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Gold-Catalyzed Transannular [4+3] Cycloaddition Reactions

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Abstract

Macrocyclic propargyl acetates containing a furan ring were prepared using the CrCl₂-promoted reaction. In the presence of either a Au(I) or a Au(III) catalyst, a tandem 3,3-rearrangement-transannular [4+3] cycloaddition reaction occurred to provide multiple fused ring systems. The transannular [4+3] cycloaddition reactions of the macrocyclic propargyl acetates 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.

Introduction

Transannular cycloaddition reactions are powerful synthetic tools to rapidly assemble 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 PtCl₂-catalyzed transannular isomerization^[3] stood in contrast to the huge number of intramolecular cycloisomerization reactions 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 about the possibility of a transannular [4+3] cycloaddition reaction to prepare the tetracyclic core structure (Figure 1).

Several conditions must be met in order for the transannular [4+3] cycloaddition to succeed. These include the efficient preparation of the macrocyclic precursor molecule, a high yield of 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 for the transannular [4+3] cycloaddition to occur and to form the center oxabicyclo [3.2.1]octene system with the simultaneous formation of two peripheral six-membered rings.

Our initial exploratory studies led us to use the epoxidation reagent dimethyl dioxirane (DMDO) and the palladium catalyst complexes on the macrocyclic allene **3** (Scheme 1).^[9] The experiments were partially successful, DMDO oxidized the furan ring and afforded the diketone **4** in 83% yield, but a 37% yield of a tetracyclic product (**5**) was isolated when compound **3** was treated with a mixture of Pd(OAc)₂, LiBr, and Cu(OAc)₂, a catalytic system developed by Backvall.^[10] The low yield of **5** prompted us to continue searching for

a more efficient initiator for the transannular [4+3] cycloaddition reaction. We now provide the details of our investigation and the achievement of high yielding reactions.

Results and Discussion

Mascarenas and co-workers reported an intramolecular [4+3] cycloaddition reaction, in which an allene functional group was selectively activated by 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 employ this method to the transannular [4+3] cycloaddition reaction with the macrocycle **3** (part of the results has appeared as a communication).^[12] We therefore treated macrocycle **3** with several different gold salts and PtCl_2 and the results are shown in Table 1.

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

The tricyclic product **8** was isolated in high yield when either the electron-deficient Au(I) complex ($[\text{Au}(\text{P}(\text{C}_6\text{F}_5)_3)\text{Cl}]$, entry 2) or PtCl_2 was used as the catalyst. A suggested mechanism for its formation is depicted in Scheme 2. We believe the transannular [4+3] cycloaddition did initially occur to give the product **6**. In the presence of the electron-deficient Au or Pt catalyst, the tetracyclic ether **6** suffers from a C-O bond scission at the double allylic position to give the tertiary, allylic carbocation **A**. A 1,2-alkyl migration with concomitant ring expansion/contraction and ketone formation forms the thermodynamically more stable **8**.

The Au(I) catalyst ($[\text{Au}(\text{P}(2,4,6\text{-PhOMe}_3)_3)\text{Cl}]$, entry 3) with an electron-rich ligand failed to initiate any reaction. In the presence of the 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 from using 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 are reported to initiate allene-diene intramolecular [4+3] cycloaddition reactions under mild conditions.^[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 made 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. Since 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. Since the CrCl₂-mediated reaction is known to produce a macrocyclic propargyl alcohol,^[29] successful implementation of this tandem sequence would provide a powerful strategy to access the tetracyclic core structure of the natural product 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 3. The known mono-substituted furans **11a,b**^[9] were converted to the 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 provided the 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 CrCl₂ in THF to yield the macrocycles **14a,b** in 78-79% yield for the two steps.^[29] Finally the propargyl alcohols were acylated to give the substrates **15a,b**.

The macrocyclization of the alkyne-aldehyde **13a,b** by the CrCl₂-promoted reaction to prepare the macrocycle **14a,b** is more efficient than the ring-closing allene metathesis reaction to prepare the corresponding macrocyclic allene **3**.^[9] It should be noted that the quality of the reagent CrCl₂ is very important to obtain a high yield of the macrocyclization products because an old bottle of CrCl₂ 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% AgSbF₆. This led to the isolation of a tricyclic ketone **17** in 82% yield. Based on the results from the reactions of macrocyclic allene **3**,^[9, 11] compound **17** should be a result of a ring opening/rearrangement from the transannular [4+3] cycloaddition product. When **15a** was treated with the Au(III) catalyst **10**,^[16] the transannular [4+3] cycloaddition product **16** was obtained as a single diastereomer in 86% yield. When **16** was treated with Au(I) catalyst **9** in the presence of AgSbF₆, the same product **17** was obtained, thus confirming the origin of **17**. The stereochemistry of **16** was confirmed by an X-ray structure analysis of its derivative (see Figure 3). In the presence of the Au(I) catalyst with a N-heterocyclic carbene ligand **18**, the reaction of **15a** gave a mixture of **16** and **17** in a ratio of 1:12 in favour of **17**.

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

The major product **20** in the Au(III)-catalyzed reaction of **15b** was converted to the known compound **23**^[12] through a sequence of reactions depicted in Scheme 4. The acetate group in compound **20** was removed and the resulting tertiary allylic alcohol was smoothly dehydrated using Burgess^[30] reagent to produce the triene **21** in high yield. Complete hydrogenation would produce compound **23**. However selective hydrogenation using Wilkinson catalyst yielded diene **22** containing the conjugated diene functionality present in the carbon core structure of cortistatins (indicated with letters in **22**).^[6, 31] This sequence of

reactions demonstrates the synthetic potential of the transannular [4+3] cycloaddition reactions. Hydrogenation of **22** under palladium on carbon gave the known 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 the product **16** and **19**, an endo-like (compact) transition state is more likely for the transannular [4+3] cycloaddition reaction (Figure 4). Each of the propargylic esters **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 the Au-allyl cations **C** and **E**.^[18] The regiochemistry of the final products is determined by the initial position of the acetoxy group. The subsequent transannular [4+3] cycloadditions give the gold carbenoid **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 alpha hydrogen atom 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**). Two major pathways may happen to the carbenoid intermediate **D** depending on the characteristics of the gold catalyst. A 1,2-acetate migration occurred when the catalyst was the cationic Au(I) catalyst to form the enol ester **19** with concomitant regeneration of the gold catalyst **9**. Such a 1,2-acetoxy migration has a relatively low activation barrier.^[4] Alternatively a 1,2-hydride shift becomes more competitive in the presence of the Au(III) catalyst to produce compound **20** and regeneration of the gold catalyst **10**. The process of 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] The presence of water molecules was suggested to lower the activation barrier. The carbenoid intermediate **D** can only undergo a 1,2-acetate migration to form the enol ester **16** because the alpha CH bond is nearly co-planar with the C=Au bond. In the presence of a cationic Au(I) catalyst such as **9**, compound **16** suffers from ether ring opening and rearrangement to give 82% of **17** according to a mechanism similar to that illustrated in Scheme 1. This was confirmed by treating compound **16** with Au(I) catalyst **9** at rt for 2 h and a complete conversion to **17** was observed. Molecular mechanics (MMFFs)^[32] calculations indicate **16** suffering from a greater strain than **19**, which explains why compound **16** rearranges to **17** under Au(I) catalysis while compound **19** is stable under the same conditions. It is remarkable that any changes in 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.

Conclusion

In summary a highly regio- and diastereoselective transannular [4+3] cycloaddition reaction has been realized using macrocyclic propargyl esters with gold catalysis. The utility of this methodology is reflected by potential synthesis of the core structures of biologically important natural products that contain a multiple ring structure, such as cortistatin A.^[6] It is noteworthy that the macrocyclic propargyl acetates **15a,b** undergo transannular [4+3] cycloaddition reactions exclusively. This is in contrast to the macrocyclic allene **3**,^[12] which gave a nearly 1:1 ratio of the transannular [4+3] and a formal [4+2] cycloaddition products, 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. While 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 the case

in macrocyclic allene **3**. As a consequence, the macrocyclic propargyl acetates **15a,b** produce exclusively the transannular [4+3] cycloaddition products in the presence of the gold catalysts **9** or **10**, while the 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 μ mol) and sodium bicarbonate (8.0 mg, 95 μ mol) was added to a flask containing CH_2Cl_2 (1.0 ml) under a nitrogen atmosphere. Macrocyclic **15a** (27.0 mg, 0.1 mmol) in CH_2Cl_2 (1.0 ml) was then added dropwise by syringe. At 2.5 h, TLC showed that no starting material was remaining and the reaction was diluted with ether and filtered through Celite. The solvent was evaporated and the residue was purified over silica gel (5-10% EtOAc/Hexane) which provided 23.3 mg (86%) of Cycloadduct **16**.

^1H NMR (500 MHz, CDCl_3): δ 1.22, 1.31 (2H, m), 1.43-1.50 (1H, m), 1.63-1.69 (1H, m), 1.76-1.94 (6H, m), 2.01-2.04 (3H, m), 2.11 (3H, s), 2.58-2.62 (1H, m), 3.09-3.13 (1H, m), 5.75-5.76 (1H, d, J = 6Hz), 6.90-6.91 (1H, d, J = 6Hz). ^{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. HRMS calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3\text{Na}$ 283.1310, found 283.1304.

Transannular [4+3] cycloaddition product (19)

Gold(I) catalyst **9** (9 mg, 17 μ mol) and silver hexafluoroantimonate (6 mg, 17 μ mol) were charged to a flask under a nitrogen atmosphere, degassed three times, and purged with nitrogen for fifteen minutes before dry methylene chloride (1 mL) was added to the reaction flask. A solution of **15b** in dry methylene chloride (1 mL) was added dropwise to the flask. After 6 h, the reaction was diluted with Et_2O and filtered through a pad of silica and Celite. The ethereal layers were concentrated and the residue was purified via silica gel chromatography (10% EtOAc:Hex) to yield 35mg (70%) of a white solid.

^1H NMR (500 MHz, CDCl_3): δ 0.96-1.06 (1H, m), 1.24-1.47 (4H, m), 1.51-1.61 (2H, m), 1.66-1.98 (8H, m), 2.10 (3H, s), 2.45-2.49 (1H, m), 2.71 (1H, d, J = 13.3 Hz), 5.97 (1H, d, J = 5.85 Hz), 6.78 (1H, d, J = 5.85 Hz). ^{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. FTIR (neat): 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 $\text{C}_{17}\text{H}_{22}\text{O}_3\text{Na}$ 297.1467, found 297.1461 ($M + \text{Na}$).

Transannular [4+3] cycloaddition product (20)

Dichloro(2-pyridinecarboxylato)gold **10** (9.4 mg, 24 μ mol) and sodium bicarbonate (40 mg, 0.47 mmol) was added to a flask containing CH_2Cl_2 (3.7 ml) under a nitrogen atmosphere. Macrocyclic **15b** (0.13 g, 0.47 mmol) in CH_2Cl_2 (1.0 ml) was then added dropwise by syringe. After 2 d, TLC showed that no starting material was remaining and the reaction was diluted with ether and filtered through Celite. The solvent was evaporated and the residue was purified over silica gel (5-10% EtOAc/Hexane) which provided 83 mg (64%) of cycloadduct **20** and 27 mg (21%) of cycloadduct **19**.

Cycloadduct **20** ^1H NMR (500 MHz, CDCl_3): δ 1.28-1.40 (3H, m), 1.58-1.69 (4H, m), 1.75-1.89 (5H, m), 1.98 (3H, s), 2.04-2.10 (2H, m), 2.24-2.30 (1H, m), 2.84-2.87 (1H, m), 5.64-5.65 (1H, d, J = 2.5Hz), 5.69-5.70 (1H, d, J = 6Hz), 6.70-6.71 (1H, d, J = 5.5Hz). ^{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. HRMS calcd for $C_{17}H_{22}O_3Na$ 297.1467, found 297.1473 (M+Na).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Retrosynthetic analysis of the potent antiangiogenesis natural product, cortistatin A, **1**.

Figure 2.
Suggested mechanism for Au(I) catalyzed transannular [4+3] cycloaddition reaction.

Figure 3. Crystal structures of the 2,4-dinitrophenylhydrazone derivatives of the ketones obtained from **16** and **19**. For details, see Supporting Information.

Figure 4.

Proposed mechanism to account for the observed reaction manifold and product stereochemistry.

Scheme 1.

Reactions of **3** with dimethyl dioxirane and the palladium catalyst system.

Scheme 2.
Suggested mechanism for the formation of **8**.

Scheme 3.
Preparation of macrocycles **15a,b**.

Scheme 4.

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

Table 1

Reactions of Macrocyclic Allene **3** under Au- and Pt-Catalysis^[a]

Entry	Catalyst	time(d)	% 6	% 7	% 8
1	9 ^[b]	0.3	38	34	0
2	[Au(P(C ₆ F ₅) ₃)Cl] ^[b]	0.1	0	0	96
3	[Au(P(2,4,6-Ph(OMe) ₃) ₃)Cl] ^[b]	3	no rxn		
4	10 (30% conversion)	5	13	16	0
5	PtCl ₂	1	0	0	80 ^[c]

^[a]Partial results appeared in reference [12].^[b]With 10% AgSbF₆.^[c]See reference [12] for more examples.

Table 2

Tandem 3,3-Rearrangement/Transannular [4+3] Cycloaddition Reactions of Macrocyclic Propargyl Ester **15a** with Different Gold Catalyst

Entry	Catalyst	time(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% AgSbF₆.

^[c] One eq NaHCO₃ was added.

Table 3

Tandem 3,3-Rearrangement/Transannular [4+3] Cycloaddition Reactions of Macrocyclic Propargyl Ester **15b** with Different Gold Catalyst

Entry	Catalyst	time(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% AgSbF₆.

^[c] One eq NaHCO₃ was added.