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Catalyst- and Substrate-Controlled Regiodivergent Synthesis of Carbazoles through Gold-Catalyzed Cyclizations of Indole-Functionalized Alkynols

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A wide variety of regioselectively substituted carbazole derivatives can be synthesized by the gold-catalyzed cyclization of alkynols bearing an indol-3-yl and an additional group at the homopropargylic positions. The regioselectivity of the process can be controlled by both the oxidation state of the gold catalyst and the electronic nature of the substituents of the alkynol moiety. The 1,2-alkyl migration in the spiroindoleninium intermediate, generated after indole attack to the activated alkyne, is favored with gold(I) complexes and for electron-rich aromatic substituents at the homopropargylic position, whereas the 1,2-alkenyl shift is preferred when using gold(III) salts and for alkyl or non-electron-rich aromatic groups.

Introduction

The carbazole heterocyclic framework is an important structural unit that has attracted considerable attention because this motif is found in a wide variety of biologically active compounds,[1] and also because carbazoles have shown tremendous potential in organic materials due to their interesting photophysical and electronic properties.[2] Therefore, the development of methods for their efficient access, mainly with regiocontrolled substitution patterns, remains an important goal in organic synthesis.[3] One of the most useful approaches for synthesizing the carbazole skeleton is the benzannulation of C-2 or C-3 alkynyl-functionalized indole derivatives, many of them being catalyzed by gold, platinum or silver complexes.[4] Gold-catalysis has become nowadays as a powerful and reliable strategy for direct access to complex molecules from simple starting materials,[5] as it has been demonstrated by its application to the functionalization of indoles,[6] in particular the annellation of C-3 alkynyl functionalized indoles.[7] Depending on the chain length of the tethered alkyne, as well as on their electronic properties, *exo*- or *endo*-cyclizations could be favored.[8] In the case of the more usual *endo* pathway, a spiroindoleninium intermediate such as **A** is assumed to be produced that usually evolves through a Wagner-Meerwein-like 1,2-migration via C3-to-C2 shift, driven by the rearomatization of the indole nucleus.[9] A competitive process can take place on **A** leading to formal 1,2-alkenyl or 1,2-alkyl migrations, being the shift of the alkenyl moiety typically more favored.[10] Only in particular cases, those in which the R^2 group is a hydroxyl or a TBDMS ether, the alternative 1,2-alkyl migration has been observed (Scheme 1a).[11]

In this field, we have reported a regioselective synthesis of 1-(indol-3-yl)carbazoles from bisindolylmethane-tethered propargyl alcohols that involves a selective formal 1,2-alkyl vs 1,2-alkenyl migration in the corresponding spirocyclic indolenimimium intermediate. This unexpected selectivity was supported by DFT calculations that reveal a key role of the second indol-3-yl group by stabilizing a carbocationic intermediate leading to a two-step pathway (Scheme 1b).[12] Later on, the analogous iodocyclization of the same starting materials was reported by Yaragorla et al., observing the same tendency for the 1,2-alkyl migration with substrates bearing an additional indolyl or 2,4,6-trimethoxyphenyl group at the homopropargylic position (Scheme 1c).[13] Following our interest in the preparation of functionalized carbazoles,[14] and considering that the nature of the additional group at the homopropargylic position could play a determinant role in the evolution of the spirocyclic intermediate, we planned to expand our study to related α-(indol-3-yl)methyl alkynols bearing different substituents looking for preparing different regioselectively substituted carbazole derivatives (Scheme 1d). Herein, we present a regiodivergent reaction, in which not only the gold catalyst, but also the nature of the substituents of the substrate affect the balance of regioisomeric products.

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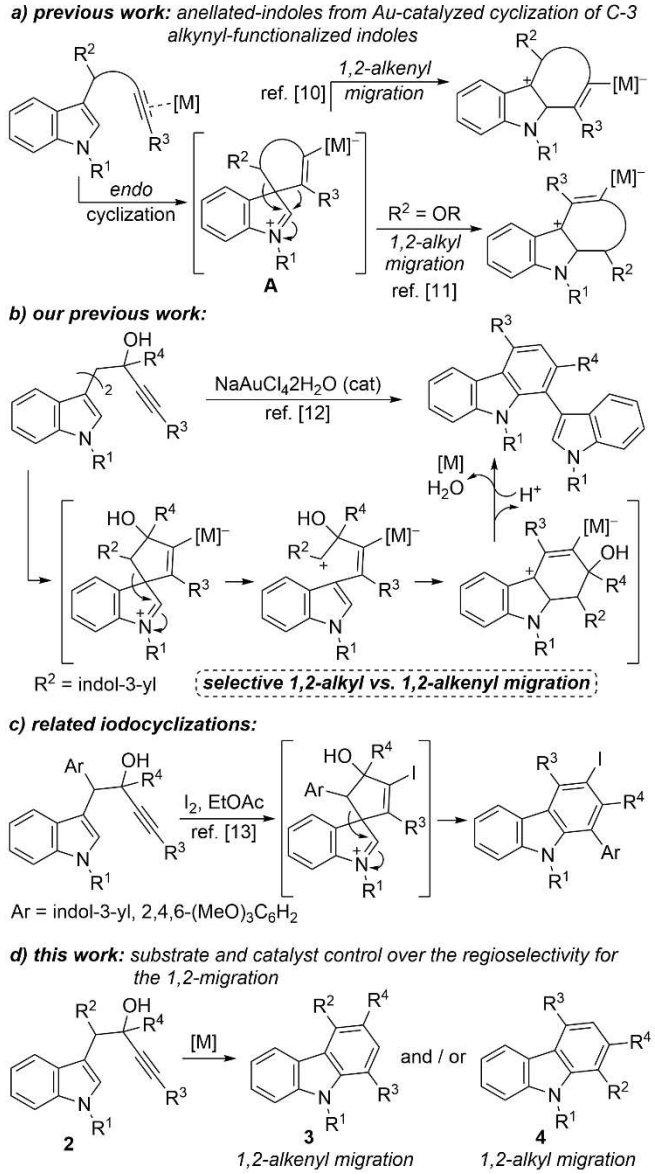
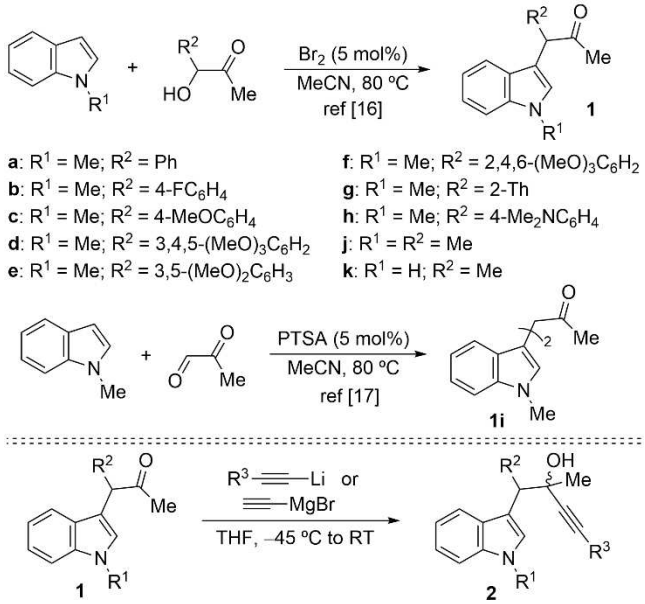


Scheme 1. Synthesis of 1-(indol-3-yl)carbazoles via selective 1,2-alkyl vs 1,2-alkenyl migration (our previous work) and proposed study for the preparation of carbazoles **3** and/or **4** from indol-3-yl-but-3-yn-2-ols **2** (this work).



Scheme 2. Synthesis of 3-homopropargyl indoles **2** from α-(indol-3-yl) ketones **1**.

Results and Discussion

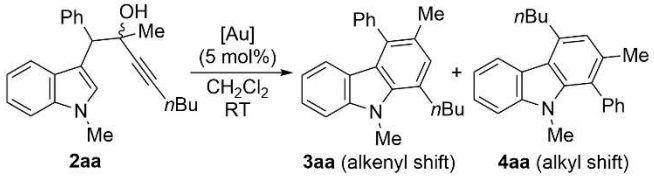
A selection of alkynols **2**, bearing aromatic groups with different electronic nature as well as alkyl ones as R^2 and R^3 substituents, was initially targeted. Their preparation was carried out by alkynylation of the corresponding α-(indol-3-yl) α-substituted ketones **1**,[15] which were previously synthesized by the bromine-catalyzed alkylation of indoles with acyloins[16] or by the Brønsted acid-catalyzed reaction of indoles with glyoxals (Scheme 2).[17]

At the beginning of our study, indole-functionalized alkynol **2aa** bearing an additional phenyl group at the homopropargylic position and a *n*-butyl as the substituent of the alkyne was selected as the model substrate to study its cyclization under gold catalysis (Table 1). Based on our previous report,[12] we chose the commercially available gold(III) complex, $NaAuCl_4 \cdot 2H_2O$, as the initial catalyst for carrying out the reaction. Under these conditions, carbazole **3aa**, derived from a formally 1,2-alkenyl migration, was selectively obtained in good yield (entry 1). However, lower yield and selectivity were obtained with other gold(III) complex like $PicAuCl_2$ (entry 2). To our excitement, when we tested Gagosz catalyst, $Ph_3PAuNTf_2$, a 1/1.8 mixture of carbazoles **3aa** and **4aa** was obtained in moderate yield, but showed a switching of the selectivity (entry 3). We then studied the reaction with other related gold(I) complexes such as $SPhosAuNTf_2$, $IPrAuNTf_2$, $XPhosAuNTf_2$, and JohnPhosAu(MeCN)SbF_6 (entries 4–7). The tendency for the switching of the selectivity was the same, favoring carbazole **4aa** derived from a 1,2-alkyl migration, compared with the use of $NaAuCl_4$ (entry 1). The best result considering both yield and selectivity was obtained with $XPhosAuNTf_2$ (entry 6). The use of silver salts for generating the cationic gold complexes from the corresponding chlorides was evaluated (entries 8–10). Although the selectivity of the 1,2-alkyl migration was slightly improved in one case, longer reaction times, no complete conversions and significantly lower yields were obtained. Finally, we also checked a gold complex bearing a phosphite ligand and $AgNTf_2$, but worse results were obtained (entries 11 and 12).

With the two sets of conditions optimized for the regiodivergent cyclization of homopropargyl indole **2aa**, we decided to study the effect of the alkyne substituent (R^3) on the selectivity of the process, as the C atom that supports this R^3 group is involved in the proposed migration (Table 2).

As above established **2aa**, bearing a butyl as R^3 group, gave rise selectively to **3aa** under Au(III) catalysis but a 1/2.2 mixture of **3aa**/**4aa** with $XPhosAuNTf_2$ (entries 1 and 2). Similar behavior

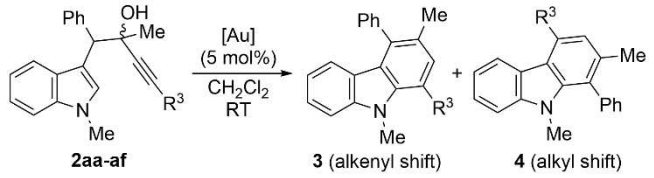
Table 1. Effect of the catalyst on the regioselectivity of the cyclization of **2aa**.[a]



Entry	Catalyst	Time (h)	Conversion[b]	Ratio **3aa**/**4aa**[b]	Yield [%][c]
1	$NaAuCl_4 \cdot 2H_2O$	16	100	12/1	73
2	$PicAuCl_2$	16	90	1.3/1	20
3	$Ph_3PAuNTf_2$	2	100	1/1.8	56
4	$SPhosAuNTf_2$	2	100	1/2.3	66
5	$IPrAuNTf_2$	2	100	1.2/1	85
6	$XPhosAuNTf_2$	2	100	1/2.2	80
7	$JohnPhosAu(MeCN)SbF_6$	2	100	1.2/1	83
8[d]	$XPhosAuCl/AgNTf_2$	16	84	1/4	50
9[d]	$XPhosAuCl/AgSbF_6$	16	90	1/1.8	61
10[d]	$IPrAuCl/AgNTf_2$	16	100	1/1.1	77
11[d]	$(PhO)_3PAuCl/AgNTf_2$	16	83	1/1.6	42
12	$AgNTf_2$	16	38	1.4/1	–[e]

[a] Reaction conditions: **2aa** (0.2 mmol), gold catalyst (0.05 mmol) in CH_2Cl_2 (2 mL) at RT. [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Combined yield of **3aa** and **4aa** determined by ^{1}H-NMR analysis using CH_2Br_2 as internal standard. [d] The gold chloride and the silver salt were stirred for 5 min prior to the addition of the substrate, without filtration of the AgCl. [e] Not determined.

Table 2. Effect of R^3 on the regioselectivity towards **3** or **4**.[a]



Entry	2	R^3	[Au] catalyst	Ratio **3**/**4**[b]	Product(s)[c]	Yield [%][d]
1	**2aa**	*n*Bu	$NaAuCl_4.2H_2O$	12/1	**3aa**	73
2	**2aa**	*n*Bu	$XPhosAuNTf_2$	1/2.2	**3aa**+**4aa**	80
3	**2ab**	$(CH_2)_2Ph$	$NaAuCl_4.2H_2O$	17/1	**3ab**	75
4	**2ab**	$(CH_2)_2Ph$	$XPhosAuNTf_2$	1/2.4	**3ab**+**4ab**	81
5	**2ac**	cC_3H_5	$NaAuCl_4.2H_2O$	>20/1	**3ac**	52
6	**2ac**	cC_3H_5	$XPhosAuNTf_2$	1/2[e]	**3ac**+**4ac**	77
7	**2ad**	Ph	$NaAuCl_4.2H_2O$	16/1	**3ad**	63
8	**2ad**	Ph	$XPhosAuNTf_2$	1/2.1[f]	**3ad**+**4ad**	79
9	**2ae**	2-$MeOC_6H_4$	$NaAuCl_4.2H_2O$	4/1	**3ae**+**4ae**	63
10	**2ae**	2-$MeOC_6H_4$	$XPhosAuNTf_2$	1/1.8	**3ae**+**4ae**	78
11	**2af**	3-Th	$NaAuCl_4.2H_2O$	18/1	**3af**	60
12	**2af**	3-Th	$XPhosAuNTf_2$	1/2.2[g]	**3af**+**4af**	73
13	**2ag**	cC_6H_9	$NaAuCl_4.2H_2O$	–	–	–[h]
14	**2ag**	cC_6H_9	$XPhosAuNTf_2$	1/4.5	**3ag**+**4ag**	74

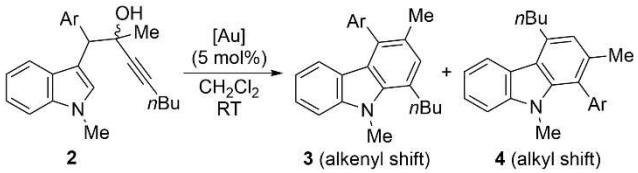
[a] Reaction conditions: **2** (0.5 mmol), [Au] catalyst (0.025 mmol) in CH_2Cl_2 (4 mL) at RT for 16 h (when using Au(III)) or 2–6 h (when using Au(I)). [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Isolated product(s) after column chromatography. [d] Isolated yield referred to the corresponding starting alkynol **2**. [e] A 2/1 ratio was obtained with $IPrAuNTf_2$. [f] A 1.7/1 ratio was obtained with $IPrAuNTf_2$. [g] A 1/1.2 ratio was obtained with $IPrAuNTf_2$. [h] Decomposition products were obtained.

was observed for **2ab** with a 2-phenylethyl substituent (entries 3 and 4). With alkynols **2ac-af**, possessing cyclopropyl and (hetero)aromatic groups as R^3 substituents, a comparable tendency was observed: carbazoles **3** were selectively obtained with $NaAuCl_4$ and mixtures of the corresponding carbazoles **3** and **4** were generated with low selectivity when using Au(I) as catalyst (entries 5–12). However, with **2ae**, lower regioselectivity towards **3ae** was obtained under Au(III)-catalysis likely due to the steric encumbrance of the *o*-methoxy group (entry 9). Finally, the alkenyl-substituted alkynol **2ag** led to decomposition with Au(III), whereas under Au(I)-catalysis, the switch of selectivity towards the corresponding carbazole **4ag** was the highest observed for this family (entry 14). Overall, the effect of the alkyne substituent (R^3) on the regioselectivity of the cyclization is not very significant, apart from slight increases or decreases in some cases (entries 9 and 14).

Our efforts were then steered to study the effect of the aromatic substituent on the homopropargylic position (R^2) because, as expected from our previous results, this group could play a crucial role in the regiochemical outcome of the process (Table 3). We selected an alkyl group (*n*-butyl) as substituent of the triple bond (R^3) for facilitating the structural elucidation of the final carbazoles through NOESY experiments.

Using alkynol **2ba** as starting material, with an electronically-poor aromatic group at the homoprogargylic position, similar results as those for model substrate **2aa** were obtained, high selectivity to **3ba** with Au(III) and low selectivity with Au(I) (entries 3 and 4). Changing to a substrate with an electron-rich aromatic group like **2ca**, bearing a *p*-methoxyphenyl group, led to a new switch on the selectivity as the amount of carbazole **4ca** clearly increases under Au(III)-catalysis, being almost exclusively obtained with $XPhosAuNTf_2$ (entries 5 and 6). Surprisingly, with alkynol **2da** (Ar = 3,4,5-trimethoxyphenyl), although the tendency was the same than for **2ca** (Ar = 4-methoxyphenyl), the switch on the selectivity was lower (entries 7 and 8). Trying to understand this effect alkynol **2ea**, with Ar = 3,5-dimethoxyphenyl, was subjected to the established catalytic conditions. With Au(III) carbazole **3ea** was selectively obtained (entry 9), thus showing that the methoxy groups at *meta*-positions do not alter the regiocontrol (entry 1 vs. 9). Disappointingly, under Au(I)-catalysis a mixture of unidentified compounds was obtained (entry 10). Increasing the electron-rich character of the aromatic group at R^2, **2fa** with a

Table 3. Effect of the aromatic group at the homopropargylic position on the regioselectivity towards **3** or **4**.[a]



2 **3** (alkenyl shift) **4** (alkyl shift)

Entry	2	Ar	[Au] catalyst	Ratio 3/4[b]	Product(s)[c]	Yield [%][d]
1	**2aa**	Ph	$NaAuCl_4.2H_2O$	12/1	**3aa**	73
2	**2aa**	Ph	$XPhosAuNTf_2$	1/2,2	**3aa** + **4aa**	80
3	**2ba**	4-FC_6H_4	$NaAuCl_4.2H_2O$	18/1	**3ba**	62
4	**2ba**	4-FC_6H_4	$XPhosAuNTf_2$	1/1.3	**3ba** + **4ba**	83
5	**2ca**	4-(MeO)C_6H_4	$NaAuCl_4.2H_2O$	1.6/1	**3ca** + **4ca**	68
6	**2ca**	4-(MeO)C_6H_4	$XPhosAuNTf_2$	1/16[f]	**4ca**	81
7	**2da**	3,4,5-$(MeO)_3C_6H_2$	$NaAuCl_4.2H_2O$	3.5/1	**3da** + **4da**	81
8	**2da**	3,4,5-$(MeO)_3C_6H_2$	$XPhosAuNTf_2$	1/3[g]	**3da** + **4da**	67
9	**2ea**	3,5-$(MeO)_2C_6H_3$	$NaAuCl_4.2H_2O$	18/1	**3ea**	76
10	**2ea**	3,5-$(MeO)_2C_6H_3$	$XPhosAuNTf_2$	–	–	–[h]
11	**2fa**	2,4,6-$(MeO)_3C_6H_2$	$NaAuCl_4.2H_2O$	1/5	**3fa** + **4fa**	55
12	**2fa**	2,4,6-$(MeO)_3C_6H_2$	$XPhosAuNTf_2$	1/2.5	**3fa** + **4fa**	70
13	**2ga**	2-Th	$NaAuCl_4.2H_2O$	1/1.5	**3ga** + **4ga**	48
14	**2ga**	2-Th	$XPhosAuNTf_2$	1/2.5	**3ga** + **4ga**	80
15	**2ha**	4-$Me_2NC_6H_4$	$NaAuCl_4.2H_2O$	< 1/20	**4ha**	82
16	**2ha**	4-$Me_2NC_6H_4$	$XPhosAuNTf_2$	< 1/20	**4ha**	85
17	**2ia**	1-Me-indol-3-yl	$NaAuCl_4.2H_2O$	< 1/20	**4ia**	90
18	**2ia**	1-Me-indol-3-yl	$XPhosAuNTf_2$	< 1/20	**4ia**	76[i]

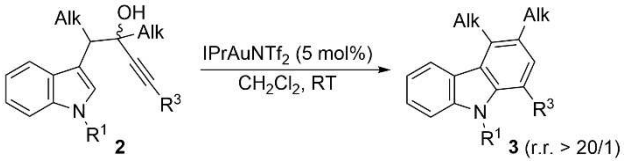
[a] Reaction conditions: **2** (0.5 mmol), gold catalyst (0.025 mmol) in CH_2Cl_2 (4 mL) at RT for 16 h (when using Au(III)) or 2–6 h (when using Au(I)). [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Isolated product(s) after column chromatography. [d] Isolated yield referred to the corresponding starting alkynol **2**. [e] 68% conversion after 16 h. [f] A 1/10 ratio was obtained with $IPrAuNTf_2$. [g] A 1/3.5 ratio was obtained with $IPrAuNTf_2$. [h] Minor amounts of **3ea** were generated along with some unidentified products. [i] An unidentified compound was also generated in minor amounts.

2,4,6-trimethoxyphenyl group was essayed. Based on the related iodocyclization reaction (see Scheme 1c),[13] the corresponding carbazole **4fa** was expected with high or complete selectivity. However, under both catalytic conditions (entries 11 and 12), **4fa** was the major compound but the selectivity was not significantly high and even worse when using Au(I). This fact could be due to a significant steric effect of the bulky 2,4,6-$(MeO)_3C_6H_2$ group on the migration step. The result for substrate **2ga**, bearing an electron-rich heteroaromatic group such as 2-thienyl, was similar to that obtained for **2ca**, with a *p*-methoxyphenyl, under Au(III)-catalysis leading to a mixture of carbazoles **3ga** and **4ga** (entry 13), which, however, was not significantly improved with Au(I) (entry 14). Using a more electron-rich aromatic group like 4-dimethylaminophenyl as Ar substituent (**2ha**), the 1,2-alkyl migration was clearly favored and the corresponding carbazole **4ha** was selectively obtained with both gold catalysts (entries 15 and 16). Finally, as expected from our previous results,[12] we checked that bisindolylmethane-tethered alkynol **2ia** regioselectively afforded the corresponding carbazole **4ia** in high yields, derived from the 1,2-alkyl migration, regardless of the gold catalyst employed (entries 17 and 18), although better results were obtained with $NaAuCl_4$. From the obtained results, it seems that the regioselectivity is mainly controlled by the electronic nature of the substituent at the homopropargylic position, with more electron-rich aromatic groups, especially with those possessing a strong +M effect such as anilines and indoles, favoring the 1,2-alkyl migration, although the gold catalyst continues to modulate this tendency being its effect more evidenced for neutral or electron-poor aromatic groups.

Considering the obtained results with an aromatic group at the homopropargylic position, we envisaged that by changing it by an alkyl group, the selectivity towards carbazoles **3**, derived from the alkenyl migration, should be higher (Table 4). After a brief screening with model alkynol **2ja**, we observed that carbazole **3ja** was selectively obtained under both catalytic conditions, but when using gold(I) complex $IPrAuNTf_2$ as catalyst, higher yields were obtained. Next, with this Au(I) catalyst a selection of 3,4-dimethylcarbazoles **3ja-jg** was synthesized in high yields bearing different alkyl or aryl groups at R^3 position, derived from the alkyne substituent of the starting homopropargyl indole **2** (Table 4, entries 1–6). An alkynol bearing an *N*H unprotected indole ring like **2ka** was also evaluated, leading to the expected carbazole **3ka**, derived from the alkenyl migration, in moderate yield as no complete conversion was observed (entry 7). Finally, the alkyl substituent of the homopropargylic position was changed from methyl to ethyl, **2la**, without any change in the selectivity, thus leading selectively to carbazole **3la** (entry 8).

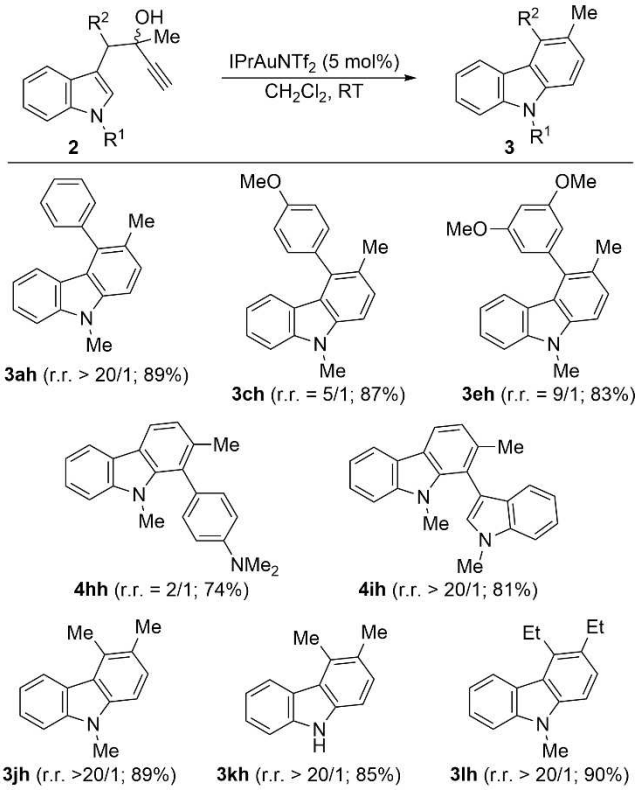
Additionally, homopropargyl indoles **2** bearing terminal alkynes were also evaluated (Scheme 3). Interestingly, in most cases, only carbazoles **3**, derived from 1,2-alkenyl migrations, were formed with a high control of the regioselectivity when using $NaAuCl_4$ or even Au(I) complexes as catalysts. No appreciable effect on the product distribution was observed by varying the catalyst. However, higher yields were achieved by employing $IPrAuNTf_2$ catalyst, affording cleaner reaction crudes. Only in a few cases, lower selectivity towards carbazole **3** was observed when employing homopropargyl indoles bearing a *p*-methoxyphenyl or a 3,5-dimethoxyphenyl substituent at position R^2, affording in these cases minor amounts of the corresponding carbazoles **4**, derived from 1,2-alkyl migration, although carbazoles **3ch** and **3eh** were respectively obtained as the major compounds. Not unexpectedly, by increasing the electron-rich character or the R^2 group, the selectivity was switched to the carbazoles **4**, as shown with alkynols **2hh** (R^2 = 4-$Me_2NC_6H_4$) and **2ih** (R^2 = indol-3-yl), which gave rise to **4hh** and **4ih** as major or exclusive products, respectively.[18] Dialkyl-substituted alkynols (**2jh**, **2kh** and **2lh**) achieved cyclization, affording carbazoles derived from alkenyl migration in high

Table 4. Regioselective synthesis of carbazoles **3** from alkyl-substituted homopropargyl indoles.[a]



Entry	2	R^1	Alk	R^3	Product	Yield [%][b]
1	**2ja**	Me	Me	*n*Bu	**3ja**	86
2	**2jb**	Me	Me	$(CH_2)_2Ph$	**3jb**	84
3	**2jc**	Me	Me	cC_3H_5	**3jc**	73
4	**2jd**	Me	Me	Ph	**3jd**	85
5	**2jf**	Me	Me	3-Th	**3jf**	85
6	**2jg**	Me	Me	cC_6H_9	**3jg**	64
7	**2ka**	H	Me	*n*Bu	**3ka**	50[c]
8	**2la**	Me	Et	*n*Bu	**3la**	85

[a] Reaction conditions: **2** (0.5 mmol), $IPrAuNTf_2$ (0.025 mmol) in CH_2Cl_2 (4 mL) at RT for 2 h. [b] Isolated yield referred to the corresponding starting alkynol **2**. [c] 70% conversion after 16 h.



Scheme 3. Gold-catalyzed cyclizations of 3-homopropargyl indoles **2** bearing terminal alkynes.

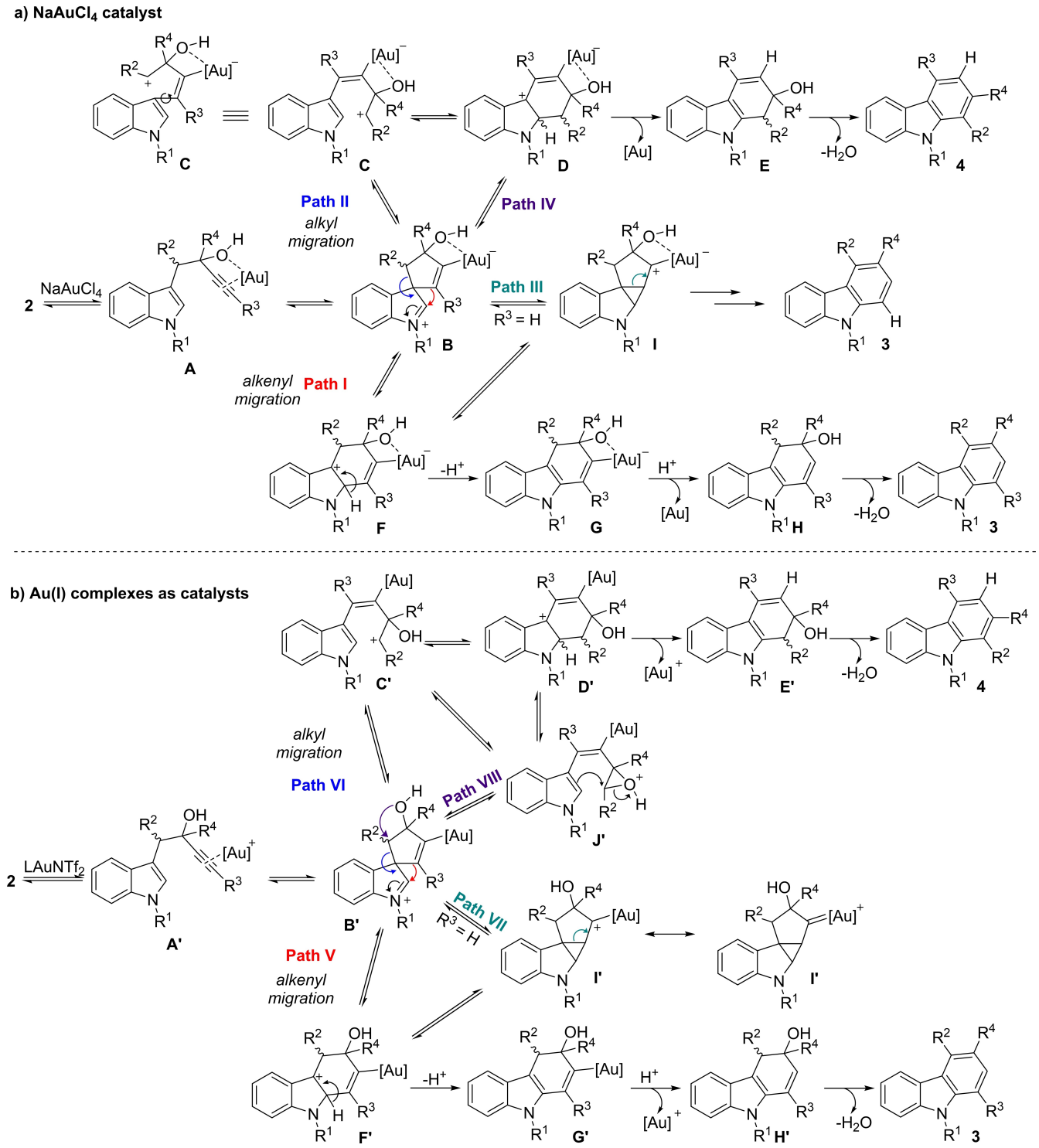
yields and with an excellent control over the regioselectivity of the process. Deuterium-labeled experiments employing the deuterated terminal alkyne **2jh-D** suggest that no gold vinylidene is formed as no deuterium shift was observed.[15]

A tentative mechanistic proposal evaluating the different plausible reaction pathways is depicted in Scheme 4, based on the obtained results and previous works on gold-catalyzed alkyne hydroarylation reaction with indoles.[7–12] In this sense, and considering the ability of gold(III) chlorides to activate alkynols,[19] coordination of the gold salt may occur at both the alkyne moiety and the hydroxyl group giving rise to intermediate **A** (Scheme 4a). Then, rapid evolution into well-established spiroindoleninium intermediates[9] takes place, affording compound **B**. Then, this spirocyclic intermediate could evolve through different reaction pathways involving 1,2-alkenyl migration (Paths I and III) or otherwise 1,2-alkyl migration (Paths II and IV). In general terms, the alkenyl moiety is more prompted to experience 1,2-migration than the alkyl substituent when spiroindoleninium intermediates are involved.[10] So, carbazole **3** is expected to be formed preferentially over carbazole **4**, once the alkenyl migration (**F**) occurs, followed by protodemetalation of **G**, affording intermediate **H**, that upon dehydration reaction liberates the carbazole **3**. Nevertheless, alkyl migration could also be a competitive reaction affording minor amounts of carbazole **4**. As shown by previous DFT calculations, 1,2-alkyl migration may occur via a stepwise mechanism involving the formation of carbocation intermediate **C** generated by C–C bond cleavage between quaternary carbon at the spiro-atom position and the alkyl fragment. Remarkably, the nature of the substituent at R^2 capable of stabilizing the carbocation could be decisive in favoring this pathway. In this sense, substrates bearing electron-rich heteroaromatics at this position (**2ia**) react almost exclusively by this route.[12] Similarly, aryl substituents decorated with methoxy groups appropriately placed (**2ca**, **2da**, and **2fa**) could also stabilize the formation of the carbocation **C** achieving a higher ratio of carbazole **4**, instead of **3**, which is preferentially formed with aryl groups at R^2 bearing halogen atoms (**2ba**), unsubstituted phenyls (**2aa**) or alkyl groups (Table 4) at this position. Then, nucleophilic attack onto this carbocation by the primary indole generates **D**, which is also the intermediate formed by a direct alkyl migration (Path IV). Similar protodemetalation and dehydration steps release the carbazole and regenerate the catalyst. In addition, when 3-homopropargyl indoles **2** bearing terminal alkynes are used as substrates, other reaction pathways that favor alkenyl migration may operate,[20] involving the formation of cyclopropane intermediate **I** that could evolve through cyclopropane ring opening reactions generating **F**.

A similar reaction mechanism could be proposed when Au(I) complexes are used as catalysts (Scheme 4b). In this case, the linear cationic Au(I) complexes are coordinated exclusively to the alkyne moiety **A'** due to their lower Lewis acid character than Au(III) species.[21] Then, analog crucial spiroindoleninium intemerdiate **B'** is also formed. Similar to the previous reaction pathways employing $NaAuCl_4$, alkenyl (Paths V, VI and VII) or alkyl migration routes could be proposed to explain the formation of both carbazoles **3** and **4**. Nevertheless, when employing the same alkynols **2**, the higher ratio of carbazoles **4**, derived from alkyl migrations, observed in these cases could be rationalized by the contribution of an additional reaction pathway (Path VIII). The carbocationic intermediate **C'**, crucial for the stepwise alkyl migration, could be stabilized by the contiguous free hydroxyl group generating **J'** that could also suffer a nucleophilic attack of the indole core to form species **D'** derived from a formal direct 1,2-alkyl migration. In addition, this pathway could also operate if Au(III) species like $PicAuCl_2$, with a lower ability to coordinate and activate OH groups of alkynols[22] are used as catalysts. Also, the reaction of 3-homopropargyl indoles **2** bearing terminal alkynes with Au(I) catalysts may proceed through intermediates involving cyclopropane rings **I'** generating almost exclusively carbazoles **3** derived from 1,2-alkenyl migrations.[23]

Conclusions

In summary, the reactivity upon activation with gold catalysts of alkynols bearing an indol-3-yl group at the homopropargylic position was studied. Under mild reaction conditions these substrates are activated forming a key spirocyclic intermediate that evolves through two main different cyclization pathways, derived from formal 1,2-alkenyl or 1,2-alkyl migrations, affording two sets of highly substituted carbazoles. The regioselectivity of the process can be controlled by a fine-tuning of both the gold



Scheme 4. Plausible reaction mechanism pathways.

catalyst employed and the nature of the substituents at the homopropargylic and terminal position of the starting alkynol, achieving a regiodivergent synthesis of carbazoles.

Experimental Section

Synthesis of 3-homopropargyl indoles 2

n-BuLi (3.0 equiv) was added to a solution of the appropriate alkyne (3.3 equiv) in THF (1.5 M) at −45 °C. The resulting solution was stirred for 30 min at 0 °C to obtain the corresponding lithium acetylide. The corresponding α-(indol-3-yl) ketone **1** (1.0 equiv) in

THF (1 M) was added dropwise to the acetylide solution at −45 °C. The resulting mixture was allowed to stir for 20 min at the same temperature and, after removal of the cooling bath, the mixture was allowed to stir at RT until the electrophile was consumed as determined by GC-MS. For the synthesis of 3-homopropargyl indoles **2** bearing terminal alkynes, ethynyl magnesium bromide (3.0 equiv. of a 0.5 M solution in THF) was directly used and the reaction mixture was allowed to stir at RT until the electrophile was consumed as determined by GC-MS. In all the cases, aqueous NH_4Cl (10 mL) was added and the resulting solution was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography using mixtures of hexane and EtOAc as eluents to obtain the corresponding 3-homopropargyl indoles **2**.

Synthesis of carbazoles 3 and 4

$NaAuCl_4 \cdot 2H_2O$ (0.05 equiv) or $XPhosAuNTf_2$ (0.05 equiv) or $IPrAuNTf_2$ (0.05 equiv), was dissolved in CH_2Cl_2 (0.012 M) and the resulting solution was allowed to stir for 5 min at RT. A solution of the corresponding alkynol **2** (1 equiv) in CH_2Cl_2 (0.25 M) was subsequently added. The reaction mixture was stirred at RT until the complete disappearance of the starting material was determined by TLC. The mixture was filtered through a short pad of silica gel and celite using a mixture of hexane/EtOAc (5/1) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography using mixtures of hexane and EtOAc as eluents to afford the corresponding carbazoles **3** and/or **4**.

Supporting Information

The Supporting Information includes characterization data and copies of the ^1H and ^{13}C NMR spectra of the prepared compounds. Additional references cited within the Supporting Information.[24–26]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbazoles · gold · homogeneous catalysis · 1,2-migration · regioselectivity

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