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Versatile Synthesis of Polyfunctionalized Carbazoles from (3-Iodoindol-2-yl)butynols via a Gold-Catalyzed Intramolecular Iodine-Transfer Reaction

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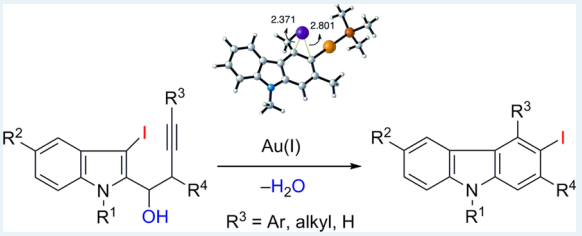
Supporting Information

ABSTRACT: The controlled gold-catalyzed preparation of 3-iodo 2,4,6-trisubstituted 9*H*-carbazoles has been developed by starting from (3-iodoindol-2-yl)butynols. These results could be explained through an initial 6-*endo*-dig alkyne carbocyclization by chemo- and regiospecific attack of the C3-indole position at the external alkyne carbon followed by a stepwise 1,3-iodine transfer and dehydration. This reaction outcome for the gold-catalyzed transformation of (3-iodoindol-2-yl)alkynols sharply contrasts with that observed for conventional metal-catalyzed processes of iodoarenes, because iodine transfer is feasible. This selective reaction has been studied experimentally; additionally, its mechanism has been investigated by means of density functional theory calculations.



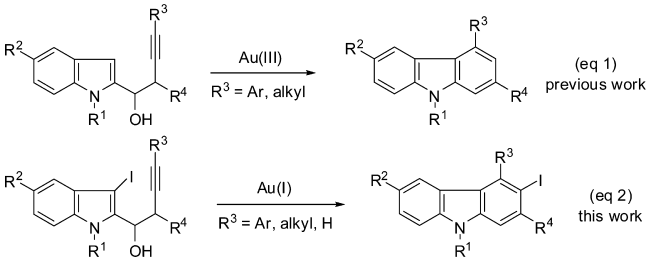
KEYWORDS: *alkynes, cyclization, density functional calculations, gold, iodine*

INTRODUCTION

The development of new chemical transformations based on the catalytic functionalization of starting materials, where as many of the atoms of the reactants as possible should end up in the final product, has great potential in organic synthesis.[1] Because of the low atom economy associated with the classical cross-coupling reactions of saturated or unsaturated halides,[2] novel activation modes of C−halogen bonds provide a prime opportunity to develop reactions paying attention to synthetic efficiency. The most successful approaches in which the halogen is reintegrated into the final product involve palladium catalysis;[3,4] only Fürstner et al., Hashmi et al., and González et al. have reported gold-catalyzed iodine transfer in 1-iodoalkynes.[5]

The carbazole nucleus is both widely distributed in nature and constitutes a key molecular motif in materials science. For these reasons, great interest has been focused on the development of new and efficient methods for the synthesis of this valuable heterocycle.[6] On the other hand, gold salts have been particularly successful at effecting activation of alkynes because of their powerful, soft Lewis acidic nature.[7] The gold-catalyzed reactions using (indol-2-yl)alkynols as substrates constitute an almost unexplored field of noble-metal catalysis.[8] The only report on the gold-catalyzed reaction of 3-alkyn-1-ol-appended indoles is the benzannulation of 1-(indol-2-yl)-3-alkyn-1-ols to provide substituted carbazoles (Scheme 1, eq 1).[9]

Scheme 1. Reactivity of 1-(Indol-2-yl)-3-alkyn-1-ols under Gold Catalysis



We were curious about the attractive possibility of divergent reactivity if the reactive C3-indole position were substituted with an iodine atom. We envisaged that, by blocking the more nucleophilic carbon of the indole ring with an easily displaced iodine moiety, the C2 side may become somewhat more reactive. We wish to report herein that to our surprise the reaction outcome for the gold-catalyzed transformation of (3-iodoindol-2-yl)alkynols is in sharp contrast with that typically observed for conventional metal-catalyzed processes involving iodoarenes, because iodine transfer is feasible, therefore

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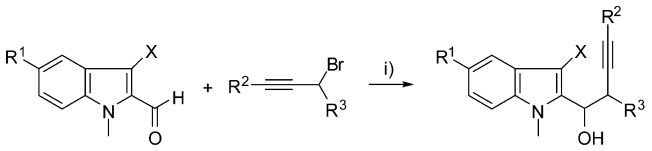
fulfilling the atom economy criterion[1] for efficient reactions (Scheme 1, eq 2). The known reports on iodine transfer reactions catalyzed by gold complexes used 1-iodoalkynes as starting materials and are based on vinylidine chemistry.[5] Our report is conceptually different (Scheme 1, eq 2).

RESULTS AND DISCUSSION

To explore the effects of various substrates on gold-catalyzed reactions, a number of new (3-haloindol-2-yl)butynols were synthesized. The starting materials, alkynes **2a−j**, were prepared from the corresponding 3-haloindole-2-carbaldehydes via zinc- or indium-mediated Barbier-type carbonyl propargylation reactions in aqueous media, in a modification of previously described methodologies.[10] A model reaction was carried out by the treatment of a THF/H_2O (1/1) solution of aldehyde **1a** with (3-bromobut-1-ynyl)benzene in the presence of indium, to give regioselectively (3-iodoindol-2-yl)butynol **2b** in 31% yield. Similar results were obtained for the indium-mediated propargylation reaction of **1a** in the system solvent THF/NH_4Cl (aqueous saturated), but the reaction times were considerably lengthened. We were pleased to find that the addition of NH_4Cl (aqueous saturated) in a 1/1.5 ratio over 1 h to a solution of **2b** and (3-bromobut-1-ynyl)benzene in THF/H_2O (1/1) improved the efficiency (60% yield). Indium was the metal of choice for the preparation of nonterminal butynols **2b,c,e,f,h**, while a conversion enhancement for the carbonyl propargylation with propargyl bromide itself was observed using zinc (Scheme 2). The reaction progress was followed by TLC but could also be noted by the disappearance of the green solution, which turns yellow. Prolonged reaction times of haloaldehydes **1** resulted in a loss of the C−X bond through exposure to the reducing metal.

Scheme 2. Regioselective Preparation of (3-Haloindol-2-yl)butynols 2a−j[a]



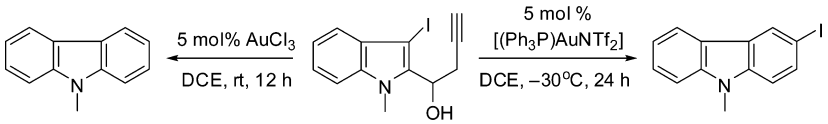
1a R^1 = H, X = I	**2a** R^2 = H, R^3 = H (69%)
1a R^1 = H, X = I	**2b** R^2 = Ph, R^3 = Me (60%)
1a R^1 = H, X = I	**2c** R^2 = Et, R^3 = Me (71%)
1b R^1 = OMe, X = I	**2d** R^2 = H, R^3 = H (61%)
1b R^1 = OMe, X = I	**2e** R^2 = Ph, R^3 = Me (54%)
1b R^1 = OMe, X = I	**2f** R^2 = Et, R^3 = Me (63%)
1c R^1 = Cl, X = I	**2g** R^2 = H, R^3 = H (55%)
1c R^1 = Cl, X = I	**2h** R^2 = Ph, R^3 = Me (88%)
1d R^1 = H, X = Cl	**2i** R^2 = H, R^3 = H (78%)
1e R^1 = H, X = Br	**2j** R^2 = H, R^3 = H (70%)

[a]Reagents and conditions: (i) 200 mol % of metal (In or Zn), THF/H_2O/NH_4Cl (aqueous saturated, 1/1/1.5), from 0 °C to room temperature; **2a** (Zn), 48 h; **2b** (In), 48 h; **2c** (In), 48 h; **2d** (Zn), 2 h; **2e** (In), 72 h; **2f** (In), 16 h; **2g** (Zn), 2 h; **2h** (In), 15 h; **2i** (Zn), 2 h; **2j** (Zn), 2 h.

Our next efforts focused on the application of gold catalysis to the selective construction of functionalized carbazoles starting from alkynols bearing a 3-iodoindole moiety. (3-Iodoindol-2-yl)butynol **2a** was chosen as a model substrate for gold-catalyzed oxycyclization reactions. Attempts to generate a tricyclic iodinated structure from **2a** by using Au(III) catalysis failed, because in the presence of $AuCl_3$ not only the iodocarbazole **3a** but also the carbazole **4a**,[11] the benzoannelation adduct, was exclusively obtained, resulting in failure of the carbocyclization−iodination sequence because the iodine transfer step was missed (Scheme 3). Despite this failure, alkynol **2a** was exposed at room temperature to different gold salts under Au(I) catalysis. However, complex reaction mixtures were obtained. Apparently, (3-iodoindol-2-yl)butynols derivatives **2** have inadequate reactivity for joint participation in the benzoannelation−iodine transfer sequence. Fortunately, an interesting and useful temperature effect emerged from the observation that cooling the reaction mixture resulted in the formation of the required 3-iodocarbazole **3a**. Our catalyst screening led to the identification of Gagosz' catalyst [$(Ph_3P)AuNTf_2$] as the most suitable promoter. AuCl and [$(Ph_3P)Au(OTf)$] were less effective for the carbocyclization−iodine transfer sequence. 1,2-Dichloroethane (DCE) was selected as the solvent of choice. It was found that [$(Ph_3P)AuNTf_2$] is an effective reagent for the iodocarbocyclization of indole-linked alkynol **2a** at −30 °C to afford the iodobenzene-fused indole **3a** in 81% yield in a totally selective fashion (Scheme 3).

In order to demonstrate the synthetic utility of this selective benzoannelation−iodine transfer process in the synthesis of substituted 3-iodocarbazole derivatives, seven additional 3-iodoindole-linked alkynols **2b−h** were employed. Both aliphatic and aromatic substitutions were well tolerated. The steric properties of the substituents in the acetylenic moiety did not significantly affect the reaction yield, with 4-aryl-functionalized but-3-yn-1-ols **2b,e** performing well in the 3-iodocarbazole formation (Scheme 4). The placement of a chlorine atom or a methoxy group at the C5 position of the indole ring was tolerated in the presence of [$(Ph_3P)AuNTf_2$] (Scheme 4), providing a handle for subsequent orthogonal reactivity. 3-Iodo 2,4,6-trisubstituted 9*H*-carbazole compounds **3b−g** were exclusively generated under these conditions (Scheme 4). Complete conversion was observed by TLC and ^1H NMR analysis of the crude reaction mixtures of alkynols **2**, and no side products were usually detected. Unfortunately, some decomposition was observed on sensitive 3-iodocarbazoles **3** during purification by flash chromatography, which may be responsible for the moderate isolated yields in some cases (**3d−g**). In particular, 3-iodocarbazoles **3d,h** were very unstable products. Adduct **3d** was isolated in very low yield, while the characterization of **3h** was not possible. The overall transformation of (3-iodoindol-2-yl)butynols into 3-iodocarbazoles

Scheme 3. Cyclization of (3-Iodoindol-2-yl)butynol 2a under Gold(III) or Gold(I) Catalysis



4a (15%; complex mixture) **2a** **3a** (81%)

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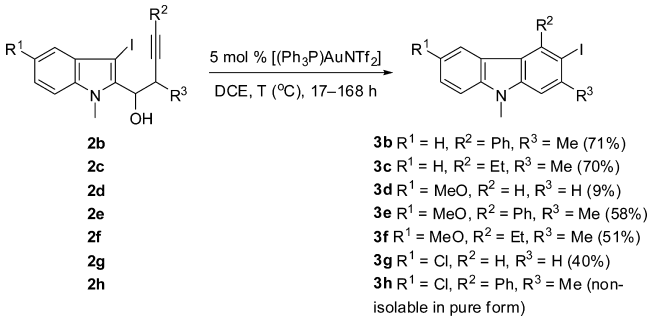
Scheme 4. Gold-Catalyzed Preparation of 3-Iodocarbazoles 3[a]

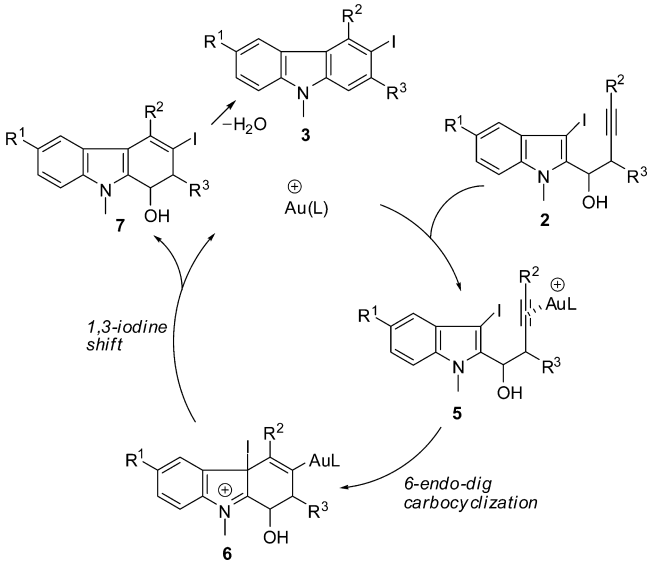


[a]Conditions: **3b**, −30 °C, 18 h; **3c**, −30 °C, 19 h; **3d**, 0 °C, 168 h; **3e**, −20 °C, 17 h; **3f**, −20 °C, 18 h; **3g**, 0 °C, 168 h; **3h**, −20 °C, 72 h.

can be roughly explained through a 6-*endo*-dig alkyne carbocyclization by chemo- and regiospecific attack of the C3-indole carbon to the external alkyne carbon followed by 1,3-iodine transfer and dehydration.

The proposed reaction pathway summarized in Scheme 5 looks valid for the formation of 3-iodocarbazoles **3** from (3-iodoindol-2-yl)butynols **2**. The initial step consists of the formation of the gold complex **5**, through coordination of the gold salt to the triple bond. A subsequent nucleophilic attack of the C3-indole position onto the above complex delivers auratetrahydrocarbazole **6** by 6-*endo* carbocyclization. This mechanistic pathway becomes attractive due to the stability of the resulting iminium cation. In the next step of the cascade, cationic intermediate **6** liberates the gold catalyst through formation of iododihydrocarbazoles **7** via 1,3-iodine shift. Finally, dehydration yields 3-iodocarbazoles **3** (Scheme 5).

Scheme 5. Mechanistic Explanation for the Gold-Catalyzed Iodocarbocyclization Reaction of (3-Iodoindol-2-yl)butynols 2

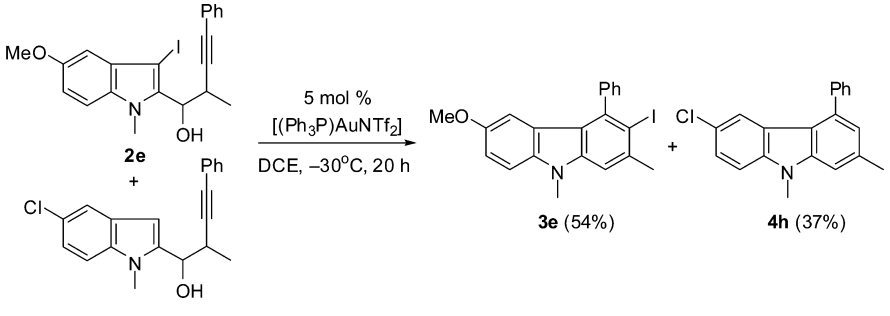


In order to test if the iodine transfer is an intramolecular or an intermolecular process, a crossover experiment was planned. Consequently, the reaction of a 1/1 mixture of 1-(3-iodo-5-methoxy-1-methyl-1*H*-indol-2-yl)-2-methyl-4-phenylbut-3-yn-1-ol (iodoalkynol **2e**) and 1-(5-chloro-1-methyl-1*H*-indol-2-yl)-2-methyl-4-phenylbut-3-yn-1-ol (alkynol without iodine substituent) was carried out. In this event, the gold-catalyzed treatment of both alkynylindoles generated 3-iodocarbazole **3e** and carbazole **4h** (Scheme 6). As the above crossover experiment did not show any appreciable formation of the chloro-substituted iodocarbazole, it can be concluded that the iodine shift occurs intramolecularly.

Density functional theory (DFT) calculations have been carried out at the dispersion-corrected PCM(DCE)-B3LYP-D3/def-TZVP//B3LYP-D3/def2-SVP level[12] to gain more insight into the reaction mechanism of the aforementioned gold(I)-catalyzed carbocyclization/iodine transfer reactions of 3-iodoindole-linked alkynols **2**. To this end, we have computed the reaction profile involving alkynol **2M** and the model gold(I) catalyst $[AuPMe_3]^+$ (see Figure 1, which gathers the corresponding relative free energies, ΔG_{298}, in dichloroethane solution).

As proposed above, the process begins with the exergonic coordination of the catalyst to the triple bond of **2M**, thus forming the initial cationic complex **INT1** ($\Delta G_{R,298}$ = −14.7 kcal/mol). From this species two alternative nucleophilic additions may occur, namely indole-C2 or indole-C3 addition to the gold(I)-coordinated external alkyne carbon atom. Our calculations suggest that, although the activation barriers of both processes (via **TS1-A** and **TS1-B**, respectively) are quite similar ($\Delta\Delta G^{\ddagger}$ = 0.3 kcal/mol), the formation of intermediate **INT2-B** is clearly thermodynamically favored over the spiranic species **INT2-A**. Moreover, whereas the formation of **INT2-B** is exergonic ($\Delta G_{R,298}$ = −3.4 kcal/mol), the process leading to **INT2-A** is endergonic ($\Delta G_{R,298}$ = 7.0 kcal/mol), which is hardly compatible with a process occurring at low temperature. Therefore, it can be concluded that the initial carbocyclization reaction does not involve a 5-*endo*-dig cyclization from the indole-C2 carbon atom but a 6-*endo*-dig process involving the indole-C3 carbon atom. Unfortunately, we were not able to locate on the potential energy surface a transition state

Scheme 6. Crossover Experiment To Assess the Intramolecular Nature of the Gold-Catalyzed Iodine Transfer



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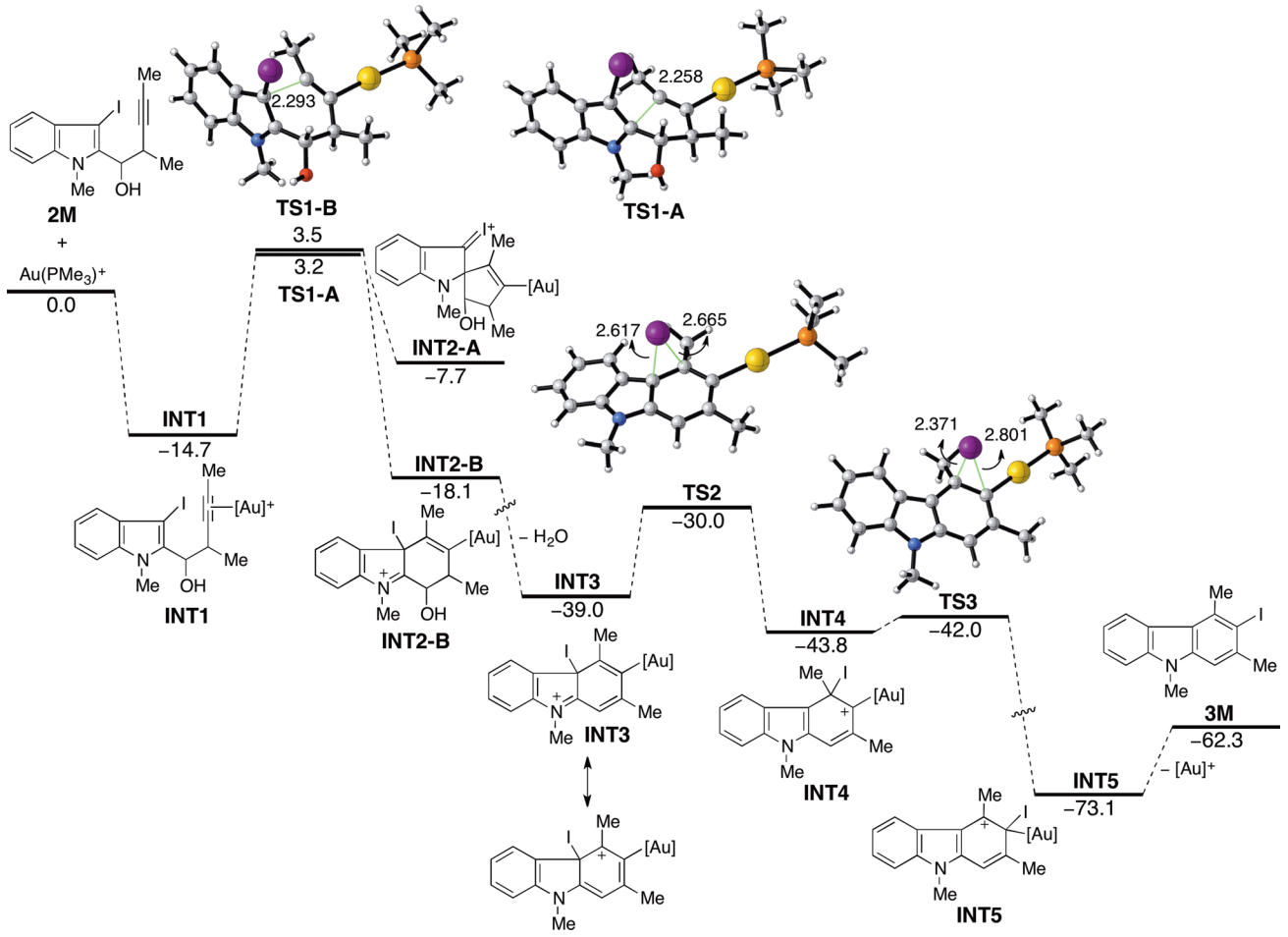
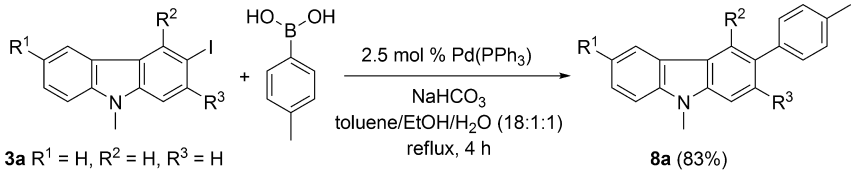


Figure 1. Computed reaction profile for the process involving alkynol **2M** and the model gold(I) catalyst $[Au(PMe_3)]^+$ (which is represented as $[Au]^+$). Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and Å, respectively. All data have been computed at the PCM(DCE)-B3LYP-D3/def-TZVP//B3LYP-D3/def2-SVP level.

Scheme 7. Functionalization of 3-Iodocarbazoles through Suzuki Cross-Coupling



3a R^1 = H, R^2 = H, R^3 = H
3e R^1 = MeO, R^2 = Ph, R^3 = Me

8a (83%)
8e (83%)

connecting **INT2-B** directly to intermediate **7** via a 1,3-iodine shift (Scheme 5). Instead, we found that a dehydration reaction occurs first, leading to **INT3** in a highly exergonic process ($\Delta G_{R,298}$ = −20.9 kcal/mol).[13] The exergonicity of this dehydration reaction is strongly related to the stabilization of the positive charge in **INT3** by conjugation (see some resonance structures in Figure 1). Then, **INT5** is formed through two consecutive 1,2-iodine shifts via transition states **TS2** ($\Delta G^{\ddagger}$ = 9.0 kcal/mol) and **TS3** ($\Delta G^{\ddagger}$ = 1.8 kcal/mol) in a strongly exergonic transformation ($\Delta G_{R,298}$ = −34.1 kcal/mol from **INT3**) instead of occurring via a direct 1,3-iodine shift. Finally, the transformation ends up with the decoordination of the gold(I) catalyst in **INT5** to produce the experimentally observed 3-iodocarbazoles **3**.

We also investigated the feasibility of the gold-catalyzed 1,3-halogen shift in (3-chloroindol-2-yl)butynol **2i** and (3-bromoindol-2-yl)butynol **2j**. However, the 1,3-iodine migration observed in iodoalkynols did not occur in their chlorine or bromine counterparts. The treatment of alkynols **2i,j** under otherwise identical conditions resulted in the recovery of the starting material along with a complicated mixture of products.

3-Iodocarbazoles **3** can undergo a further derivatization reaction through a Pd-catalyzed process to give the corresponding Suzuki coupling products. The Pd-catalyzed coupling between 3-iodocarbazole derivatives **3a,e** and 4-tolylboronic acid afforded products **8a,e**; even Suzuki coupling on the 3-iodocarbazole precursor where the iodine is flanked by two substituents works efficiently (Scheme 7). The capture of the iodine in a tandem sequence is more troublesome, because the reaction of (3-iodoindol-2-yl)butynols **2a,e** with 4-tolylboronic acid under a bimetallic Au−Pd catalytic system resulted in a complicated mixture.

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CONCLUSIONS

In conclusion, the controlled benzoannelation−iodine transfer process of 3-iodoindole-tethered alkynols into 3-iodo 2,4,6-trisubstituted 9*H*-carbazoles has been realized by using gold catalysis. This reaction sequence has been studied experimentally; additionally, its mechanism has been investigated by a DFT study. The overall transformation can be rationalized through a 6-*endo*-dig alkyne carbocyclization by chemo- and regiospecific attack of the C3 indole carbon to the external alkyne carbon followed by dehydration and two consecutive 1,2-iodine transfers. We hope that these selective cyclization reactions can be used in the efficient preparation of other types of heterocyclic compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00471.

Experimental procedures, characterization data of new compounds, copies of NMR spectra, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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(11) The major proton source for the protodeauration step in the formation of carbazole **4a** would be water, generated in situ in the aromatization step (in addition to moisture).

(12) See Computational Details in the Supporting Information.

(13) It is very unlikely that this dehydration reaction proceeds through a single transition state associated with the direct elimination of −OH and −H from the adjacent sp^3 carbons. Instead, we think that the process is assisted by a new molecule of [Au](NTf$_2$), where the [Au]$^+$ would coordinate the OH moiety (increasing its nucleofugacity) and the NTf$_2^-$ would act as a base.

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