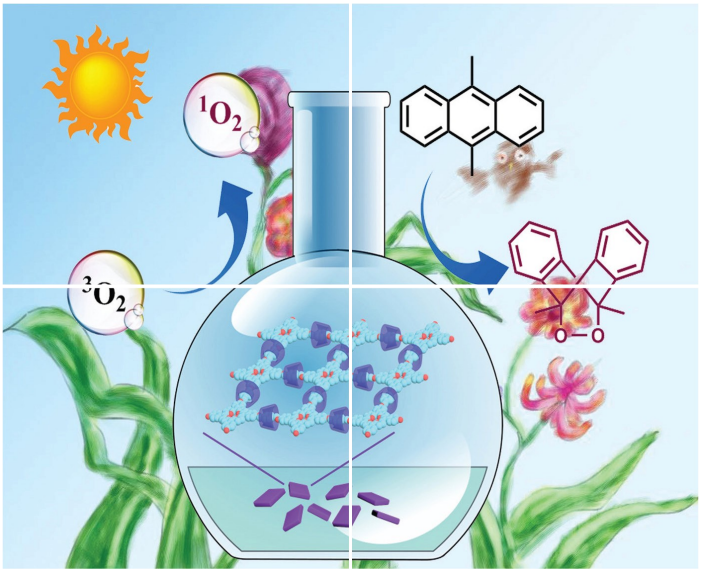
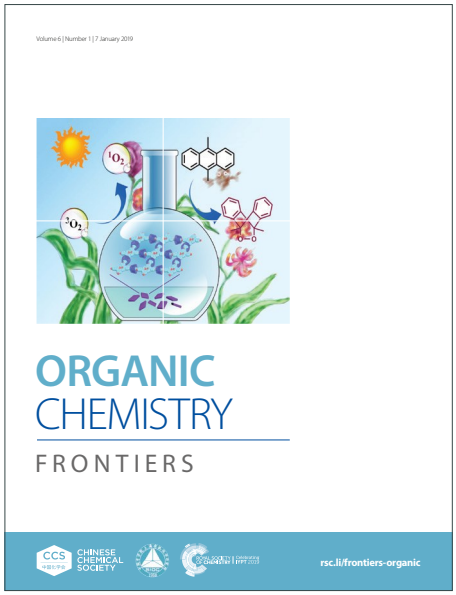
ORGANIC CHEMISTRY

FRONTIERS

Accepted Manuscript




This article can be cited before page numbers have been issued, to do this please use: F. Martínez-Lara, A. Suárez, S. Suárez-Pantiga, M. J. Tapia Estévez and R. Sanz, *Org. Chem. Front.*, 2020, DOI: 10.1039/D0QO00405G.



ORGANIC CHEMISTRY FRONTIERS

View Article Online
DOI: 10.1039/D0QO00405G

RESEARCH ARTICLE

# Straight access to highly fluorescent angular indolocarbazoles *via* merging Au- and Mo-catalysis

Fernando Martínez-Lara, Anisley Suárez, Samuel Suárez-Pantiga, M. José Tapia, and Roberto Sanz*

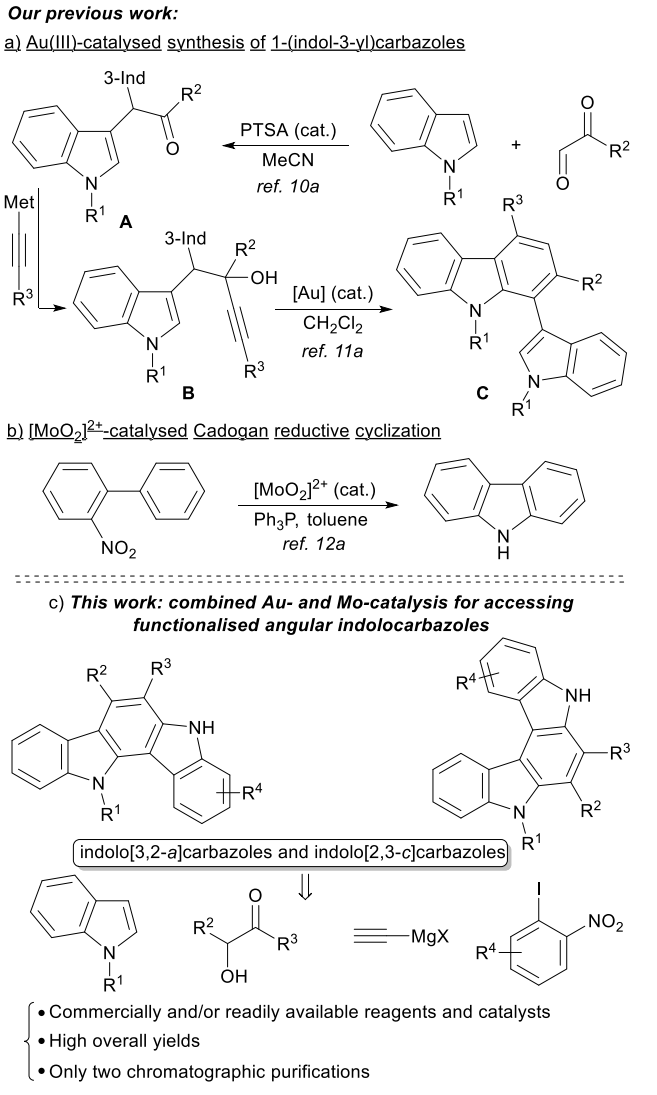
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A straightforward and efficient synthesis of the two less explored types of indolocarbazoles has been developed. Two different processes for the carbazole nucleus preparation, a gold-catalysed regioselective cyclization followed by the dioxomolybdenum-catalysed version of Cadogan reductive cyclization, enables the sequential construction of two carbazole cores. The procedure features total regioselectivity and high overall yields. The required starting α-indol-3-ylalkyl propargylic alcohols are easily and efficiently accessed from commercially available reagents. In addition, the photoluminescent properties of two indolo[2,3-*c*]carbazoles, with fluorescence quantum yields around 0.7, have been studied.

## Introduction

Indolocarbazoles are privileged scaffolds that possess a wide range of biological activities[1] and diverse applications in organic electronics.[2] Five different isomers have been recognized depending on the position and orientation of the fusion between the indole and the carbazole units.[3] Among them, angular indolocarbazoles, such as indolo[3,2-*a*]carbazoles[4] and, mainly, indolo[2,3-*c*]carbazoles[5] have been studied in much lesser extension than the linear isomers likely due to the lack of efficient methods for their preparation. Even though some reports have revealed the potential of the indolo[2,3-*c*]carbazole core as fairly promising OLEDs and other interesting optoelectronic properties,[2b,6] the synthesis of these molecules appear limited and frequently focused in simple examples.[7] Moreover, most of the reported procedures afford substrates with both nitrogen atoms equally substituted. Recently, few methods have been designed to synthesize functionalised indolo[2,3-*c*]carbazoles with the aim of achieving a fine-tuning of the optical properties.[6a-c] By contrast, carbazole synthesis has experienced an outstanding development.[8,9] Into this regard, we have described the Au(III)-catalysed[10] cyclization of 1,1-bis(indol-3-yl)-3-alkyn-2-ols **B**, prepared from readily accessible α,α-bis(indol-3-yl) ketones **A**,[11] affording a wide range of 1-(indol-3-yl)carbazoles **C** through a selective 1,2-rearrangement involving an alkyl migration over the alkenyl migration (Scheme 1a).[12] Due to the elevated functional group tolerance of this reaction, carbazoles bearing 2-nitroaryl substituents could be easily accessed opening the possibility to subsequently carry out Cadogan reductive cyclization, such as




**Scheme 1** Our previous work: Au(III)-catalysed synthesis of indolylcarbazoles and $[MoO_2]^{2+}$-catalysed reductive cyclization of 2-nitrobiaryls. This work: synthesis of regioselectively-functionalised angular indolocarbazoles.

*Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain. E-mail: rsd@ubu.es; Fax: (+34) 947258831*

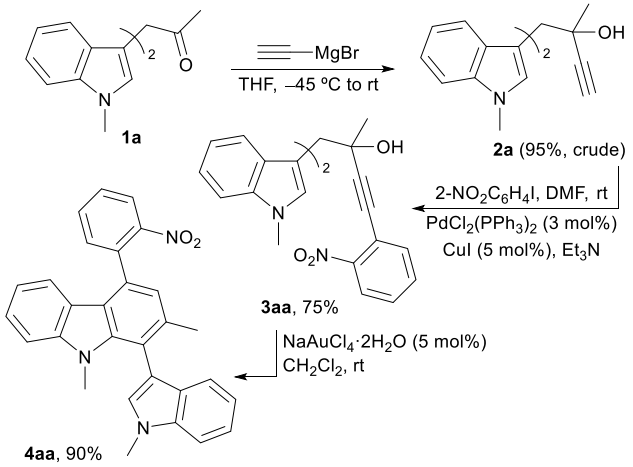
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, complementary photophysical studies, and NMR spectra. See DOI: 10.1039/x0xx00000x

the Mo-catalysed one developed by our group and widely used by other authors (Scheme 1b).[13] At this point, we envisaged that indolocarbazoles could be synthesized by an initial gold-catalysed carbazole synthesis followed by a $[MoO_2]^{2+}$-catalysed Cadogan reaction. This strategy of synthesis is based on using readily available reagents such as indole, Grignard reagents, α-hydroxyketones, and 2-nitro-1-halobenzenes (Scheme 1c). Interestingly, the regioselectivity of the migration step during the carbazole generation under gold-catalysis could determine which of the two proposed indolocarbazole cores could be synthesized.

## Results and discussion

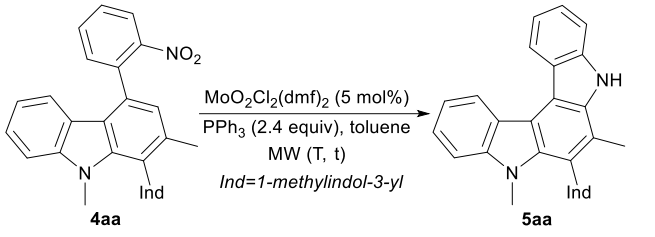
Initially, to test the feasibility of our strategy, α,α-bis(indol-3-yl)ketone **1a** was prepared in gram scale (5.5 g, 17.6 mmol) upon treatment of *N*-methylindole and pyruvaldehyde with catalytic amounts of *p*-toluenesulfonic acid.[11a] After the addition of ethynylmagnesium bromide, the 1,1-bis(indol-3-yl)-3-alkyn-2-ol **2a** was almost quantitatively obtained (Scheme 2). Interestingly, the crude alkynol was successfully subjected to a standard Sonogashira-type reaction to install the 2-nitroaryl moiety leading to the nitro-functionalised alkynol **3aa**. After performing the first purification by column chromatography, the synthesis of the carbazole derivative was evaluated. When compound **3aa** was treated with $NaAuCl_4.2H_2O$ under the disclosed reaction conditions,[12a] the desired cyclization proceeds smoothly affording carbazole **4aa**. After the initial tests, the reaction was successfully scaled up to gram scale, providing pure enough carbazole in 90% yield (1.3 g, 3 mmol) (Scheme 2).

With an efficient access to **4aa** just developed, we evaluated the planned Cadogan reaction (Table 1). Based on our previous experience in molybdenum catalysed reduction of nitroarenes,[13a,14] we selected $MoO_2Cl_2(dmf)_2$ as a suitable catalyst. Initial experiments revealed that under microwave irradiation at 150 °C in toluene after 30 min, the desired indolo[2,3-*c*]carbazole **5aa** was obtained (entry 1). Although in




**Scheme 2** Preparation of model indolylcarbazole **4aa** from α,α-bis(indol-3-yl)ketone **1a**.

**Table 1** Reaction conditions for the reductive cyclization of indolylcarbazole **4aa**. Synthesis of indolocarbazole **5aa**[a]



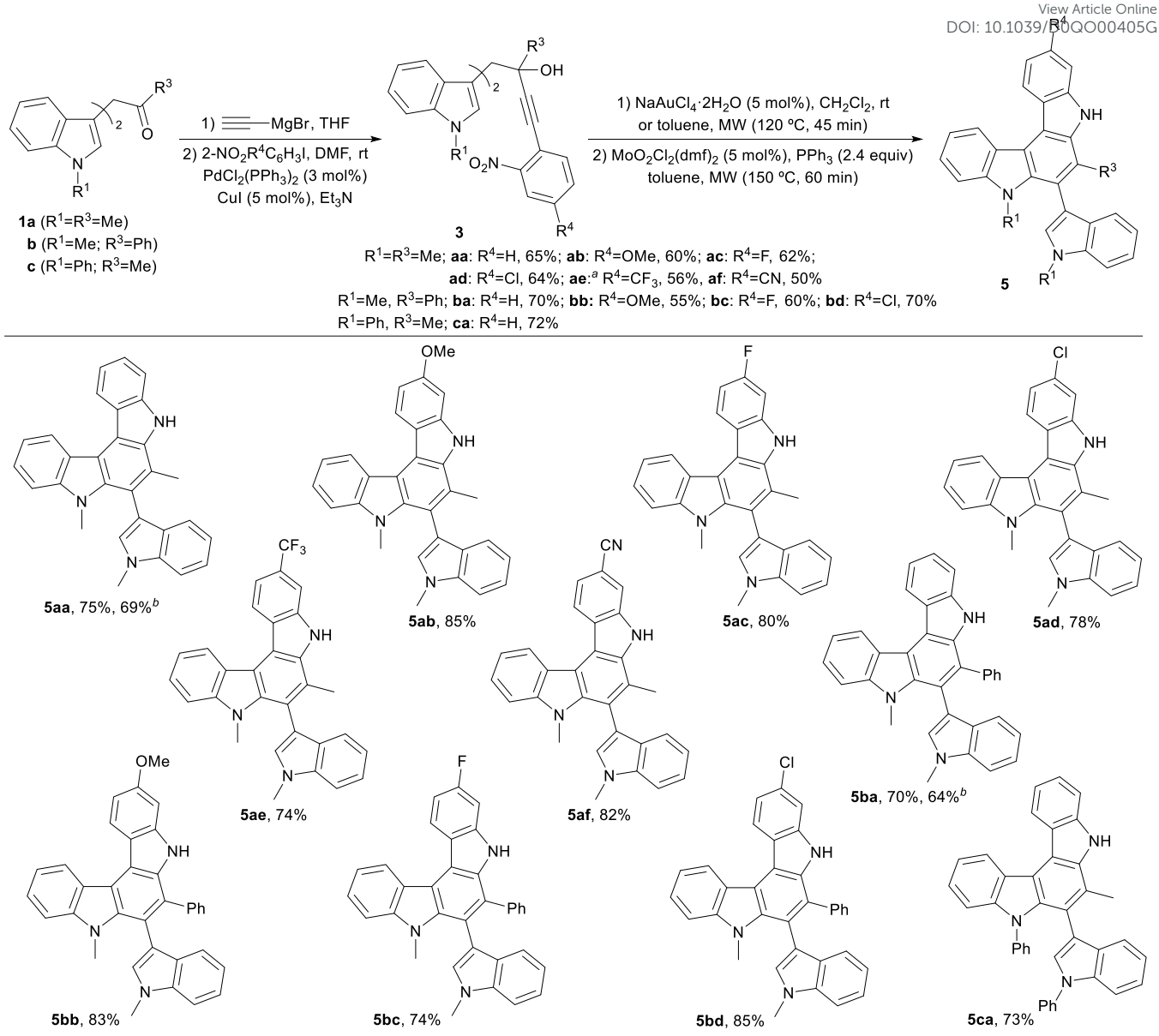

| Entry | T (°C) | t (min) | Conversion[b] (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 150 | 30 | 73 | 60 |
| 2 | 150 | 45 | 93 | 80 |
| 3 | 150 | 60 | 100 | 88 (82)[c] |
| 4 | 180 | 60 | 100 | 83 |
| 5[d] | 110 | overnight | 100 | 82 |
| 6[e] | 150 | 60 | 32 | 20 |

[a] Reaction conditions: **4aa** (0.3 mmol), $PPh_3$ (0.72 mmol), $MoO_2Cl_2(dmf)_2$ (5 mol%) in toluene (0.6 mL). [b] Determined by $^1H$ NMR using $CH_2Br_2$ as an internal standard. [c] Isolated yield after column chromatography. [d] Carried out under conventional refluxing conditions. [e] The reaction was performed in absence of the catalyst.

this case full conversion is not reached, it could be easily achieved by increasing the reaction time (entries 2–3). Just after 60 min (entry 3), the complete conversion was observed affording compound **5aa** in 88% yield (82% isolated). Higher temperatures do not provide any improvement (entry 4), and slightly lesser yields are obtained. Interestingly, the reaction could also be performed under conventional heating by refluxing in toluene (110 °C) for 24 h (entry 5). The increased reaction times cause some degradation of **5aa**, affording slightly lower yields. Finally, in the absence of the molybdenum catalyst, the desired indolocarbazole **5aa** was obtained in low yields (entry 6). Increasing reaction times in the absence of the catalyst does not lead to any improvement in the process.

With suitable catalytic conditions for both the gold and molybdenum-catalysed steps, we turned our attention to evaluate the applicability of this strategy to the synthesis of different indolo[2,3-*c*]carbazoles **5** (Scheme 3). A selection of 1,1-bis(indol-3-yl)-3-alkyn-2-ols **3** was readily prepared by varying the indole ($R^1$), the starting glyoxal ($R^3$), and the 2-nitroaryl moiety ($R^4$). Then, these compounds underwent a cyclization reaction, promoted by $NaAuCl_4$, affording the corresponding carbazoles **4**. Without further purification, the crude carbazoles were directly subjected to Mo-catalysed Cadogan reaction delivering the desired indolocarbazoles **5**. Starting indoles bearing *N*-methyl (**5aa-af**, **5ba-bd**) or *N*-phenyl (**5ca**) substituents are well tolerated. Modification of the nature of $R^3$ does not have a significative influence over the performance of both steps, and the indolocarbazoles derived from methyl or phenyl substituted glyoxals were obtained in similar yields. The presence of electron-donating or electron-withdrawing groups over the 2-nitroaryl moiety was also tolerated allowing access to methoxy-functionalised indolocarbazoles (**5ab**, **5bb**) or halogenated and cyano-functionalised indolocarbazoles (**5ac-af**, **5bc-bd**), respectively, in high yields.

Organic Chemistry Frontiers ARTICLE
View Article Online
DOI: 10.1039/D0QO00405G

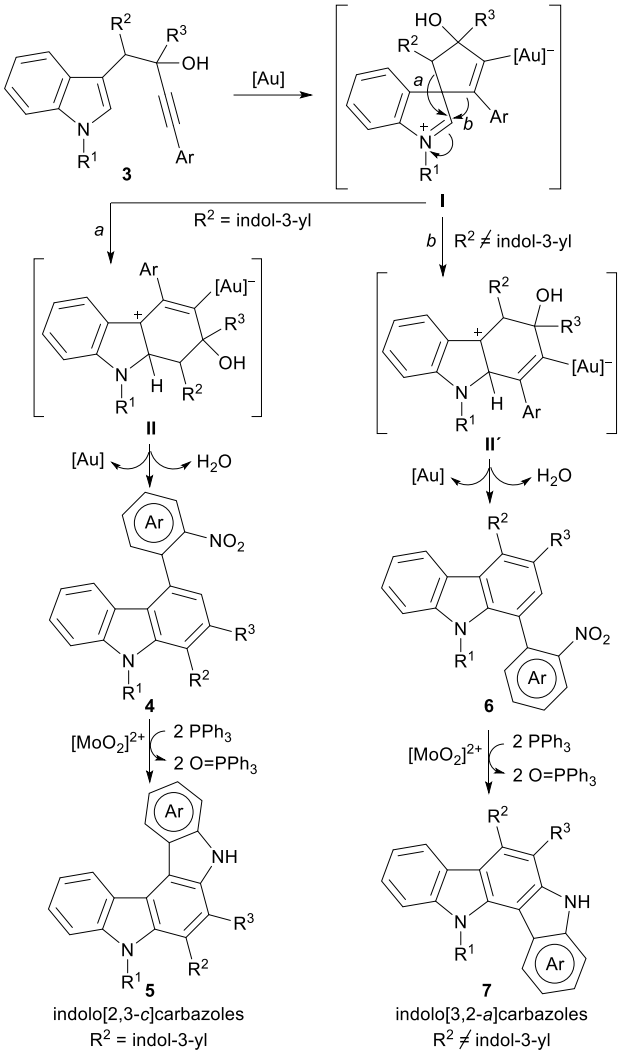



**Scheme 3** Synthesis of indolo[2,3-*c*]carbazoles **5**. [a]Prepared from 1-bromo-2-nitro-4-(trifluoromethyl)benzene at 70 °C. [b]Reaction performed in a one-pot two step sequence using toluene as solvent for the Au- and Mo-catalysed reactions.

At this stage and taking advantage of the high efficiency and reliability of the Au(III)-catalysed cyclization step, we hypothesized that the design of a one-pot procedure for this tandem sequence, involving carbazole formation followed by Cadogan reaction, could be suitable.

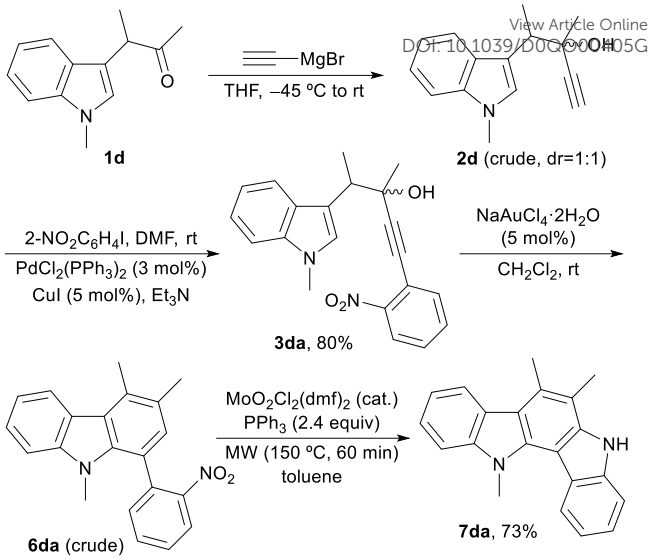
After some screening, it was revealed that whereas the molybdenum-catalysed Cadogan reaction could be performed efficiently only by using toluene as solvent, the gold-catalysed cyclization demonstrated to have a lower dependence with the solvent and, interestingly, it could be successfully accomplished in toluene. Moreover, under microwave irradiation at 120 °C the Au(III)-catalysed cyclization takes place within 45 min. Under these reoptimized conditions, we were able to perform the one-pot synthesis of indolocarbazoles **5aa** and **5ba** in high yields from their parent alkynols **3** (Scheme 3).

In the overall sequence, the gold-catalysed cyclization plays a decisive role in accessing indolo[2,3-*c*]carbazoles **5**. According to our previously described mechanism proposal (Scheme 4), the alkynol **3** after coordination with the gold catalyst delivers the spirocyclic intermediate **I**.[15] Then, this compound could evolve onto two competitive pathways. On the one hand, through path *a* an alkyl 1,2-migration takes place generating intermediate **II**, which through aromatization and loss of one molecule of water delivers carbazole **4**. Subsequent Cadogan cyclization affords the desired indolo[2,3-*c*]carbazoles **5**. Interestingly, in an alternative way, a 1,2-alkenyl migration could take place (Scheme 4, path *b*) obtaining the intermediate




**Scheme 4** Mechanistic proposal for the synthesis of indolo[2,3-*c*]carbazoles **5** and proposed approach for the preparation of indolo[3,2-*a*]carbazoles **7**.

**II'**. Then, a similar evolution of **II'** through aromatization and dehydration provides a different type of carbazole **6** in which the 2-nitroaryl moiety is found in position 1 instead of position 4 as previously described for the route *a*. Interestingly, carbazoles **6** are also plausible substrates for Cadogan reaction, but in this case, the cyclization would afford indolo[3,2-*a*]carbazoles **7**. In fact, if the control of one migration over the other would be possible, the assembly of two differentiated indolocarbazoles moieties could be achieved. Considering our previous mechanistic studies,[12a] we hypothesized[16] the nature of substituent $R^2$ as a critical factor in achieving this goal. DFT studies prove that when this substituent is an indol-3-yl group, the cleavage of the bond between the spiranic carbon and the alkyl fragment is considerably more favoured because of the resulting carbocation is stabilized by conjugation with the vicinal indole. Thus, it is likely to think that replacing this substituent by another group possessing less electronic density will render in promoting the competitive 1,2-alkenyl migration. To provide access to indolo[3,2-*a*]carbazoles **7** from alkynols **3**, we envisioned that if $R^2$ is a simple alkyl group, the 1,2-alkenyl migration is more likely to take place and therefore carbazoles




**Scheme 5** Synthesis of indolo[3,2-*a*]carbazole **7da** from α-indolylketone **1d**.

**6** would be obtained. To test our hypothesis, we efficiently synthesized 3-(1-methyl-1*H*-indol-3-yl)butan-2-one **1d** from *N*-methylindole and acetoin by using catalytic amounts of molecular bromine (Scheme 5).[11c] Then, the crude compound **1d** was subjected to the developed synthetic sequence. After reacting with an excess of ethynylmagnesium bromide, the corresponding alkynol **2d** was obtained as a 1:1 mixture of diastereoisomers. The crude **2d** affords, under the previously established Sonogashira reaction conditions, the alkynol derivative **3da** that possesses only one indole ring. Next, **3da** was treated with catalytic amounts of $NaAuCl_4.2H_2O$ in $CH_2Cl_2$, according to the general procedure. The reaction proceeded smoothly, affording only one compound identified, after NMR analysis, as carbazole **6da**. Remarkably, the process takes place with total control of the regioselectivity. As it was hypothesized, by merely replacing the $R^2$ substituent in **1** from an indole (**1a**) to a methyl group (**1d**), the 1,2-alkenyl migration is favoured and, so, carbazole **6da** was selectively obtained. Additionally, the reaction proceeds so efficiently that the crude carbazole could be used in the next step without further purification.

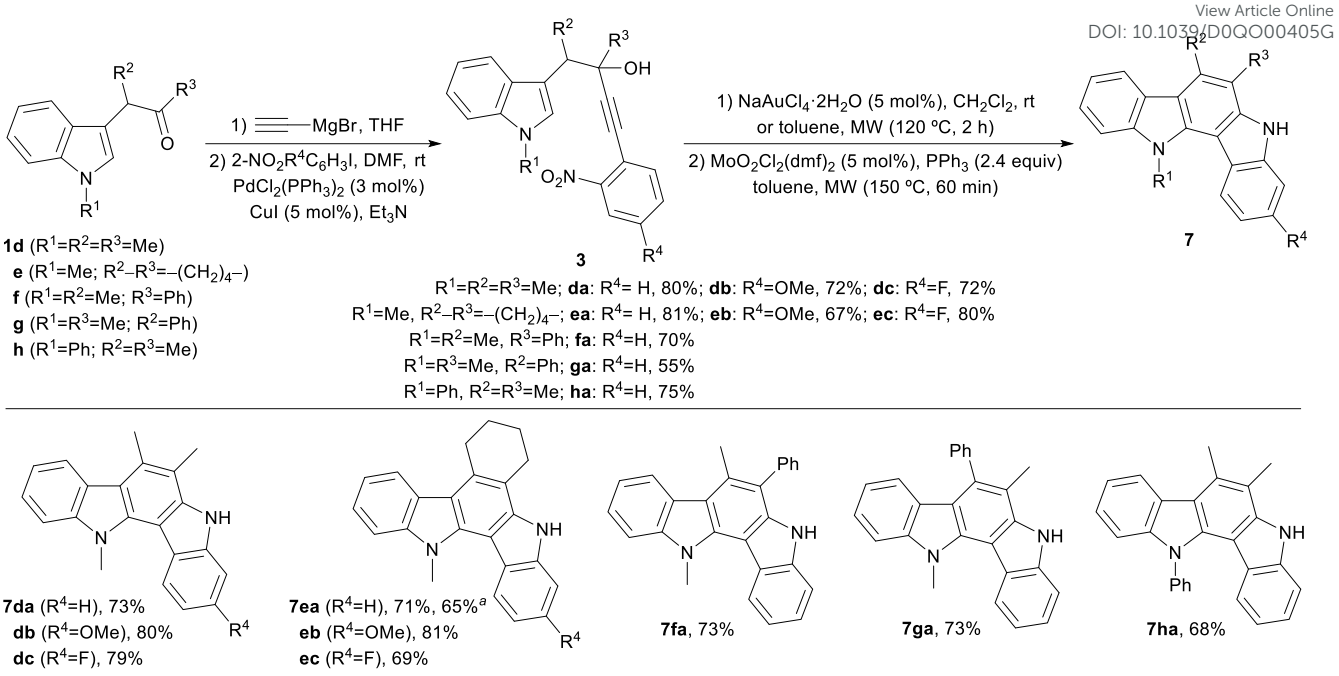
Finally, we tested the Cadogan cyclization. Under the optimized reaction conditions, carbazole **6da** is efficiently converted into indolo[3,2-*a*]carbazole **7da** in high yield referred to alkynol **3da** (Scheme 5).

Once it was demonstrated that indolo[3,2-*a*]carbazoles could also be accessed from the corresponding alkynols **3**, we decided to synthesize a variety of compounds bearing this scaffold to test the influence of different substituents (Scheme 6). Initially, we focused on the substitution of the initial indole. Both *N*-methyl (**7da-dc**, **7ea-ec**, **7fa**, **7ga**) and *N*-phenyl (**7ha**) substituted indoles could be used as starting materials. Additionally, the influence of substituents $R^2$ and $R^3$ was also studied. The transformation was proved to be general with both alkyl (**7da-dc**) or cycloalkyl (**7ea-ec**) groups achieving in all cases similar yields. Besides, an alkynol with $R^2$=Me and $R^3$=Ph (**3fa**) delivered the desired carbazole **7fa** in a 73% yield. By swapping both groups, the reaction takes place, and in the same



View Article Online
DOI: 10.1039/D0QO00405G




**Scheme 6** Synthesis of functionalised indolo[3,2-*a*]carbazoles **7**. [a]Reaction performed in a one-pot two step sequence using toluene as solvent for the gold- and molybdenum-catalyzed reactions.

extension affording carbazole **7ga** (Scheme 6). The effect of electron-donating and moderate electron-withdrawing groups over the 2-nitroaryl moiety was studied by placing methoxy and fluorine substituents. The presence of methoxy substituents delivered the corresponding indolocarbazoles in slightly higher yields (**7db**, **7eb**). Alkynols **3** having the 2-nitroaryl substituent bearing fluorine atoms behave similarly to unfunctionalised substrates allowing the access to fluorinated indolocarbazoles **7dc** and **7ec**. Finally, we decided to evaluate the one-pot procedure to access indolo[3,2-*a*]carbazoles from 1-(indol-3-yl)-3-alkyn-2-ols **3**. To our delight, the synthesis of compound **7ea** was successfully accomplished merging gold-catalysed cyclization and molybdenum-catalysed Cadogan reaction in a one-pot manner using toluene as solvent for both processes.

### Photophysical properties of compounds

The photoluminescent properties of two selected indolo[2,3-*c*]carbazoles, **5aa** and **5ba**, were investigated in DMSO in order to gain insight into the effect that the substituent at the C-7 position of the indolocarbazole skeleton (methyl in **5aa**, and phenyl in **5ba)** has on the photophysical properties of these compounds (Table 2). The absorbance and the emission intensity of both chromophores at the absorption and emission spectrum maximum wavelengths grow linearly for a concentration range between $5 \times 10^{-7}$ and $4 \times 10^{-6}$ M.

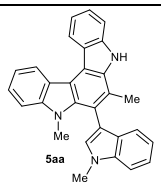
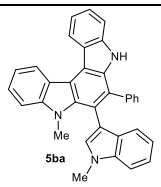
The normalized absorption and emission spectra of both compounds in DMSO are shown in Figure 1. The absorption spectra show two main bands at 351 and 397 nm for the methyl-substituted compound (**5aa**) and at 354 and 402 nm for the phenyl-substituted one (**5ba**) (Table 2), which shows a wider absorption range (Figure 1). Closely similar spectra are reported in the literature for *N,N´*-dimethylindolo[2,3-*c*]carbazole[5a] and for a phenyl-substituted *N,N´*-dimethylindolo[2,3-*c*]carbazole[7h] indicating that these bands are characteristics of the indolo[2,3-*c*]carbazoles, regardless the grade of nitrogen methylation.

Since extended conjugated systems lead to high absorption and emission wavelengths,[14] the red shifts of the spectra upon phenyl substitution (**5ba**) in comparison to the methylated compound (**5aa**), which is of 3 nm for the 351 nm band and 5 nm for the 397 nm band, suggest that the phenyl substituent is conjugated with the indolo[2,3-*c*]carbazoles molecular framework. Additionally, provided the absorption band at 397 nm experiments a higher shift to the red than the band at 351 nm, when methyl is changed by phenyl in the carbazole moiety, indicates that the band at 397 nm is likely to be due to the carbazole absorption. Moreover, the higher conjugation of carbazole in comparison to that of indole would also justify that the absorption linked to the carbazole segment of the chromophore appears at higher wavelengths. Moreover, the pendant indole moiety from the carbazole group in **5aa** and **5ba** does not seem to induce significant changes in the absorption maximum wavelengths when compared to the spectra of *N,N´*-dimethylindolo[2,3-*c*]carbazoles.[5a,7h]

Similarly, the emission band is 24 nm red shifted when the methyl-substituted **5aa** (407 nm) and the phenyl-substituted **5ba** (424 nm) are compared (Table 2), supporting the idea that the phenyl group is conjugated with the rest of the indolo[2,3-*c*]carbazole π-system.

View Article Online
DOI: 10.1039/D0QO00405G

**Table 2.** Maximum absorption wavelength ($\lambda_{abs}$), molar absorptivity at the absorption maximum wavelengths ($\varepsilon_{max}$), maximum emission wavelength ($\lambda_{em}$), fluorescence quantum yield ($\phi_f$), average lifetime ($\tau$), and fluorescence ($k_f$) and non-radiative ($k_{nr}$) rate constants of selected **5aa** and **5ba** in DMSO

| Compound | $\lambda_{abs}$ (nm) | $\varepsilon_{max}$ ($L\ mol^{-1}\cdot cm^{-1}$) | $\lambda_{em}$ (nm) | $\phi_f$ | $\tau$ (ns) | $k_f$ ($10^7\ s^{-1}$) | $k_{nr}$ ($10^7\ s^{-1}$) |
|---|---|---|---|---|---|---|---|
|  **5aa** | 338 | 20700 ± 300 | 407 | 0.72 ± 0.04 | 7.4 ± 0.1 | 9.54 ± 0.10 | 3.89 ± 0.04 |
| | 351 | 23700 ± 300 | | | | | |
| | 377 | 6900 ± 200 | | | | | |
| | 397 | 8200 ± 200 | | | | | |
|  **5ba** | 342 | 16700 ± 200 | 424 | 0.69 ± 0.02 | 6.4 ± 0.1 | 10.77 ± 0.05 | 4.84 ± 0.02 |
| | 354 | 20000 ± 200 | | | | | |
| | 384 | 6500 ± 100 | | | | | |
| | 402 | 7500 ± 100 | | | | | |

The fluorescence quantum yields of **5aa** and **5ba** in DMSO, around 0.70 (Table 2), are highly remarkable because more than double the 0.31 of the methyl-substituted *N,N´*-dimethylindolo[2,3-*c*]carbazole in $CH_2Cl_2$.[7h] Although these chromophores do not have the same nitrogen methylation grade and the solvent is different, it is likely that the pendent indole substituent in the carbazole moiety of **5aa** and **5ba** could play a crucial role in this dramatic increase in the emission quantum yields by increasing the molecular rigidity.

Moreover, fluorescence decays of **5aa** and **5ba** in DMSO were also registered at several wavelengths (emission maxima and shoulders), as detailed in Table S1. The decays in the emission maxima of **5aa** and **5ba** are also shown in Figure S1 (see ESI for details). Mono-exponential decays were obtained for all the cases, and the average lifetimes are shown in Table 2. Although the lifetime is slightly lower for the phenyl derivative (**5ba**), the difference is not significant.

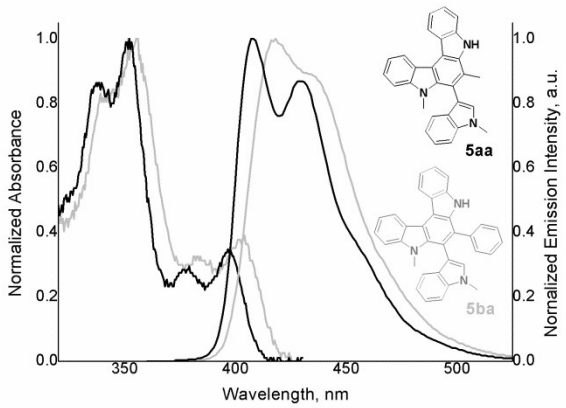



**Figure 1** Normalized absorption and emission spectra of **5aa** (black) and **5ba** (grey) indolo[2,3-*c*]carbazoles ($4 \times 10^{-6}$ M) in DMSO. Excitation wavelengths: 351 and 354 nm, respectively.

From the fluorescence quantum yield and lifetimes, the fluorescence ($k_f$) and non-radiative ($k_{nr}$) rate constants can be calculated (in the absence of bimolecular processes) by combining Eq. S1 and Eq S2 (see ESI for details).[17] The values of both constants are shown in Table 2. Both fluorophores have a similar rate constant, and the fluorescence constants double the non-radiative ones, showing the higher efficiency of the radiative channel to deactivate the first electronic states of both chromophores with respect to the non-radiative ones.

## Conclusions

In conclusion, we have developed a new methodology to access two different angular indolocarbazole moieties by merging gold- and molybdenum-catalysis through two sequential carbazole formation reactions. It is remarkable that the nature of the substituent at the propargylic position of the starting alkynol plays a decisive role in the regioselectivity of the migration step in the intermediate spirocyclic indolenine. Thus, when alkyl migration is favoured indolo[2,3-*c*]carbazoles are obtained, whereas if alkenyl migration dominates the process indolo[3,2-*a*]carbazoles are accessed. In addition, the indolocarbazoles could also be synthesized through a single-pot tandem operation using toluene as a solvent. The methyl-substituted (**5aa**) and phenyl-substituted (**5ba**) indolo[2,3-*c*]carbazoles (the latter with a wider absorption wavelength range) show fluorescence quantum yields ($\phi_f$) around 0.7 in DMSO, doubling the $\phi_f$ of similar compounds in the literature. The high extinction coefficient and fluorescence quantum yields of these compounds make them potentially useful for optoelectronic applications.

DOI: 10.1039/D0QO00405G

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support from Junta de Castilla y León and FEDER (BU291P18) and Ministerio de Ciencia e Innovación and FEDER (CTQ2016-75023-C2-1-P) is gratefully acknowledged. F. M.-L. and S. S.-P. thank Junta de Castilla y León and FSE and FEDER for predoctoral and postdoctoral contracts, respectively.

## Notes and references

1 (*a*) C. Sánchez, C. Méndez and J. A. Salas, Indolocarbazole natural products: occurrence, biosynthesis, and biological activity, *Nat. Prod. Rep.*, 2006, **23**, 1007–1045; (*b*) C. Olano, C. Méndez and J. A. Salas, Antitumor Compounds from Marine Actinomycetes, *Mar. Drugs*, 2009, **7**, 210–248; (*c*) H. Nakano and S. Ômura, Chemical biology of natural indolocarbazole products: 30 years since the discovery of staurosporine, *J. Antibiot.*, 2009, **62**, 17–26; (*d*) J.-N. Wang, H.-J. Zhang, J.-Q. Li, W.-J. Ding and Z.-J. Ma, Bioactive Indolocarbazoles from the Marine-Derived Streptomyces sp. DT-A61, *J. Nat. Prod.*, 2018, **81**, 949–956.

2 (*a*) C.-C. Lai, M.-J. Huang, H.-H. Chou, C.-Y. Liao, P. Rajamalli and C.-H. Cheng, m-Indolocarbazole Derivative as a Universal Host Material for RGB and White Phosphorescent OLEDs, *Adv. Funct. Mater.*, 2015, **25**, 5548–5556; (*b*) R. Gómez-Bombarelli, J. Aguilera-Iparraguirre, T. D. Hirzel, D. Duvenaud, D. Maclaurin, M. A. Blood-Forsythe, H. S. Chae, M. Einzinger, D. G. Ha, T. Wu, G. Markopoulos, S. Jeon, H. Kang, H. Miyazaki, M. Numata, S. Kim, W. L. Huang, S. I. Hong, M. Baldo, R. P. Adams and A. Aspuru-Guzik, Design of Efficient Molecular Organic Light-Emitting Diodes by a High-Throughput Virtual Screening and Experimental Approach, *Nat. Mater.*, 2016, **15**, 1120–1128.

3 For reviews about the chemistry and applications, see: (*a*) T. Janosik, N. Wahlström and J. Bergman, Recent progress in the chemistry and applications of indolocarbazoles, *Tetrahedron*, 2008, **64**, 9159–9180; (*b*) T. Janosik, A. Rannug, U. Rannug, N. Wahlström, J. Slätt and J. Bergman, Chemistry and Properties of Indolocarbazoles, *Chem. Rev.*, 2018, **118**, 9058–9128.

4 For seminal contribution see: (*a*) M. L. Tomlinson, Preparation of indolocarbazoles. IV. The preparation of indolo(3',2':1,2)carbazole, *J. Chem. Soc.*, 1951, 809–811; (*b*) J. A. Hall and S. G. P. Plant, Preparation of indolocarbazoles. V. Synthesis of indolo(3',2':1,2)carbazole and its 3-methyl derivative, *J. Chem. Soc.*, 1953, 116–119. For the first isolated indolo[3,2-*a*]carbazole natural product, see: (*c*) K. M. Meragelman, L. M. West, P. T. Northcote, L. K. Pannell, T. C. McKee, and M. R. Boyd, Unusual Sulfamate Indoles and a Novel Indolo[3,2-*a*]carbazole from *Ancorina* sp., *J. Org. Chem.*, 2002, **67**, 6671–6677.

5 For pionering work see: (*a*) H. Weller and K. H. Grellmann, On the Photochemical Synthesis of *N*,*N*′-dimethylindolo[2,3-*c*]carbazole and the Mechanism of Its Formation from *N*,*N*′-dimethyl-*N*,*N*′-diphenyl-1,4-phenylenediamine, *J. Am. Chem. Soc.*, 1983, **105**, 6268-6273; (*b*) E. Desarbre and J. Bergman, Synthesis of symmetric and non-symmetric indolo[2,3-*c*]carbazole derivatives: preparation of indolo[2,3-*c*]pyrrolo[3,4-*a*]carbazoles, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2009–2016; (*c*) J. Bergman, T. Janosik, L. Yudina, E. Desarbre, G. Lidgren and L. Venemalm, Reactions of 1,2-Bis(1*H*-indol-2-yl)ethane: Formation of Indolo[2,3-*c*]carbazole and Cyclohept[1,2-*b*:5,4-*b*′]bisindole Derivatives, *Tetrahedron*, 2000, **56**, 1911–1916.

6 (*a*) T. Suzuki, Y. Tokimizu, Y. Sakano, R. Katoono, K. Fujiwara, S. Naoe, N. Fujii and H. Ohno, 5,10-Dihydrobenzo[*a*]indolo[2,3-*c*]carbazole: A Highly Fluorescent Disk-shaped Electron Donor Exhibiting Dual UV–vis–NIR and Fluorescence Spectral Changes upon Electrolysis, *Chem. Lett.*, 2013, **42**, 1001–1003; (*b*) T. Suzuki, Y. Sakano, Y. Tokimizu, Y. Miura, R. Katoono, K. Fujiwara, N. Yoshioka, N. Fujii and H. Ohno, Wurster's Blue-type Cation Radicals Framed in a 5,10-Dihydrobenzo[*a*]indolo[2,3-*c*]carbazole (BIC) Skeleton: Dual Electrochromism with Drastic Changes in UV/Vis/NIR and Fluorescence, *Chem. Asian J.*, 2014, **9**, 1841–1846; (*c*) S.-G. Ihn, N. Lee, S. O. Jeon, M. Sim, H. Kang, Y. Jung, D. H. Huh, Y. M. Son, S. Y. Lee, M. Numata, H. Miyazaki, R. Gómez-Bombarelli, J. Aguilera-Iparraguirre, T. Hirzel, A. Aspuru-Guzik, S. Kim and S. Lee, An Alternative Host Material for Long-Lifespan Blue Organic Light-Emitting Diodes Using Thermally Activated Delayed Fluorescence, *Adv. Sci.*, 2017, **4**, 1600502; (*d*) M. Daniels, F. de Jong, K. Kennes, C. Martin, J. Hofkens, M. Van der Auweraer and W. Dehaen, Promising Molecules for Optoelectronic Applications: Synthesis of 5,10-Dihydrobenzo[*a*]indolo[2,3-*c*]carbazoles by Scholl Reaction of 1,2-Bis(indol-2-yl)benzenes, *Eur. J. Org. Chem.*, 2018, 4683–4688; (*e*) F. de Jong, M. Daniels, L. Vega-Castillo, K. Kennes, C. Martin, G. de Miguel, M. Cano, M. Perez-Morales, J. Hofkens, W. Dehaen and M. Van der Auweraer, 5,10-Dihydrobenzo[a]indolo[2,3-*c*]carbazoles as Novel OLED Emitters, *J. Phys. Chem. B*, 2019, **123**, 1400–1411.

7 [3,2-*a*]-isomers: (*a*) T. Janoszik and J. Bergman, Reactions of 2,3′-biindolyl: Synthesis of indolo[3,2-*a*]carbazoles, *Tetrahedron*, 1999, **55**, 2371–2380; (*b*) N. Wahlström and J. Bergman, Synthesis of 2,3′-biindolyls and indolo[3,2-*a*]carbazoles, *Tetrahedron Lett.*, 2004, **45**, 7273–7275; (*c*) V. Nair, V. Nandialath, K. G. Abhilash and E. Suresh, An efficient synthesis of indolo[3,2-*a*]carbazoles via the novel acid catalyzed reaction of indoles and diaryl-1,2-diones, *Org. Biomol. Chem.*, 2008, **6**, 1738–1742; (*d*) G. Dupeyre, P: Lemoine, N. Ainseba, S. Michel and X. A. Cachet, A one-pot synthesis of 7-phenylindolo[3,2-*a*]carbazoles from indoles and β-nitrostyrenes, via an unprecedented reaction sequence, *Org. Biomol. Chem.*, 2011, **9**, 7780–7790; (*e*) X. Zheng, L. Lv, S. Lu, W. Wang and Z. Li, Benzannulation of Indoles to Carbazoles and Its Applications for Syntheses of Carbazole Alkaloids, *Org. Lett.*, 2014, **16**, 5156–5159; (*f*) C. Yang, K. Lin, L. Huang, W.-d. Pan and S. Liu, Facile synthesis of indolo[3,2-*a*]carbazoles via Pd-catalyzed twofold oxidative cyclization, *Beilstein J. Org. Chem.*, 2016, **12**, 2490–2494. [2,3-*c*]-isomers: (*g*) M. Viji and R. Nagarajan, $RuCl_3/SnCl_2$ mediated synthesis of pyrrolo[2,3-*c*]carbazoles and consequent preparation of indolo[2,3-*c*]carbazoles, *Tetrahedron*, 2012, **68**, 2453–2458; (*h*) Y. Nagase, H. Shirai, M. Kaneko, E. Shirakawa and T. Tsuchimoto, Indium-catalyzed annulation of 3-aryl- and 3-heteroarylindoles with propargyl ethers: synthesis and photoluminescent properties of aryl- and heteroaryl[*c*]carbazoles, *Org. Biomol. Chem.*, 2013, **11**, 1456–1459; (*i*) Y. Carvajal-Miranda, R. Pérez-Salazar, J. A. Varela, Synthesis of Dihydroindolo[2,3-*c*]carbazole as Potential Telomerase Inhibitor, *J. Heterocycl. Chem.*, 2016, **53**, 762–766; (*j*) E. Sankar, P. Raju, J. Karunakaran and A. K. Mohanakrishnan, Synthetic Utility of Arylmethylsulfones: Annulative π-Extension of Aromatics and Hetero-aromatics Involving Pd(0)-Catalyzed Heck Coupling Reactions, *J. Org. Chem.*, 2017, **82**, 13583–13593; (*k*) Y. Kawada, S. Ohmura, M. Kobayashi, W. Nojo, M. Kondo, Y. Matsuda, J. Matsuoka, S. Inuki, S. Oishi, C. Wang, T. Saito, M. Uchiyama, T. Suzuki and H. Ohno, Direct synthesis of aryl-annulated [*c*]carbazoles by

gold(I)-catalysed cascade reaction of azide-diynes and arenes, *Chem. Sci.*, 2018, **9**, 8416–8425.

8 For selected reviews, see: (*a*) J. Roy, A. K. Jana and D. Mal, Recent trends in the synthesis of carbazoles: an update, *Tetrahedron*, 2012, **68**, 6099–6121; (*b*) A. W. Schmidt, K. R. Reddy and H. J. Knölker, Occurrence, Biogenesis, and Synthesis of Biologically Active Carbazole Alkaloids, *Chem. Rev.*, 2012, **112**, 3193–3328; (*c*) T. Aggarwal, Sushmita and A. K. Verma, Recent advances in the synthesis of carbazoles from indoles, *Org. Biomol. Chem.*, 2019, **17**, 8330–8342.

9 For selected recent examples see: (*a*) S. Chen, Y. Li, P. Ni, H. Huang and G.-J. Deng, Indole-to-Carbazole Strategy for the Synthesis of Substituted Carbazoles under Metal-Free Conditions, *Org. Lett.*, 2016, **18**, 5384–5387; (*b*) B. Guo, X. Huang, C. Fu and S. Ma, Carbazoles from the [4C+2C] Reaction of 2,3-Allenols with Indoles, *Chem. Eur. J.*, 2016, **22**, 18343–18348; (*c*) Y.-W. Huang, X.-Y. Li, L.-N. Fu and Q.-X. Guo, Procedure for the Synthesis of Polysubstituted Carbazoles from 3-Vinyl Indoles, *Org. Lett.*, 2016, **18**, 6200–6203; (*d*) H. Wang, Z. Wang, Y.-L. Wang, R.-R. Zhou, G.-C. Wu, S.-Y. Yin, X. Yan and B. Wang, *N*-Bromosuccinimide (NBS)-Catalyzed C–H Bond Functionalization: An Annulation of Alkynes with Electron Withdrawing Group (EWG)-Substituted Acetyl Indoles for the Synthesis of Carbazoles, *Org. Lett.*, 2017, **19**, 6140–6143; (*e*) S. Choi, V. Srinivasulu, S. Ha and C.-M. Park, *Chem. Commun.*, Synthesis of carbazoles based on gold–copper tandem catalysis, 2017, **53**, 3481–3484; (*f*) T. Zhou, B. Li and B. Wang, Rhodium-catalyzed C2 and C4 C-H activation/annulation of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles with internal alkynes: a facile access to substituted and fused carbazoles, *Chem. Commun.*, 2017, **53**, 6343–6346; (*g*) Y. Gu, W. Huang, S. Chen and X. Wang, Bismuth(III) Triflate Catalyzed Three-Component Reactions of Indoles, Ketones, and α-Bromoacetaldehyde Acetals Enable Indole-to-Carbazole Transformation, *Org. Lett.*, 2018, **20**, 4285–4289; (*h*) S. Kundu, A. Banerjee and M. S. Maji, *J. Org. Chem.*, 2019, Brønsted Acid-Catalyzed Tandem Pinacol-Type Rearrangement for the Synthesis of α-(3-Indolyl) Ketones by Using α-Hydroxy Aldehydes, *J. Org. Chem.*, 2019, **84**, 16003–16012. For the synthesis of carbazoles from indole-derived (homo)propargyl alcohols, see: (*i*) Y. Qiu, W. Kong, C. Fu and S. Ma, Carbazoles via $AuCl_3$-Catalyzed Cyclization of 1-(Indol-2-yl)-3-alkyn-1-ols, *Org. Lett.*, 2012, **14**, 6198–6201; (*j*) Z. Zhang, X. Tang, Q. Xu and M. Shi, Gold-catalyzed cyclization of 1-(indol-3-yl)-3-alkyn-1-ols: Facile synthesis of diversified carbazoles, *Chem. Eur. J.*, 2013, **19**, 10625–10631; (*k*) Y. Qiu, J. Zhou, C. Fu and S. Ma, A General Diversified Synthesis of Carbazoles and the First Synthesis of Karapinchamine A, *Chem. Eur. J.*, 2014, **20**, 14589–14593; (*l*) B. Alcaide, P. Almendros, J. M. Alonso, E. Busto, I. Fernández, M. P. Ruiz and G. Xiaokaiti, Versatile Synthesis of Polyfunctionalized Carbazoles from (3-Iodoindol-2-yl)butynols via a Gold-Catalyzed Intramolecular Iodine-Transfer Reaction, *ACS Catal.*, 2015, **5**, 3417–3421; (*m*) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O´Brien, R. J. K. Taylor and W. P. Unsworth, Silver(I)-Catalyzed Dearomatization of Alkyne-Tethered Indoles: Divergent Synthesis of Spirocyclic Indolenines and Carbazoles, *Org. Lett.*, 2015, **17**, 4372–4375; (*n*) J. Zhou, Y. Qiu, J. Li, C. Fu, X. Zhang and S. Ma, $PtCl_4$-catalyzed skeleton rearrangement–cyclization of tertiary indolyl-3-alkynols, *Chem. Commun.*, 2017, **53**, 4722–4725.

10 For early results on gold(III) catalysis, see: (*a*) Y. Fukuda and K. Utimoto, Effective Transformation of Unactivated Alkynes into Ketones or Acetals by Means of Au(III) Catalyst, *J. Org. Chem.*, 1991, **56**, 3729–3731; (*b*) A. S. K. Hashmi, L. Schwarz, J.-H. Choi and T. M. Frost, A New Gold-Catalyzed C–C Bond Formation, *Angew. Chem. Int. Ed.*, 2000, **39**, 2285–2288; (*c*) A. S. K. Hashmi, T. M. Frost and J. W. Bats, Highly Selective Gold-Catalyzed Arene Synthesis, *J. Am. Chem. Soc.*, 2000, **122**, 11553–11554. For general reviews on gold catalysis see: (*d*) A. S. K. Hashmi, Gold-Catalyzed Organic Reactions, *Chem. Rev.*, 2007, **107**, 3180–3211; (*e*) A. Corma, A. Leyva-Pérez and M. J. Sabater, Gold-Catalyzed Carbon-Heteroatom Bond Forming Reactions, *Chem. Rev.*, 2011, **111**, 1657–1712; (*f*) R. Dorel and A. M. Echavarren, Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity, *Chem. Rev.*, 2015, **115**, 9028–9072.

11 (*a*) A. Suárez, F. Martínez, S. Suárez-Pantiga and R. Sanz, PTSA-Catalyzed Reaction of Indoles with 2-Oxoaldehydes: Synthesis of α,α-Bis(indol-3-yl) Ketones, *ChemistrySelect*, 2017, **2**, 787–790. For other syntheses of α-(indol-3-yl)ketones, see: (*b*) T. Liang, Z. Zhang and J. C. Antilla, Chiral Brønsted Acid Catalyzed Pinacol Rearrangement, *Angew. Chem. Int. Ed.*, 2010, **49**, 9734–9736; (*c*) D. Liang, X. Li, Y. Li, Y. Yang, S. Gao and P. Cheng, $Br_2$-Catalyzed regioselective dehydrative coupling of indoles with acyloins: direct synthesis of α-(3-indolyl) ketones, *RSC Adv.*, 2016, **6**, 29020–29025; (*d*) N. Chalotra, A. Ahmed, M. A. Rizvi, Z. Hussain, Q. N. Ahmed and B. A. Shah, Photoredox Generated Vinyl Radicals: Synthesis of Bisindoles and β-Carbolines, *J. Org. Chem.*, 2018, **83**, 14443–14456; (*e*) F. Turnu, A. Luridiana, A. Cocco, S. Porcu, A. Frongia, G. Sarais and F. Secci, Catalytic Tandem Friedel–Crafts Alkylation/C4–C3 Ring-Contraction Reaction: An Efficient Route for the Synthesis of Indolyl Cyclopropanecarbaldehydes and Ketones, *Org. Lett.*, 2019, **21**, 7329–7332.

12 (*a*) A. Suárez, S. Suárez-Pantiga, O. Nieto-Faza and R. Sanz, Gold-Catalyzed Synthesis of 1-(Indol-3-yl)carbazoles: Selective 1,2-Alkyl vs 1,2-Vinyl Migration, *Org. Lett.*, 2017, **19**, 5074–5077. For a related iodocyclization reactions, see: (*b*) S. Yaragorla, D. Bag, R. Dada and K. V. J. Jose, Iodo-Cycloisomerization of Aryl(indol-3-yl)methane-Tethered Propargyl Alcohols to 3-Iodocarbazoles via Selective 1,2-Alkyl Migration, *ACS Omega*, 2018, **3**, 15024–15034. For other syntheses of (indol-3-yl)carbazoles, see: (*c*) Y.-W. Huang, X.-Y. Li, L.-N. Fu and Q.X. Guo, Procedure for the Synthesis of Polysubstituted Carbazoles from 3-Vinyl Indoles, *Org. Lett.*, 2016, **18**, 6200–6203; (*d*) G. Ranjani and R. Nagarajan, Metal-Free C–H Functionalization and Aromatization Sequence for the Synthesis of 1-(Indol-3-yl)carbazoles and Total Synthesis of 7-Bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole, *Org. Lett.*, 2019, **21**, 675–678.

13 (*a*) R. Sanz, J. Escribano, M. R. Pedrosa, R. Aguado and F. J. Arnáiz, Dioxomolybdenum(VI)-Catalyzed Reductive Cyclization of Nitroaromatics. Synthesis of Carbazoles and Indoles, *Adv. Synth. Catal.*, 2007, **349**, 713–718. For reports from other groups using the Mo-catalysed Cadogan reaction, see for instance: (*b*) N V. Borrero, L. G. DeRatt, L. F. Barbosa, K. A. Abboud and A. Aponick, Tandem Gold-Catalyzed Dehydrative Cyclization/Diels–Alder Reactions: Facile Access to Indolocarbazole Alkaloids, *Org. Lett.*, 2015, **17**, 1754–1757; (*c*) Y Yamamoto, E. Ohkubo and M. Shibuya, Synthesis of 3-Aryl-2-(trifluoromethyl)indoles via Copper-Catalyzed Hydroarylation and Subsequent Cadogan Cyclization, *Adv. Synth. Catal.*, 2017, **359**, 1747–1751; (*d*) H. Kang, X. Xiao, C. Huang, Y. Yuan, D. Tang, X. Dai and X. Zeng, Potent aromatase inhibitors and molecular mechanism of inhibitory action, *Eur. J. Med. Chem.*, 2018, **143**, 426–437.

14 (*a*) N. García, R. Rubio-Presa, P. García-García, M. A. Fernández-Rodríguez, M. R. Pedrosa, F. J. Arnáiz and R. Sanz, A selective, efficient and environmentally friendly method for the oxidative cleavage of glycols, *Green Chem.*, 2016, **18**, 2335–2340; (*b*) R. Rubio-Presa, M. A. Fernández-Rodríguez, M. R. Pedrosa, F. J. Arnáiz and R. Sanz, Molybdenum-Catalyzed Deoxygenation of Heteroaromatic N-Oxides and Hydroxides using Pinacol as Reducing Agent, *Adv. Synth.*



View Article Online
DOI: 10.1039/D0QO00405G



*Catal.*, 2017, **359**, 1752–1757; (*c*) R. Rubio-Presa, M. R. Pedrosa, M. A. Fernández-Rodríguez, F. J. Arnáiz and R. Sanz, Molybdenum-Catalyzed Synthesis of Nitrogenated Polyheterocycles from Nitroarenes and Glycols with Reuse of Waste Reduction Byproduct, *Org. Lett.*, 2017, **19**, 5470–5473; (*d*) R. Hernández-Ruiz and R. Sanz, Dichlorodioxomolybdenum(VI) Complexes: Useful and Readily Available Catalysts in Organic Synthesis, *Synthesis*, 2018, **50**, 4019–4036; (*e*) R. Rubio-Presa, S. Suárez-Pantiga, M. R. Pedrosa and R. Sanz, Molybdenum-Catalyzed Sustainable Friedlander Synthesis of Quinolines, *Adv. Synth. Catal.*, 2018, **360**, 2216–2220; (*f*) S. Suárez-Pantiga, R. Hernández-Ruiz, C. Virumbrales, M. R. Pedrosa and R. Sanz, Reductive Molybdenum-Catalyzed Direct Amination of Boronic Acids with Nitro Compounds, *Angew. Chem. Int. Ed.*, 2019, **58**, 2129–2133.

15 Such spirocyclic intermediates have been observed before, see: (*a*) A. S. K. Hashmi, W. Yang and F. Rominger, Gold(I)-Catalyzed Formation of Benzo[*b*]furans from 3-Silyloxy-1,5-enynes, *Angew. Chem. Int. Ed.*, 2011, **50**, 5762–5765; (*b*) A. S. K. Hashmi, W. Yang and F. Rominger, Gold-Catalysis: Highly Efficient and Regio-Selective Carbonyl Migration in Alkynyl-Substituted Indole-3-Carboxamides Leading to Azepino[3,4-b]indol-1-ones, *Adv. Synth. Catal.*, 2012, **354**, 1273–1279; (*c*) A. S. K. Hashmi, W. Yang and F. Rominger, Gold(I)-Catalyzed Rearrangement of 3-Silyloxy-1,5-enynes: An Efficient Synthesis of Benzo[*b*]thiophenes, Dibenzofurans, and Indole Derivatives, *Chem. Eur. J.*, 2012, **18**, 6576–6580; (*d*) A. S. K. Hashmi, T. Häffner, W. Yang, S. Pankajakshan, S. Schäfer, L. Schultes, F. Rominger and W. Frey, Gold Catalysis: Non-Spyrocyclic Intermediates in the Conversion of Furanynes by the Formal Insertion of an Alkyne into an Aryl-Alkyl C–C Single Bond, *Chem. Eur. J.*, 2012, **18**, 10480–10486.

16 A. S. K. Hashmi, Homogeneous Gold Catalysis Beyond Assumptions and Proposals–Characterized Intermediates, *Angew. Chem. Int. Ed.*, 2010, **49**, 5232–5241.

17 J. R. Lakowicz, *Principles of Fluorescence Spectroscopy*, Springer, Baltimore, **2006**.