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ARTICLE TYPE

Iodine recycling via 1,3-migration in iodoindoles under metal catalysis

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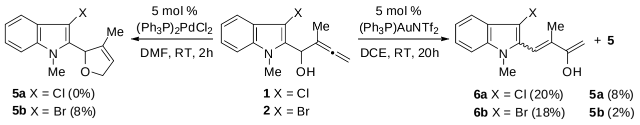
3-Substituted (indol-2-yl)-α-allenols show divergent patterns of reactivity under metal catalysis. An unprecedented intramolecular 1,3-iodine migration is described.

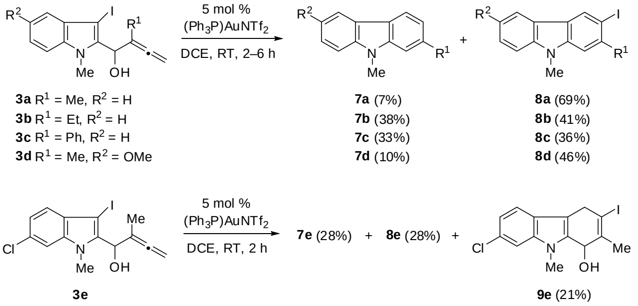
Despite that aryl halides are used in many metal-catalysed synthetic developments,[1] low atom economy is a disadvantage because the heteroatom is usually eliminated. A great challenge to be accomplished is the conversion of readily available aryl halides into halogenated products in which the heteroatom is not eliminated but reintegrated in the reaction product.[2] Recently, we have successfully reported metal-catalysed carbocyclizations of 3-unsubstituted (indol-2-yl)-α-allenols for the direct preparation of the relevant carbazole nucleus.[3] We envisioned that different behaviour of indole-tethered allenols might be achieved if the reactive C3-indole position was substituted with an activating group. Herein, we report our findings starting from 3-halo- and 3-phenoxy-(indol-2-yl)-α-allenols **1–4**.

To explore the possibility of a 1,3-heteroatom migration, chloro- and bromoallenes **1** and **2** were initially chosen. Unfortunately, 2,5-dihydrofurans **5**, formed through usual palladium-catalysed oxycyclization reaction,[4] and dienes **6**, formed via gold-catalysed rearrangement, were the only products formed (Scheme 1). The above experiments suggested that the halide recycling is troublesome.



Scheme 1 Metal-catalysed reactions of 3-chloro/bromo (indol-2-yl)-α-allenols **1** and **2**.

We thought that the use of a iodo-alkenyl rather than a Cl(Br)-species to initiate the allene functionalization could make the halogen recycling reaction possible.[2] We first investigated the reactions of allenols **3a–e** bearing a C3-iodosubstituent at the indole nucleus under our previously optimized gold-catalysed conditions. Interestingly, a separable mixture of carbazoles **7a–e** and iodocarbazoles **8a–e** were obtained (Scheme 2). The iodocyclization of allenol **3a** afforded the corresponding 3-iodocarbazole **8a** in 69% yield and carbazole **7a** in 7% yield. Diminished iodocarbazole/carbazole selectivity of ethyl- and phenyl-substituted reactans **3b** and **3c**, were observed with respect to methyl-substituted allenes **3a**, **3d** and **3e**. In addition of the expected carbazole **7e** and iodocarbazole **8e**, 1-hydroxy-3-iododihydrocarbazole **9e** was also formed from chloroderivative **3e**. It should be noted, that in our previous work on metal-catalyzed carbocyclizations 3-unsubstituted (indol-2-yl)-α-allenols, we were not able to form iodocarbazoles **8** by trapping the postulated organometallic intermediate with halogenated reagents.[3a] Considering the versatility of organic iodides in chemical transformations, iodinated carbazoles **8** are potentially interesting building blocks for further manipulation.[5] The structure of 3-iodocarbazole **8d** was unambiguously confirmed with the help of a X-ray diffraction analysis on suitable crystals of this compound (Figure 1).[6]



Scheme 2 Synthesis of carbazoles **7**, 3-iodocarbazoles **8**, and 3-iododihydrocarbazole **9e** through carbocyclization/halogen recycling reactions of iodoallenols **3** under gold catalysis.

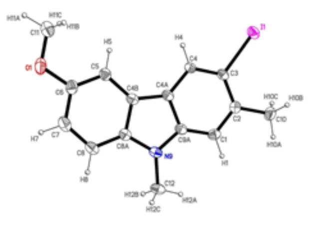
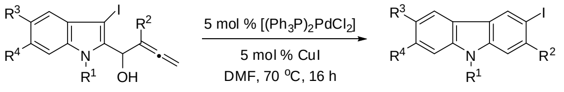


Figure 1 ORTEP drawing of 3-iodocarbazole **8d**.

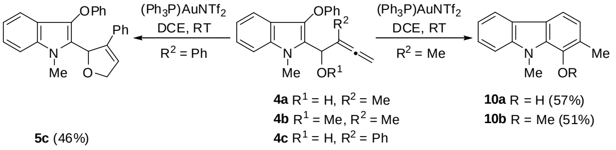
In an attempt to improve the iodocarbocyclization efficiency under related metal-catalysed conditions, we screened a different catalytic system such as $PdCl_2(PPh_3)_2$ on reacting with 3-iodo-(indol-2-yl)-buta-2,3-dienol **3a**. While the Pd-catalysed reaction proceeded with an optimal product distribution (100:0 ratio of the desired 1,3-iodine migration product to the non-iodinated carbazole), the isolated yield of 3-iodocarbazole **8a** was poor (38%). Therefore, we moved to a different catalytic system. Finally, compound **8a** was prepared in acceptable yield (61%) via the reaction of **3a** in the presence of a Pd–Cu bimetallic system in DMF. Nicely, indoles **3a**, **3e**, **3f** and **3h**, bearing a methyl substituent on the allene moiety, furnished exclusively 3-iodocarbazoles **8a**, **8e**, **8f** and **8h** (Scheme 3). Unfortunately, attempts to use phenyl-substituted substrates **3c** and **3g** proved to be unsuccessful for the construction of the corresponding iodocarbazoles, possibly because of both unfavourable steric factors as well as a direct interaction of the π-aromatic system with the metal center from the catalyst. In addition to atom economy and bond-forming efficiency, the above metal-catalysed cases in Scheme 2 and Scheme 3, may be considered as examples of the rare recycling of halogen groups via 1,3-halogen migration.[7]



3a R^1 = Me, R^2 = Me, R^3 = R^4 = H	**8a** (61%)
3c R^1 = Me, R^2 = Ph, R^3 = R^4 = H	**8c** (0%)
3e R^1 = Me, R^2 = Me, R^3 = H, R^4 = Cl	**8e** (50%)
3f R^1 = H, R^2 = Me, R^3 = R^4 = H	**8f** (52%)
3g R^1 = H, R^2 = Ph, R^3 = R^4 = H	**8g** (0%)
3h R^1 = H, R^2 = Me, R^3 = OMe, R^4 = H	**8h** (75%)

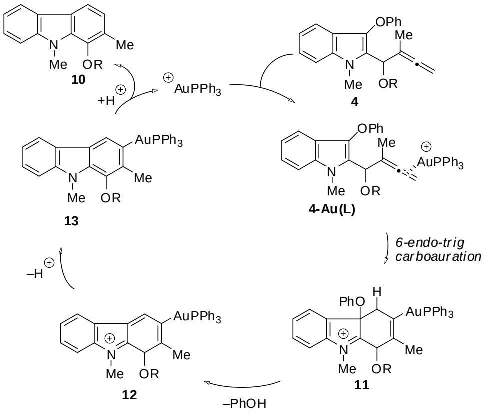
Scheme 3 Synthesis of 3-iodocarbazoles **8** through carbocyclization/halogen recycling reactions of iodoallenols **3** under palladium catalysis.

Next, the annulations of 3-phenoxy-(indol-2-yl)-α-allenols **4** were examined (Scheme 4). To test the reactivity of allenes **4**, we started the initial investigation on the gold-catalysed reaction of allene **4a** under otherwise identical reaction conditions used for its iodocounterpart **3a**. Interestingly, it was found that substrate **4a** was exclusively transformed into the 1-hydroxycarbazole **10a** (Scheme 4). This interesting transformation can be explained through a gold-catalysed allenic carbocyclization with concomitant hydrodephenoxylation (see below). Thus, it was encountered that the synthesis of structurally interesting 1-oxygenated carbazoles, could be controlled by the C3-substituent on the indole ring in allenes of type **1–4**. Next, 3-phenoxy-(indol-2-yl) allenes **4b** and **4c** were examined in this reaction (Scheme 4). Allene **4b** was successfully converted to 1-methoxycarbazole **10b** in fair yield in the presence of the Gagosz' catalyst.[8] On the contrary, phenyl-substituted allene **4c** could not lead to the formation of the corresponding 1-hydroxycarbazole, affording instead the 2,5-dihydrofuran **5c**. Hence, the hydroxy group in phenyl-substituted 3-phenoxy-(indol-2-yl)-α-allenol **4c** exclusively suffers 5-*endo* oxycyclization reaction, instead of 6-*endo* carbocyclization.



Scheme 4 Synthesis of 1-oxygenated carbazoles **10** through carbocyclization/hydrodephenoxylation reaction of phenoxyallenols **4** under gold catalysis.

A possible pathway[9] for the gold-catalysed generation of 1-oxygenated carbazoles **10** is outlined in Scheme 5. Initially, the formation of a complex **4**-Au(L) through coordination of the gold salt to the distal allenic double bond may be involved. Species **4**-Au(L) suffers an intramolecular chemo- and regioselective 6-*endo*-trig carbocyclization reaction to produce the auratetrahydrocarbazole **11**. This nucleophilic attack from the C3-indole site occurs as a result of the stability of the intermediate iminium type cation **11**. Next, a phenol elimination[10] step occurs in tricycle **11** through C3–OPh bond cleavage to generate the dihydrocarbazolium **12**. Aromatization by loss of proton generates neutral species **13**, which followed by protonolysis of the carbon–gold bond afforded 1-oxygenated carbazoles **10** with concurrent regeneration of the gold catalyst (Scheme 5).



Scheme 5 Mechanistic explanation for the Au(I)-catalyzed synthesis of 1-oxygenated carbazoles **10** from phenoxyallenols **4**.

Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP//B3LYP/def2-SVP level[11] to gain more insight into the reaction mechanism of the above discussed transition metal-catalysed carbocyclization/halogen recycling reactions of iodoallenols **3**. Thus, the corresponding computed reaction profile of the reaction of allenol **3a** and the model catalyst $AuPMe_3^+$ is shown in Figure 2, which gathers the respective free energies, ΔG_{298}, in dichloroethane solution.

The process begins with the exergonic coordination of the catalyst to the distal allenic double bond of **3a** to form intermediate **INT1** ($\Delta G_{R,298}$ = -11.9 kcal/mol). Then, the nucleophilic attack of the C3-indole position onto the gold(I)-activated double-bond delivers auratetrahydrocarbazole **INT2**. This carbocyclization reaction occurs through transition state **TS1** with an activation barrier of $\Delta G^{\neq}_{298}$ = 14.0 kcal/mol in an exergonic transformation ($\Delta G_{R,298}$ = -6.6 kcal/mol), which is compatible with a process at room temperature. Alternatively, it has been recently suggested that species related to **INT2** may be formed from spiranic species **INT2'** through a 1,2-migration reaction.[12] However, our calculations indicate that the initial formation of **INT2'** via **TS1'**, a saddle point associated with the C2-indole nucleophilic attack, is kinetically and thermodynamically less favoured than the process involving **TS1**, which makes the alternative pathway non-competitive. The origins of this behaviour are found in the well-known activation of the C3-carbon atom by the nitrogen atom of the indole.[13] Once **INT2** is formed, it is transformed into the iodonium species **INT3** through **TS2** (activation barrier of $\Delta G^{\neq}_{298}$ = 16.8 kcal/mol) in an exergonic process ($\Delta G_{R,298}$ = -2.7 kcal/mol). As shown in Figure 2, **TS2** is associated with the 1,3-migration of the iodine atom to the endocyclic double bond of the adjacent six-membered ring. This step resembles that for typical electrophilic halogen addition to alkenes. Indeed, the computed positive NBO-charge at iodine atom in **INT3** (q = +0.35e) clearly confirms the cyclic-iodonium cation nature of this species. Therefore, this step can be viewed as an unprecedented intramolecular iodine cation addition to a metal-activated double bond. The next step of the transformation involves the liberation of the metal catalyst through formation of the corresponding iododihydrocarbazoles **9** from **INT4**. Subsequent aromatization by dehydration would produce the observed 3-iodocarbazoles **8**. Although the isolation of tricycle **9e** from the reaction of **3e** outlined in Scheme 2 was fortuitous, the result argues in favour of the suggested reaction mechanism, because an observable intermediate of type **9** was formed.

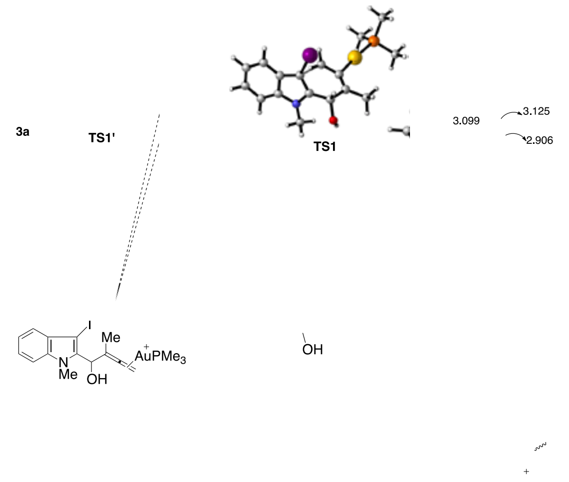


Figure 2 Computed reaction profile (PCM(dichloroethane)-M06/def2-SVP// B3LYP/def2-SVP level) for the reaction between **3a** and $AuPMe_3^+$. Relative free energies are given in kcal/mol and bond distances in the transition states in angstroms.

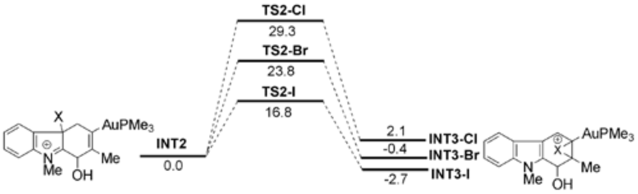


Figure 3 Comparison of the migratory aptitude of halogen atoms in the proposed 1,3-shift. Relative free energies are given in kcal/mol. All data have been computed at the PCM(dichloroethane)-M06/def2-SVP// B3LYP/def2-SVP levels.

Finally, we have also investigated why chlorine or bromine substituted allenols **1** and **2** do not undergo a similar 1,3-migration to that found for iodoallenols **3**. As clearly seen in Figure 3, the computed activation barriers associated with the 1,3-halogen shifts involving chlorine and bromine atoms are much higher than the barrier associated with the migration of iodine ($\Delta G^{\neq}_{298}$ = 29.3 and 23.8 kcal/mol for Cl and Br, respectively). Therefore, our calculations suggest that the migratory aptitude of halogen atoms in this transition metal-mediated process follows the order I >> Br > Cl, which is in nice agreement with the experimental findings.[14]

In conclusion, in salient contrast to the reaction of 3-phenoxy-(indol-2-yl) allenes, which were transformed into 1-oxygenated carbazoles, 3-iodo-(indol-2-yl) allenes afforded 3-iodocarbazoles through rare recycling of halogen groups via 1,3-halogen migration. Besides, a computational study suggested the intermediacy of an iodonium cation species formed through an unprecedented intramolecular iodine cation addition to a metal-activated double bond.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds, computational details, and copies of NMR spectra. See DOI: 10.1039/b000000x/

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