Palladium-Catalyzed Hydroarylation of Homopropargyl Iodoindoles with Concurrent Alkyl and Iodonium Migrations

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Abstract. A selective palladium-catalyzed C(sp) arylation/carbocyclization/iodonium migration reaction sequence has been accomplished. Novel 2-iodo-1-aryl-9*H*-carbazoles are now easily available. As this result is contrary to the selectivity observed using gold catalysis, the formation of 2-iodo-carbazoles is noticeable, suggesting a metal-controlled cyclization through chemo- and regioselective 1,2-alkyl migration and 1,4-iodonium migration.

Keywords: carbazole; cyclization; homogeneous catalysis; iodonium migration; palladium

The carbazole core is a fundamental type of nucleus due to the widespread occurrence of this heterocycle in bioactive compounds, advanced materials, and natural products.^[1] Because the relevance of this framework, there is still a demand for the development of straightforward and efficient synthesis of the functionalized carbazole motif.

On the other hand, haloalkenes and haloarenes are widely used in metal-catalyzed cross-coupling reactions.^[2] However, the halogenated functionality is normally expelled, which diminished the synthetic utility of the obtained products. To surpass this limitation, the reintegration of the halogen atom into the target molecule has evolve into a challenging yet interesting issue.^[3] Hashmi et al. have described the preparation of disubstituted alkynes from terminal (indol-2-yl)butynols under Sonogashira conditions and its gold-catalyzed cyclization (Scheme 1a).^[4a] In the same year Ma reported the synthesis of carbazoles via Au(III)-catalyzed cyclization of 1-(indol-2-yl)-3-alkyn-1-ols.^[4b] while we have recently described the gold-

catalyzed intramolecular 1,3-iodine transfer reaction in (3-iodoindol-2-yl)butynols for the synthesis of polyfunctionalized carbazoles (Scheme 1b).^[5] Taking into account that the above iodine migration as well as the direct iodination of the carbazole nucleus occurred at the C3 position,^[6] the discovery of new protocols for the controlled preparation of iodinated carbazoles at different positions is challenging. Notwithstanding the significant progress attained in this area, the reported protocols suffer from drawbacks such as the necessity of preparation of sophisticated precursors. Our aim was the adoption of Pd-catalytic conditions in a tandem Sonogashira–carbocyclization process for the straightforward preparation of iodocarbazoles in a more efficient manner. Herein, we report an unprecedented palladium-catalyzed synthesis of 2-iodo-1-aryl-9*H*-carbazoles coupled to a selectivity switch in comparison with gold catalysis^[7] (Scheme 1c).

Previous work

Current work (c)

Scheme 1. Previous studies and current design for the metal-catalyzed hydroarylation reactions of C2-alkyne-tethered iodoindoles.

Table 1. Reaction of 1-(3-iodoindol-2-yl)but-3-yn-1-ol **1a** with iodoarene **2a** under modified metal-catalyzed conditions.

entry	catalyst	base	solvent	T (°C)	time (h) ^a	yield (%) ^b
1	Pd(OAc) ₂	K ₂ CO ₃	ethanol	80	1.5	3a (0)/ 4a (0)
2	Pd(OAc) ₂	DABCO	acetonitrile	40	2	3a (12)/ 4a (2)
3	Pd(OAc) ₂ /CuI	Et ₃ N	Et ₃ N	40	2	3a (15)/ 4a (2)
4	Pd(PPh ₃) ₂ Cl ₂ /CuI	Et ₃ N	Et ₃ N	40	2	3a (44)/ 4a (5)
5	Pd(PPh ₃) ₂ Cl ₂ /CuI	DABCO	acetonitrile	40	2	3a (35)/ 4a (3)
6	Pd(PPh ₃) ₂ Cl ₂ /CuI	Na ₂ CO ₃	DMF	60	2	3a (21)/ 4a (2)
7	CuI	Et ₃ N	Et ₃ N	40	2	3a (0)/ 4a (0)
8	NiI ₂ (PPh ₃) ₂ /Mn	-	toluene	80	2	3a (5)/ 4a (1) ^c

^a) Reaction progress was followed by TLC. ^b) Yield of pure, isolated product with correct analytical and spectral data. ^c) 40% of non-iodinated **1a** was recovered.

Initially, the reaction between 1-(3-iodo-1-methyl-1*H*-indol-2-yl)but-3-yn-1-ol **1a** and 1-iodo-4-methoxybenzene **2a** was evaluated. To our satisfaction, when the process was catalyzed by a palladium complex, the 1-aryl-2-iodo-9*H*-carbazole **3a** was obtained as the dominating product (Table 1). Worth of note, carbazole **3a** is an unanticipated product which should arise from a Sonogashira/skeletal reorganization sequence. The formation of **3a** contrasts with the previously reported gold-catalyzed sequence^[5] and is a nice example of diverting selectivity through the judicious election of metal catalyst. Taking into account the role of bases and ligands in Pd-catalyzed reactions, the optimizations of the reaction conditions was performed by the use of different palladium-based salts, bases, and solvents. The experiments in Table 1 disclosed that Pd(PPh₃)₂Cl₂ as the palladium source and CuI as co-catalyst led to the best result, and carbazole **3a** was achieved in 44% yield (Table 1, entry 4). Control experiments revealed that the cross-coupling/carbocyclization/rearrangement/iodine migration sequence was not detected in the absence of the palladium complex (Table 1, entry 7). The copper co-catalyst is necessary for the reaction to proceed because in the absence of the copper salt little or none carbazole product was obtained. Organic bases such as Et₃N and DABCO performed better than inorganic bases

(Na₂CO₃ and K₂CO₃). Solvent screening showed that the use of Et₃N both as base as well as solvent was very effective. Nickel salts provided a poor outcome (Table 1, entry 8). 1-Iodo-4-methoxybenzene **2a** could be substituted by 1-bromo-4-methoxybenzene, but carbazole **3a** was obtained with a diminished yield.

Next, the electronic effects imparted by the presence of different substituents at the iodoarene were evaluated using iodoalkynol **1a** as the model substrate. From results in Scheme 2, it became evident that the electronic nature of the iodoarene partner could modulate the selectivity outcome. The presence of electron-donating substituents such as methoxy on the benzene ring have a marked directing effect of the formed iodocarbazole products, with the main product being the 1-aryl-2-iodo-9*H*-carbazole **3** isomer. When iodoarenes **2** bearing an electron-withdrawing substituent such as nitro on the benzene ring were used, the selectivity was reverted in favour of the 4-aryl-3-iodo-9*H*-carbazole counterpart **4**. Afterwards, the generality of this cross-coupling/skeletal reorganization sequence was studied using heteroaryl iodides such as 2-iodothiophene and 3-iodo-1*H*-indole-2-carbaldehydes. When the optimized reaction conditions were applied to these heteroaryl iodides and iodoalkynol **1a**, chromatographically separable mixtures of carbazoles **3** and **4** were obtained. In case whereas

the competing reaction could not be fully suppressed. the practical application of this method in organic synthesis was obvious because

both isomeric carbazoles could be easily separated by bench column chromatography.

Scheme 2. Controlled preparation of iodocarbazoles **3a-j,p** under palladium catalyzed conditions.

Next, the scope of the above transformation was assessed through the reaction between substituted indoles **1** and iodoarenes **2** (Scheme 3). Employing the optimized conditions, the preparation of various iodocarbazole derivatives was accomplished starting from 1-(3-iodo-1*H*-indol-2-yl)but-3-yn-1-ols **1b-d** bearing substitution at the benzene ring of the indole nucleus. The cross-coupling/skeletal reorganization sequence was amenable to the presence of neutral or electron-rich benzenoid rings at the indole framework such as in precursors **1a-c**. However, but-3-yn-1-ol **1d** with a fluorine atom at the indole moiety did react under our conditions to afford the classical Sonogashira product **1da** rather than the challenging cross-coupling/carbocyclization/rearrangement/iodine migration adduct. Fortunately, by forcing conditions (heating at 60 °C), iodocarbazole **3o** could be obtained (Scheme 3). Oxidative addition of the indole C–I bond does not occur. Complete conversion was observed, but some dimerization of the starting alkynols **1** was detected (Glaser

coupling), which may be responsible for the moderate isolated yields of carbazoles **3** and **4**. An alternative procedure for the formation of 1-aryl-2-iodocarbazoles which takes advantage of the iodocyclization reaction between 1-(indol-2-yl)but-3-yn-1-ols and electrophilic iodinated reagents has previously been reported.^[8] By contrast with our protocol, Liang's group starts from non-iodinated precursors and the iodination arises from an external reagent.

Taking into account the interesting reactivity of homopropargyl iodoindoles while preserving the synthetically valuable iodo functionality in the final carbazole products, we decided to take advantage of iodo-functionalized adducts **3** and **4** for further transformations through Suzuki reaction. Thus, the coupling reaction of selected iodocarbazoles **3a,b,d,f** and **4a,d,f** with (4-methoxyphenyl)boronic acid was performed. As shown in Scheme 4, the corresponding 1,2-diaryl- or 3,4-diaryl-carbazoles **5** and **6** which cannot be easily prepared by alternative synthetic routes, were smoothly obtained in fair yields. Heck reaction between iodocarbazole **3a** and styrene

was also successfully accomplished resulting in 1-aryl-2-styryl-carbazole **7**.

Scheme 3. Controlled preparation of iodocarbazoles **3k–o** under palladium-catalyzed conditions.

Bearing in mind the isolation of homopropargylic alcohol **1da**, we decided to study the possible isolation of Sonogashira products as putative intermediates for the iodocarbazole formation. Indeed, under otherwise identical reaction conditions for the formation of iodocarbazoles **3** and **4** but after a short reaction time (15 min), the coupling between iodoalkynol **1a** and iodoarene **2a** yielded the corresponding Sonogashira adduct **1aa** (Scheme 5). We presumed that adducts of type Sonogashira could be transformed into iodocarbazoles. As expected, a further exposure of compound **1aa** to the palladium-catalyzed conditions generated iodocarbazoles **3a** and **4a** in 60% and 7% yields, respectively (Scheme 5). Consequently, it should be concluded that alkynes substituted at the terminal end are intermediates for the generation of iodocarbazoles. An additional control experiment which consisted in the metal-catalyzed reaction of **1aa** but in the absence of $\text{Pd(PPh}_3)_2\text{Cl}_2$ resulted in no formation of the carbazole products while the disappearance of CuI did not affect the reaction, thus disfavoring the Cu-activation scenario in this step (Scheme 5). Unsurprisingly, the reaction of the deuterium-labeled alkyne **1d1-1a** with iodoarene **2a** under optimized conditions resulted in the formation of non-deuterated iodocarbazoles **3a** and **4a** (Scheme 5).

A conceivable justification that explains the construction of 2-iodocarbazoles **3** is depicted in Scheme 6. Sonogashira adducts **INT-1** should

initially be formed under palladium catalysis from (3-iodoindol-2-yl)butynols **1** and iodoarenes **2**. Thus, the first catalytic cycle is completed. Iodoarenes **2** are selectively cross-coupled with alkynols **1**, but there is no homo-coupling of the alkyne moiety in **1** with the heteroaryl iodide of a second molecule of **1** probably because of the steric hindrance imparted by the butynol side chain in (3-iodoindol-2-yl)butynols **1**. Next, coordination of the palladium salt to the alkyne moiety brings about palladium complex **INT-1-Pd**, which provokes further spirocyclization through 5-*endo-dig*-carbopalladation by nucleophilic attack of the C2 indole carbon atom. Based on recent DFT studies on related systems which support that the 5-*endo-dig* path rather than the 6-*endo-dig* path is kinetically favourable^[9] we proposed a 5-*endo-dig* carbopalladation with the C2 (less nucleophilic position of indole) rather than attack from the 3-position of the indole ring to give 6-*endo-dig* carbopalladation.^[10] The so-formed pallada-spirocyclopentene intermediate **INT-2** suffers a chemo- and regioselective 1,2-alkyl migration to generate iodotetrahydrocarbazolium species **INT-3**. Consecutive 1,4-iodonium migration provided 2-iodo-1-aryl-4,9-dihydro-3*H*-carbazol-4-ols **INT-4** along with the regeneration of the palladium catalyst in the second catalytic cycle. The direct 1,4-iodonium migration did not probably occur and it may be better described as a formal 1,4-iodonium migration composed of several

consecutive 1,2 shifts, which are thermally allowed and would ultimately result in a formal 1,4-I migration. After dehydration, intermediates **INT-4** afforded aromatic 2-iodo carbazole derivatives **3**. The C–I bond within the product may be formed by reductive elimination; however taking into account the previous report on the gold-catalyzed synthesis of iodocarbazoles in which this step is not feasible,^[5] we believe that iodine transfer may be operative. The C–I bond within the product may also be formed by initial iodonium lost during the aromatization process

and further C–Pd bond cleavage, but a related iodine transfer is being supported by DFT in a previous report.^[5] We feel that there are not two independent mechanisms (5-*endo-dig* cyclization for isomer **3** versus 6-*endo-dig* cyclization for isomer **4**) simultaneously operating; we rather think that the mixture of products **3** and **4** arises from competitive 1,2-migrations (alkyl versus alkenyl), and the formation of **INT-3** is favoured by electron-donating aryl groups.

Scheme 4. Synthesis of 1,2(3,4)-diaryl-9*H*-carbazoles **5,6** and 1-aryl-2-styryl-carbazole **7** under Suzuki or Heck reaction conditions.

Scheme 5. Control experiments.

Scheme 6. Feasible pathway for the palladium-catalyzed preparation of 2-iodocarbazoles **3** from yodoindoles **1**.

In summary, a novel approach to build 2-iodo-1-aryl-9*H*-carbazoles through a convenient Pd-catalyzed C(sp)-H arylation/carboacylation/iodonium migration domino reaction has been developed. This protocol reveals that palladium not only can conduct the Sonogashira reaction on terminal (indol-2-yl)butynols but also provides distinct selectivity compared with gold. This sequence is complementary to the Au-catalyzed process, as we possess now a divergent strategy to form each isomer of the carbazole products, namely 2-iodo-1-aryl-9*H*-carbazoles and 3-iodo-4-aryl-9*H*-carbazoles,^[11] with high selectivity. The formation of these iodocarbazoles is also of interest because the aryl iodide moiety of the so-obtained iodocarbazoles can be further functionalized via Suzuki cross-coupling.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Reaction of 1-(3-iodo-1-methyl-1*H*-indol-2-yl)but-3-yn-1-ols; Synthesis of 2-iodo-1-aryl-9*H*-carbazoles 3a/4a.

A solution of alkynol **1** (50 mg, 0.154 mmol) in Et₃N (0.22 mL, 1.54 mmol) was added dropwise to a stirred solution of 4-iodoanisole (40 mg, 0.169 mmol), CuI (0.6 mg, 0.00308 mmol) and PdCl₂(PPh₃)₂ (1 mg, 0.00154 mmol) in Et₃N (0.39 mL, 2.8 mmol) at room temperature. Then, the reaction was heated at 40°C after disappearance of the starting material (TLC). The mixture was washed with NH₄Cl (3 x 20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extract was washed with brine (2 x 15 mL), dried (MgSO₄) and concentrated under reduced pressure. A mixture of two carbazoles in a ratio (90:10) was obtained. After chromatography of the residue using *n*-hexane/ethyl acetate (9:1) as eluent, a less polar compound **3a** (28 mg, 44 %) and a more polar compound **4a** (3 mg, 5%) were obtained. **Iodocarbazole 3a**. Colorless oil; ¹H NMR (300 MHz, CDCl₃, 25°C) δ: 8.10 (1H, d, *J* = 7.7 Hz, H Ar), 7.79 (2H, s, H Ar), 7.49 (1H, ddd, *J* = 8.3, 7.2, 1.1 Hz, H Ar), 7.32-7.23 (4H, m + AA'XX', H Ar + 2 CH Ar PMP), 7.06-7.03 (2H, AA'XX', 2 CH Ar PMP), 3.93 (3H, s, O-CH₃), 3.19 (3H, s, N-CH₃); ¹³C NMR (75 MHz, CDCl₃, 25°C) δ: 159.5 (C Ar), 141.5 (C Ar), 139.0 (C Ar), 134.9 (C Ar), 131.9 (2 x CH Ar), 129.3 (C Ar), 129.2 (CH Ar), 126.3 (CH Ar), 123.6 (C Ar), 122.1 (C Ar), 120.6 (CH Ar), 120.0 (CH Ar), 119.4 (CH Ar), 113.5 (2 x CAr), 108.9 (CH Ar), 100.2 (C Ar), 55.3 (O-CH₃), 32.0 (N-CH₃); IR (CDCl₃, cm⁻¹): ν 2926 (Ar, C-H), 2853 (O-CH₃), 1512 (Ar), 1245 (Ar); HRMS (ES): calcd for C₂₀H₁₇NO [M + H]⁺: 414.03493; found: 414.03413. **Iodocarbazole 4a**. Colorless oil; ¹H NMR (700 MHz, CDCl₃, 25°C) δ: 7.98 (1H, d, *J* = 8.5 Hz, H Ar), 7.42-7.39 (1H, m, H Ar), 7.37 (1H, d, *J* = 8.1 Hz, H Ar), 7.28-7.27 (2H, AA'XX', 2 CH Ar PMP), 7.18 (1H, d, *J* = 8.6 Hz, H Ar), 7.12-7.11 (2H, AA'XX', 2 CH Ar PMP), 6.95 (1H, ddd, *J* = 8.1, 6.5, 1.7 Hz, H Ar), 6.78 (1H, d, *J* = 8.0 Hz, H Ar), 3.96 (3H, s, O-CH₃), 3.87 (3H, s, N-CH₃); ¹³C NMR (175 MHz, CDCl₃, 25°C) δ: 159.3 (CAr), 140.9 (CAr), 140.8 (CAr), 140.7 (CAr), 135.0 (CHAr), 130.4 (2xCHAr), 126.0 (CHAr), 122.8 (CAr), 122.4 (CHAr), 122.2 (CAr), 119.1 (CHAr), 114.1 (2xCHAr), 109.4 (CHAr), 108.2 (CHAr), 89.3 (CAr), 55.3 (O-CH₃), 29.2 (N-CH₃); IR (CDCl₃, cm⁻¹): ν 2924 (Ar, C-H), 2853 (O-CH₃), 1243 (Ar).

Supporting Information Available: Experimental procedures, characterization data of new compounds, and

copies of NMR spectra. This material is available free of charge on the ACS Publication website at DOI: .

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- [10] Besides, the direct 6-*endo-dig* carbopalladation could only explain the formation of minor carbazole isomers **4** but not major rearranged isomers **3**.
- [11] 2D NMR spectra and NOE experiments allowed the unequivocal identification of isomeric carbazoles **3** and **4**. It should be noted that the relative ¹H NMR chemical shift of the *N*-CH₃ protons for the **3** and **4** iodocarbazoles is a useful check of the regiochemistry; for any pair of **3** and **4** isomers, the *N*-CH₃ hydrogens of 3-iodocarbazoles **4** were approximately 0.4–0.7 ppm downfield of the analogous hydrogens of 2-iodocarbazoles **3**.

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