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$PtCl_4$-Catalyzed Cyclization Reaction of β-Allenols in the Presence of Indoles

Wangqing Kong,[†] Jie Cui,[‡] Yihua Yu,[‡] Guofei Chen,[†] Chunling Fu,[†] and Shengming Ma*,[†]

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China, and Shanghai Key Laboratory of Functional Magnetic Resonance Imaging, Department of Physics, East China Normal University, Shanghai 200062, People's Republic of China

masm@mail.sioc.ac.cn

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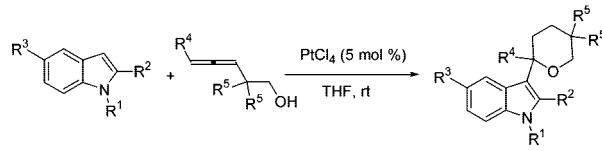
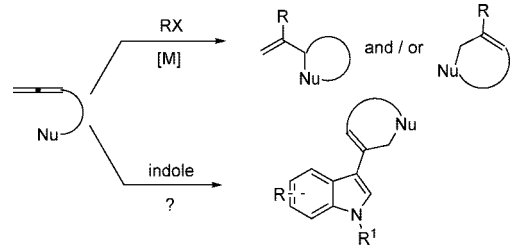
ABSTRACT



The highly regioselective $PtCl_4$-catalyzed reaction of indoles with β-allenols in THF at room temperature afforded indole derivatives containing a six-membered ether ring at the 3-position in moderate isolated yields. On the basis of a D-labeling experiment, a mechanistic rationale was proposed.

Indoles are key structural units in many natural products and important pharmaceuticals.[1] The development of new, efficient, and selective synthetic methods for the functionalization of indoles continues to receive considerable attention.[2] Recently, we and others have developed the cyclization of functionalized allenes in the presence of organic halides.[3] Considering the easy functionalization at the 3-position of indoles,[4] we envisioned the cyclization of allenes with a nucleophilic functional group in the presence of indoles (Scheme 1). In this paper, we report our unexpected observation that β-allenols may be cyclized in the presence of indoles to give an indole derivative with a saturated six-membered cyclic ether group at the 3-position.

Scheme 1



Our initial investigation was focused on the reaction of indole **1a** and 3,4-undecadien-1-ol **2a** in THF under the catalysis of $AuCl_3$ (5 mol %), resulting in cycloisomerization of **2a** to afford 2-hexyl-5,6-dihydro-2*H*-pyran **4aa** in 84% isolated yield (entry 1, Table 1).[5]

When $AuCl_3$ was replaced with $AuCl(PPh_3)$, 89% of indole **1a** and 92% of β-allenol **2a** were recovered (entry 2, Table

[†] Zhejiang University.
[‡] East China Normal University.

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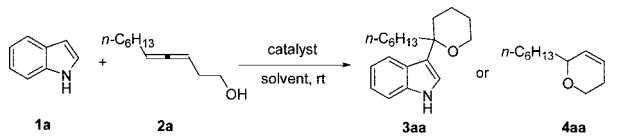
Table 1. Effect of Catalyst and Solvent on the Cyclization Reaction of 3,4-Undecadien-1-ol **2a** in the Presence of Indole **1a**



entry	catalyst (mol %)	solvent	**2a** (equiv)	time (h)	NMR yield (%) of **3aa**[a]
1	$AuCl_3$ (5)	THF	1.2	4	[b]
2	$AuCl(PPh_3)$ (5)	THF	1.2	27	[c]
3	$PtCl_4$ (5)	THF	1.2	4	77 (74[d])
4	$PtCl_4$ (5)	DMSO	1.2	19	[e]
5	$PtCl_4$ (5)	CH_3CN	1.2	3.5	60
6	$PtCl_4$ (5)	$ClCH_2CH_2Cl$	1.2	4	64
7	$PtCl_4$ (5)	toluene	1.2	7	72
8	$PtCl_4$ (5)	MeOH	1.2	24	[f]
9	$PtCl_4$ (5)	THF	1.0	6	60[d]
10	$PtCl_4$ (3)	THF	1.2	22.5	59[d]

[a] ^1H NMR yield using CH_2Br_2 as the internal standard. [b] **3aa** was not formed, and the reacion afforded **4aa** in 84% isolated yield. [c] The recoveries of indole **1a** and β-allenol **2a** were 89% and 92%, respectively. [d] Isolated yield. [e] The recoveries of indole **1a** and β-allenol **2a** were 100% and 94%, respectively. [f] The recovery of indole **1a** was 80%, and β-allenol **2a** decomposed.

1). Fortunately, when $PtCl_4$ was applied, an unexpected 1:1 cyclization product was isolated in 77% NMR yield (entry 3, Table 1). The structure was further established by the X-ray studies of this product[6] to be 3-(2-hexyl-tetrahydro-2*H*-pyran-2-yl)-1*H*-indole **3aa**, indicating the β-allenols were cyclized to form a six-membered ring, which was attached to the 3-position of indole **1a**. Surprisingly, the connection to indole was made at the 5-position of the starting alcohol **2a**; i.e., the hydrogen atom at this position was removed, and no C=C bond remained in the final product (Figure 1).

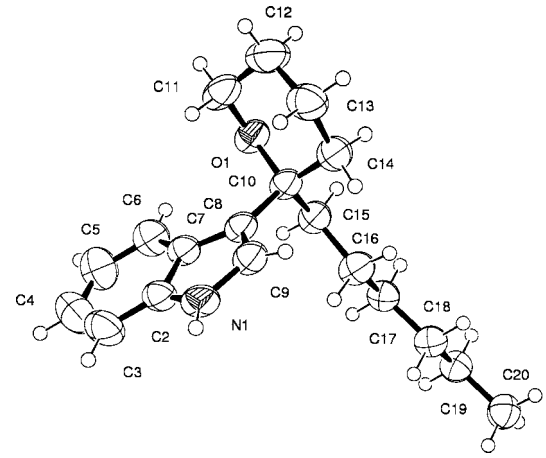


Figure 1. ORTEP representation of the product **3aa**.

In terms of solvent effect, THF is better than other solvents screened, such as DMSO, CH_3CN, DCE, toluene, etc. We also observed that 1.2 equiv of β-allenol **2a** is necessary (compare entry 9 with entry 3, Table 1). When 3 mol % of $PtCl_4$ was used, the yield of **3aa** was lower with a prolonged reaction time (compare entry 10 with entry 3, Table 1). Thus, we defined the experimental protocol for the cyclization of β-allenols with indoles under the catalysis of 5 mol % of $PtCl_4$ in THF at room temperature as the standard reaction conditions to afford indole derivatives with a cyclic ether at the 3-position.

This new transformation was quite general. Some of the typical results are listed in Table 2. With the N-unprotected simple indole **1a**, the cyclization of β-allenols **2a**−**2d** afforded the products **3aa**−**3ad** in 71−74% isolated yields (entries 1−4, Table 2). Other N-unprotected indoles with substituents at the 5-position **1b**−**1d** can also successfully afford the corresponding products **3ba**−**3da** (entries 5−8, Table 2). A methyl group may be introduced to the 2-position of indole (entry 8, Table 2). The 1-position of indoles may also be substituted with an alkyl (entries 9−13, Table 2) as well as a phenyl group (entries 14 and 15, Table 2). However, a tosyl group inhibited this cyclization reaction (entry 16, Table 2).

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(6) Crystal data for **3aa**: $C_{19}H_{27}NO$, MW = 285.43, Monoclinic, space group P2(1)/c, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0377, wR2 = 0.0881, *a* = 7.4333(5) Å, *b* = 15.8825(13) Å, *c* = 15.0972(10) Å, α = 90°, β = 106.1198(16)°, γ = 90°, *V* = 1712.3(2) Å^3, *T* = 296(1) K, *Z* = 4, number of reflections collected/unique: 3868/1300 (*R*int = 0.077), number of observations [$I > 2\sigma(I)$] 3868, parameters: 191. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC702025.

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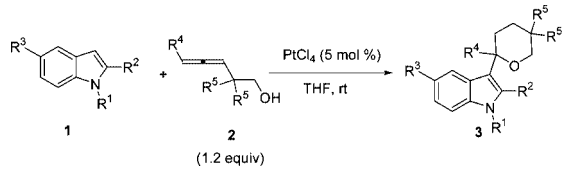
Table 2. $PtCl_4$-Catalyzed Cyclization Reaction of β-Allenols in the Presence of Indoles

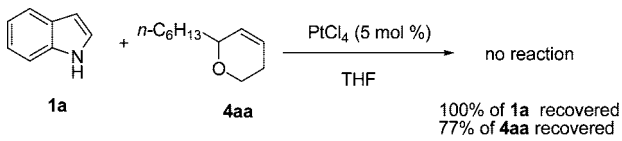


	1			2		time	yield (%) of
entry	R^1	R^2	R^3	R^4	R^5	(h)	**3**[a]
1	H	H	H (**1a**)	n-C_6H_{13}	H (**2a**)	4	74 (**3aa**)
2	H	H	H (**1a**)	n-C_5H_{11}	H (**2b**)	10	74 (**3ab**)
3	H	H	H (**1a**)	CH_3	H (**2c**)	11	74 (**3ac**)
4	H	H	H (**1a**)	Ph	CH_3 (**2d**)	21.3	71 (**3ad**)
5	H	H	OH (**1b**)	n-C_6H_{13}	H (**2a**)	4.6	67 (**3ba**)
6	H	H	OH (**1b**)	n-C_5H_{11}	H (**2b**)	1.8	77 (**3bb**)
7	H	H	OBn (**1c**)	n-C_6H_{13}	H (**2a**)	5	72 (**3ca**)
8[b]	H	CH_3	Cl (**1d**)	n-C_6H_{13}	H (**2a**)	19	42 (**3da**)
9	CH_3	H	H (**1e**)	n-C_6H_{13}	H (**2a**)	14.2	70 (**3ea**)
10	CH_3	H	H (**1e**)	n-C_5H_{11}	H (**2b**)	6	50 (**3eb**)
11	CH_3	H	H (**1e**)	CH_3	H (**2c**)	12	68 (**3ec**)
12	CH_3	H	H (**1e**)	Ph	CH_3 (**2d**)	23	47 (**3ed**)
13	n-C_4H_9	H	H (**1f**)	n-C_6H_{13}	H (**2a**)	19	55 (**3fa**)
14	Ph	H	H (**1g**)	n-C_6H_{13}	H (**2a**)	10	50 (**3ga**)
15	Ph	H	H (**1g**)	n-C_5H_{11}	H (**2b**)	12	55 (**3gb**)
16	Ts	H	H (**1h**)	n-C_6H_{13}	H (**2a**)	18.6	[c]

[a] Isolated yield. [b] $PtCl_4$ (10 mol %) and **2** (2 equiv) were added. [c] The recovery of indole **1h** was 100%, and β-allenol **2a** decomposed.

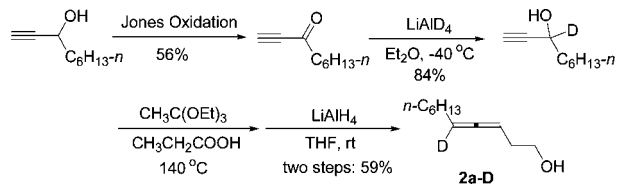
Further study revealed that no reaction was observed between indole **1a** and 2-hexyl-5,6-dihydro-2*H*-pyran **4aa**, which rules out the possibility of initial cyclization of β-allenol followed by the subsequent connection to indole (Scheme 2).

Scheme 2



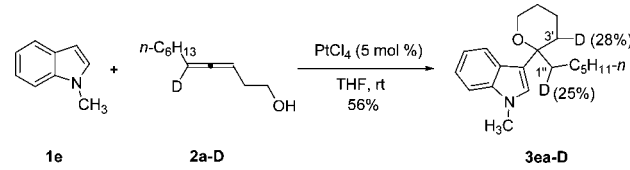
To gain further insight into the mechanism, we prepared the deuterium-labeled β-allenol **2a-D**. First, Jones oxidation of non-1-yn-3-ol afforded the corresponding alkynyl ketone,[7] which was subsequently reduced by $LiAlD_4$.[8] Finally, an ortho-Claisen rearrangement followed by reduction with $LiAlH_4$ afforded **2a-D** (Scheme 3).[9]

Scheme 3



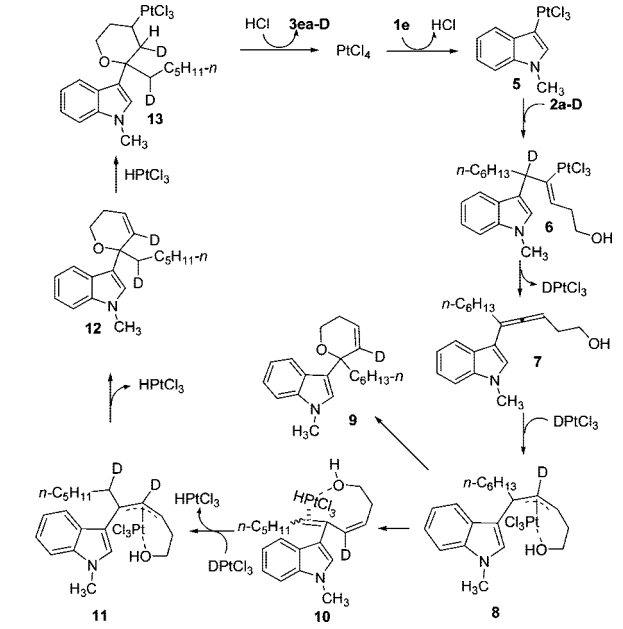
An isotopic distribution experiment was performed on the reaction of *N*-methyl indole **1e** and β-allenol **2a-D**. To our surprise, the result showed that 28% and 25% D incorporated into the C3′ and C1″ position (Scheme 4, see Supporting Information file for the determination of isotopic distribution).

Scheme 4



With this evidence in hand, we proposed a rationale for this transformation (Scheme 5). The reaction of $PtCl_4$ with **1e** would form indolyl platinum trichloride **5**, which would undergo carbometalation with allenol **2a-D** to afford vinylic platinum intermediate **6**. Subsequent β-D elimination would afford indole-containing allenol **7**. Hydrometalation of **7** with $DPtCl_3$ would afford π-allylic platinum **8**,[10] which may undergo β-H elimination to afford conjugated diene **10**.

Scheme 5



Hydrometalation of **10** with $DPtCl_3$ with a reversed regioselectivity would afford π-allylic platinum intermediate **11**,

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which would undergo intermolecular allylic substitution,[11] hydrometalation of **12**, and protonolysis[12] to afford the product **3ea-D** with regeneration of the catalytically active species $PtCl_4$. Of course, intermediate **8** may also cyclize to afford the monocyclic **9**, which undergoes similar transformation of **12** to afford the 3′-monodeuterated product **3**. Likewise, the 1″-monodeuterated product may also be formed from **7** via hydrometalation with $HPtCl_3$, β-hydrometalation, hydrometalation with $DPtCl_3$, etc. The lower level of D-incorporation may be caused by the coexistence of $HPtCl_3$ and $DPtCl_3$ (Scheme 5).

In summary, we have observed a unique cyclization of β-allenols in the presence of indoles. Due to the easy availability of the starting allenols[9] and indoles and the potential of the products, this method may be useful in organic synthesis. We also proposed a possible mechanism based on a D-labeling study. Further studies in this area are being carried out in our laboratory.

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Note Added after ASAP Publication. The version published ASAP on February 12, 2009 contained errors. In the version published ASAP on February 18, 2009, a correction was made to entry 9 in Table 1 and the last sentence was added to the acknowledgment.

Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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