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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.

metal catalysis[†]

Despite the fact 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 into 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 a 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, chloroand bromoallenes 1 and 2 were initially chosen. Unfortunately, 2,5-dihydrofurans 5, formed through the usual palladiumcatalysed 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.

We thought that the use of an iodo-alkenyl rather than a Cl(Br)species to initiate the allene functionalization could make the

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Iodine recycling via 1,3-migration in iodoindoles under

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

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 was 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 reactants 3b and 3c, were observed with respect to methyl-substituted allenes 3a, 3d and 3e. In addition to the expected carbazole 7e and iodocarbazole 8e, 1-hydroxy-3-iododihydrocarbazole 9e was also formed from the chloroderivative 3e. It should be noted, that in our previous work on metal-catalyzed carbocyclization of 3-unsubstituted (indol-2-yl)- α -allenols, we were not able to obtain 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



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

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Fig. 1 ORTEP drawing of 3-iodocarbazole 8d.

3-iodocarbazole **8d** was unambiguously confirmed with the help of X-ray diffraction analysis on suitable crystals of this compound (Fig. 1).⁶

In an attempt to improve the iodocarbocyclization efficiency under related metal-catalysed conditions, we screened a different catalytic system such as PdCl₂(PPh₃)₂ in the reaction with 3-iodo-(indol-2-yl)buta-2,3-dienol 3a. While the Pd-catalysed reaction proceeded with an optimal product distribution (a 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, exclusively furnished 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, shown in Schemes 2 and 3, may be considered as examples of the rare recycling of halogen groups via 1,3-halogen migration.⁷

Next, the annulation of 3-phenoxy-(indol-2-yl)- α -allenols 4 was 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 1-hydroxycarbazole 10a (Scheme 4). This interesting transformation can be explained through a goldcatalysed allenic carbocyclization with concomitant hydrodephenoxylation (see below). Thus, it was found 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



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



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

1-methoxycarbazole **10b** in fair yield in the presence of Gagosz's catalyst.⁸ In contrast, 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 undergoes the 5-*endo* oxycyclization reaction, instead of 6-*endo* carbocyclization.

A possible pathway⁹ 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) undergoes 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 elimination¹⁰ 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 carbongold bond afforded 1-oxygenated carbazoles **10** with concurrent regeneration of the gold catalyst (Scheme 5).

Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP//B3LYP/def2-SVP level¹¹ 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 AuPMe₃⁺ is shown in Fig. 2, which shows 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** ($\Delta G_{\text{R},298} = -11.9$ kcal mol⁻¹). Then, the nucleophilic attack of



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



Fig. 2 Computed reaction profile (PCM(dichloroethane)-M06/def2-SVP//B3LYP/ def2-SVP level) for the reaction between **3a** and AuPMe₃⁺. Relative free energies are given in kcal mol⁻¹ and bond distances in the transition states in angstroms.

the C3-indole position on the gold(1)-activated double-bond delivers auratetrahydrocarbazole INT2. This carbocyclization reaction occurs through the transition state TS1 with an activation barrier of $\Delta G^{\neq}_{298} = 14.0 \text{ kcal mol}^{-1}$ in an exergonic transformation ($\Delta G_{R,298} =$ -6.6 kcal mol⁻¹), which is compatible with the 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** (an activation barrier of ΔG^{\neq}_{298} = 16.8 kcal mol⁻¹) in an exergonic process ($\Delta G_{R,298} = -2.7 \text{ kcal mol}^{-1}$). As shown in Fig. 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 of the typical electrophilic halogen addition to alkenes. Indeed, the computed positive NBO-charge at the 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 metalactivated 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 as 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.

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 shown in Fig. 3, the computed activation barriers associated with the **1**,3-halogen shifts



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

involving chlorine and bromine atoms are much higher than the barrier associated with the migration of iodine (ΔG^{\neq}_{298} = 29.3 and 23.8 kcal mol⁻¹ 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 \gg 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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