Communication

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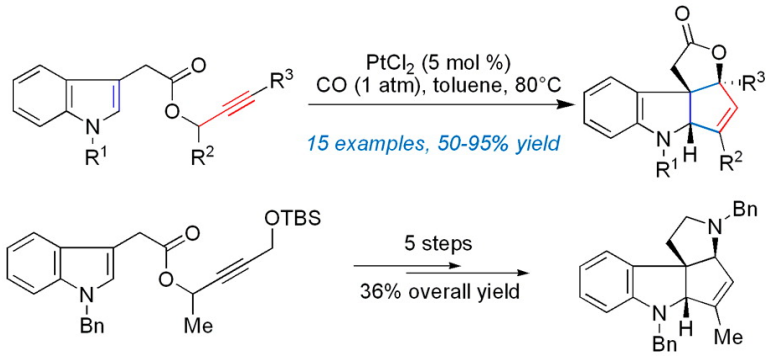

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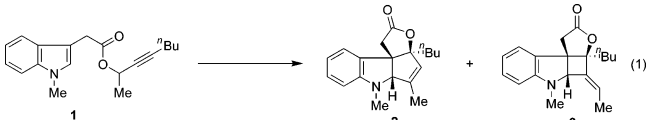
$PtCl_2$-Catalyzed Rapid Access to Tetracyclic 2,3-Indoline-Fused Cyclopentenes: Reactivity Divergent from Cationic Au(I) Catalysis and Synthetic Potential

Guozhu Zhang, Vincent J. Catalano, and Liming Zhang*

Department of Chemistry/216, University of Nevada, Reno, 1664 North Virginia Street, Reno, Nevada 89557

Received June 21, 2007; E-mail: lzhang@chem.unr.edu

Au catalysts have attracted much attention lately owing to their unique capacity in activating π systems for various useful transformations.[1] Pt catalysts, mostly $PtCl_2$, often catalyze, to a varying extent, similar reactions.[2] Examples of divergent reactivities of these two different metals are rare.[3] Herein, we report a $PtCl_2$-catalyzed highly selective formation of 2,3-indoline-fused cyclopentenes from propargylic 3-indoleacetates, in sharp contrast to our previously reported Au^I-catalyzed cyclobutane formation.[4]



Catalyst and reaction conditions	2	3
$ClAu(PPh_3)/AgSbF_6$ (5 %), CH_2Cl_2, rt , 0.5 h	< 2	83%
Dichloro(pyridine-2-carboxylato)gold(III) (5 %), THF, reflux, 2 h	52%	14%
$PtCl_2$ (5 %), toluene, 80°, 7h	57% (81% conversion)	<2
$PtCl_2$ (5 %), toluene, CO (1 atm), rt, 24 h	38 (40% conversion)	<2
$PtCl_2$ (5 %), toluene, CO (1 atm), 80°C, 1.5 h	94	<2
HBF_4 (5 %), CH_2Cl_2, 24 h	no reaction	

We previously reported a Au^I-catalyzed tandem 3,3-rearrangement/[2+2]-cycloaddition reaction of propargylic 3-indoleacetates and tetracyclic 2,3-indoline-fused cyclobutanes (e.g., **3**, eq 1) were formed in good to excellent yields,[4] highlighting the power of Au catalysis in rapidly enhancing molecular complexity. In our effort to apply this method in total synthesis, we isolated a tetracyclic cyclopentene product **2** along with **3** (**2**/**3** = 3.7) when (1-methyl-1*H*-indol-3-yl)acetate **1** was treated with dichloro(pyridine-2-carboxylato)gold(III)[5] in refluxing THF (eq 1). Of note, compound **2** was not observed when $[Au(PPh_3)]^+SbF_6^-$ was used. The indoline-fused cyclopentene structure of **2** was elucidated via extensive NMR studies and verified by X-ray crystallography (Figure 1). Attempts to enhance the selectivity of cyclopentene **2** over cyclobutane **3** were marginally successful using other Au^{III} catalysts; however, we were surprised to discover that no cyclobutane **3** was observed when $PtCl_2$ was used as catalyst and the yield of **2** was 57% with 19% of **1** left after 7 h. As far as we know, this drastic contrast of selectivities between cationic Au^I and $PtCl_2$ is unprecedented. Moreover, this change of selectivities was not caused by different reaction temperatures as $PtCl_2$ at room temperature again did not furnish **3**. The efficiency of this $PtCl_2$-catalyzed reaction was substantially improved when CO (1 atm) was used as additive,[6] and cyclopentene **2** was isolated in 94% yield. Of note, Brønsted acids[7] such as HBF_4 did not catalyze this reaction.

The mechanism of this Pt^{II}-catalyzed reaction is proposed in Scheme 1. Similar to the tandem transformations in Au catalysis,[8] an initial Pt-catalyzed 3,3-rearrangement of **1** should lead to carboxyallene **4**, which can be activated further by the same catalyst to yield oxocarbenium **A**. Electrophilic attack of the indole 3-position by the intramolecular oxocarbenium moiety would form the metal-containing lactone **B**, which diverges into different products. In contrast to the formation of a cyclobutane ring in the case of cationic Au^I (route a), $PtCl_2$ catalysis should follow route b, that is, a 5-*exo* cyclization yielding cyclopentane **C** containing

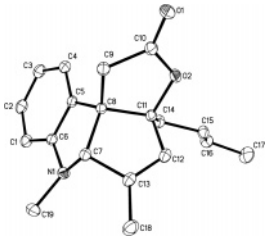
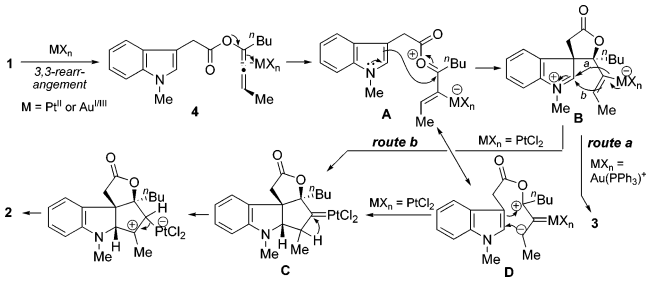


Figure 1. Thermal ellipsoid (50%) depiction of compound **2**.

Scheme 1. Proposed Mechanism for $PtCl_2$-Catalyzed Formation of Cyclopentene **2**



a Pt carbenoid moiety. Cyclopentene **2** is then formed via hydride migration and elimination of the Pt catalyst. Besides this stepwise cyclization mechanism, the allene moiety in **4** can form a mesomeric all-carbon 1,3-dipole in **D** upon Pt^{II} activation, and hence, an intramolecular, concerted 1,3-dipolar cycloaddition could also lead to carbenoid **C**.[9] Notably, the propargyl moiety in **1** acts as a C_3 unit for the intramolecular [3+2]-cycloaddition. This mechanistic hypothesis reveals substantial difference in the reactivities of alkenylplatinum(II) and alkenylgold(I): the former tends to react at the β-position and forms a Pt carbenoid, and the latter shows preferential nucleophilicity at the α-position.

While this remarkable reactivity divergence is worthy of detailed theoretic study,[10] the scope of this chemistry is shown in Table 1. Hence, ester **5a** prepared from the parent 3-indoleacetic acid (R^1 = H) and oct-3-yn-2-ol underwent selective [3+2]-cycloaddition, yielding the corresponding cyclopentene in 70% yield (entry 1). Again, the corresponding 2,3-indoline-fused cyclobutane was not observed. In anticipation of likely application of this chemistry in alkaloid synthesis, we chose to protect the indole nitrogen atom with a benzyl group (i.e., R^1 = Bn).[11] Gratifyingly, ester **5b** underwent smooth transformation, and cyclopentene **6b** was isolated in 95% yield (entry 2). Further scope studies with propargylic (1-benzyl-1*H*-indol-3-yl)acetates revealed a rather clear trend. Substrates with primary alkyl groups substituted at both ends of the propargyl moiety underwent highly efficient transformation, and the corresponding tetracyclic cyclopentenes were formed in excellent yields (entries 3−8). Notably, these substituents (i.e., R^2 and R^3) can be functionalized, including a C−C double bond (entry 4), protected hydroxyl groups (entries 5 and 6), a benzene ring (entry

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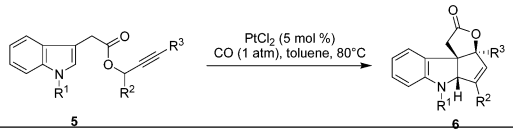
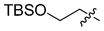
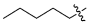
Table 1. Scope Study

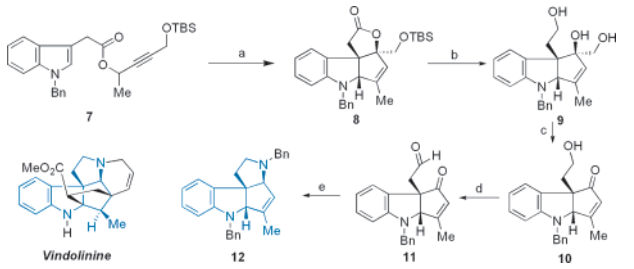


5 6

Entry	Ester **5**[a]	R^1	R^2	R^3	Time (h)	Yield of **6** (%)[b,c]
1	**5a**	H	Me	^{n}Bu	24	70
2	**5b**	Bn	Me	^{n}Bu	2	95
3	**5c**	Bn		Me	1	93
4	**5d**	Bn		^{n}Bu	0.5	94
5	**5e**	Bn	TBSO 	^{n}Bu	1	88
6	**5f**	Bn			1.5	90
7	**5g**	Bn	Bn	^{n}Bu	2	94
8	**5h**	Bn			1	92
9	**5i**	Bn	isopropyl	^{n}Bu	5	67[d]
10	**5j**	Bn	Me	Ph	1.5	70[d]
11	**5k**	Bn	Ph	^{n}Bu	1.5	50[d,e]
12	**5l**	Bn	Me	cyclohexyl	2	53[d,f]
13	**5m**	Bn		cyclopropyl	1	83

[a] The substrate concentration was 0.05 M. [b] Isolated yield. [c] No cyclobutane product was observed. [d] $NaHCO_3$ (2 equiv) was added. [e] Cyclobutane (20%) was isolated. [f] The reaction temperature was 100 °C.

Scheme 2. Synthesis of the Tetracyclic Core of Vindolinine[a]



7 8 9 10 11 12

[a] Reagents and conditions: (a) $PtCl_2$ (5 mol %), CO (1 atm), toluene, 80 °C, 2 h, 88%; (b) LAH, THF, rt, 90%; (c) $NaIO_4$, 75%; (d) TPAP (10 mol %), NMO (2 equiv), MS 4Å, CH_2Cl_2, 73%; (e) $NaBH(OAc)_3$ (10 equiv), $BnNH_2$ (5 equiv), HOAc (1 equiv), $ClCH_2CH_2Cl$, 83%.

7), and a bromide (entry 8). Interestingly, no intramolecular cyclopropanation was observed with ester **5d**,[12] and desilylation did not happen under these reaction conditions (entry 5).[13] When the R^2 or R^3 is a sterically more demanding alkyl group (entries 9 and 12) or a phenyl group (entries 10 and 11), the efficiency of this reaction decreased, and cyclopentene **6** was isolated in yields ranging from 50 to 70% in the presence of $NaHCO_3$.[14] Noteworthy is the formation of a small amount of the cyclobutane product from ester **5k** containing a phenyl group at the propargylic position. A cyclopropyl group was amendable for this reaction, and due to its decreased steric size, the corresponding cyclopentene was isolated in 83% yield. Substrates with R^3 = H and R^2 = Me led to a rather sluggish reaction, and the isolated yield was only 25%.

The densely functionalized, 2,3-indoline-fused tetracyclic structure of **6** coupled with its ready access provides an excellent starting point for synthesis of indoline-containing alkaloids. As a preliminary exploration of its synthetic application, Scheme 2 illustrates a short synthesis of the tetracyclic core of vindolinine (i.e., pyrrolidine **12**).[15] (1-Benzyl-1*H*-indol-3-yl)acetate **7** with a TBS-protected propargylic hydroxyl group underwent the $PtCl_2$-catalyzed tandem reaction smoothly, affording cyclopentene **8** in 88% yield. LAH reduction of **8** with concurrent desilylation resulted in triol **9**, which was subjected to oxidative cleavage by $NaIO_4$. The resulting hydroxycyclopentenone **10** was converted into aldehyde **11** using TPAP/NMO,[16] and subsequent double reductive amination[17] installed the desired pyrrolidine ring in tetracycle **12**.

In summary, a $PtCl_2$-catalyzed 3,3-rearrangement/[3+2]-cycloaddition employing a propargyl moiety as the C_3 unit is developed. Besides the efficient formation of highly functionalized tetracyclic cyclopentenes, the reactivity is dramatically divergent from that catalyzed by cationic Au^I. Moreover, the synthetic potential of this method is demonstrated by a short synthesis of the tetracyclic core of vindolinine.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray files. This material is available free of charge via the Internet at http://pubs.acs.org.

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