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Brønsted Acid-Catalyzed Straightforward Synthesis of Benzo[*b*]carbazoles from 2,3-Unsubstituted Indoles

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Abstract: Described is a general and efficient synthesis of valuable benzo[*b*]carbazoles by Brønsted acid-catalyzed reactions between simple C-2,C-3-unsubstituted indoles and *ortho*-[α-(hydroxy)benzyl]benzaldehyde acetals. Highly selective migration processes are involved as key steps in the overall cascade sequence that involves the one-pot formation of two new bonds and a cycle in a regioselective fashion.

Keywords: 1,2-alkyl shift; benzo[*b*]carbazoles; Brønsted acid catalysis; heterocycles; synthetic methods

Aryl- and heteroaryl-condensed carbazoles have attracted considerable interest because of their broad spectrum of useful biological activities.[1] Among the benzocarbazole frameworks, annulated[*b*]carbazoles, such as ellipticine and its derivatives,[2] are relevant due to their interesting pharmacological activities[3] as well as their utility in the field of material chemistry.[4] Different approaches for accessing this type of heterocyclic compounds have been described, although most of them imply multi-step sequences and restricted substitution patterns. In this regard, benzo[*b*]carbazoles are commonly constructed from either properly functionalized indoles or carbazoles,[5] substituted naphthalenes,[6] or more particularly from ketenimines and imidoyl selanides by radical cyclizations,[7] or from ynamides by dehydro Diels–Alder reactions.[8] However, to the best of our knowledge, there are no general methodologies developed for the direct synthesis of (hetero)aryl[*b*]carbazoles starting from simple C-2,C-3-unsubstituted indoles (Figure 1).[9]

On the other hand, the reaction of indoles with carbonyl derivatives, including acetals,[10] in the presence of Lewis or protic acids is the most general method for the synthesis of symmetrical 3,3′-bisindolylmethanes (3,3′-BIMs) (**II**). Their formation is proposed to proceed through the intermediacy of an azafulvenium species such as **I** (with Nu = H) that undergoes further addition of a second indole molecule (Scheme 1).[11] When intermediates **I** are functionalized with an additional nucleophilic group such as an electron-rich aromatic (Nu = Ar), a second Friedel–Crafts alkylation process can take place affording products like **III** (Scheme 1).[12] Alternatively, it is well known that neutral alkylideneindolenine intermediates related with **I** (Nu = H), commonly formed from precursors having a suitable leaving group at the benzylic position of 3-substituted indoles, are able to add external nucleophiles in a conjugate fashion.[13]

Herein we wish to report our results on the Brønsted acid-catalyzed reaction between indoles and aromatic aldehyde acetals possessing an α-(hydroxy)benzyl group at the *ortho*-position, which enables a facile entry into the synthesis of regioselectively functionalized benzo[*b*]carbazoles through an unprecedented cascade sequence.

In the last years, we have been interested in the development of new methodologies for the direct C-3 alkylation of indoles with alcohols.[14] As part of this research, we studied the reaction between *N*-methylindole **1a** and [2-(diethoxymethyl)phenyl]-(phenyl)methanol **2a**[15] using various acid catalysts (Scheme 2). The use of selected σ-Lewis acids, previously employed for the reaction of indoles with carbonyl derivatives, afforded isobenzofuran derivative **3aa**, obtained as a mixture of diastereoisomers, as the only product without formation of the corresponding 3,3′-BIM. Surprisingly, the same reaction under Brønsted acid catalysis (20 mol% of PTSA) selectively afforded a new product, the benzo[*b*]carbazole de-

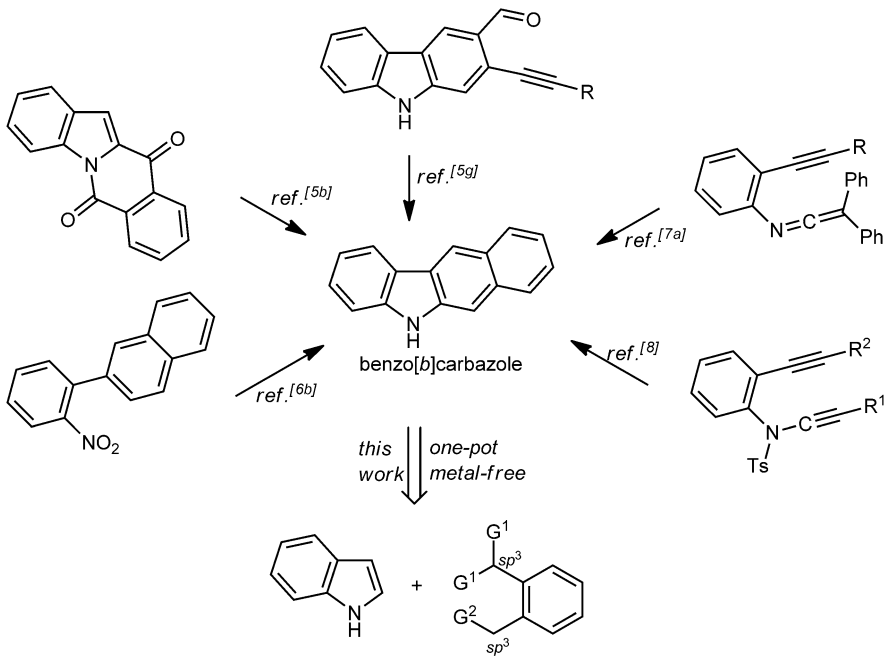
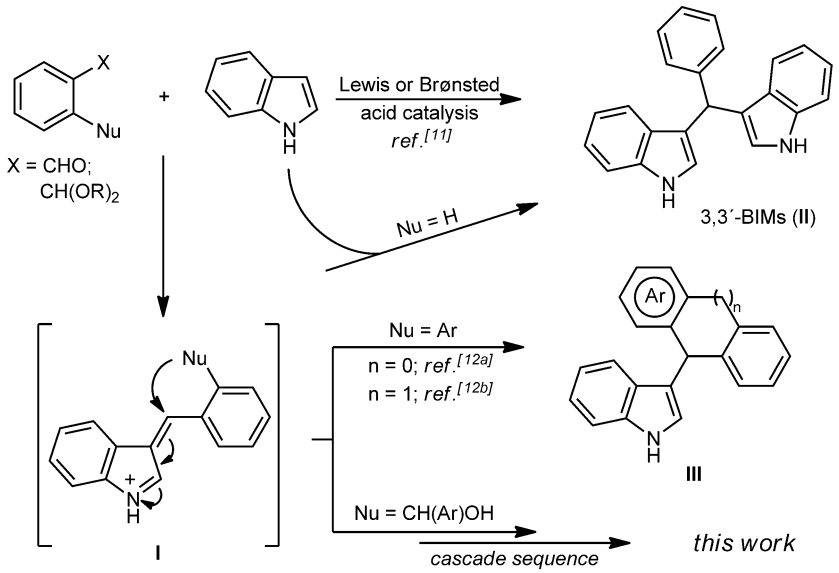


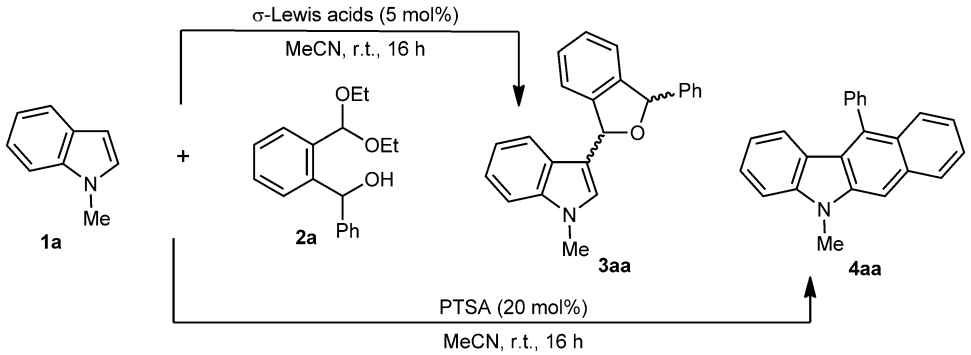
Figure 1. Synthetic routes to benzo[*b*]carbazoles.



Scheme 1. Reported reactions of indoles and benzaldehyde derivatives: synthesis of 3,3′-BIMs (**II**) and C-3-carbocyclic-functionalized indoles (**III**).

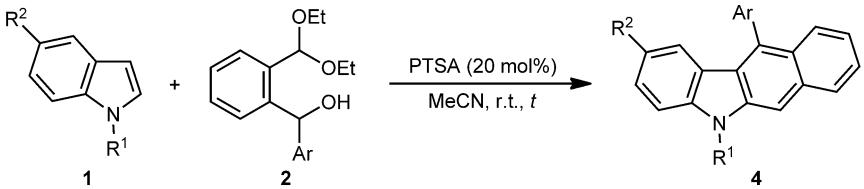
rivative **4aa**, which was isolated in 78% yield.[16] Remarkably, its formation formally involves two consecutive and selective Friedel–Crafts-type reactions of a C-2,C-3-unsubstituted indole with a bis(electrophile) bearing an alcohol as sp^3-type acceptor and an acetal as carbonyl-type acceptor. Interestingly, whereas the preparation of annulated indolic frameworks by the formal C-2-hydroarylation of indoles with sp^2- or *sp*-type acceptors, such as Michael substrates[17] or gold-activated alkynes,[18] has been well established, the corresponding reactions with sp^3-type acceptors like halides or alcohols through the Ciamician–Plancher rearrangement have been scarcely reported.[19]

Having found mild conditions to efficiently and directly access **4aa** from readily available *N*-methylindole we decided to check if this methodology could be general for the synthesis of a variety of benzo[*b*]-carbazoles. First, *N*-methylindole **1a** was treated with selected benzylic alcohols **2a–i**, prepared from 2-lithiobenzaldehyde diethyl acetal and selected (hetero)ar-



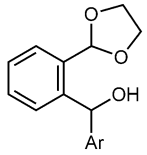
Scheme 2. Acid-catalyzed reaction of *N*-methylindole **1a** with diethyl acetal **2a**. Selective formation of **3aa** and **4aa**.

Table 1. Synthesis of benzo[*b*]carbazoles **4**.

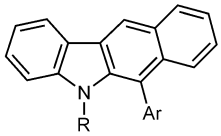


Entry	**1**	R^1	R^2	**2**	Ar	*t* [h]	Product	Yield [%][a]
1	**1a**	Me	H	**2a**	Ph	16	**4aa**	78
2[b]	**1a**	Me	H	**2b**	4-ClC_6H_4	24	**4ab**	89
3[b]	**1a**	Me	H	**2c**	4-BrC_6H_4	16	**4ac**	65
4[b]	**1a**	Me	H	**2d**	2-naphthyl	3.5	**4ad**	58
5	**1a**	Me	H	**2e**	4-$MeOC_6H_4$	16	**4ae**	85[c]
6	**1a**	Me	H	**2f**	2,3,4-$(MeO)_3C_6H_2$	0.5	**4af**	90
7	**1a**	Me	H	**2g**	2-thienyl	2	**4ag**	73
8	**1a**	Me	H	**2h**	3-methyl-2-thienyl	1.5	**4ah**	71
9	**1a**	Me	H	**2i**	5-methyl-2-furyl	2	**4ai**	51[d]
10[b]	**1b**	H	H	**2a**	Ph	5	**4ba**	65
11[b]	**1b**	H	H	**2d**	2-naphthyl	4	**4bd**	50
12	**1b**	H	H	**2e**	4-$MeOC_6H_4$	16	**4be**	92
13	**1b**	H	H	**2f**	2,3,4-$(MeO)_3C_6H_2$	0.5	**4bf**	98
14	**1b**	H	H	**2i**	5-methyl-2-furyl	3.5	**4bi**	68[d]
15	**1c**	H	Br	**2e**	4-$MeOC_6H_4$	4	**4ce**	48
16	**1d**	H	NO_2	**2f**	2,3,4-$(MeO)_3C_6H_2$	1	**4df**	85
17	**1e**	H	Cl	**2f**	2,3,4-$(MeO)_3C_6H_2$	1	**4ef**	94
18	**1f**	H	CO_2Me	**2f**	2,3,4-$(MeO)_3C_6H_2$	1	**4ff**	80

[a] Yield of isolated products **4** based on the starting indole **1**.
[b] Carried out with 50 mol% of PTSA.
[c] Same yield was obtained in a related reaction starting from alcohol **2′e** bearing an ethylene acetal moiety instead of a diethyl acetal one.
[d] 7–10% of the corresponding 6-arylbenzo[*b*]carbazole **5** was also isolated and characterized.



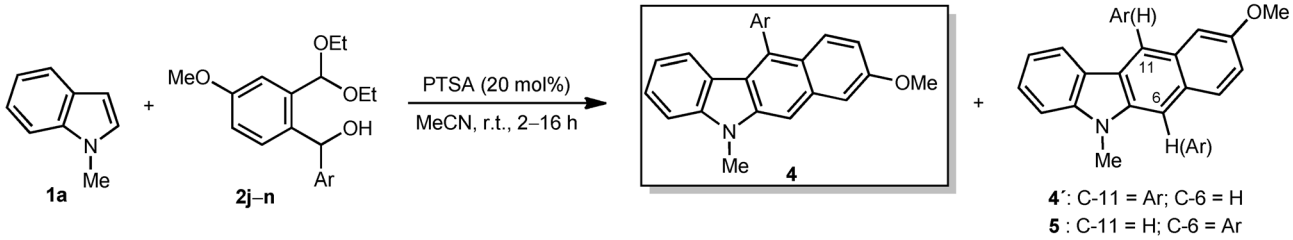
2e′: Ar = 4-$MeOC_6H_4$



5

yl carboxaldehydes. As shown in Table 1, both EDG and EWG substituents on the Ar group, as well as heteroaromatics, were adequately tolerated in the process and 11-aryl-5*H*-benzo[*b*]carbazoles **4aa–ai**[20] were obtained typically in high yields. Reactions with highly activated benzylic alcohols bearing EDG groups proceed faster and with a lower amount of the Brønsted acid catalyst (entries 5–9 *vs.* 1–4). Interest-

Table 2. Brønsted acid-catalyzed reaction of *N*-methylindole **1a** with functionalized acetals **2j–n**. Competitive formation of benzo[*b*]carbazoles **4** *vs.* **4′** and **5**.



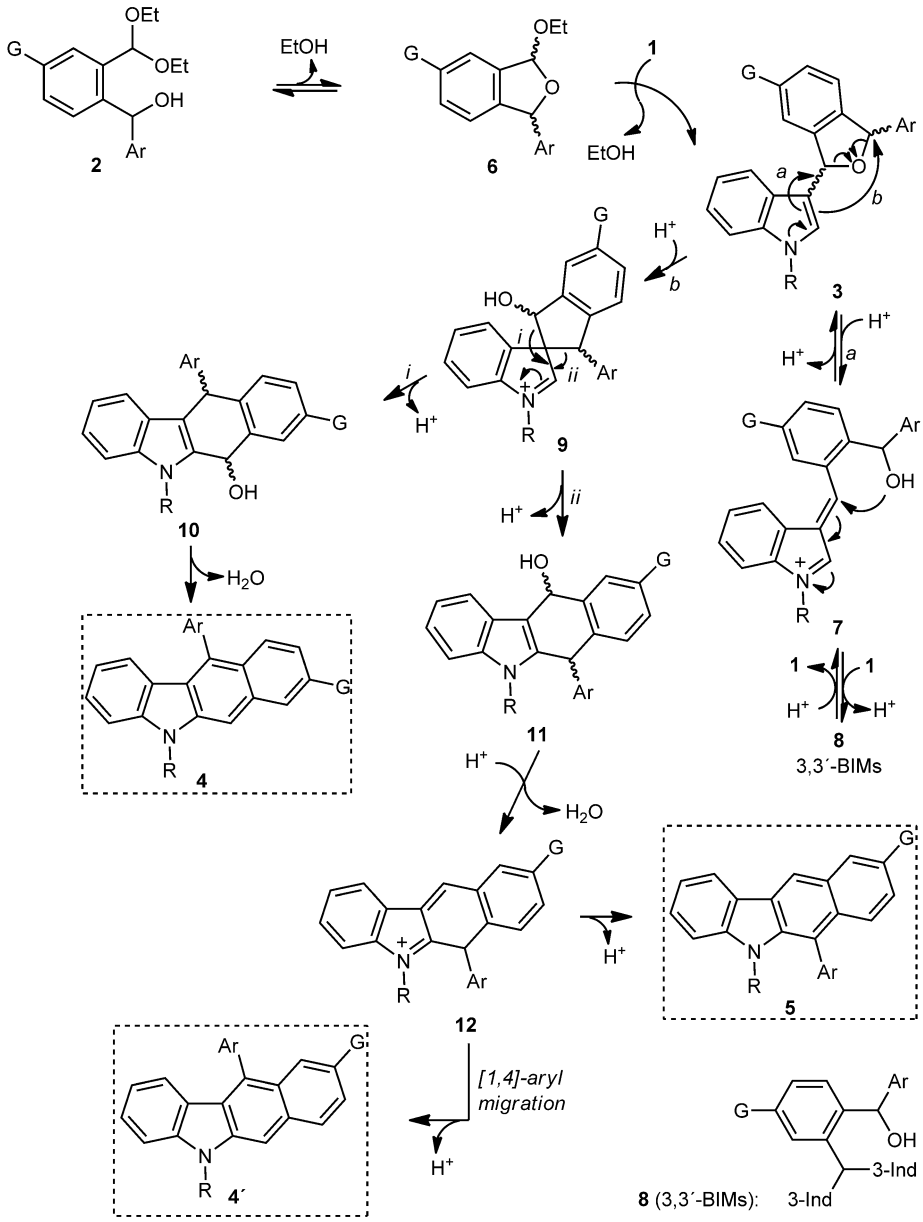
Entry	**2**	Ar	Product(s)[a]	Yield [%][b]
1	**2j**	Ph	**4aj**	60[c]
2	**2k**	4-ClC_6H_4	**4ak**	68[c]
3	**2l**	4-$MeOC_6H_4$	**4al**	73[d]
4	**2m**	2,3,4-$(MeO)_3C_6H_2$	**4am**+**4′am** (1/1.7)	82[e]
5	**2n**	2-thienyl	**4an**+**4′an** (2/1)	75[f]

[a] When two regioisomers were generated, the ratio (in brackets) was determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Yield of isolated product **4** based on the starting *N*-methylindole **1a**.
[c] *Ca.* 5% of the corresponding 6-arylbenzo[*b*]carbazole **5** was also isolated and characterized.
[d] Trace amounts of **4′al** and **5al** were also formed.
[e] Yield for the mixture of regioisomers. The major one was isolated and characterized.
[f] 56% of **4an** and 19% of **4′an** were isolated and characterized.

ingly, no influence in the process or yield was observed by varying the acetal moiety as we determined in the synthesis of benzo[*b*]carbazole **4ae** from **2e** and **2′e** (entry 5). In addition, NH-indole **1b** also reacted with selected hydroxyacetals **2** to furnish benzocarbazole derivatives **4ba–bi** in good yields (entries 10–14). Moreover, even the less nucleophilic 5-functionalized indoles **1c–f** are able to participate in this reaction allowing the regioselective preparation of benzo[*b*]carbazoles **4ce** and **4df–ff** in moderate to high yields (entries 15–18). However, the presence of an aromatic group (Ar) as substituent in the starting alcohol **2** seems to be mandatory for the success of the reaction as substrates bearing alkyl (*n*-Bu), cyclopropyl, (*E*)-β-styrenyl (CH=CHPh), or phenylethynyl (C≡CPh) only gave rise to decomposition products under the standard reaction conditions.

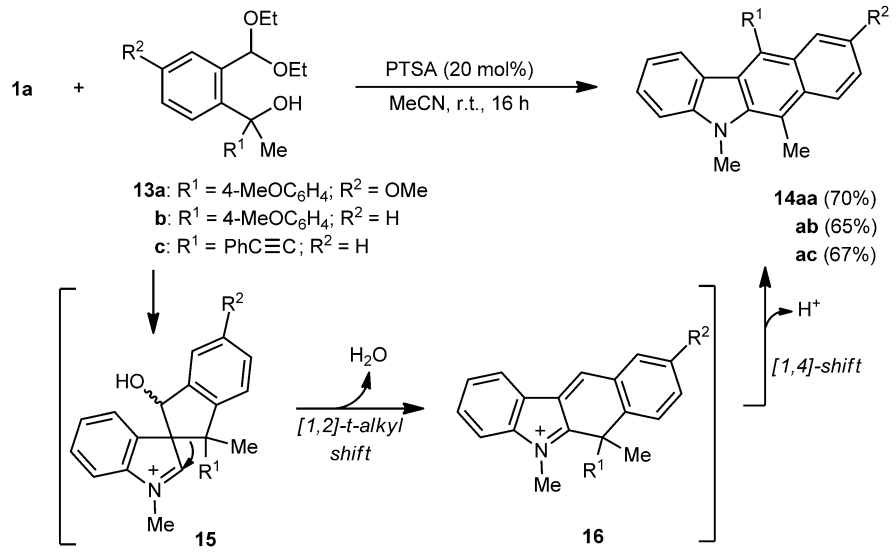
Remarkably, all these reactions selectively occurred to form 11-aryl-5*H*-benzo[*b*]carbazoles **4** while the corresponding regioisomeric 6-aryl-substituted benzo[*b*]carbazoles **5** were only observed in trace to minor amounts in some cases (entries 9 and 14). Intrigued by these particular results, we decided to further explore this process by using hydroxyacetals **2j–n** functionalized with a methoxy group at the aryl ring that contains the acetal group and with different aryl groups at the benzylic position. Their reactions with *N*-methylindole **1a** under the standard conditions, PTSA (20 mol%) in MeCN at room temperature, mainly gave rise to the expected 11-aryl-5*H*-benzo[*b*]carbazoles **4** that could be isolated in synthetically useful yields (Table 2). With hydroxyacetals **2j–l** bearing neutral, moderately electron-rich, or electron-poor aryl substituents (entries 1–3), the corresponding benzo[*b*]carbazoles **4** were almost exclusively obtained. However, in the case of highly activated hydroxyacetals **2m** and **2n**, with a 2-thienyl or a trimethoxyphenyl group as Ar substituent, variable amounts of regioisomeric benzo[*b*]carbazoles **4′**, differing on the final position of the methoxy group initially located at a defined position in the starting hydroxyacetal **2**, were obtained (entries 4 and 5).

With all these results in hand, a catalytic cycle that could account for the formation of benzo[*b*]carbazoles **4**, **4′**, and **5** is shown in Scheme 3. Initially, an equilibrium between hydroxyacetal **2** and cyclized acetal **6** is established in the acidic medium. Its reaction with the corresponding indole **1** would afford isobenzofuran derivatives **3**, as it was observed when using several σ-Lewis acids or lower amounts of PTSA (see Table in the Supporting Information).[21] Probably favoured by the presence of the Brønsted acid, these isobenzofurans **3** are in equilibrium with the corresponding 3,3′-BIMs **8** through the iminium intermediate **7** (path *a*).[22] This hypothesis was supported by previous reports[12] and by isolation of bisindole **8ab** (Ar=4-ClC_6H_4; G=H), along with **3ab**, when carrying out the reaction with 5 mol% of PTSA for 30 min. Reactions under the conditions reported in Table 1 (entry 2) of both isolated dihydroisobenzofuran **3ab** and bisindole **8ab** furnished benzo[*b*]carbazole **4ab**. Having proved the intermediacy of **3**, as well as its equilibrium with **8** in the reaction media, the formation of benzo[*b*]carbazole **4** would be ex-



Scheme 3. Proposed mechanism for the formation of benzo[*b*]carbazoles **4**, **4′**, and **5**.

plained by an alternative path *b* which would imply a nucleophilic addition of C-3 of the indole that would generate spiro species **9**. This key intermediate could undergo two different 1,2-alkyl shifts (Ciamician–Plancher rearrangement) to recover aromaticity after loss of a proton.[23] Migration of the hydroxyalkyl group (path *i*) would lead to alcohol **10** that upon loss of water would afford benzo[*b*]carbazole **4**. On the other hand, a competitive migration of the benzylic group (path *ii*) would lead to regioisomeric alcohol **11** that would provide the corresponding benzo[*b*]carbazole **5** after protonation and loss of water, probably through the iminium intermediate **12**, and subsequent aromatization by further removal of a proton. However, both pathways do not account for the generation of benzo[*b*]carbazoles **4′**, in which the relative position of the G substituent and the Ar group have changed with respect to the starting alcohol **2**. So, we propose that the iminium intermediate **12** could also evolve through an alternative pathway involving a [1,4]-aryl migration. Subsequent loss of a proton would explain the formation of benzo[*b*]carbazoles **4′**. This competitive process seems to be partially operative exclusively when the hydroxymethyl group is located at C-3 (intermediate **11** *vs.* **10**), probably due to the high stabilization of iminium intermediate **12**. On the basis of this proposal the two 1,2-alkyl shifts (pathways *i* and *ii*) could not be distinguished for non-



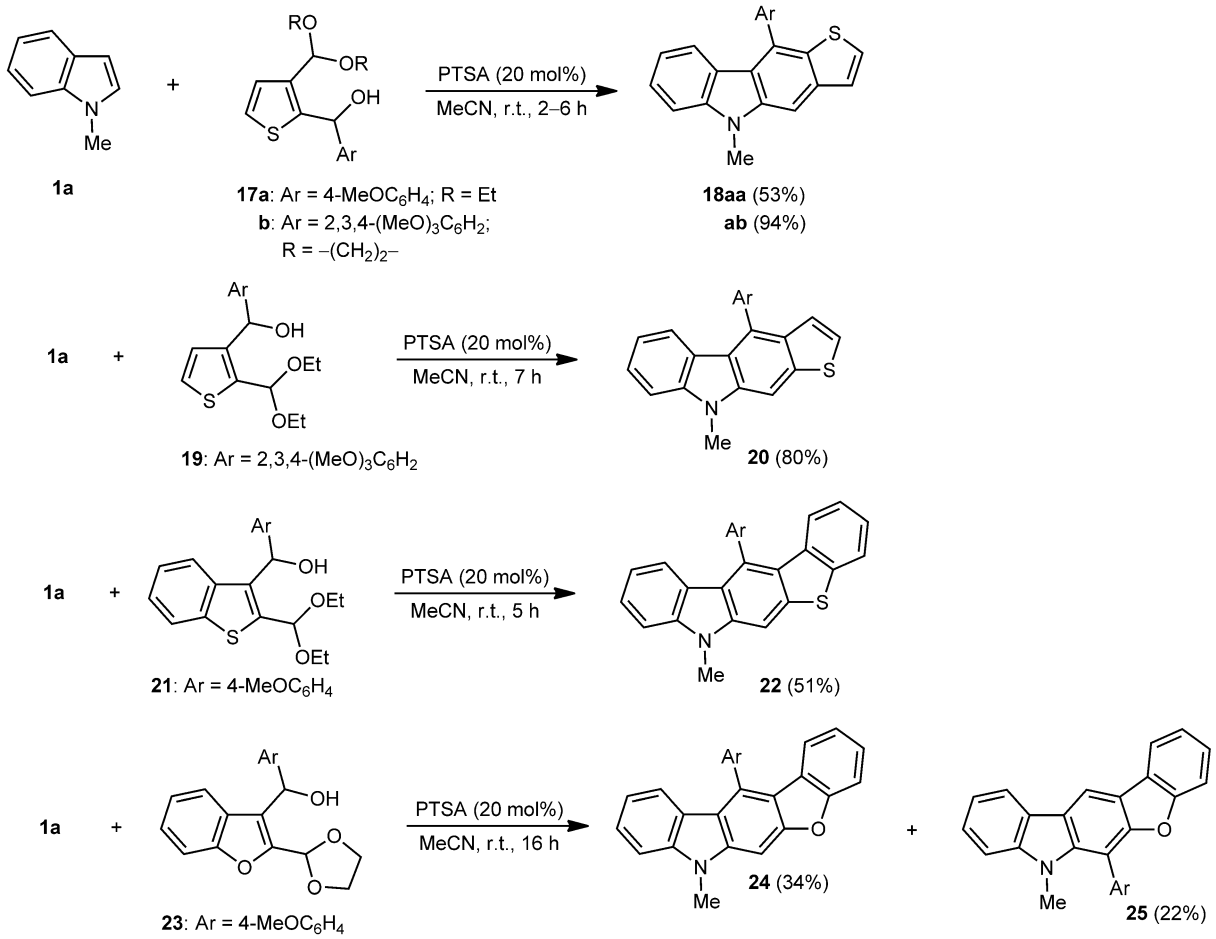
Scheme 4. Reactions of **1a** with tertiary alcohols **13a–c**. Synthesis of 6,11-disubstituted-5*H*-benzo[*b*]carbazoles **14**.

functionalized hydroxyacetals **2** (G = H) as both of them collapse to the same product (**4′** = **4** for G = H). From the results of Table 2 it seems that pathway *i* is the preferred one whereas the benzyl migration (pathway *ii*) resulted to be competitive only for highly activated substrates [G = OMe and Ar = 2-thienyl or 2,3,4-$(MeO)_3C_6H_2$] with an increased carbocation stabilization ability at the benzylic position. Also, the subsequent [1,4]-aryl migration on intermediate species **12** is favoured for electron-rich aromatics as Ar substituents. In the other cases, only trace amounts of regioisomers **5** are formed.

Based in our proposed mechanism we envisioned that acetal derivatives **13** bearing a tertiary benzylic hydroxy group could be potential precursors of 6,11-disubstituted benzo[*b*]carbazoles thus expanding the scope of the reported benzocarbazole synthesis. Gratifyingly, treatment of indole **1a** with hydroxyacetals **13a–c** under the standard Brønsted acid catalysis selectively afforded the aimed 6,11-disubstitued benzo[*b*]carbazole derivatives **14** (that correspond with **4′** in the general mechanism depicted in Scheme 3) in good yields (Scheme 4).[24] It is interesting to note that for these acetals **13** the scope of the substitution at the benzylic carbon bearing the hydroxy group is not limited to aromatic substituents, like in secondary alcohols **2**, as shown for **13ac** having an alkynyl group that affords the corresponding benzo[*b*]carbazole **14ac**. As we anticipated, by increasing the migratory aptitude of the benzylic carbon in intermediate **15** (tertiary in **15** *vs.* secondary in **9**) an initial selective migration of the *tert*-alkyl group (pathway *ii* in Scheme 3) occurred to form iminium species **16**. These intermediates, in contrast with related ones **12** in Scheme 3, could only evolve by a formal [1,4]-migration to recover the aromaticity after loss of a proton (Scheme 4). Interestingly, the observed [1,4]-aryl or alkynyl shift has no precedent and opens the door to future developments in this field. Specially significant is the result of the migration of an alkynyl group in the formation of **14ac** as the low migratory aptitude of these groups in carbocation rearrangements is known.[25]

Moreover, the reported methodology resulted to be also useful for the synthesis of heteroaryl-fused carbazoles. So, 10-aryl-5*H*-thieno[3,2-*b*]carbazoles **18** were selectively prepared under the standard Brønsted acid catalysis from thiophene-based hydroxyacetals **17a** and **17b** (Scheme 5). Interestingly, starting from regioisomeric hydroxyacetal **19**, the corresponding thieno[2,3-*b*]carbazole derivative **20**, was exclusively formed (Scheme 5). In addition, benzo[4,5]thieno[2,3-*b*]carbazole **22** as well as benzofuro[2,3-*b*]carbazole **24** could also be prepared with this methodology from a properly functionalized benzo[*b*]thiophene **21** and benzo[*b*]furan **23**, respectively (Scheme 5). The formation of all of these carbazole derivatives could be understood in the same way as benzo[*b*]carbazoles **4**, thus involving initial hydroxyalkyl shift (pathway *i* in Scheme 3) followed by loss of water. Furthermore, the synthesis of these adducts was completely selective with the exception of carbazole derivative **24** the formation of which was accompanied with the regioisomeric benzofuro[2,3-*b*]carbazole **25** in a *ca.* 1.6:1 ratio (Scheme 5).[26] On the contrary, hydroxyacetals bearing N-heterocycles such as pyridines or indoles led to no reaction or decomposition under the established conditions (Figure 2).[27]

In conclusion, we have described a straightforward and regioselective synthesis of aryl-functionalized (hetero)aryl-annulated[*b*]carbazoles from easily available starting materials such as indoles and *ortho*-[α-



Scheme 5. Synthesis of heteroaryl[*b*]carbazoles **18**, **20**, **22**, **24** and **25**.

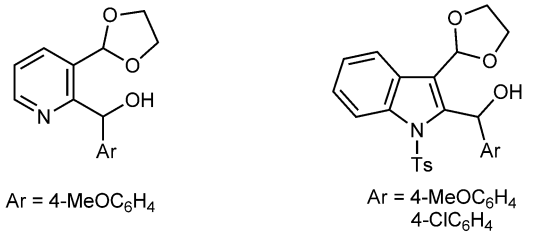


Figure 2. Not successful N-heterocycles-functionalized hydroxyacetals.

(hydroxy)benzyl]benzaldehyde acetals under simple Brønsted acid catalysis through a new cascade sequence. This efficient and metal-free methodology complements the current synthetic scenario for the preparation of benzo[*b*]carbazoles by adding a new strategy that allows the direct use of C-2,C-3-unsubstituted indoles. Further studies to prove the proposed mechanism of this new transformation and to extend its synthetic scope are currently in progress in our laboratory.

Experimental Section

General Remarks

All reactions involving air-sensitive compounds were carried out under an N_2 atmosphere (99.99%). All glassware was oven-dried (120 °C), evacuated and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers (VWR, Alfa and Aldrich) and used without any further purification. Solvents were dried by standard methods. Hexane and ethyl acetate were purchased as extra pure grade reagents and used as received. For the preparation of starting alcohols see the Supporting Information. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator; the chromatograms were visualized under ultraviolet light and/or by staining with a Ce/Mo reagent and subsequent heating. R_f values are reported on silica gel. Flash column chromatography was carried out on silica gel 60, 230–240 mesh. NMR spectra were measured on Varian Mercury-Plus 300 MHz and Varian Inova-400 MHz spectrometers. High resolution-mass spectra (HR-MS) were recorded on a Micromass Autospec spectrometer using EI at 70 eV. Melting points were measured on a Gallenkamp apparatus using open capillary tubes and are uncorrected. GC-MS and low resolution mass spectra (LR-MS) measurements were recorded on an Agilent

6890N/5973 Network GC System, equipped with an HP-5 MS column.

General Procedure for the PTSA-Catalyzed Synthesis of Benzo[*b*]carbazoles 4, 4′, and 5

To a mixture of the corresponding acetal derivative **2** (1 mmol) and the corresponding indole **1** (1 mmol) in MeCN (1 mL) was added PTSA (20 mol%, 38 mg). The reaction mixture was stirred at room temperature until complete disappearance of the acetal derivative was observed by TLC (0.5–24 h), then it was quenched with a 0.5 M aqueous solution of NaOH, and extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The remaining residue was purified by flash chromatography on silica gel using mixtures of hexane/EtOAc as eluents. The corresponding benzo[*b*]carbazoles **4**, **4'**, and **5** were isolated in the yields reported in the text. Characterization data and NMR spectra are presented in the Supporting Information.

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[21] The initial formation of isobenzofuran derivatives **3** precludes the possibility of an alternative mechanism involving a prior direct substitution of the hydroxy group by the indole through C-3 and further direct cyclization by attack of C-2 to the carbonyl.

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[27] Treatment of **1a** with pyridine- or indole-functionalized hydroxyacetal (Figure 2) led to no reaction under catalytic (20 mol%) or excess (120 mol%) amounts of PTSA.

