

2,3-Diodocarbazoles by a Domino Iodocyclization/Iodo-Translocation of (3-Iodoindolyl)butynols

Irene Martín-Mejías,^a A. Sonia Petcu,^a José M. Alonso,^{b,*}
Cristina Aragoncillo,^{b,*} and Pedro Almendros^{a,*}

^a Instituto de Química Orgánica General, IQOG, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain

E-mail: palmendros@iqog.csic.es

^b Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain

E-mail: caragoncillo@quim.ucm.es; josalo08@ucm.es

Manuscript received: May 25, 2022; Revised manuscript received: September 27, 2022;

Version of record online: November 7, 2022



Supporting information for this article is available on the WWW under <https://doi.org/10.1002/adsc.202200564>

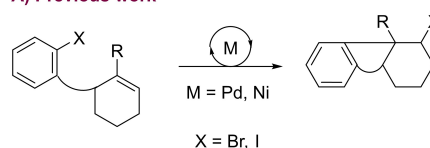
© 2022 The Authors. Advanced Synthesis & Catalysis published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Abstract: A controlled access to 1-aryl 2,3-diiodo-carbazoles involving iodine transposition has been accomplished directly from acyclic precursors. The 2,3-diiodo-carbazole core was prone to further chemoselective decoration at C3–I or double di-functionalization.

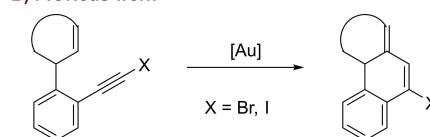
Keywords: carbazole; cascade reactions; cyclization; iodine translocation; metal-free

The classical and widespread cross-coupling reactions of organic compounds bearing a C–X (X = halogen) bond proceed through an oxidative addition of the organohalide to the metal and imply X loss.^[1] Taking into account the interest in organohalides and chiefly iodinated arenes,^[2] the transfer of the halogen atom into the newly prepared molecule is appealing but difficult. In this context, the reintegration of the X atom of halogenated molecules through metal-catalyzed carbohalogenations via reductive elimination is an emerging strategy (Scheme 1A).^[3] A less explored methodology is the gold-catalyzed iodine recycling during 1-iodoalkyne carbocyclization (Scheme 1B).^[4] Recently, we reported the iodine transfer across an indole nucleus under gold- and palladium-catalyzed conditions (Scheme 1C).^[5] As only metal-catalyzed halogen translocation is available in literature, we were curious to explore the metal-free unexplored path. It should be mentioned that although halogenation of C3

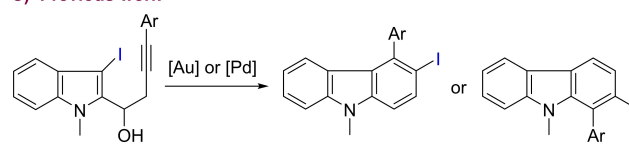
A) Previous work



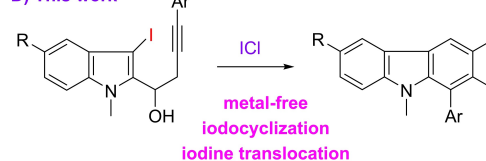
B) Previous work



C) Previous work



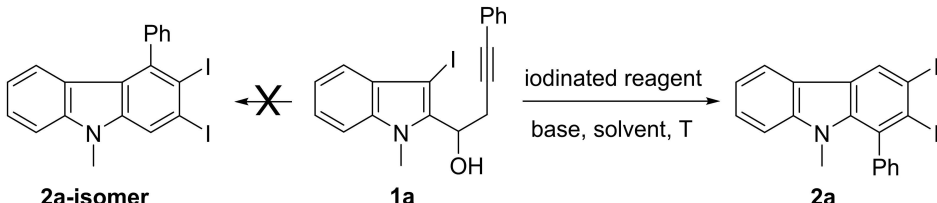
D) This work



Scheme 1. Prior art and current strategy.

position is attainable, the halogenation at C2 is intrinsically difficult because of the steric and electronic properties of carbazoles.^[6] Besides, simultaneous halo-

Table 1. Iodination-carbocyclization-iodine migration of (iodoindolyl)butynol **1a** under modified reaction conditions.



entry	Iodinated reagent ^[a]	base	solvent	T (°C)	yield 2a (%) ^[b]
1	I ₂	K ₂ CO ₃	<i>i</i> PrOH	−15	12
2	NIS	K ₂ CO ₃	<i>i</i> PrOH	−15	8
3	ICl	K ₂ CO ₃	<i>i</i> PrOH	−15	60
4	Ipy ₂ BF ₄	K ₂ CO ₃	<i>i</i> PrOH	−15	7
5	ICl ^[c]	K ₂ CO ₃	<i>i</i> PrOH	−15	50
6	ICl	K ₂ CO ₃	<i>i</i> PrOH	0	19
7	ICl	K ₂ CO ₃	<i>i</i> PrOH	20	6
8	ICl	Et ₃ N	<i>i</i> PrOH	−15	28
9	ICl	DBU	<i>i</i> PrOH	−15	21
10	ICl	K ₂ CO ₃	EtOH	−15	44
11	ICl	K ₂ CO ₃	MeCN	−15	20
12	ICl	K ₂ CO ₃	1,4-dioxane	−15	15

^[a] The reactions were run using **1a** (0.1 mmol) and iodinated reagent (0.25 mmol).

^[b] Yield of pure, isolated product with correct analytical and spectral data.

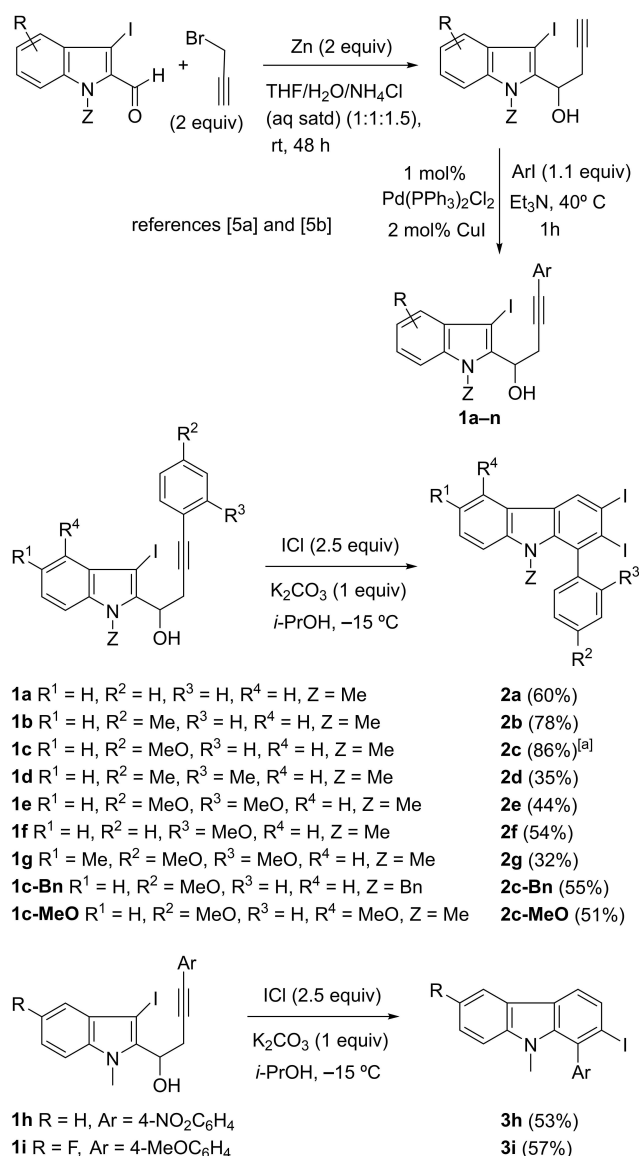
^[c] 0.11 mmol of ICl were used.

genation of C3 and C2 positions has not yet been developed. Herein, we report a catalyst-free access to 1-aryl 2,3-diiodo-carbazoles^[7,8] involving iodine transposition (Scheme 1D). Noteworthy, our protocol allows for the controlled functionalization of the carbazole core at three contiguous positions,^[9] namely, C1, C2 and C3.

Cyclization precursors, (iodoindolyl)alkynols **1a–n**, were prepared from the appropriate indole-2-carbaldehyde using known procedure.^[5] Our journey started with the study of the reaction of phenyl-substituted alkynol **1a** as model substrate (Table 1).^[10] We explored the reaction of **1a** with several iodinated reagents such as I₂, NIS, ICl and Ipy₂BF₄. The tandem iodocyclization-iodine translocation was effectively attained through the use of ICl^[11] in isopropanol at −15 °C in presence of sodium carbonate. The utilization of 1.1-fold excess of ICl provided tricycle **2a** in 50% yield (Table 1, entry 5) while the use of 2.5-fold excess produced the desired heterocycle in 60% yield (Table 1, entry 3). Total conversion was observed by TLC and ¹H NMR analysis of the crude reaction mixture, and no side-products or polymerisation reactions were detected. However, some decomposition was observed during purification of 2,3-diiodo-carbazole **2a** by column chromatography, which may be responsible for the moderate isolated yield. Noteworthy, the rearranged 1-phenyl-2,3-diiodo-carbazole **2a** was obtained as the only regioisomer. The use of organic bases instead K₂CO₃ or different solvents

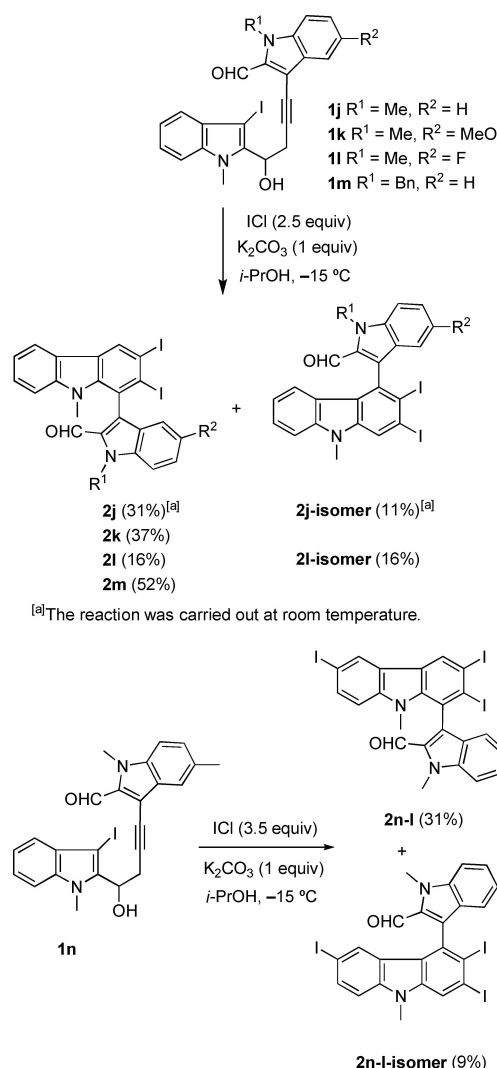
generated 2,3-diiodo-carbazole **2a** in diminished yield (Table 1).

With the optimal conditions in hand, we next studied the generality of the process (Scheme 2). The presence at the alkyne end of electron-rich aromatic moieties such as 4-tolyl in **1b** or 4-anisyl in **1c** was beneficial because the corresponding 2,3-diiodo-carbazoles **2b** and **2c** were achieved in 78% and 86% yields, respectively. Besides, the sequence displayed steric tolerance as evidenced by the formation of 2,3-diiodo-carbazole **2f** bearing an *ortho*-methoxyphenyl moiety. However, 2,3-diiodo-carbazoles **2d** and **2e** having 2,4-dimethylphenyl or 2,4-dimethoxyphenyl substituents were achieved in diminished yields (35% and 44%) in comparison with parent **2a**. 4-Arylbut-3-yn-1-ol **1g** linked to a 5-methyl substituted indole nucleus reacted to provide 2,3-diiodo-carbazole **2g**. Replacing the N-methyl group with a N-benzyl moiety such as in **1c-Bn** smoothly formed product **2c-Bn** in total selectivity, while the reaction of precursors having a carbamate or a sulfonamide group failed. Disappointingly, the reaction of free (NH)-indoles with ICl resulted in a complicated mixture, thus avoiding its use for accessing 2,3-diiodo-carbazoles. 1-(3-Iodo-4-methoxy-indol-2-yl)-4-but-3-yn-1-ol **1c-MeO** was transformed into 5-methoxy-carbazole **2c-MeO** in a competent way (Scheme 2), which evidenced that it is also possible to prepare 2,3-diiodo-C5-substituted carbazoles through our iodocyclization/iodo-translocation strategy. Unfortunately, neither the presence of an



Scheme 2. Synthesis of 2,3-diiodo-carbazoles **2a–g**.^[a]The reaction was carried out at room temperature.

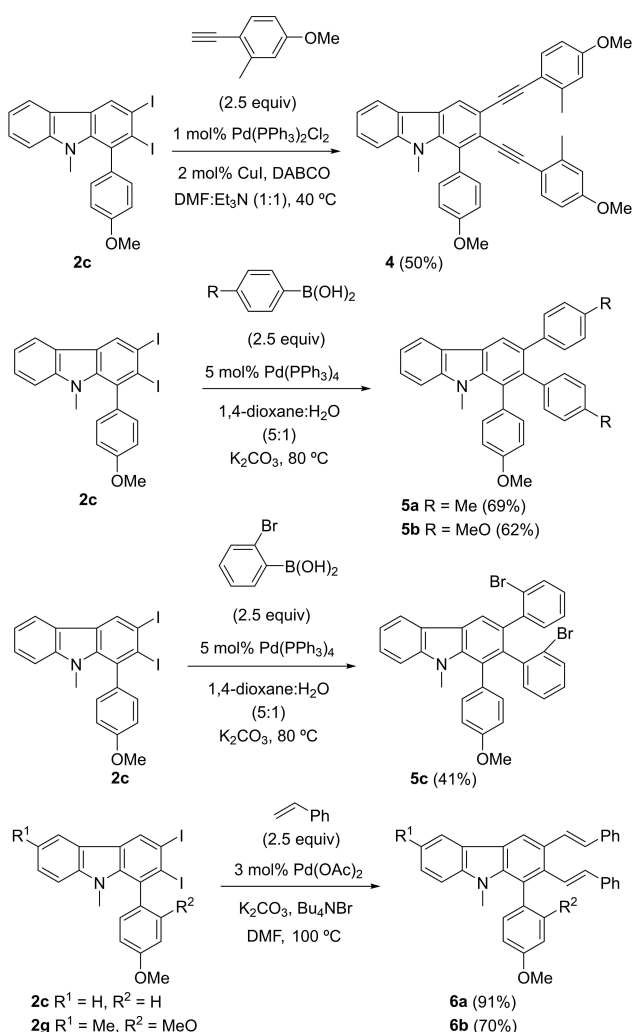
electron-poor 4-nitrophenyl substituent at the alkyne end nor a fluorine atom at the C5 indole nucleus were tolerated, because in both cases the exclusive formation of 2-iodo-carbazoles **3h** and **3i** was detected (Scheme 2). Interestingly, sterically congested (iodoindolyl)alkynols **1j–n** bearing an extra indole nucleus at the alkyne end were well accommodated and were transformed into 2,3-diiodo-carbazoles **2j–n** and 2,3,6-triiodo-carbazole **2n-I** (Scheme 3). In some cases (**1j,l,n**), chromatographically separable regioisomeric C4-indolyl carbazoles (**2j,l,n-I-isomer**) were isolated as minor components. The positional selectivity in 1-aryl carbazoles **2c**, **2j** and **2j-isomer** was identified through selective NOE irradiation of the N-9-CH₃ protons, which resulted in enhancement in the



Scheme 3. Synthesis of 2,3-diiodo-carbazoles **2j–m** and 2,3,6-triiodo-carbazole **2n–I**.

signals of the aromatic protons of the 4-MeOC₆H₄ group at C1 in **2c**, in enhancement in the signal of the aldehydic proton in **2j**, and in enhancement in the signals of C1–H and C8–H in **2j-isomer** (see ESI).

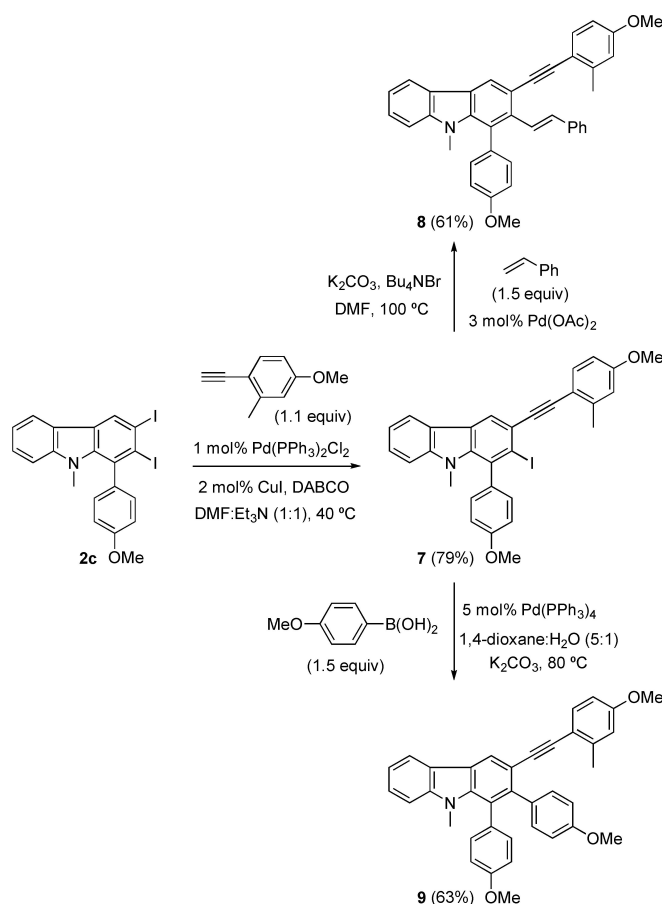
Having suitably exemplified the cyclization reaction to give 2,3-diiodocarbazoles **2**, we decided to investigate the reactivity under Pd-catalyzed cross-coupling reactions. By subjecting selected 1-aryl-2,3-diiodo-carbazoles **2** to Sonogashira, Suzuki or Heck protocols, the corresponding 1,2,3-trifunctionalized carbazoles **4–6** were obtained in reasonable yields through double functionalization reactions (Scheme 4). Even sterically encumbered 2-bromophenylboronic acid allowed the simultaneous two-fold customization at C2 and C3 in **2c** resulting in the formation of triarylated carbazole **5c**, but with a slightly lesser efficiency. Similarly, precursor **2g** having a bulky aromatic ring conveniently afforded polysubstituted



Scheme 4. Two-fold functionalization of 2,3-diiodo-carbazoles **2**.

heterocycle **6b** after treatment with styrene under Pd catalysis.

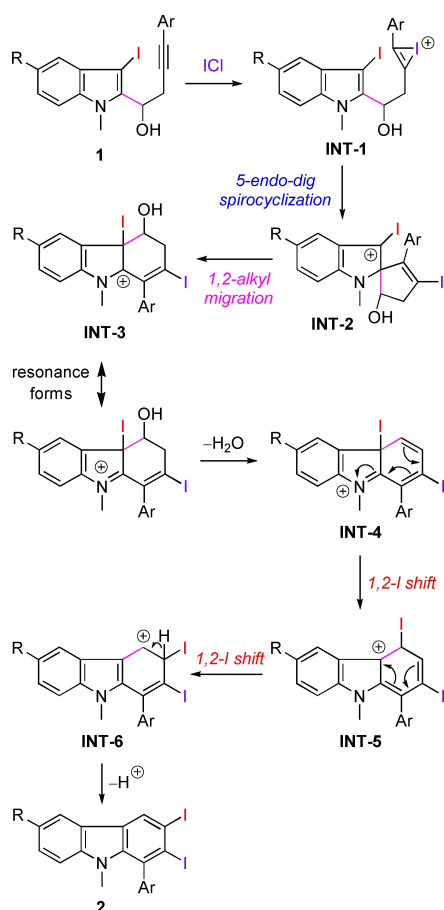
Haloarenes bearing several halogen functionalities such as 2,3-diiodo-carbazoles **2** are challenging substrates for chemoselective cross-coupling reactions due to site selectivity problems. Having successfully accomplished two-fold cross coupling reactions in **2**, we decide to pursue a controlled monofunctionalization. Pleasingly, chemoselective Sonogashira mono-coupling reaction was attained in 2,3-diiodo-carbazole **2c** at the C3 position, giving rise to 3-alkynyl-1-aryl-2-iodo-carbazole **7** in 79% yield. NMR data analysis demonstrated to be a convenient tool to establish the linking position of the alkyne moiety on alkynyl-iodocarbazole **7** (see ESI), allowing full structural assignment.^[12] The chemoselective C3–I activation was probably dictated by steric factors, taking place at the less hindered position. Nicely, heterocycle **7** was prone to further functionalization at C2–I through



Scheme 5. Controlled mono-functionalization of 2,3-diiodo-carbazole **2c**.

Heck reaction with styrene, leading to 1-aryl-2-alkenyl-3-alkynyl carbazole **8** in 61% yield (Scheme 5). In addition of the Heck functionalization, Suzuki-type termination was successfully accomplished in the mono- Sonogashira adduct **7**, which smoothly provided 1,2-diaryl-3-alkynyl carbazole **9** (Scheme 5). In this way, many 1,2,3-trifunctionalized carbazoles could be conveniently constructed in a predictable fashion.

A reasonable pathway for the ICl-assisted genesis of 2,3-diiodo-carbazoles **2** is depicted in Scheme 6. The transformation is speculated to hold an ionic nature, with the initial formation of the three-membered iodonium intermediate **INT-1** by reaction of the alkyne moiety with the cationic iodine atom of ICl. **INT-1** evolves to spirocyclic species **INT-2** through nucleophilic attack of the C2 indole position into the external carbon atom of the iodonium **INT-1**. After the 5-*endo-dig* spirocyclization, the formation of indolinium intermediate **INT-3** should occur by selective 1,2-alkyl migration. The driving force of this migration may well be the stability of the so-formed indolinium intermediate **INT-3**. Next, water release occurs to form



Scheme 6. Mechanistic explanation for the ICl-promoted synthesis of 2,3-diiodo-carbazoles **2**.

iminium species **INT-4** which is followed by a further 1,2-iodine migration. The generation of intermediate **INT-5** should be followed by an additional 1,2-iodine migration to build carbocationic species **INT-6**. Finally, loss of proton creates the neutral and aromatic 2,3-diiodo-carbazoles **2**.^[13] Our guess is that the mixture of positional isomers **2j/2j-isomer**, **2l/2l-isomer** and **2n/2n-isomer** arises from competitive 1,2-migrations (alkyl *versus* alkenyl) in intermediates **INT-2** (1,2-alkyl migration for compounds **2** and 1,2-alkenyl migration for isomers **2-isomer**). The iodocyclization/de-iodination pathway followed by precursors **1h,i** to form mono-iodo carbazoles **3h,i** may be explained from an increased tendency to iodonium elimination in intermediates **INT-4** due to the presence of electron-withdrawing substituents.

In conclusion, we report the metal-free iodination-carbocyclization-iodine migration of (iodoindolyl)butynols as a direct and controlled access to the elusive 2,3-diiodo-carbazole core. Both, further chemoselective functionalization at C3–I as well as two-fold cross-coupling reactions were applicable and

a number of 1,2,3-trifunctionalized carbazoles were built.

Experimental Section

General Procedure for the Synthesis of 2,3-Di-iodo-1-aryl-9H-carbazoles **2**

K₂CO₃ (1 equiv.) was added to a solution of the appropriate (iodoindolyl)butynol **1** (1 equiv.) in *i*PrOH (38 mL/mmol) at –15 °C. After five minutes, ICl (2.5 equiv.) dissolved in *i*PrOH was added dropwise, under argon atmosphere. Then, the reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction as indicated by TLC, the mixture was poured into Na₂S₂O₃ and extracted with EtOAc (3 × 10 mL). The organic extract was washed with water (3 × 10 mL), dried (MgSO₄) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/*n*-hexane mixtures gave analytically pure diiodocarbazoles **2**.

2,3-Diiodo-1-(4-methoxyphenyl)-9-methyl-9H-carbazole 2c. From 93 mg (0.215 mmol) of alkynol **1c**, and after flash chromatography of the residue using *n*-hexane/ethyl acetate (6:1) as eluent, compound **2c** (97 mg, 86%) was obtained as a pale-yellow thick gum; ¹H NMR (300 MHz, CDCl₃): δ = 8.38 (1H, d, *J* = 1.7 Hz, CH_{Ar}), 7.79 (1H, d, *J* = 8.2 Hz, CH_{Ar}), 7.72–7.69 (2H, m, CH_{Ar}), 7.24–7.20 (2H, AA'XX', 2 × CH_{Ar}PMP), 7.08–7.03 (3H, m, CH_{Ar} and 2 × CH_{Ar}PMP), 3.93 (3H, s, O-CH₃), 3.14 (3H, s, N-CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 159.5 (C_{Ar}), 140.6 (C_{Ar}), 138.8 (C_{Ar}), 135.5 (C_{Ar}), 134.4 (CH_{Ar}), 131.8 (2 × CH_{Ar}), 129.7 (CH_{Ar}), 129.6 (C_{Ar}), 128.8 (CH_{Ar}), 124.6 (C_{Ar}), 122.3 (C_{Ar}), 120.7 (CH_{Ar}), 113.5 (2 × CH_{Ar}), 111.0 (CH_{Ar}), 101.2 (C_{Ar}), 81.9 (C_{Ar}), 55.3 (O-CH₃), 32.1 (N-CH₃); IR (CHCl₃): ν = 1512, 1544 cm^{–1}; HRMS (ES): calcd for C₂₀H₁₆I₂NO [*M*+H]⁺: 539.93158; found: 539.92909.

Supporting Information Available

Experimental procedures, characterization data of new compounds, and copies of NMR spectra.

Acknowledgements

This work was supported in part by MCIN/AEI /10.13039/501100011033/FEDER (Project PGC2018-095025-B-I00). I. M. thanks MCIN for a predoctoral contract. A. S. P. thanks CAM and FEDER (YEI) for a contract.

References

- [1] a) L. Xue, Z. Lin, *Chem. Soc. Rev.* **2010**, *39*, 1692–1705; b) M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4879–5203; c) A. Biffis, P. Centomo, A. D. Del Zotto, M. Zecca, *Chem. Rev.* **2018**, *118*, 2249–2295.
- [2] a) Y. Sasson, Formation of Carbon-Halogen Bonds (Cl, Br, I) in *Halides, Pseudo-Halides and Azides*; Eds.: P. Patai, Z. Rappoport, John Wiley and Sons: New York, 1995; b) G. W. Gribble, *J. Chem. Educ.* **2004**, *81*, 1441–

- 1449; c) F. C. Kupper, M. C. Feiters, B. Olofsson, T. Kaiho, S. Yanagida, M. B. Zimmermann, L. J. Carpenter, G. W. Luther, Z. Lu, M. Jonsson, L. Kloo, *Angew. Chem. Int. Ed.* **2011**, *50*, 11598–11620; *Angew. Chem.* **2011**, *123*, 11802–11825; d) J. M. Schomaker, R. D. Grigg, *Synlett* **2013**, *24*, 401–407; e) C. Chen, X. Tong, *Org. Chem. Front.* **2014**, *1*, 439–446; f) L. Zani, A. Dessi, D. Franchi, M. Calamante, G. Reginato, A. Mordini, *Coord. Chem. Rev.* **2019**, *392*, 177–236; g) L. Xu, J. Zhang, L. Yin, X. Long, W. Zhang, Q. Zhang, *J. Mater. Chem. C* **2020**, *8*, 6342–6349.
- [3] For seminal reviews, see: a) D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003–8104; b) D. J. Jones, M. Lautens, G. P. McGlacken, *Nat. Catal.* **2019**, *2*, 843–851; c) D. Bag, S. Mahajan, S. D. Sawant, *Adv. Synth. Catal.* **2020**, *362*, 3948–3970.
- [4] a) V. Mamane, P. Hennenand, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575; b) P. Nösel, T. Lauterbach, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 8634–8641; c) P. Morán-Poladura, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2015**, *54*, 3052–3055; *Angew. Chem.* **2015**, *127*, 3095–3098; d) S. Mader, L. Molinari, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2015**, *21*, 3910–3913; e) P. Nösel, V. Müller, S. Mader, S. Moghimi, M. Rudolph, I. Braun, Rominger, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2015**, *357*, 500–506.
- [5] a) B. Alcaide, P. Almendros, J. Alonso, E. Busto, I. Fernández, M. P. Ruiz, G. Xiaokaiti, *ACS Catal.* **2015**, *5*, 3417–3421; b) I. Martín-Mejías, C. Aragoncillo, P. Almendros, *Adv. Synth. Catal.* **2021**, *363*, 1449–1456.
- [6] For an elegant synthesis of 2-iodo-carbazoles, see: S. Yaragorla, R. Dada, D. Bag, *Eur. J. Org. Chem.* **2019**, 6983–6988.
- [7] For the use of halogenated carbazoles as precursors of bioactive compounds and advanced materials, see: a) S. Yaragorla, D. Bag, R. Dada, K. V. J. Jose, *ACS Omega* **2018**, *3*, 15204–15034 and references therein; b) J. R. Dobscha, H. D. Castillo, Y. Li, R. E. Fadler, R. D. Taylor, A. A. Brown, C. Q. Trainor, S. L. Tait, A. H. Flood, *J. Am. Chem. Soc.* **2019**, *141*, 17588–17600; c) M. H. Ghom, M. S. Naykode, V. T. Humne, P. D. Lokhande, *Tetrahedron Lett.* **2019**, *60*, 1029–1031 and references therein; d) L. Przypis, K. Z. Walczak, *J. Org. Chem.* **2019**, *84*, 2287–2296 and references therein.
- [8] Vicinal dihalogenated arenes have attracted considerable interest due to their biological properties and usefulness both as building blocks as well as organocatalysts in organic synthesis: a) M. Wienhold, J. J. Molloy, C. G. Daniliuc, R. Gilmour, *Angew. Chem. Int. Ed.* **2021**, *60*, 685–689; *Angew. Chem.* **2021**, *133*, 695–699 and references therein; b) T. Kaehler, A. John, T. Jin, M. Bolte, H.-W. Lerner, M. Wagner, *Eur. J. Org. Chem.* **2021**, 5847–5851 and references therein; c) R. M. Al-Zoubi, R. M. Altamimi, W. K. Al-Jammal, K. Q. Shawkfeh, M. S. Al-Zoubi, M. J. Ferguson, A. Zarour, A. Yassin, A. Al-Ansari, *Synthesis* **2021**, *53*, 2665–2675; d) L. Habert, K. Cariou, *Angew. Chem. Int. Ed.* **2021**, *60*, 171–175; *Angew. Chem.* **2021**, *133*, 173–177 and references therein.
- [9] The functionalization of the carbazole nucleus is a difficult task due to its poor reactivity, by virtue of the high stability imparted by the extended delocalization of the π -electrons. For selected reports on the introduction of substituents at the carbazole core, see: a) B. Urones, R. Gómez-Arrayás, J. C. Carretero, *Org. Lett.* **2013**, *15*, 1120–1123; b) T. Okada, K. Nobushige, T. Satoh, M. Miura, *Org. Lett.* **2016**, *18*, 1150–1153; c) J. A. Leitch, C. J. Heron, J. McKnight, G. Kociok-Kohn, Y. Bhonoah, C. G. Frost, *Chem. Commun.* **2017**, *53*, 13039–13042; d) S. Samala, J. Shin, J. Y. Shim, E. J. Yoo, *Asian J. Org. Chem.* **2017**, *6*, 998–1002; e) X.-T. Wu, E.-K. Xiao, F. Ma, J. Yin, J. Wang, P. Chen, Y.-J. Jiang, *J. Org. Chem.* **2021**, *86*, 6734–6743; f) S. S. Bera, S. B. Bahukhandi, C. Empel, R. M. Koenigs, *Chem. Commun.* **2021**, *57*, 6193–6196; g) E.-K. Xiao, X.-T. Wu, F. Ma, L.-W. Miao, Y.-J. Jiang, P. Chen, *Chem. Commun.* **2021**, *57*, 7148–7151; h) I. A. Pocock, A. M. Alotaibi, K. Jagdev, C. Prior, G. R. Burgess, L. Male, R. S. Grainger, *Chem. Commun.* **2021**, *57*, 7252–7255.
- [10] For a review on the cyclization of heteroarene-tethered alkynes, see: D. Bag, S. D. Sawant, *Chem. Eur. J.* **2021**, *27*, 1165–1218.
- [11] For a review on the synthetic utility of ICl, see: D. P. Day, N. I. Alsenani, A. A. Alsimaree, *Eur. J. Org. Chem.* **2021**, 4299–4307.
- [12] Incorporation of one alkyne unit into 2,3-diiodo-carbazole **2c** to generate 3-alkynyl-1-aryl-2-iodo-carbazole **7** provokes a shielding effect in the C4–H proton of the mono cross-coupling product compared to the starting material, while no remarkable effect is observed on the chemical shift of the hydrogen signals belonging to the *para*-methoxyphenyl substituent. The C4–H proton of **2c** resonates at 8.38 ppm while C4–H proton of **7** is shifted upfield to 8.25 ppm.
- [13] Taking into consideration that 3-membered iodonium-alkyne complexes **INT-1** are unlikely to be intermediates (a combined DFT and experimental study has concluded that the iodonium ion attacks the alkyne moiety directly to give an open iodovinyl cation: R. Volpe, L. Aurelio, M. G. Gillin, E. H. Krenseke, B. L. Flynn, *Chem. Eur. J.* **2015**, *21*, 10191–10199), a reviewer suggested an alternative mechanism to Scheme 6. This alternative mechanism (Scheme S1, Supporting Information) also replaces the spontaneous elimination of water from the cationic intermediates **INT-3** that is followed by two consecutive 1,2-iodine migration steps, with a proton migration to drive water elimination, followed by an iodonium ion release and re-attack. The formation of mono-iodo species **3h,i** from substrates bearing electron-withdrawing substituents, may then arise from a reduced susceptibility of **3h,i** to iodonium re-attack.