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Electronic Effect Directed Au(I)-Catalyzed Cyclic C2−H Bond Functionalization of 3-Allenylindoles

Bo Chen,[†] Wu Fan,[‡] Guobi Chai,[§] and Shengming Ma*[,†,‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China, Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai 200062, P. R. China, and Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, P. R. China

masm@sioc.ac.cn

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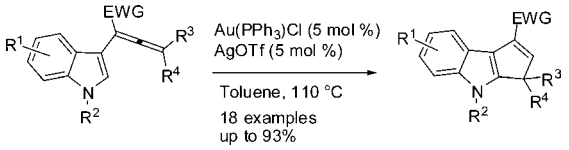
ABSTRACT



Gold-catalyzed cyclization reactions of indoles with an electron-deficient allene at the 3-position led to formation of dihydrocyclopenta[*b*]indole derivatives in moderate to excellent yields via C2−H bond functionalization of the indole unit. The presence of the electron-withdrawing alkoxycarbonyl, dialkoxyphosphono, or phenyl is crutial for this transformation. The potential synthetic dihydrocyclopenta[*b*]indole with the electron-withdrawing group has been demonstrated by applying a [3 + 2] cycloaddition reaction to construct the tretracycloskeleton.

Among heterocyclic compounds, indoles are probably the most ubiquitous scaffolds.[1] Because of their great structural diversity and important biological activity, indoles have become a privileged structure in numerous areas such as pharmaceuticals, fragrances, agrochemicals, pigments, and materials science.[2] Of particular interest is the cyclopenta[*b*]indole structural unit that occurs in a large number of indole alkaloids such as paxilline, paspaline, penitrems, janthitrems, lolitrems, monoterpenoid alkaloid yeuhchukene, Fischer indoles, and some reduced cyclopenta[*b*]indoles (Figure 1).[3] They display a variety of biological activities: penitrem A and paxilline have become recognized and used pharmacologically as a selective blocker of high conductance calcium-activated potassium channels.[3b] Thus, the development of simple, efficient, and general methods to synthesize the cyclopenta[*b*]indole skeleton are of high interest.[4]

On the other hand, the transition-metal-catalyzed C−H bond functionalization has received rapidly growing attention during the past decades because of its synthetic efficiency and environmental friendliness.[5] In this area, enormous efforts have also been devoted to the development of the directed C−H bond functionalization of indole compounds.[6]

[†] Shanghai Institute of Organic Chemistry.
[‡] East China Normal University.
[§] Zhejiang University.

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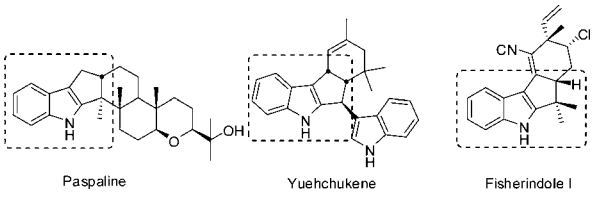
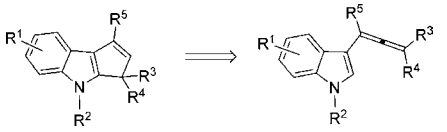


Figure 1. Some biologically active compounds containing the cyclopenta[*b*]indole unit.

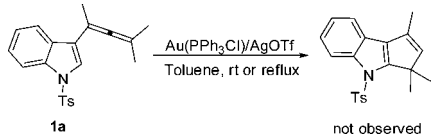
It is well-known that the C2-position of indoles is much less reactive than the C3 site. The C2−H bond functionalization of indoles followed by a coupling reaction with a halide,[7a−e] organometallic reagent,[7f,g] arene,[7h,i] terminal alkyne,[7j] radical,[7k−m] or carbometalation with carbon−carbon double[8] or triple bonds[9] has been well documented. However, such a reaction with allenes has not been well established as pioneered by Barluenga and Toste et al. with the cyclization of *N*-allenylindoles.[10] We envisioned that 3-allene-substituted indoles could offer an efficient approach to the cyclopenta[*b*]indole skeleton. The cyclic C=C bond may provide further opportunity to build an extra ring via cycloaddition reaction (Scheme 1). However, because of the high strain of the dihydrocyclopenta[*b*]-indole product and the less nucleophilicity of C2-indole, it would be a challenge to realize such a cyclization reaction. Herein, we disclose our recent realization of such an approach using a gold catalyst.[11,12]

Scheme 1. Allene Approach to Cyclopenta[*b*]indole



At first, we chose indole−allene **1a** as a model to explore such a concept. However, after many screenings, the formation of this desired product was not observed and an unknown product was formed (Scheme 2).

Scheme 2. Initial Experiments



We then switched to indole−allenoate **1b** with an electron-withdrawing methoxycarbonyl group. We were pleased to observe that when the reaction was conducted with 5 mol % each of $Au(PPh_3)Cl$ and $AgBF_4$ in toluene,

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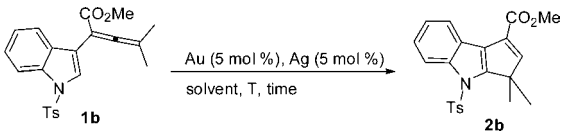
the expected product **2b** was cleanly formed albeit in 37% NMR yield after 19 h at 130 °C, while 48% of the starting material was unreacted as determined by NMR analysis (entry 1, Table 1). The structure of compound **2b** was further unambiguously confirmed by the X-ray crystal diffraction study.[13] Next, we focused our attention on the effect of different silver salts and observed that by applying AgOTf the yield of product **2b** was improved to 95% NMR yield (entries 1–3, Table 1)! In the absence of $Au(PPh_3)Cl$ or AgOTf, the transformation did not occur (entries 4–5, Table 1). $AuCl_3$ showed a poor catalytic activity in this reaction (entry 6, Table 1). We also examined the solvent effect and observed that toluene is the best (entries 7–10, Table 1). When the reaction was conducted at 110 °C, **2b** was also formed in 95% NMR yield (entry 11, Table 1). The reaction was very slow at 80 °C or room temperature (entries 14 and 15, Table 1). Therefore, we defined entry 11 in Table 1 as the standard conditions.

Table 1. Optimization of the Reaction Conditions[a]



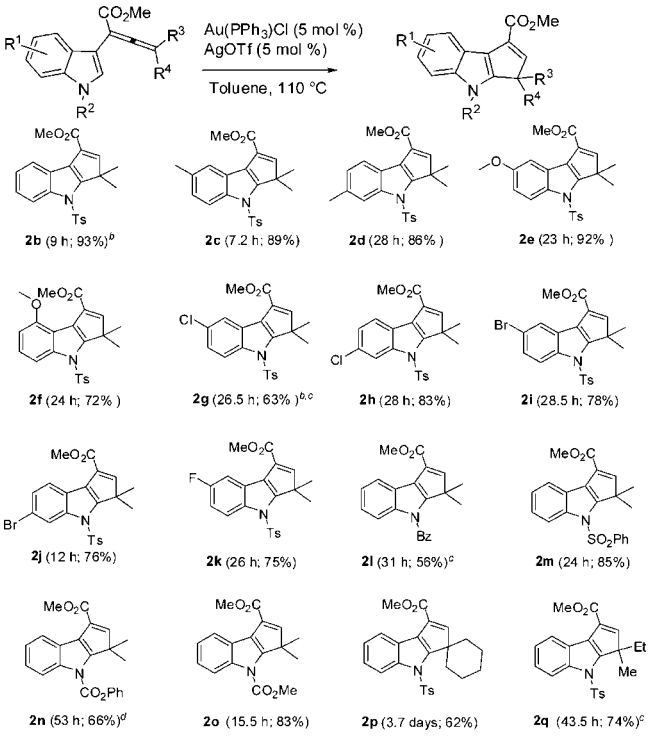
entry	Au	Ag	temp (°C)	solvent	time (h)	**2b**[b] (%)	**1b**[b] (%)
1	$Au(PPh_3)Cl$	$AgBF_4$	130	toluene	19.3	37	48
2	$Au(PPh_3)Cl$	$AgSbF_6$	130	toluene	19	80	13
3	$Au(PPh_3)Cl$	AgOTf	130	toluene	19.3	95	0
4	–	AgOTf	130	toluene	24	0	85
5	$Au(PPh_3)Cl$	–	130	toluene	24	0	80
6	$AuCl_3$	–	130	toluene	24	8	76
7	$Au(PPh_3)Cl$	AgOTf	130	mesitylene	21	63	0
8	$Au(PPh_3)Cl$	AgOTf	130	1,4-dioxane	10	75	0
9	$Au(PPh_3)Cl$	AgOTf	130	DMSO	21	0	23
10	$Au(PPh_3)Cl$	AgOTf	130	DMF	22.5	0	12
11	$Au(PPh_3)Cl$	AgOTf	110	toluene	9	95	0
12	(JohnPhos)-AuCl	AgOTf	110	toluene	9	94	0
13	(IPr)AuCl	AgOTf	110	toluene	9	92	0
14	$Au(PPh_3)Cl$	AgOTf	80	toluene	22	16	78
15	$Au(PPh_3)Cl$	AgOTf	rt	toluene	22	5	73

[a] The reaction was carried out using **1b** (0.2 mmol) in toluene (2 mL) in a Schlenk tube. [b] The yields were determined by NMR using mesitylene or CH_2Br_2 as internal standard.

The scope of this transformation was investigated under the standard conditions. Various differently substituted indolylallenes may afford the cyclopenta[*b*]indole derivatives in moderate to excellent yields (Table 2). The substituent on the indole unit (R^1) may be an alkyl, alkoxy, or halide group (**2b**–**k**); the protecting group on the nitrogen atom R^2 may be Ts, Bz, SO_2Ph, CO_2Ph, or CO_2Me (**2l**–**o**); when R^3 and R^4 are different alkyl or cycloalkyl groups, **2p** and **2q** were also formed in good yields.

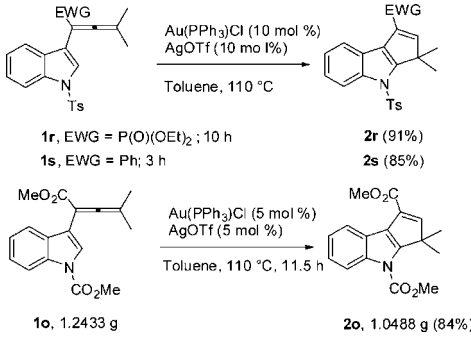
The electron-withdrawing group may also be $PO(OEt)_2$ (**2r**) or Ph (**2s**). In addition, the reaction may be easily conducted on a scale of 1 g of the substrate **1o** in a similar yield (Scheme 3). It should be noted that when the terminal sp^2 allene carbon atom is monoalkyl substituted, the reaction became complicated.

Table 2. Substrate Scope[a]



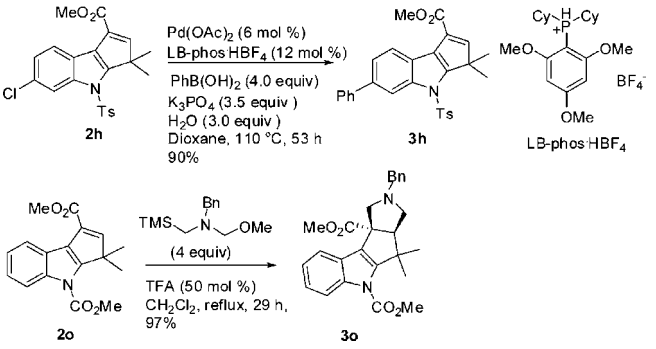
[a] The reaction was carried out by using 0.5 mmol of **1**, 5 mol % of $Au(PPh_3)Cl$, and 5 mol % of AgOTf in 2 mL of toluene in a Schlenk tube. [b] 0.2 mmol of **1b** and **1g** was used. [c] 10 mol % of $Au(PPh_3)Cl$ and 10 mol % of AgOTf were used. [d] The reaction was carried out at 115 °C.

Scheme 3. Reaction of Substrates with Other Electron-Withdrawing Groups and the Gram-Scale Reaction of **1o**



(13) Crystal data for **2b**: $C_{22}H_{21}NO_4S$, MW = 395.46, monoclinic; space group *C*2/*c*, final *R* indices [$I > 2\delta(I)$], R1 = 0.0362, wR2 = 0.0950; a = 15.4952(6) Å, b = 19.4413(8) Å, c = 13.8414(6) Å, α = 90°, β = 107.3010(10) °, γ = 90 °, V = 3981.0(3) A^3, T = 173(2) K, Z = 8. Reflections collected/unique 22907/3517 [R(int) = 0.0251], number of observations [$>2\delta(I)$] 3152, parameters: 257. CCDC 873147 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Synthetic Applications

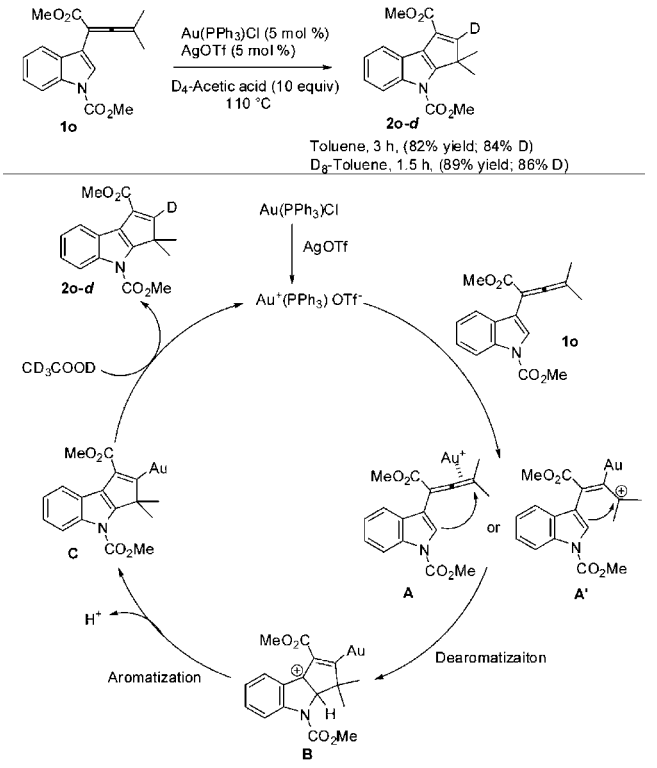


The C−Cl bond in the indole skeleton in **2h** may smoothly undergo a Suzuki-coupling reaction with organoboronic acid under the catalysis of $Pd(OAc)_2$-LB-phos (Scheme 4).[14] As expected, the dihydrocyclopenta[*b*]indole **2o** may further undergo a 1,3-dipolar cycloaddtion reaction to construct the tretracycloskeleton **3o** (Scheme 4).[15]

Running the reaction of **1o** in the presence of 10 equiv of d_4-acetic acid in toluene provided **2o-*d*** in 82% isolated yield with 84% *d*-incorporation, while the same reaction in d_8-toluene afforded the **2o-*d*** in 89% isolated yield with 86% *d*-incorporation (Scheme 5), indicating the formation of a vinylgold intermediate which was quenched with d_4-acetic acid. On the basis of this observation, a possible reaction mechanism was proposed as shown in Scheme 5. The relatively electron-rich C=C bond in the allene moiety, selectively activated by the coordination with the cationic gold atom, would be attacked by the indole C2 atom via the intermediacy of **A** and/or **A′** to afford vinylgold complex **B.** During this process, the aromaticity of the indole ring is broken.[16] Subsequent deprotonative rearomatization and demetalation would afford **2o-*d*** and regenerate the cationic gold catalyst.[17]

In summary, we have demonstrated a gold(I)-catalyzed cyclization reaction of 3-allene-substituted indoles providing an efficient entry to cyclopenta[*b*]indole derivatives via C2−H bond functionalization of the indole unit. The electron-withdrawing group in the allene moiety is crucial for this transformation for the selective activation of the two C=C bonds in the allene moiety. The cyclopenta[*b*]indole derivatives **2o** could further undergo a [3 + 2] cycloaddition reaction affording the tetracycloskeleton. The electron-withdrawing functionality may also provide

Scheme 5. Isotopic Labeling Experiments and Possible Mechanism



further opportunities of synthetic elaboration. Because of the potential of the products[3] and the ready availability of the starting materials,[18] this method may be useful in organic synthesis and medicinal chemistry. Further research in this area including the synthetic application is ongoing in our laboratory.

Acknowledgment. Financial support from the Major State Basic Research Development Program (2009CB825300) and National Natural Science Foundation of China (21172192) is greatly appreciated. We thank Mr. Qiu Youai in this group for reproducing the results presented for **2e**, **2k**, and **2l** in Table 2.

Supporting Information Available. Detailed experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.