolecular [4+3] cycloaddition reactions under mild conditions were reported.[14,17] However, even with the much improved conditions, the reported allene–diene [4+3] cycloaddition reactions appear to be limited to intramolecular reactions with a

three-atom tether. In all examples reported, the tether is composed of three atoms and the products are universally a seven-membered cycle fused with a five-membered ring.

With the goal of controlling regioselectivity, we sought to employ a different starting material than the allene–diene type. Because a furan moiety is necessary to provide the oxabicyclo[3.2.1]octene core structure, a different functional group is required to replace the allene as the three-carbon component. Gold-catalyzed tandem reactions of propargyl esters have been established as an efficient protocol for generating an acetyloxyallene intermediate,[15,18–28] however, a tandem 3,3-rearrangement followed by a [4+3] cycloaddition reaction sequence has not been reported. Because the $CrCl_2$-mediated reaction is known to produce a macrocyclic propargyl alcohol,[29] successful implementation of this tandem sequence would provide a powerful strategy for accessing the tetracyclic core structure of the family of cortistatins (**1**).[6]

Our study of the tandem reaction sequence begins with the preparation of the macrocyclic propargyl esters (**15a**,**b**) as shown in Scheme 5. Known monosubstituted furans



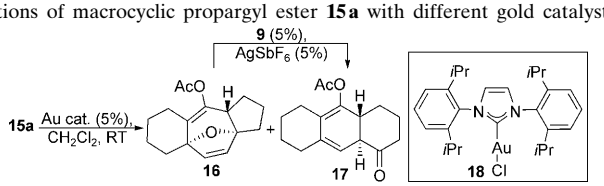
Scheme 5. Preparation of macrocycles **15a**,**b**. Conditions: i) a) BuLi, b) 1,4-dibromobutane; ii) ≡—Na, DMF (*N*,*N*-dimethylformamide); iii) TsOH, MeOH; iv) PCC (pyridinium chlorochromate), NaOAc; v) NIS (*N*-iodosuccinamide), $AgNO_3$; vi) $CrCl_2$ (10 equiv)/$NiCl_2$; vii) AcCl, pyridine.

11a,**b**[9] were converted to disubstituted furans **12a**,**b** by alkylation of 1,4-dibromobutane with the lithiated furan, followed by alkynylation of the resulting bromide. Removal of the tetrahydropyranyl ether protecting group from **12** followed by PCC oxidation gave aldehyde **13**. After iodination of the terminal alkyne, the key macrocyclization was carried out in THF with slow addition of the substrate to a suspension of $CrCl_2$ in THF to yield macrocycles **14a**,**b** in 78–79% yield for the two steps.[29] Finally the propargyl alcohols were acylated to give substrates **15a**,**b**.

The macrocyclization of alkyne–aldehydes **13a**,**b** by the $CrCl_2$-promoted reaction to prepare macrocycles **14a**,**b** is more efficient than the ring-closing allene metathesis reaction to prepare corresponding macrocyclic allene **3**.[9] It should be noted that the quality of the $CrCl_2$ reagent is very important for obtaining a high yield of the macrocyclization products because an old bottle of $CrCl_2$ gave consistently lower yields of the macrocycle.

The 13-membered macrocycle **15a** was first treated with 5% Au^I catalyst **9** (Table 2)[13] and 5% $AgSbF_6$. This led to

Table 2. Tandem 3,3-rearrangement/transannular [4+3] cycloaddition reactions of macrocyclic propargyl ester **15a** with different gold catalysts.



Entry	Catalyst	*t* [h]	**16** [%][a]	**17** [%][a]
1	**9**[b]	2	0	82
2	**10**[c]	2.5	86	0
3	**18**[b]	2	6	70

[a] Isolated yields. [b] With 5% $AgSbF_6$. [c] One equivalent of $NaHCO_3$ was added.

the isolation of tricyclic ketone **17** in 82% yield. Based on the results from the reactions of macrocyclic allene **3**,[9,11] compound **17** should be the result of a ring-opening/rearrangement from the transannular [4+3] cycloaddition product. When **15a** was treated with Au^{III} catalyst **10**,[16] transannular [4+3] cycloaddition product **16** was obtained as a single diastereomer in 86% yield. Product **17** was also obtained when **16** was treated with Au^I catalyst **9** in the presence of $AgSbF_6$, thus confirming the origins of **17**. The stereochemistry of **16** was confirmed by an X-ray structure analysis of its derivative (see Figure 1). In the presence of the Au^I catalyst with N-heterocyclic carbene ligand **18**, the reaction of **15a** gave a mixture of **16** and **17** in the ratio 1:12.

In contrast, 14-membered macrocycle **15b** underwent the transannular [4+3] cycloaddition reaction in the presence of Au^I catalyst **9** to give tetracyclic product **19** in 70% yield as a single diastereomer (Table 3). Interestingly, a mixture of **19** and **20** was isolated in a ratio of 1:3 in the presence of Au^{III} catalyst **10**. The stereochemistry of compound **19** was confirmed by X-ray structure analysis of its derivative (Figure 1). The stereochemistry of compound **20** was assigned based on two-dimensional NMR spectroscopy analysis.

Compound **20**, the major product in the Au^{III}-catalyzed reaction of **15b**, was converted to known compound **23**[12] by the sequence of reactions depicted in Scheme 6. The acetate group in compound **20** was removed and the resulting tertiary allylic alcohol was smoothly dehydrated by using Burgess[30] reagent to produce triene **21** in high yield. Complete hydrogenation produced compound **23**. However selective hydrogenation by using Wilkinson catalyst gave diene **22**, which contains the conjugated diene functionality present in the carbon core structure of cortistatins (indicated by labels A,B,C,D in **22**).[6,31] This sequence of reactions demonstrates

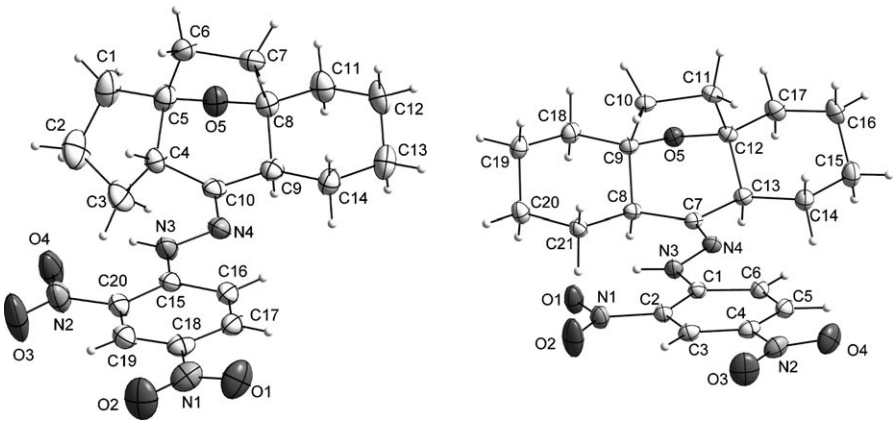
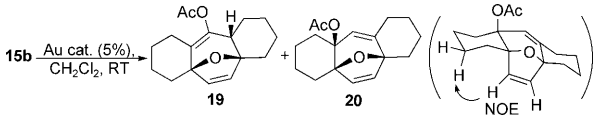


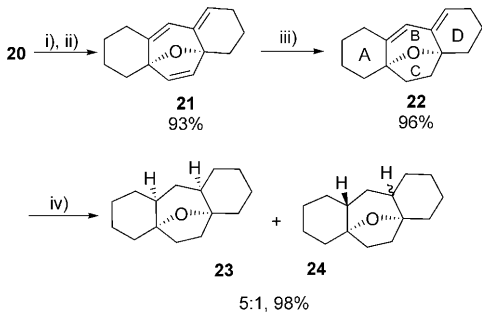
Figure 1. Crystal structures of the 2,4-dinitrophenylhydrozone derivatives of the ketones obtained from **16** (left) and **19** (right). For details, see the Supporting Information.

Table 3. Tandem 3,3-rearrangement/transannular [4+3] cycloaddition reactions of macrocyclic propargyl ester **15b** with different gold catalysts.



Entry	Catalyst	t [h]	**19** [%][a]	**20** [%][a]
1	**9**[b]	6	70	0
2	**10**[c]	48	21	64
3	**18**[b]	3	56	0

[a] Isolated yields. [b] With 5% $AgSbF_6$. [c] One equivalent of $NaHCO_3$ was added.

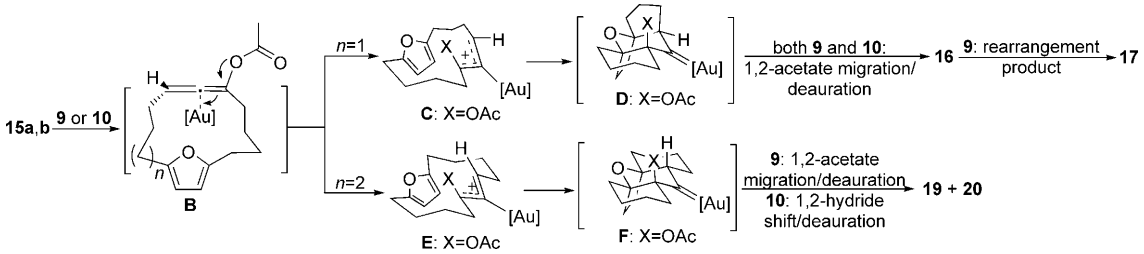


Scheme 7. Conversion of product **20** to the carbon tetracyclic core structure of cortistatin A (**22**).

itial position of the acetoxy group. The subsequent transannular [4+3] cycloadditions give gold carbenoids **D** and **F** depending on the ring size.[14] The tether length controls the stereochemistry of the attack with the following results: due to the geometric requirement of the forming tetracyclic ring, the hydrogen atom alpha to the C=Au bond should be *trans* to the furan oxygen if the forming peripheral ring is 5-membered (as in **D**) and it should be *cis* if the forming ring is 6-membered (as in **F**). Carbenoid intermediate **F** may then follow one of two major pathways depending on the characteristics of the gold catalyst. If the catalyst is cationic Au^I catalyst **9**, a 1,2-acetate migration occurs to form enol ester **19** with concomitant regeneration of **9**. This 1,2-acetoxy migration has a relatively low activation barrier.[4] Alternatively, in the presence of Au^{III} catalyst **10**, the 1,2-hydride shift to give compound **20** and regenerate **10** becomes more competitive. The process of the 1,2-hydride shift in the gold-catalyzed tandem 3,3-rearrangement/Nazarov reaction sequence has been studied computationally and it appears to have a relatively high barrier.[27] It was suggested that the presence of water molecules lower the activation barrier. Carbenoid intermediate **D** can only undergo a 1,2-acetate migration to form enol ester **16**

the synthetic potential of the transannular [4+3] cycloaddition reactions. Hydrogenation of **22** by using palladium on carbon gave compound **23** and a small amount of diastereomers **24**.[12]

A synchronous *exo*-like (extended) transition state has been proposed for the intramolecular allene-diene [4+3] cycloaddition reaction.[14] Judging from the stereochemistry of products **16** and **19**, an *endo*-like (compact) transition state is more likely for the transannular [4+3] cycloaddition reaction (Scheme 7). Each propargylic ester **15a**,**b** undergoes an initial gold-catalyzed 3,3-rearrangement to form carboxyallene **B**, which should be further activated by the same gold catalyst in situ to generate Au–allyl cations **C** and **E**.[18] The regiochemistry of the final products is determined by the in-



Scheme 6. Proposed mechanism to account for the observed reaction manifold and product stereochemistry. Conditions: i) K_2CO_3, MeOH; ii) Burgess reagent, C_6H_6, 50 °C; iii) $[RhCl(PPh_3)]$, H_2, C_6H_6; iv) H_2, Pd/C.

because the alpha CH bond is almost co-planar with the C=Au bond. In the presence of a cationic Au^I catalyst, such as **9**, compound **16** undergoes ether ring opening and rearrangement to give **17** in 82% yield according to a mechanism similar to that illustrated in Scheme 2. This was confirmed by treating compound **16** with **9** at room temperature for 2 h; a complete conversion to **17** was observed. Molecular mechanics (MMFFs)[32] calculations indicate that **16** is under greater strain than **19**, which explains why compound **16** rearranges to **17** under Au^I catalysis whereas compound **19** is stable under the same conditions. It is remarkable that any changes to the structure of the substrate and/or the catalyst will lead to a different reaction manifold. One can take advantage of the versatility of the gold-catalyzed transannular [4+3] cycloaddition reactions to produce desired target compounds.

Conclusions

In summary, a highly regio- and diastereoselective transannular [4+3] cycloaddition reaction has been realized by using macrocyclic propargyl esters with gold catalysis. The utility of this methodology is reflected by the possibility of synthesizing the core structures of biologically important natural products that have a multiple-ring structure, such as cortistatin A.[6] It is worth noting that macrocyclic propargyl acetates **15a**,**b** exclusively undergo transannular [4+3] cycloaddition reactions. This is in contrast to macrocyclic allene **3**,[12] which gave a nearly 1:1 ratio of the transannular [4+3] product and a formal [4+2] cycloaddition product (Table 1). The difference between the substrates suggests that the gold carbenoid intermediates (**D** and **F**) generated from propargyl esters are more suitable for [4+3] cycloaddition reactions than the corresponding Au–carbenoids generated from allenes. Whereas a 1,2-acetoxy migration occurs preferentially in intermediates such as **D** and **F**, a 1,2-alkyl migration would compete strongly in intermediates generated from allenes such as **3**. As a consequence, macrocyclic propargyl acetates **15a**,**b** exclusively give the transannular [4+3] cycloaddition products in the presence of gold catalysts **9** or **10**, whereas macrocyclic allene **3** gave a mixture of [4+3] and formal [4+2] cycloaddition products.

Experimental Section

Transannular [4+3] cycloaddition product (16): Dichloro(2-pyridinecarboxylato)gold **10** (2 mg, 5 μmol) and sodium bicarbonate (8.0 mg, 95 μmol) were added to a flask containing CH_2Cl_2 (1.0 mL) under a nitrogen atmosphere at room temperature. Macrocycle **15a** (27.0 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was then added dropwise with stirring. At 2.5 h, TLC showed that no starting material remained and the reaction was diluted with diethyl ether and filtered through Celite. The solvent was evaporated and the residue was purified on silica gel (5–10% EtOAc/hexane) to give cycloadduct **16** (23.3 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22, 1.31 (m, 2H), 1.43–1.50 (m, 1H), 1.63–1.69 (m, 1H), 1.76–1.94 (m, 6H), 2.01–2.04 (m, 3H), 2.11 (s, 3H), 2.58–2.62 (m, 1H), 3.09–3.13 (m, 1H), 5.75–5.76 (d, J = 6 Hz, 1H), 6.90–6.91 ppm (d, J = 6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 20.2, 20.4, 23.5, 24.0, 24.5, 30.6, 32.0, 47.8, 86.5, 90.9, 129.0, 131.3, 140.0, 144.7, 168.9 ppm; HRMS: m/z calcd for $C_{16}H_{20}O_3Na$: 283.1310; found: 283.1304.

Transannular [4+3] cycloaddition product (19): Gold(I) catalyst **9** (9 mg, 17 μmol) and silver hexafluoroantimonate (6 mg, 17 μmol) were added to a flask under a nitrogen atmosphere at room temperature, degassed three times, and purged with nitrogen for fifteen minutes before addition of dry methylene chloride (1 mL). A solution of **15b** in dry methylene chloride (1 mL) was added dropwise to the flask with stirring. After 6 h, the reaction was diluted with diethyl ether and filtered through a pad of silica and Celite. The ethereal layers were concentrated and the residue was purified by using silica gel chromatography (10% EtOAc/hexane) to give the product as a white solid (35 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96–1.06 (m, 1H), 1.24–1.47 (m, 4H), 1.51–1.61 (m, 2H), 1.66–1.98 (m, 8H), 2.10 (s, 3H), 2.45–2.49 (m, 1H), 2.71 (1H, d, J = 13.3 Hz), 5.97 (d, J = 5.85 Hz, 1H), 6.78 ppm (d, J = 5.85 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 23.1, 23.4, 24.0, 24.2, 24.3, 25.9, 32.1, 34.9, 46.6, 83.6, 86.1, 129.2, 129.9, 139.5, 143.2, 168.7 ppm; FTIR (neat): $\tilde{\nu}$ = 3079, 2940, 2932, 2865, 2853, 1748, 1671, 1444, 1370, 1210, 1178, 1160, 1143, 1120, 1054, 1040, 1018, 971, 944, 897, 887, 822, 755, 745 cm^{-1}; HRMS: m/z calcd for $C_{17}H_{22}O_3Na$: 297.1467; found: 297.1461 [M+Na].

Transannular [4+3] cycloaddition product (20): Dichloro(2-pyridinecarboxylato)gold **10** (9.4 mg, 24 μmol) and sodium bicarbonate (40 mg, 0.47 mmol) were added to a flask containing CH_2Cl_2 (3.7 mL) under a nitrogen atmosphere at room temperature. Macrocycle **15b** (0.13 g, 0.47 mmol) in CH_2Cl_2 (1.0 mL) was then added dropwise with stirring. After 2 d, TLC showed that no starting material remained and the reaction was diluted with diethyl ether and filtered through Celite. The solvent was evaporated and the residue was purified on silica gel (5–10% EtOAc/hexane) to give cycloadducts **20** (83 mg, 64%) and **19** (27 mg, 21%).

*Cycloadduct **20***: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28–1.40 (m, 3H), 1.58–1.69 (m, 4H), 1.75–1.89 (m, 5H), 1.98 (s, 3H), 2.04–2.10 (m, 2H), 2.24–2.30 (m, 1H), 2.84–2.87 (m, 1H), 5.64–5.65 (d, J = 2.5 Hz, 1H), 5.69–5.70 (d, J = 6 Hz, 1H), 6.70–6.71 ppm (d, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 21.5, 22.2, 23.6, 24.8, 30.9, 31.1, 31.4, 32.2, 79.4, 85.5, 87.2, 119.2, 134.1, 142.3, 145.8, 170.1 ppm; HRMS: m/z calcd for $C_{17}H_{22}O_3Na$: 297.1467; found: 297.1473 [M+Na].

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