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Gold-catalyzed transannular [4+3] cycloaddition reactions

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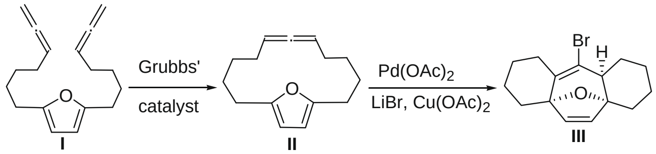
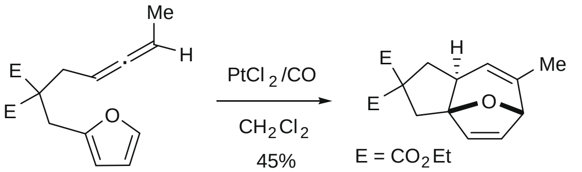
ABSTRACT

In the presence of a catalytic amount of Au(I) and Ag(I) salts, the 14-membered furanophane **II** with an allene function located across the ring undergoes both a transannular [4+3] and [4+2] cycloaddition. Secondary rearrangement products containing a tricyclic ring system were isolated when the catalyst was $PtCl_2$.

We recently described a transannular [4+3] cycloaddition reaction catalyzed by a palladium catalyst system.[1] Furanophane **II** was transformed into the tetracyclic compound **III** in 37% yield. The stereochemistry of **III** was ascertained by an X-ray structure analysis. The transannular [4+3] cycloaddition reaction is largely unexplored in contrast to its counterpart in Diels–Alder reactions. Many natural products contain polycyclic systems with a center seven-membered ring which can be efficiently synthesized with a transannular [4+3] cycloaddition reaction.

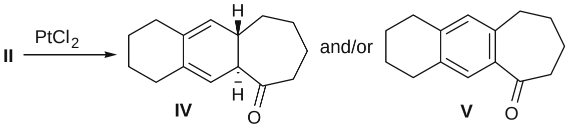


It was of interest to improve the yield of the transannular [4+3] cycloaddition reaction in an effort of developing a practical method aimed at the synthesis of natural products such as cortistatin A.[2] In the last decade, widespread interest has developed in the application of gold and platinum catalysis.[3–6] Mascarenas and co-workers have reported platinum-catalyzed intramolecular [4+3] cycloaddition reactions in which an allene function is activated by $PtCl_2$.[7] In general the successful substrates for the $PtCl_2$ catalyst were allene–dienes. However a fair yield of intramolecular [4+3] cycloaddition reaction product was also reported from an allene-furan substrate (Eq. 1).



(1)

It appeared promising that $PtCl_2$ may also promote the transannular [4+3] cycloaddition reaction of **II**. Under the reported conditions,[7] macrocycle **II** was treated with 10 mol % $PtCl_2$ in CH_2Cl_2 under an atmosphere of carbon monoxide. The products isolated were identified as **IV** and **V** (Eq. 2). The results were disappointing, but were consistent with the suggestion by Mascarenas that possible metal-induced secondary products were formed with furan containing substrates.[7] Echavarren has reported that divergent pathways for $PtCl_2$-catalyzed enyne cyclizations were observed in different solvents.[8] In an attempt to suppress the secondary process, we tried various solvents and ran the reaction at different temperatures. As shown in Eq. 2 and Table 1, the secondary rearrangement products tricyclic ketones **IV** and **V** were unfortunately the solely isolated products with $PtCl_2$ as the catalyst.



(2)

Considering the significant progress in the area of gold-catalyzed cyclizations,[3,4,9] we next turned our attention to gold catalysis. Nelson reported asymmetric Au(I)-catalyzed pyrrole additions to allenes in his synthesis of (−)-rhazinilam.[10] Toste and Zhang have independently reported gold-catalyzed intramolecular [2+2] and [3+2] cycloaddition reactions, respectively.[11,12] In each of these reports, an allene function was activated by a cationic gold catalyst to initiate the formal cycloadditions. Based on the suggested mechanism, it seems reasonable that the allene function in compound **II** should also be activated by a cationic gold catalyst and the furan moiety would trap the cationic intermediate leading to formal [4+3] cycloaddition reactions. With anticipation, we set out to try the Au(I) catalyst (**3**) first employed by Echavarren.[13] We are pleased to find that the transannular [4+3] cycloaddition reaction of **II** can indeed be promoted by this cationic gold catalyst to give a higher combined yield of products than the palladium catalyst system recently reported.[1]

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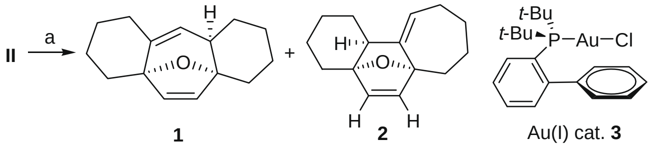
Table 1
$PtCl_2$-catalyzed transannular cycloaddition reactions of **II**

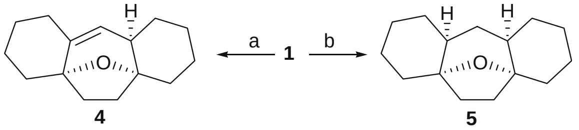
Entry	Solvent	Conditions	Ratio **II**:**IV**:**V**	Yield %
1	CH_2Cl_2	1 atm CO, 23 °C, 24 h	0:8:1	90
2	Toluene	1 atm CO, 23 °C, 24 h	43:41:0	41
3	Toluene	1 atm CO, 110 °C, 8 h	0:0:100	81
4	1,4-Dioxane	1 atm N_2, 70 °C, 24 h	0:0:100	62
5	Acetone	1 atm CO, 60 °C, 48 h, 2 equiv $NaHCO_3$	100:0:0	na
6	CH_2Cl_2	1 atm CO, 23 °C, 24 h, 2 equiv $NaHCO_3$	0:50:20	70



Key: a. 10% Au(I) cat. **3**, $AgSbF_6$, CH_2Cl_2, rt., **1** 38%, **2** 34%.

The reaction of macrocycle **II** in the presence of the Au(I) catalyst **3**[13] with the bulky ligand[14] resulted in the formation of two products at room temperature, the transannular [4+3] cycloaddition product **1** and the [4+2] reaction product **2**. The combined yield of the two reaction products is 72% without the observation of the secondary rearrangement products. The major product **1**, unlike the product obtained using the palladium catalyst system (**III**), has no bromoatom incorporated, which could potentially eliminate one synthetic operation in a total synthesis scheme.

The stereochemistry of **1** was established by its transformation to the known compound **4**[1] by selective hydrogenation of the disubstituted double bond using Wilkinson's catalyst.[15] When compound **1** was fully hydrogenated in the presence of palladium on carbon, the symmetrical tetracyclic compound **5** was obtained, further confirming the stereochemistry of **1**. The stereochemistry of the [4+2] cycloaddition product **2** was assigned based on two dimensional NMR studies. No cross-peaks were observed in the NOESY spectrum between the allylic bridgehead proton and the vinyl protons.



Key: (a) 96%, 10 mol% $Rh(PPh_3)_3Cl$, 1 atm. H_2, C_6H_6; (b) 91%, 5% Pd/C, 1 atm. H_2.

The cationic nature of the gold catalyst suggests a stepwise mechanism.[4,3,16] Our working hypothesis for the gold-catalyzed transannular [4+3] cycloaddition reactions is depicted in Figure 1. The initial activation of the allene function by the Au(I) catalyst should generate a cationic intermediate (**B**).[17] Intermediate **B** can undergo either a [4+2] reaction from trapping of the carbocation in **B** or a direct reaction with the carbon–gold bond to generate cation **C**′.[11] Alternatively a [4+3] cycloaddition could arise from cationic intermediate **C** which could be stabilized as the carbenoid resonance structure **D**. A 1,2-hydride shift followed by elimination of the gold catalyst would produce the transannular [4+3] cycloaddition product **1**.

In summary, we have found a Au(I) catalyst that can initiate a transannular [4+3] cycloaddition reaction at rt. Future work will be directed at an optimization of the ligand structure to improve the cycloaddition yield. We are currently exploring several macrocyclization reactions to more efficiently prepare the precursors for the transannular cycloadditions.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures, NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.138.

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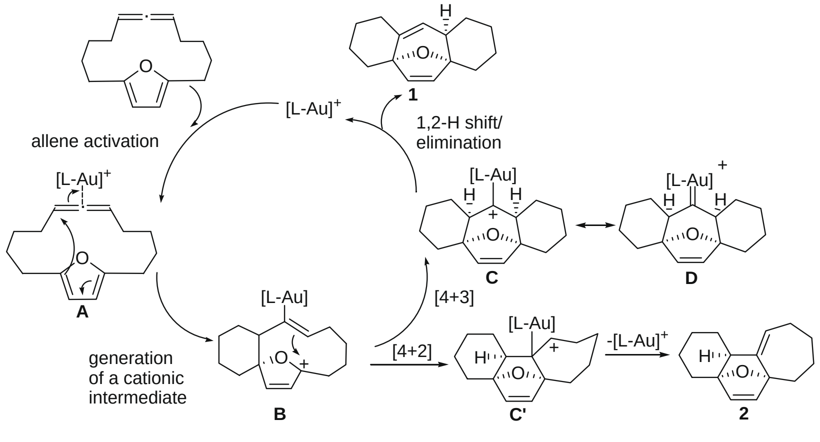

Figure 1. Plausible mechanism for Au(I)-catalyzed transannular [4+3] cycloaddition reaction.

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