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Gold- or Palladium-Catalyzed Allene Carbocyclization/Functionalization: Simple and Efficient Synthesis of Carbazoles

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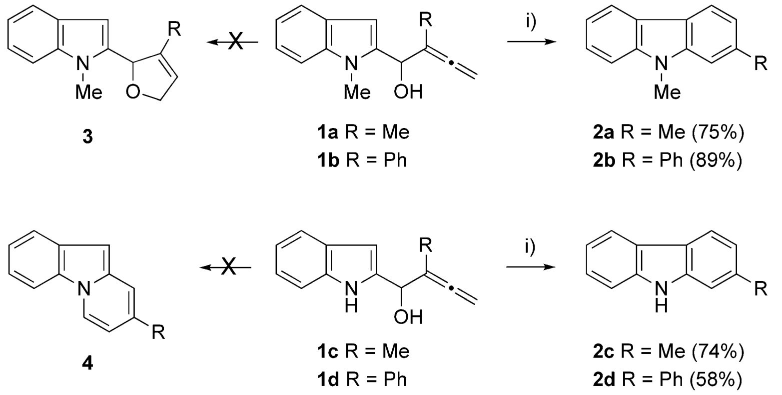
Abstract: Gold- and palladium-catalyzed cyclization of easily accessible indole-tethered allenols allows the efficient synthesis of carbazole derivatives under mild conditions.

Keywords: allenes; chemoselectivity; gold; heterocycles; palladium

The carbazole nucleus represents a key molecular motif with widespread occurrence in nature and featuring peculiar biological activities.[1] Besides, the carbazole substructure is present in many mono- and polymeric materials that exhibit interesting physical properties.[2] On the other hand, the last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acidic nature.[3,4] Allenes are a class of compounds with two cumulated carbon-carbon double bonds, which are versatile synthetic intermediates in organic synthesis.[5] Indole is an electron-rich heterocycle showing high reactivity in Friedel–Crafts-type processes. However, surprisingly, gold-catalyzed cyclizations of indoles bearing allenic moieties have rarely been mentioned.[6] Thus, while the platinum-catalyzed cyclization of 1-(indol-2-yl)-2,3-allenols has been accomplished, the same transformation was unable to be catalyzed by gold salts.[7] On the other hand, despite the rich chemistry of palladium,[8,9] the Pd-catalyzed cyclizations of indole-tethered allenes find rare precedents in the literature; only Broggini has recently reported the N-cyclization of indole-2-carboxylic acid allenamides.[10]

A process which involves a selective chemical reaction, even if the structure of the substrate suggests numerous possibilities for reactivity, represents an attractive strategy.[11] NH-Indole-tethered allenols have diverse reactive sites, at which different transformations (C-cyclization *versus* O-cyclization *versus* N-cyclization) can take place. The controlled preparation of a cycle from these multifunctional allenes requires selective catalytic systems. Otherwise, a mixture of at least three different products is possible. In continuation of our interest in heterocyclic and allene chemistry,[12] we present here a preliminary account dealing with the Au- and Pd-catalyzed 6-*endo* carbocyclization/functionalization (with concomitant dehydration) of indolyl allenols, as an efficient synthetic tool to obtain added-value compounds, such as carbazole derivatives.

We employed three different gold salts in our initial screening of catalysts for the model system, the indole-tethered allenol **1a**.[13] A mixture of at least two different products arising from competitive C-cyclization *versus* O-cyclization is possible. Initially, the use of $AuCl_3$ was tested. Next, both $Ph_3PAuNTf_2$ and AuCl were investigated. Substrate **1a** gave full conversion in all cases; carbazole **2a** being isolated in 71% ($AuCl_3$), 74% ($Ph_3PAuNTf_2$), and 75% (AuCl) yields, in a totally selective fashion. AuCl was selected as the gold source of choice. Solvent screening demonstrated that 1,2-dichloroethane was the best choice for the reaction. Worthy of note, despite the fact that gold-based catalysts are well known for their ability



Scheme 1. Controlled carbocyclization reaction of indole-tethered allenols **1a–d** to carbazole derivatives **2a–d** under selective gold-catalyzed conditions. *Reagents and conditions:* i) 5 mol% AuCl, DCE, room temperature, 2 h.

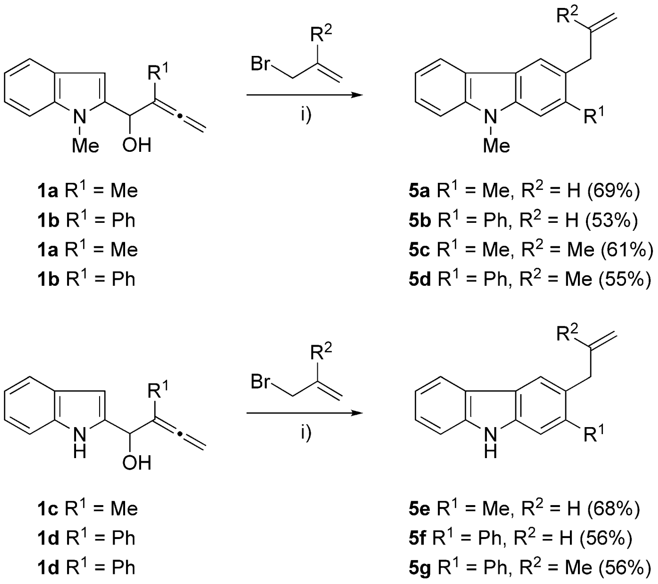
to promote the O-cyclization of α-allenols, no traces of dihydrofuran **3** were detected.[14] Thus, it is obvious from the experiments that in our functionalized system competitive processes are not operating. Indolyl allenol **1b** with a phenyl substituent on the allene moiety, also gave high yield of the carbacyclization adduct **2b** (Scheme 1). The 5-*endo* cyclization of α-functionalized allenes to five-membered heterocycles is normally faster than the formation of their six-membered counterparts from β-functionalized allenes through 6-*endo* cyclization.[15] Probably, in our case, the carbazole formation must be driven by the higher stability associated with the aromatic six-membered carbocycle; being thermodynamically favored the 6-*endo* carbocyclization reaction.

We further found that this activation mode was also quite successful in the direct cyclization reaction of NH-indolyl allenols. As shown in Scheme 1, under gold(I) catalysis, the exclusive C-cyclization products **2c** and **2d** could be smoothly isolated in isomerically pure form from NH-indolyl allenols **1c** and **1d**. The investigation of allenic-NH-indoles in this reaction revealed that NH-carbazoles were produced as the sole reaction products; pyrido[1,2-*a*]indole derivatives **4** not even being detected as trace products. Indeed, unlike their allenamine counterparts that have been shown to suffer azacyclization when exposed to gold salts,[16] these NH-indolyl allenols undergo carbocyclization. Probably, the azacyclization reaction is clearly kinetically disfavored with respect to the corresponding carbocyclization process due to the much higher activation barrier of the former transformation. The efficient participation of the indole ring rather than the nucleophilic oxygen or nitrogen functionalities in the cyclization reaction is an interesting result.

A control experiment that would rule out the participation of H^+ as the active catalyst was undertaken. A strong difference of reactivity using AuCl and methanesulfonic acid (MsOH) as catalysts was observed. When indolyl allenol **1b** was treated with MsOH with the same catalyst ratio, just a 5% yield of carbazole **2b** was obtained from a messy reaction mixture; highlighting the efficiency of AuCl in the catalytic process. The role of the gold salt seems obvious, and a Brønsted acid catalysis seems very unlikely.

Attempts to develop a gold-catalyzed carbocyclization/cross-coupling process in the presence of unsaturated halides failed, carbocyclization adducts **2** being always obtained. Achieving selectivity in the Pd-catalyzed cyclization of indolyl allenols **1** would present a valuable tool for the synthesis of functionalized carbazoles. To screen the reactivity of the allenolic indole moiety under different palladium-based catalysts, the palladium-catalyzed cyclizative coupling reaction of indole-tethered allenols **1** with aryl and alkenyl halides was explored. Cyclization was initially attempted by the exposure of allene **1a** to Pd(0) catalysis and iodobenzene. When the reaction was conducted in the presence of 0.05 equiv. of $Pd(PPh_3)_4$ and 4 equiv. of K_2CO_3 in DMF (either at room temperature or at 80 °C), we did not obtain the desired carbazole. Other solvents, such as DMSO and acetonitrile and use of different bases also failed. As next step, we investigated the reaction of indolyl allenol **1a** with allyl bromide in the presence of palladium(II) chloride (5 mol%) in DMF at room temperature. To our delight, under these conditions substrate **1a** was totally consumed and smoothly converted into carbazole **5a**, which was isolated in 69% yield. Interestingly, the use of phenyl-allenols and allenic-NH-indoles proceeded similarly to afford functionalized carbazoles **5b–g** (Scheme 2).

Because of the ability of dimers to increase the affinity for biological targets, with significant consequences *in vivo* as has been documented,[17] we decided to test the reactivity of bis(indole-tethered allenols) **6** under gold- or palladium-catalyzed conditions. Attempts to achieve cyclization using various gold-catalyzed conditions gave unsatisfactory results and polymeric material was obtained in most of the cases.



1a R^1 = Me → **5a** R^1 = Me, R^2 = H (69%)
1b R^1 = Ph → **5b** R^1 = Ph, R^2 = H (53%)
1a R^1 = Me → **5c** R^1 = Me, R^2 = Me (61%)
1b R^1 = Ph → **5d** R^1 = Ph, R^2 = Me (55%)

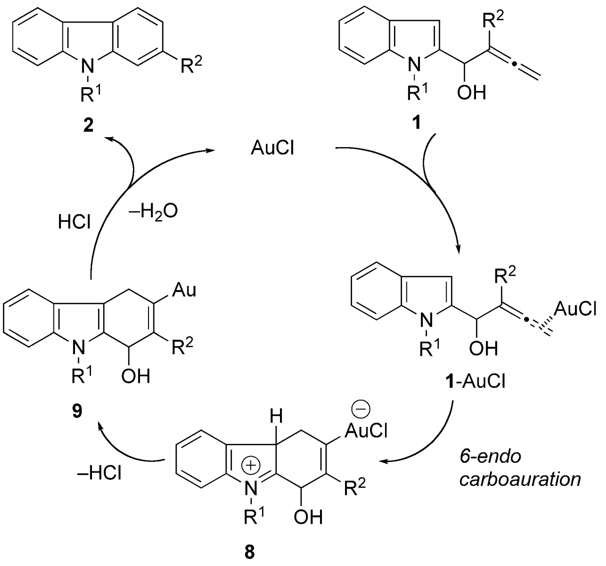
1c R^1 = Me → **5e** R^1 = Me, R^2 = H (68%)
1d R^1 = Ph → **5f** R^1 = Ph, R^2 = H (56%)
1d R^1 = Ph → **5g** R^1 = Ph, R^2 = Me (56%)

Scheme 2. Controlled carbocyclization-functionalization reaction of indole-tethered allenols **1a–d** to carbazole derivatives **5a–g** under selective palladium-catalyzed conditions. *Reagents and conditions:* i) 5 mol% $PdCl_2$, DMF, room temperature, 2 h.

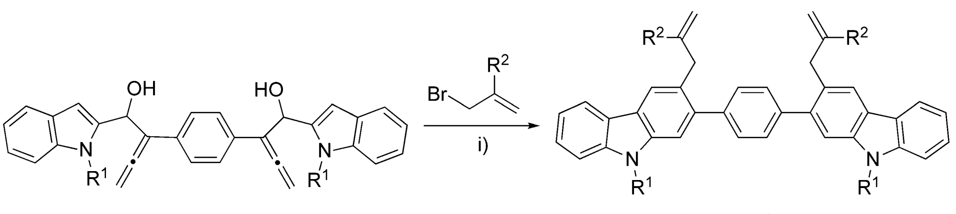
Happily, when we examined the reaction of allene **6a** with allyl bromide under palladium catalysis, the bis(carbazole) **7a** was obtained in reasonable yield. The same methodology was also extended to various bis(indole-tethered allenols) **6** and allyl bromides under optimized conditions to afford the dimeric carbazoles **7** (Scheme 3). Although complete conversion was observed by TLC and ^1H NMR analysis of the crude reaction mixtures, some decomposition was observed of sensitive NH-bis(carbazoles) **7** during purification by flash chromatography, which may be responsible for the moderate isolated yields.

A possible pathway for the gold-catalyzed formation of carbazoles **2** from indole-tethered allenols **1** may initially involve the formation of a complex **1**-AuCl through coordination of the gold chloride to the distal allenic double bond. Next, chemo- and regioselective 6-*endo* carboauration forms the zwitterionic species **8**. Attack at the 3-position of the indole occurs as a result of the stability of the intermediate iminium cation type **8**. Loss of HCl generates the neutral species **9**, which, followed by protonolysis of the carbon-gold bond and dehydration, afforded carbazoles **2** with concurrent regeneration of the gold catalyst (Scheme 4).

A likely mechanism for the palladium-catalyzed generation of functionalized carbazoles **5** is outlined in Scheme 5. Initial Pd(II) coordination to the 1,2-diene moiety gave an allenepalladium complex **1**-PdX_2. Species **1**-PdX_2 suffers an intramolecular chemo- and regioselective 6-*endo* carbocyclization reaction to give the intermediate palladadihydrocarbazole **10**, which reacted with allyl bromide *via* **11** to

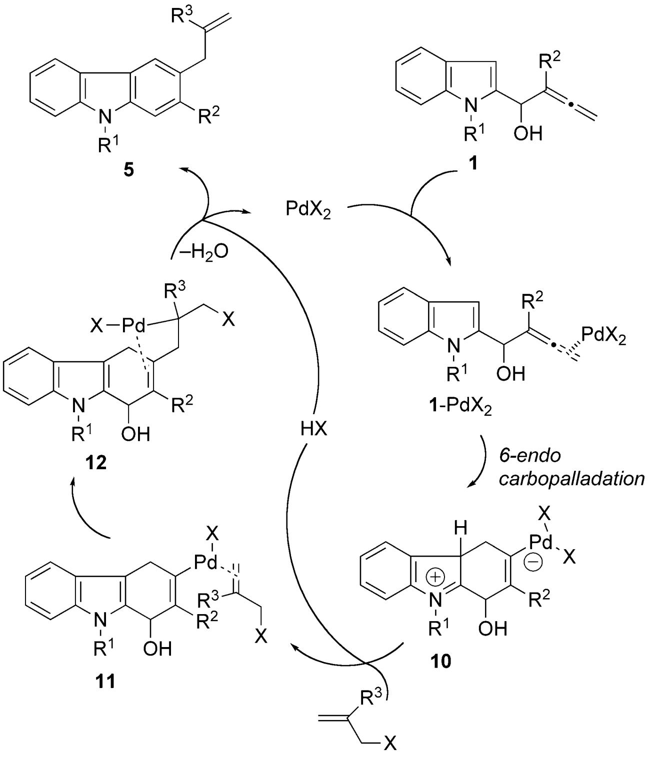


Scheme 4. Mechanistic explanation for the gold-catalyzed carbocyclization reaction of indolyl allenols **1**.



6a R^1 = Me → **7a** R^1 = Me, R^2 = H (60%)
6a R^1 = Me → **7b** R^1 = Me, R^2 = Me (54%)
6b R^1 = H → **7c** R^1 = H, R^2 = H (31%)
6b R^1 = H → **7d** R^1 = H, R^2 = Me (48%)

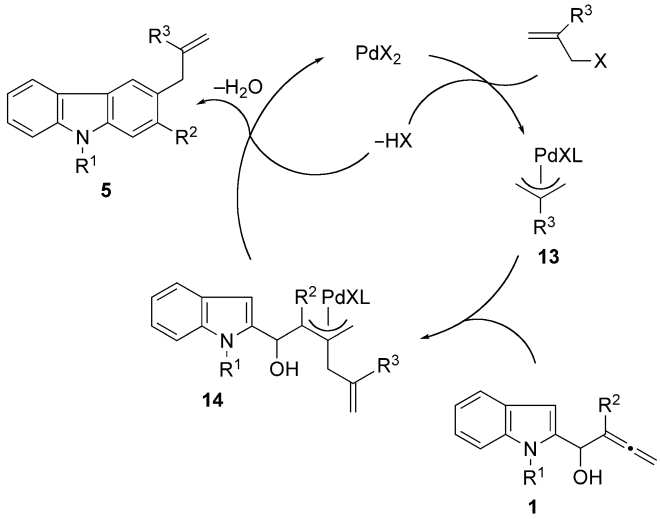
Scheme 3. Controlled carbocyclization-functionalization reaction of bis(indole-tethered allenols) **6a**,**b** to dimeric carbazole derivatives **7a–d** under selective palladium-catalyzed conditions. Reagents and conditions: i) 5 mol% $PdCl_2$, DMF, room temperature, 2 h.



Scheme 5. Mechanistic explanation for the palladium-catalyzed carbocyclization-functionalization reaction of indolyl allenols **1**.

form intermediate **12**. A *trans* β-heteroatom elimination with concurrent dehydration under the reaction conditions generates carbazoles of type **5** with concomitant regeneration of the palladium(II) catalyst (Scheme 5).[18] Here, the liberated HX plays a very important role in promoting the dehalopalladation and inhibiting the β-H elimination.[19] It has been postulated that halide ions would assist the β-heteroatom elimination, through an E2-like mechanism promoted by halide ion coordination to Pd.[20]

On the basis of some literature precedents,[21] an alternative mechanism for the observed Pd-catalyzed carbocyclization-functionalization of indolyl allenols to produce carbazoles could be proposed (Scheme 6). Accordingly, it is also possible that the oxidative addition reaction of the allyl bromide with palladium proceeds to form a π-allyl palladium complex **13**, which adds to the central carbon of the 1,2-diene moiety through carbopalladation giving rise to a new π-allyl palladium complex **14**. Intermediate **14** evolves by an intramolecular 6-*endo* carbocyclization reaction with concomitant dehydration to give functionalized carbazoles **5** and regenerates the palladium species.



Scheme 6. Alternative mechanistic explanation for the palladium-catalyzed carbocyclization-functionalization reaction of indolyl allenols **1**.

In conclusion, efficient gold- and palladium-catalyzed synthetic routes to carbazole derivatives from easily accessible indole-tethered allenols under mild conditions have been reported. The reactions were found to proceed with complete chemoselectivity control (carbocyclization *versus* oxycyclization *versus* azacyclization). Further exploration of the mechanism, scope, and synthetic applications of the present reactions are currently underway.

Experimental Section

Typical Procedure for the Pd(II)-Catalyzed Carbocyclization/Cross-Coupling between Allenols 1 and Allyl Bromides

Palladium(II) chloride (0.0165 mmol) was added to a stirred solution of allenol **1a** (70 mg, 0.33 mmol) and allyl bromide (1.65 mmol) in *N*,*N*-dimethylformamide (2.0 mL). The reaction mixture was stirred under an argon atmosphere until disappearance of the starting material (TLC). Water (1.5 mL) was added before the mixture was extracted with ethyl acetate (3×12 mL). The organic phase was washed with water (2×6 mL), dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 13:1) to afford product **5a** as a pale brown syrup; yield: 53 mg (69%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.96$ (d, $J = 7.7$ Hz, 1H, Ar), 7.76 (s, 1H, Ar), 7.33 (m, 1H, Ar), 7.24 (d, $J = 7.9$ Hz, 1H, Ar), 7.08 (m, 2H, Ar), 5.99 (m, 1H, *CH*=CHH), 4.98 (m, 2H, CH=*CHH*), 3.69 (s, 3H, NMe), 3.45 (m, 2H, CH_2), 2.41 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 141.1$ (*C* Ar), 140.2 (*C* Ar), 137.7 (*C*H Ar), 129.1 (*C* Ar), 125.1 (*C*H Ar), 122.9 (*C* Ar), 121.1 (*C* Ar), 120.6 (*C*H Ar), 120.0 (*C*H=CHH), 118.6 (*C*H Ar), 115.3 (CH=*C*HH), 109.6 (*C*H Ar), 108.3 (*C*H Ar), 37.9 (CH_2), 29.0 (Me), 20.6 (Me); IR ($CHCl_3$): $\nu = 1473$, 1251, 708 cm^{-1}; HR-MS (ES): $m/z = 235.1359$. calcd. for $C_{17}H_{17}N$ $[M]^+$: 235.1361.

Acknowledgements

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