

PtCl₄-Catalyzed Cyclization Reaction of β -Allenols in the Presence of Indoles

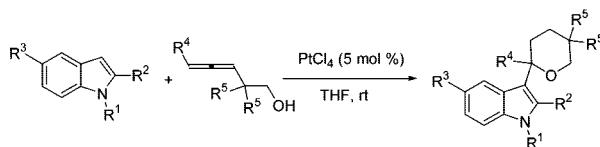
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ABSTRACT

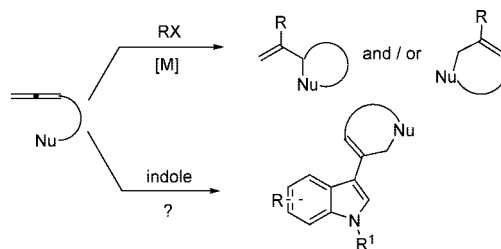


The highly regioselective PtCl₄-catalyzed reaction of indoles with β -allenols in THF at room temperature afforded indole derivatives containing a six-membered ether ring at the 3-position in moderate isolated yields. On the basis of a D-labeling experiment, a mechanistic rationale was proposed.

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 AuCl₃ (5 mol %), resulting in cycloisomerization of **2a** to afford 2-hexyl-5,6-dihydro-2H-pyran **4aa** in 84% isolated yield (entry 1, Table 1).⁵

When AuCl₃ was replaced with AuCl(PPh₃), 89% of indole **1a** and 92% of β -allenol **2a** were recovered (entry 2, Table

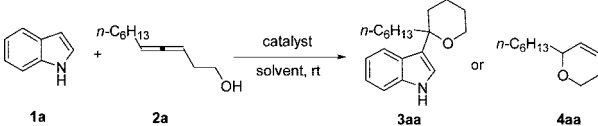
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Table 1. Effect of Catalyst and Solvent on the Cyclization Reaction of 3,4-Undecadien-1-ol **2a** in the Presence of Indole **1a**



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 ₃ CN	1.2	3.5	60
6	PtCl ₄ (5)	ClCH ₂ CH ₂ Cl	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 CH₂Br₂ as the internal standard. ^b **3aa** was not formed, and the reaction 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 PtCl₄ 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 product⁶ to be 3-(2-hexyl-tetrahydro-2H-pyran-2-yl)-1H-indole **3aa**, indicating the β -allenols were cyclized to form a six-membered ring, which was attached

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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).

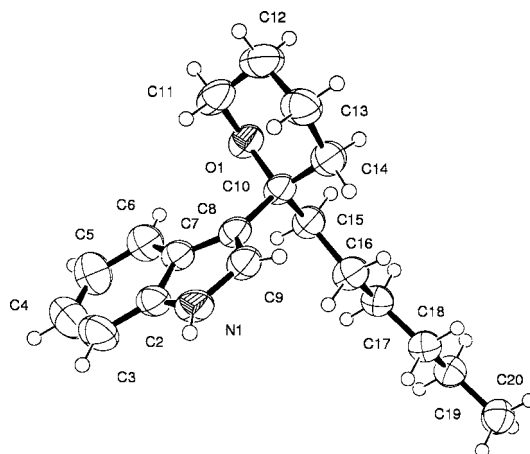


Figure 1. ORTEP representation of the product **3aa**.

In terms of solvent effect, THF is better than other solvents screened, such as DMSO, CH₃CN, 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 PtCl₄ 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 PtCl₄ 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).

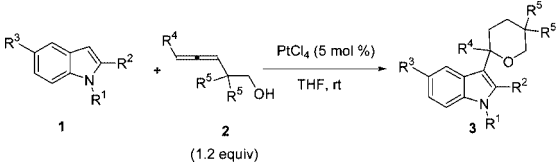
(6) Crystal data for **3aa**: C₁₉H₂₇NO, MW = 285.43, Monoclinic, space group P2(1)/c, final *R* indices [*I* > 2 σ (*I*)], *R*₁ = 0.0377, *wR*₂ = 0.0881, *a* = 7.4333(5) Å, *b* = 15.8825(13) Å, *c* = 15.0972(10) Å, α = 90°, β = 106.1198(16)°, γ = 90°, *V* = 1712.3(2) Å³, *T* = 296(1) K, *Z* = 4, number of reflections collected/unique: 3868/1300 (*R*_{int} = 0.077), number of observations [*I* > 2 σ (*I*)] 3868, parameters: 191. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC702025.

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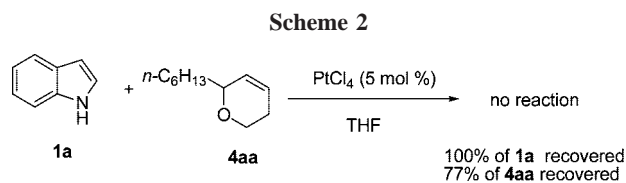
Table 2. PtCl₄-Catalyzed Cyclization Reaction of β -Allenols in the Presence of Indoles



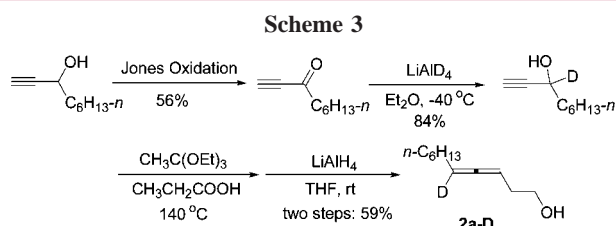
entry	1			2		time (h)	yield (%) of 3 ^a
	R ¹	R ²	R ³	R ⁴	R ⁵		
1	H	H	H (1a)	<i>n</i> -C ₆ H ₁₃	H (2a)	4	74 (3aa)
2	H	H	H (1a)	<i>n</i> -C ₅ H ₁₁	H (2b)	10	74 (3ab)
3	H	H	H (1a)	CH ₃	H (2c)	11	74 (3ac)
4	H	H	H (1a)	Ph	CH ₃ (2d)	21.3	71 (3ad)
5	H	H	OH (1b)	<i>n</i> -C ₆ H ₁₃	H (2a)	4.6	67 (3ba)
6	H	H	OH (1b)	<i>n</i> -C ₅ H ₁₁	H (2b)	1.8	77 (3bb)
7	H	H	OBn (1c)	<i>n</i> -C ₆ H ₁₃	H (2a)	5	72 (3ca)
8 ^b	H	CH ₃	Cl (1d)	<i>n</i> -C ₆ H ₁₃	H (2a)	19	42 (3da)
9	CH ₃	H	H (1e)	<i>n</i> -C ₆ H ₁₃	H (2a)	14.2	70 (3ea)
10	CH ₃	H	H (1e)	<i>n</i> -C ₅ H 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	<i>n</i> -C ₄ H ₉	H	H (1f)	<i>n</i> -C ₆ H ₁₃	H (2a)	19	55 (3fa)
14	Ph	H	H (1g)	<i>n</i> -C ₆ H ₁₃	H (2a)	10	50 (3ga)
15	Ph	H	H (1g)	<i>n</i> -C ₅ H ₁₁	H (2b)	12	55 (3gb)
16	Ts	H	H (1h)	<i>n</i> -C ₆ H ₁₃	H (2a)	18.6	^c

^a Isolated yield. ^b PtCl₄ (10 mol %) and 2 (2 equiv) were added. ^c The recovery of indole 1h was 100%, and β -allenol 2a decomposed.

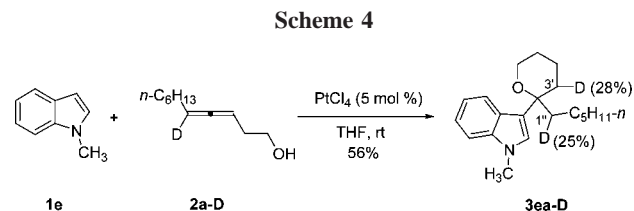
Further study revealed that no reaction was observed between indole 1a and 2-hexyl-5,6-dihydro-2H-pyran 4aa, which rules out the possibility of initial cyclization of β -allenol followed by the subsequent connection to indole (Scheme 2).



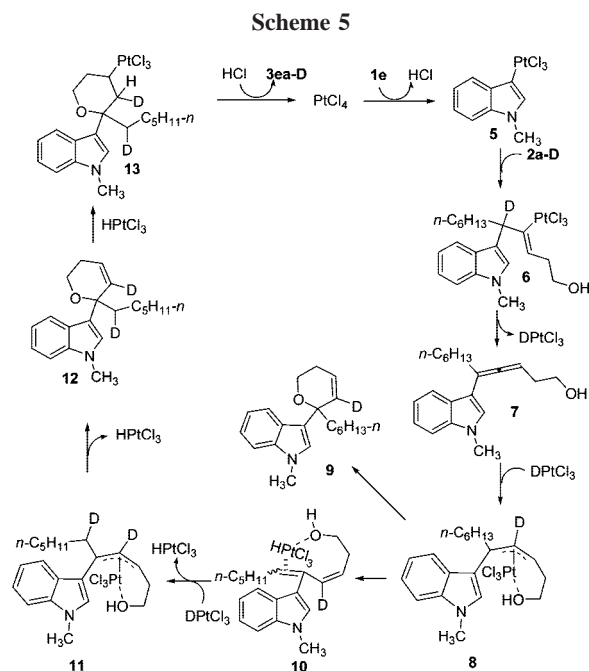
To gain further insight into the mechanism, we prepared the deuterium-labeled β -allenol 2a-D. First, Jones oxidation of non-1-yn-3-ol afforded the corresponding alkynyl ketone,⁷ which was subsequently reduced by LiAlD₄.⁸ Finally, an ortho-Claisen rearrangement followed by reduction with LiAlH₄ afforded 2a-D (Scheme 3).⁹



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).



With this evidence in hand, we proposed a rationale for this transformation (Scheme 5). The reaction of PtCl₄ 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 DPtCl₃ would afford π -allylic platinum 8,¹⁰ which may undergo β -H elimination to afford conjugated diene 10.



Hydrometalation of 10 with DPtCl₃ 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 protonolysis¹² to afford the product **3ea-D** with regeneration of the catalytically active species PtCl₄. 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 HPtCl₃, β -hydrometalation, hydrometalation with DPtCl₃, etc. The lower level of D-incorporation may be caused by the coexistence of HPtCl₃ and DPtCl₃ (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 allenols⁹ and indoles and the potential of the products, this method may be useful in organic synthesis. We also proposed a possible mechanism

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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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