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Lewis Acid Mediated Aminobenzannulation Reactions of δ-Ketoalkynes: Synthesis of 1-Aminocarbazoles and 9-Aminopyrido[1,2-*a*]indoles

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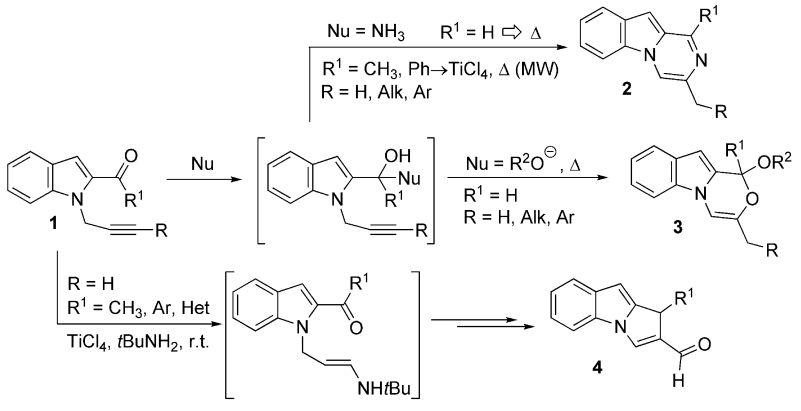
2-Acyl-*N*-propargylindoles **1** and 2-acyl-3-propargylindoles **5** undergo aminobenzannulation reactions with pyrrolidine in the presence of an appropriate Lewis acid to give 9-aminopyrido[1,2-*a*]indoles **6** and 1-aminocarbazoles **7**, respectively. The selection of the appropriate Lewis acid, $TiCl_4$ or $GaCl_3$ for **1** and $InCl_3$ for **5**, allows the domino process involving the initial formation of an enamine intermediate, followed by a regioselective 6-*exo*-*dig* intramolecular nucleophilic attack of the nucleophilic terminus of the unsaturated system (the β-carbon of the enamino moiety) to the carbon–carbon triple bond. Moreover, several features concerning the reaction mechanism and the role of both catalysts, in connection with the electronic properties of the reacting alkynes, are reported.

Introduction

2-Acyl-*N*-propargylindole derivatives **1** have been recently proposed by our research group as useful building blocks for the construction of *a*-fused polycyclic indoles, that is, pyrazino[1,2-*a*]indoles **2**,[1] [1,4]oxazino[4,3-*a*]-indoles **3**,[2] and pyrrolo[1,2-*a*]indole-2-carbaldehydes **4**[3] (Scheme 1). For the synthesis of pyrazino- and oxazino-indoles **2** and **3** this goal was achieved through domino catalyzed or uncatalyzed addition/annulation reactions involving two sequential inter/intramolecular carbon–heteroatom bond formations in the presence of ammonia or alkoxide. Thus, as reported in Scheme 1, these reactions involve a double heteronucleophilic attack on the electrophilic side of the carbonyl group and consequently over the carbon–carbon triple bond and can be thermally induced, Lewis acid/water scavenger catalyzed, and/or accelerated by the use of alternative heating methodologies (microwaves), when necessary.

Moreover, pyrroloindole derivatives **4** have been prepared by sequential hydroamination/carbon–carbon bond formation reactions. The reaction proceeds under *tert*-butylamine/titanium tetrachloride catalysis through initial hydroamination of the triple bond followed by an intramolecular carbon–carbon bond formation reaction.

Starting from these results, we exploited the possibility of performing the addition/annulation sequence with 2-acyl-*N*- or 3-propargylindoles **1** and **5** in the presence of a



Scheme 1.

secondary amine (Scheme 2). The second step should be in this case a carbocyclization reaction (aminobenzannulation), that is, the whole process should involve the formation of an enamine intermediate followed by regioselective

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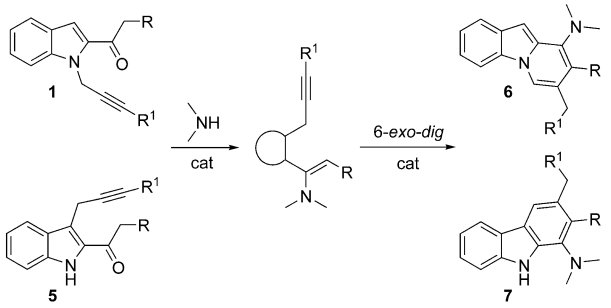
6-*exo-dig* intramolecular nucleophilic attack of the β-carbon of the enamino moiety to the carbon–carbon triple bond to yield 1-aminocarbazoles **6** and 9-aminopyrido[1,2-*a*]indoles **7**, respectively.



Scheme 2.

In particular, starting from δ-ketoalkynes **1** and **5**, the enamine, which represents the nucleophilic terminus of the unsaturated system, could be easily synthesized in the presence of a Lewis acid able to enhance the reactivity of the acyl group towards nucleophilic attack by formation of a complex with the lone pairs of the carbon–oxygen double bond. The second step of the reaction requires activation of the carbon–carbon triple bond by a catalyst able to act as a coordination partner with the π-electrons of the alkyne. However, the entire sequence could be catalyzed by suitable salts that exhibit dual activation properties and operate both as σ and π Lewis acid catalysts. For instance, the synthesis of the enamine could be catalyzed by the same palladium(II) salts, which act as promoters for the carbopalladation[4] or benzannulation step.[5] Moreover, detailed results concerning the electrophilic behavior of alkynes in carbon–carbon bond formation reactions promoted by electrophilic Lewis acids such as Au^{I} and Au^{III},[6] In^{III},[7] Ga^{III},[8] or Ti^{IV}[1b,3,9] salts have been recently reported by several authors. To the best of our knowledge, there are no reports on the behavior of δ-ketoalkynes in aminobenzanulation reactions, whereas several reports dealing with related reactions of γ-ketoalkynes have been published.[5,10–12] In particular, a 6-*endo-dig* aminobenzannulation reaction of *o*-alkynylacetophenones with pyrrolidine or diethylamine takes place in the presence of a catalytic amount of palladium chloride, copper iodide, and triphenylphosphane to give rise to aminonaphthalene derivatives.[5] The reaction is strongly substrate dependent and works only with alkynyl-substituted acetophenone and in the presence of the above-mentioned amines. Moreover, the 6-*endo-dig* aminobenzannulation reaction has been reported to occur starting from 2-alkynyl-3-acetylquinolines, 2-alkynyl-3-acetylindoles, 2-alkynyl-3-acetylpyridines, and 2-alkynyl-3-acetylbenzofuranes and pyrrolidine in the presence of 4 Å molecular sieves, yielding, respectively, 1-aminoacridines, 4-aminocarbazoles, 5-aminoquinolines, and 1-aminobenzofurans.[10] For some other secondary amines, neutral Al_2O_3 or $PtCl_2$ catalysts are required.[10] Recently, we described a copper(II) or gold(III) salt catalyzed 6-*endo-dig* cyclization/aromatization reaction of 5-en-1-ynes (*N*-propargylenamines) giving rise in a one-pot approach to functionalized pyridines.[11] Finally, related aminobenzannulation reactions of γ-ketoalkynes based on the 6-*exo-dig* mechanism have been reported involving the deprotonation of 2-(1-alkynyl)-benzaldimines and afforded, through a multistep rearrangement cascade mechanism, aminonaphthalenes.[12]

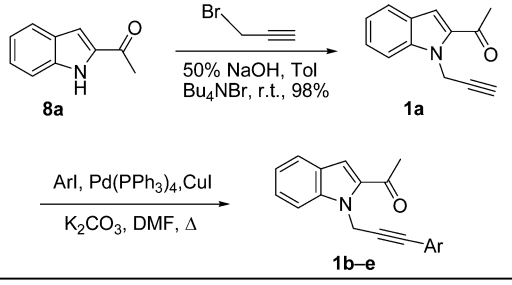
Although a number of routes are available for the preparation of substituted carbazoles, there are only few reports on the synthesis of 1-amino derivatives. The reported methods involve sequential electrophilic nitration/hydrogenation reactions on the carbazole nucleus,[13] reductive amination of the corresponding 1-oxo derivatives,[14] intramolecular Pd^{II}-mediated oxidative coupling of diphenylamine derivatives,[15] and cycloaddition reactions of C-heteroarylimines with α,β-unsaturated Fischer carbene complexes.[16] 1-Aminocarbazoles have been tested as inhibitors of Bcl-2 proteins[17] and as NPY5 antagonists.[18]

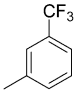
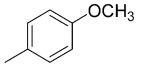
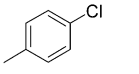
Also, 9-aminopyrido[1,2-*a*]indoles are relatively unknown compounds and have been prepared by intra- or intermolecular cycloaddition reactions,[19] by intramolecular Pauson–Khand reactions,[20] intramolecular reductive cyclizations, and Curtius rearrangements.[21] 9-Aminopyrido[1,2-*a*]indoles have been tested for the treatment of cognitive impairments.[22]

Results and Discussion

We initiated our survey with δ-ketoalkynes **1a**–**e** (Table 1) and **5a**–**g** (Table 2). 2-Acyl-*N*-propargyl-1*H*-indole **1a** was prepared from readily accessible 2-acyl-1*H*-indole[23] **8a** and propargyl bromide under PTC (phase-transfer catalysis) conditions, followed by, for compounds **1b**–**e**, functionalization of the terminal alkyne under Sonogashira conditions.[1]

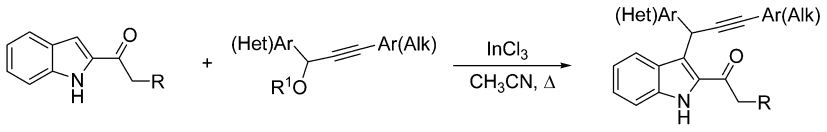
Table 1. 2-Acyl-*N*-propargyl-1*H*-indoles **1a**–**e**.



	Ar	Yield [%][a]		Ar	Yield [%]
1b		91	**1d**		92
1c		73	**1e**		83

[a] Isolated yields after chromatographic purification.

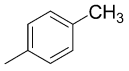
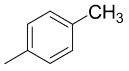
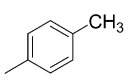
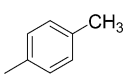
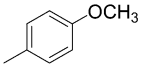
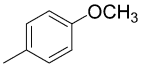
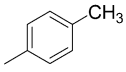
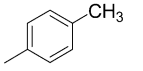
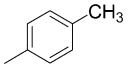
Table 2. 2-Acyl-3-propargyl-1*H*-indoles **5a**–**g**.



8a, R = H
8b, R = Ph

9a–e

5a–g

	Ar or Het	Ar or Alk	R^1	Yield [%][a]		Ar or Het	Ar or Alk	R	Yield [%][a]
9a			Ac	84	**5a**			H	71
9b			Ac	94	**5b**			H	67
9c			H	60	**5c**			H	79
9d			H	87	**5d**			H	94
9e		$-C_5H_{11}$	H	74	**5e**		$-C_5H_{11}$	H	67
					5f				63
					5g				59

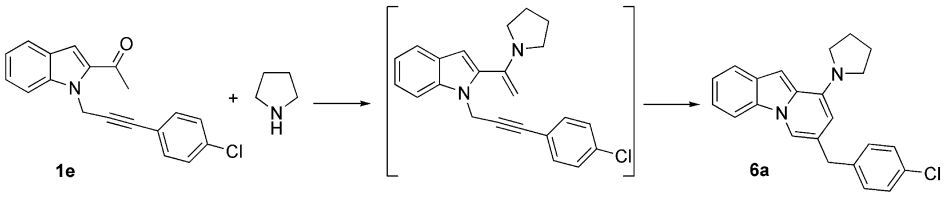
[a] Isolated yields after chromatographic purification.

2-Acyl-3-propargyl-1*H*-indoles **5a**–**g** were prepared from 2-acyl-1*H*-indole **8a** or 1-(1*H*-indol-2-yl)-2-phenylethanone[24] **8b** by $InCl_3$-catalyzed propargylation with propynyl acetates **9a**,**b** or propynyl alcohols **9c**–**e** (Table 2).[25] Compounds **9** can be easily obtained by reaction between the appropriate aldehyde and the terminal alkyne in the presence of butyllithium.[26]

Initially, with the use of *N*-propargylindole **1e** and pyrrolidine as a model system, the study was focused on the appropriate choice of the catalyst(s) able to induce or to accelerate the formation of the enamine and the subsequent carbocyclization reaction giving rise to 9-amino-pyrido[1,2-*a*]indole **6a**. A survey of the catalysts and reaction conditions employed, in addition to the obtained results, are reported in Table 3.

Treatment of **1e** with pyrrolidine in the presence of catalytic amounts of Au^{III} and Pd^{II} salts gave **6a** in very low yields (Table 3, Entries 1–3) and also in the presence of triethylorthoformate as a water scavenger for the formation of the enamine intermediate. Better results could be obtained by using a stoichiometric amount of Pd^{II} (Table 3, Entry 4). Shifting our attention to Lewis acids (Table 3, Entries 5 and 6), and finally to Lewis acids with reported dual activation properties (Table 3, Entries 7–9), desired 9-amino-pyrido[1,2-*a*]indole **6a** was obtained in 0–87% yield. In particular, $AlCl_3$ and $ZnCl_2$ gave the worst results even if they were used in large excess and could thus act also as water scavengers. In the presence of $InCl_3$, **6a** was isolated in poor yields, whereas $GaCl_3$ and $TiCl_4$ gave the best results. Nevertheless it is worth noting that in order to achieve the desired trans-

Table 3. Review of the reactions conditions for the domino synthesis of pyrido[1,2-*a*]indole **6a**.



Entry	Catalyst	Additive	Molar ratio[a]	Solvent	Temp. [°C]	Time [h]	Yield of **6a** [%]
1	$NaAuCl_4$	–	1:3:0.15	EtOH	80	24	–
2	$NaAuCl_4$	$HC(OEt)_3$	1:3:0.15:3	Toluene	100	24	10
3	$Pd(OAc)_2$	$HC(OEt)_3$	1:3:0.05:3	Toluene	100	24	5
4	$Pd(OAc)_2$	$HC(OEt)_3$	1:6:1:6	Toluene	60	24	52
5	$AlCl_3$	–	1:4:2.4	Toluene	70	24	–
6	$ZnCl_2$	–	1:4:2.4	Toluene	70	24	5
7	$InCl_3$	–	1:1.2:0.1	Toluene	80	48	11
8	$GaCl_3$[b]	–	1:2.4:1.2	Toluene	100	4	87
9	$TiCl_4$	–	1:3:0.5	Toluene	80	4	71

[a] **1e**/pyrrolidine/catalyst/(additive). [b] Used as a 0.26 M solution in toluene.

formation, $GaCl_3$ must be used in a 1:1.2 ratio, whereas $TiCl_4$ can be used in substoichiometric quantities. In particular, in this latter case, the molar ratios between **1e**, pyrrolidine, and catalyst parallels those reported by White and Weingarten in their pioneering work on the synthesis of enamines.[27]

Thus, in order to evaluate the scope and limitation of the reactions catalyzed by gallium and titanium salts, the addition/annulation sequences were carried out under the conditions reported in Table 3 (Entries 8 and 9) with *N*-propargyl-1*H*-indoles **1a**–**e** and pyrrolidine or morpholine as secondary amines (Table 4).

Compounds **1** gave the corresponding 9-aminopyrido[1,2-*a*]indoles **6** in moderate to good yields with both catalysts. Only the reaction with **1d**, bearing an electron-donating substituent on the triple bond failed to give the corresponding pyridoindole **6e**. Moreover, it is worth noting that compounds **6** are quite unstable under acidic conditions. Thus, in order to avoid decomposition of the products, they must be purified by flash chromatography in the presence of a little amount of triethylamine (1% v/v), and the proton and carbon spectra must be recorded in $CDCl_3$ immediately after sample preparation or alternatively by using C_6D_6 as the solvent.

Next, we turned our attention to the addition/annulation reactions of 2-acyl-3-propargyl-1*H*-indoles **5a**–**g** with secondary amines. By using 3-propargylindole **5a** and pyrrolidine as a model system, we chose to test several catalysts employed in the first part of this study. A survey of the catalysts and reaction conditions employed, in addition to the obtained results, are reported in Table 5.

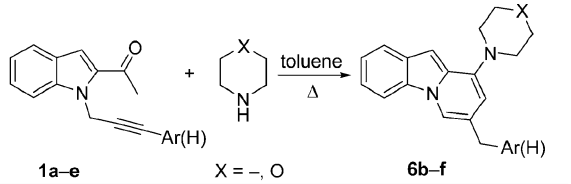
Good results were obtained by using $InCl_3$ as well as $GaCl_3$ and $TiCl_4$ (Table 5, Entries 1–3), and the desired carbazole **7a** was obtained in 65–78% yield. Next, we choose to evaluate the scope and limitations of the reactions catalyzed in particular by $InCl_3$, which is not moisture sensitive as other Lewis acid/carbon–carbon triple bond activators, for example, $GaCl_3$ and $TiCl_4$, and can be used in substoichiometric quantities even in the presence of water arising from the first condensation step.[28] Under the optimized reaction conditions [**5** (1 equiv.), $InCl_3$ (0.1 equiv.), pyrrolidine (1.2 equiv.), dry acetonitrile (0.1 M), 75 °C] **5b**–**e** gave rise to the expected 1-(pyrrolidin-1-yl)-9*H*-carbazoles **7b**–**e** in good yields, whereas the reaction performed with 3-propargylindoles **5f**–**g** resulted in the isolation of 1-hydroxy-9*H*-carbazoles **7f**,**g** in 85 and 70% yield, respectively (Table 6).

The reactions of propargylindoles **5f**,**g** probably proceed through the base-catalyzed formation of an enolate intermediate, stabilized by the adjacent phenyl ring, as demonstrated by the experimental observation that the reaction proceeds only in the presence of both $InCl_3$ and pyrrolidine. In fact, when a solution of **5g** and $InCl_3$ in dry acetonitrile was allowed to react at 75 °C for several hours TLC analysis showed the presence of the sole starting compound. Moreover, the addition of 1 equiv. of pyrrolidine to the same solution resulted in the formation of **7g** in 4 h.

In this work, both δ-ketoalkynes **1** and **5** contained a heteroaromatic scaffold undergoing two sequential inter- and intramolecular nucleophilic attacks at the two electrophilic sites, that is, the carbonyl group and C–C triple bond. The reactions proceed in the presence of the appropriate catalytic system through a proposed dual activation sequence. The overall work deals with the first report of C–C bond formation realized through a 6-*exo*-*dig* cyclization of an enaminic carbon nucleophile over a carbon–carbon triple bond. Note that 6-*endo*-*dig* cyclization patterns have been reported on related ketoalkyne systems.[10]

In the first example, 2-acyl-*N*-propargylindoles **1a**–**c**,**e** give rise to 9-aminopyrido[1,2-*a*]indoles **6a**–**d**,**f**. The reactions proceed in good yield in the presence of $TiCl_4$ or $GaCl_3$ as catalysts. Probably in this case both catalysts operate as Lewis acids and water scavengers in the first step of the reaction to give rise to enamine **10** (Scheme 3, path a). Enamine intermediate **10** regioselectively attacks the activated alkyne to give rise to carbometalation adduct **11**,

Table 4. Pyrido[1,2-*a*]indoles **6b–f**.

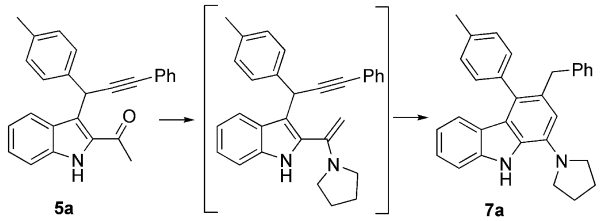


1a–e X = –, O **6b–f**

Starting compound	Product	Yield [%][a] $GaCl_3$	Yield [%][a] $TiCl_4$
1a	**6b**	56	61
1b	**6c**	55	42
1c	**6d**	56	61
1d	**6e**	–	–
1e	**6f**	65	59

[a] Isolated yields after chromatographic purification.

Table 5. Review of the reaction conditions for the domino synthesis of 1-aminocarbazole **7a**.

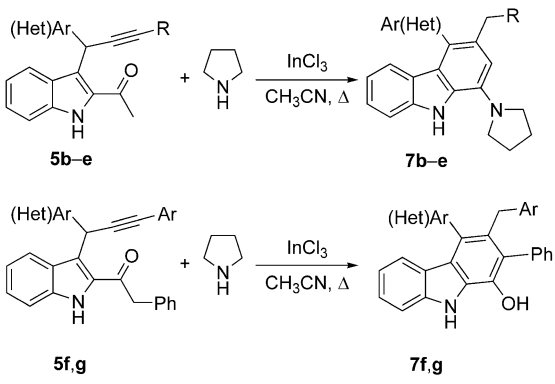


5a **7a**

Entry	Catalyst	Molar ratio[a]	Solvent	Temp. [°C]	Time [h]	Yield [%][c]
1	$InCl_3$	1:1.2:0.1	CH_3CN	80	5	78
2	$GaCl_3$[b]	1:2.4:1.2	Toluene	80	4	65
3	$TiCl_4$	1:3:0.5	Toluene	80	4	72

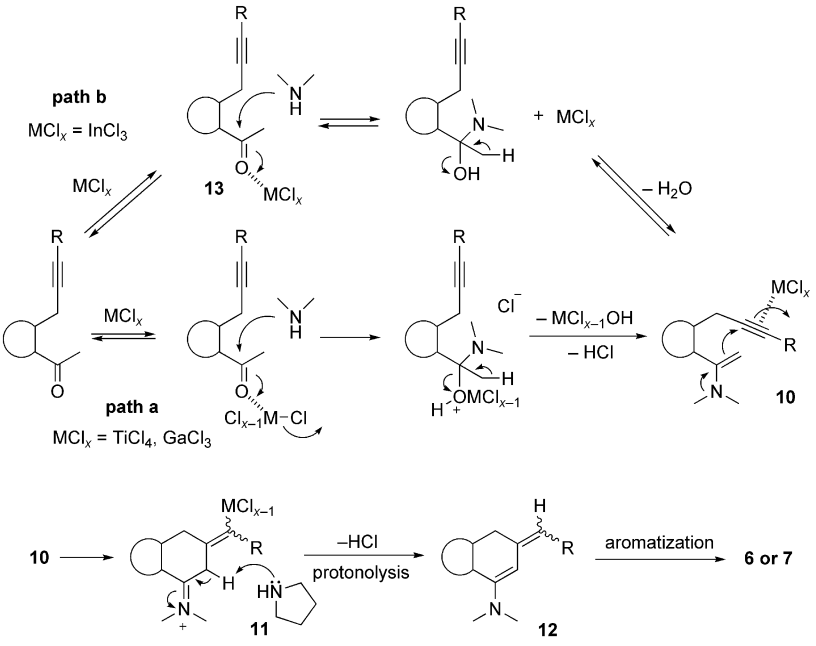
[a] **5a**/pyrrolidine/catalyst. [b] Used as a 0.26 M solution in toluene. [c] Isolated yields after chromatographic purification.

Table 6. 1-Aminocarbazoles **7b–e** and 1-hydroxy-9*H*-carbazoles **7f,g**.



Starting compound	Product	Yield [%][a]
5b	**7b**	80
5c	**7c**	83
5d	**7d**	77
5e	**7e**	71[b]
5f	**7f**	85
5g	**7g**	78

[a] Isolated yields after chromatographic purification. [b] The purified compound consists of a 3:1 mixture of **7e** and **7′e** (see Experimental Section).



Scheme 3.

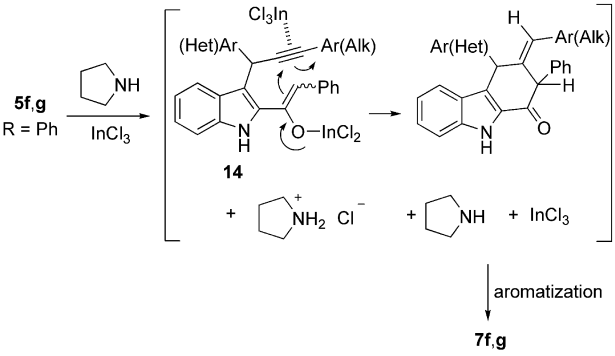
which after base-mediated deprotonation (pyrrolidine), protonolysis of the carbon–metal bond (**12**), and aromatization affords 6-*exo*-*dig* adduct **6**.

The ability of $TiCl_4$ and $GaCl_3$ to activate carbonyl groups and carbon–carbon triple bonds towards nucleophiles is well documented.[29,30] In particular, the catalytic interaction of carbon–oxygen double bonds and carbon–carbon triple bonds with $GaCl_3$ and $TiCl_4$ has been proven by ^1H and ^{13}C NMR spectroscopic measurements.[29a,30b]

Finally, the intermediacy of vinyltitanium[31] and vinylgallium[8e,8f,8h] species like **11** is supported by literature references. Moreover it is worth noting that, as reported in Table 3 (Entries 8 and 9), the reactions performed in the presence of $GaCl_3$ and $TiCl_4$ require 1.2 and 0.5 equiv. of catalyst, respectively. This experimental evidence could be ascribed to the high stability of the vinylgallium intermediate that does not undergo direct protonolysis in the reaction medium, thus regenerating the catalyst, but only during the final acidic workup.

In the second example, 2-acyl-3-propargylindoles **5a**–**e** gave rise to 1-(pyrrolidin-1-yl)-9*H*-carbazoles **7a**–**e** under $InCl_3$ catalysis. We propose a reaction mechanism that involves dual activation of both electrophilic sites by the catalyst (Scheme 3, path b). The proposed mechanism parallels in part the mechanism proposed for gallium- and titanium-catalyzed reactions with a single difference. The indium salt is a water-tolerant Lewis acid, stable under hydrolytic conditions and does not work as a water scavenger in the first step of the reaction.[28] Thus, enamine **10** is formed through a reversible process involving nucleophilic attack of the secondary amine on $InCl_3$ complex **13**[32] followed by loss of water. Working with 2-acyl-3-propargylindole **5e** and pyrrolidine, intermediate **12** was detected by NMR spectroscopy in addition to 1-amminocarbazole **7e** (see Experimental Section).

Moreover, working with 2-acyl-3-propargylindoles **5f**,**g** the formation of indium enolate **14** (Scheme 4) stabilized by the adjacent phenyl ring could be the driving force for the intramolecular cyclization that gives rise to 1-hydroxy-9*H*-carbazoles **7f**,**g**. The reaction proceeds only in the presence of a base (pyrrolidine) able to act as a proton acceptor/proton donor.



Scheme 4.

The intermediacy of vinylindium species[7a–7c] (Scheme 3, path b) and indium enolates[7d–7g] (Scheme 4) has been reported by several authors. Moreover, the dual role exerted by the catalyst was demonstrated by Ohshima and Shibasaki[7m] and by Takemoto[7o] by IR, ^1H NMR, and ^{13}C NMR spectroscopic measurements.

However, more intriguing than the simple elucidation of the single reaction mechanisms is the understanding of the different catalysts required by similar systems **1** and **5** in the aminobenzannulation reactions. Several observations can be made by analysis of the ^{13}C NMR spectra of **1e** and **5a** performed on pure compounds and in the presence of 1 equiv. of $InCl_3$ or $TiCl_4$ (Figure 1).

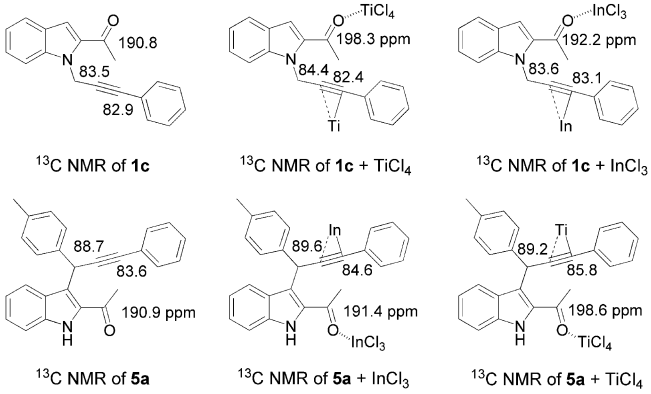


Figure 1. ^{13}C NMR (500 MHz, $CDCl_3$) were recorded in sequence on the same sample by adding $InCl_3$ or $TiCl_4$ at the end of the first acquisition. Reported chemical shifts are the average of three different acquisitions.

It is worth noting that the sp carbon atom involved in the cyclization step is more deshielded and thus more electrophilic in **5a** than in **1c**. In our opinion, the only meaningful effect is the high frequency shift of the carbonyl carbon atom observed for both compounds in the presence of $TiCl_4$. Actually, $InCl_3$ seems to act as a weak σ- and π-electrophilic Lewis acid, whereas $TiCl_4$ acts as a weak π-electrophilic catalyst and as a strong σ-electrophilic catalyst.[33] With these data in hand it may be assumed that the irreversible formation of enamine intermediate **10**, promoted by a strong Lewis acid/water scavenger such as $TiCl_4$, is essential to promote the cyclization reaction of substrates **1** involving the less electrophilic carbon–carbon triple bond.

Conclusions

We described here the synthesis of relatively unknown 1-aminocarbazole[13–16] and 9-aminopyrido[1,2-*a*]indole[19–21] derivatives starting from pyrrolidine and easily achievable 2-acyl-3-propargylindoles and 2-acyl-*N*-propargylindoles, respectively, under Lewis acid catalysis. The reactions proceed through a domino addition/annulation strategy allowing the coupling of two simple and flexible building blocks in a one-pot operation and giving rise to complex structures by simultaneous formation of two bonds.

Moreover, the reactions are catalyzed by simple Lewis acids that are able to catalyze the different reaction steps exerting double activation. All performed reactions deal with the first report of a 6-*exo*-*dig* intramolecular attack of an enaminic carbon nucleophile over a carbon–carbon triple bond activated by a Lewis acid and open up new suggestions for the use of alkyne derivatives in ring-formation reactions. In addition, interesting insight into the capability of different Lewis acids to enhance the reactivity of the same functional groups in different chemical environments is reported, and all reported findings corroborate that electronic properties play a central role in the carbon–carbon bond-forming step.

Experimental Section

General Details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F_{254} thin-layer plates were employed for thin-layer chromatography (TLC). Silica gel 40–63 micron/60 Å was employed for flash column chromatography. Melting points were measured with a Perkin–Elmer DSC 6 calorimeter at a heating rate of 5 °C min^{-1} and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer FTIR 16 PC spectrometer by using KBr tablets or NaCl disks. ^{1}H and ^{13}C NMR spectra were determined with a Varian-Gemini 200 or a Bruker 500 Avance spectrometer at room temperature in $CDCl_3$, CD_3CN, or C_6D_6 with residual solvent peaks as the internal reference. The APT or DEPT sequences were used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ advantage AP electrospray/ion trap equipped instrument by using a syringe pump device to directly inject sample solutions. 2-Acylindoles **8a**,**b** are known compounds and were prepared as reported in ref.[23,24] 2-Acyl-*N*-propargyl indoles **1a**–**c**,**e** are known compounds.[1] Compound **1d** is new and was prepared as reported in ref.[1] starting from **1a** (2.0 mmol).

1-{1-[3-(4-Methoxyphenyl)prop-2-ynyl]-1*H*-indol-2-yl}ethanone (1d): Reaction time: 2 h. Eluent for chromatography: *n*-hexane/EtOAc, 95:5. Yield: 558 mg, 92%. White solid. M.p. 104–105 °C. IR (KBr): $\tilde{\nu}$ = 1655, 1604, 1509, 1249 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3), 5.69 (s, 2 H, CH_2), 6.76 and 7.29 (AA′BB′ system, ^3J = 8.8 Hz, 2 H, arom.), 7.20 (t, ^3J = 8.8 Hz, 1 H, arom.), 7.32 (s, 1 H, arom.), 7.43 (dt, ^3J = 8.6 Hz, ^4J = 0.7 Hz, 1 H, arom.), 7.61 (d, ^3J = 8.4 Hz, 1 H, arom.), 7.71 (d, ^3J = 8.0 Hz, 1 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.2 (CH_3), 35.2 (CH_2), 55.4 (CH_3), 83.2, 83.8 (C≡C), 111.3, 113.4, 114.0, 121.4, 123.2, 126.5, 133.5 (C_{sp^2}-H), 115.0, 126.4, 133.9, 139.8, 159.8, 191.7 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 326 (100) [M + Na]$^+$. $C_{20}H_{17}NO_2$ (303.35): calcd. C 79.19, H 5.65, N 4.62; found C 78.84, H 5.48, N 4.85.

Propynyl acetates **9a**,**b** were prepared according to literature methods;[25] propynyl alcohols **9c**–**e** were prepared as acetates **9a**,**b** by avoiding the final acylation step. All compounds were prepared starting from 5.0 mmol of the appropriate alkyne.

1-(4-Methylphenyl)-3-phenylprop-2-ynyl Acetate (9a): Eluent for chromatography: *n*-hexane/EtOAc, 98:2. Yield: 1109 mg, 84%. Yellow oil. IR (NaCl): $\tilde{\nu}$ = 2924, 2330, 1743, 1491 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 6.81 (s, 1 H, C_{sp^3}-H), 7.30–7.38 (m, 4 H, arom.), 7.54–7.63 (m, 5 H, arom.) ppm. ^{13}C NMR (50.3 MHz, CD_3CN): δ = 20.5 (2 C, CH_3), 65.8 (C_{sp^3}-H), 86.3, 86.6 (C≡C), 127.8, 128.9, 129.4, 129.6, 131.8 (C_{sp^2}-H), 122.1, 134.7, 139.3 (quat. C_{sp^2}), 169.8 (C=O) ppm. MS (APCI+): *m*/*z* (%) = 205 (100) [M – CH_3COO]$^+$.

1-(4-Methylphenyl)-3-[3-(trifluoromethyl)phenyl]prop-2-ynyl Acetate (9b): Eluent for chromatography: *n*-hexane/EtOAc, 70:30. Yield: 1662 mg, 94%. Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3468, 2927, 1908, 1744 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.13 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 6.65 (s, 1 H, C_{sp^3}-H), 7.21–7.28 (m, 2 H, arom.), 7.40–7.74 (m, 6 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3, 21.5 (CH_3), 66.0 (C_{sp^3}-H), 85.4, 87.7 (C≡C), 123.9 (q, $^1J_{C,F}$ = 272.4 Hz, CF_3), 125.6 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 129.0 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 128.0, 129.1, 129.7, 135.2 (C_{sp^2}-H), 123.4, 134.1, 139.4, (quat. C_{sp^2}), 131.2 (q, $^2J_{C,F}$ = 32.7 Hz, quat. C_{sp^2}), 170.0 (C=O) ppm. MS (ESI+): *m*/*z* (%) = 273 (100) [M – CH_3COO]$^+$. $C_{19}H_{15}F_3O_2$ (332.32): calcd. C 68.67, H 4.55; found C 68.52, H 4.37.

3-Phenyl-1-thien-2-ylprop-2-yn-1-ol (9c):[34] Eluent for chromatography: *n*-hexane/EtOAc, 95:5. Yield: 639 mg, 60%. Dark-yellow solid. M.p. 56–58 °C. IR (KBr): $\tilde{\nu}$ = 3436, 3099, 2228, 1630, 1489 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.45 (d, J = 5.9 Hz, 1 H, OH), 5.89 (d, J = 5.9 Hz, 1 H, C_{sp^3}-H), 6.99–7.03 (m, 1 H, arom.), 7.24–7.37 (m, 5 H, arom.), 7.45–7.52 (m, 2 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 61.0 (C_{sp^3}-H), 86.3, 88.4 (C≡C), 125.9, 126.4, 127.1, 128.6, 129.1, 132.1 (C_{sp^2}-H), 122.4, 145.0 (quat. C_{sp^2}) ppm. MS (ESI+): m/z (%) = 197 (100) $[M - OH]^+$.

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (9d):[34,35] Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 1035 mg, 87%. Yellow solid. M.p. 68–70 °C. IR (KBr): $\tilde{\nu}$ = 3379, 2962, 2229, 1883, 1614, 1517 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.22 (d, J = 6.2 Hz, 1 H, OH), 3.83 (s, 3 H, OCH_3), 5.65 (d, J = 6.2 Hz, 1 H, C_{sp^3}-H), 6.90–6.97 (m, 2 H, arom.), 7.29–7.36 (m, 3 H, arom.), 7.43–7.59 (m, 4 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 64.9 (C_{sp^3}-H), 86.7, 89.3 (C≡C), 114.3, 128.5, 128.6, 128.8, 132.0 (C_{sp^2}-H), 122.8, 133.3, 159.9 (quat. C_{sp^2}) ppm. MS (ESI+): m/z (%) = 239 (60) $[M + H]^+$, 221 (100) $[M - OH]^+$.

1-(4-Methylphenyl)oct-2-yn-1-ol (9e): Eluent for chromatography: *n*-hexane/EtOAc, 95:5. Yield: 799 mg, 74%. Pale-yellow oil. IR (NaCl): $\tilde{\nu}$ = 3360, 2956, 2869, 1903 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.85–1.75 (m, 9 H, aliph.), 2.17–2.30 (m, 2 H, aliph.), 2.03 (d, J = 5.87 Hz, 1 H, OH), 2.36 (s, 3 H, CH_3), 5.42 (d, J = 5.87 Hz, 1 H, C_{sp^3}-H), 7.13–7.23 (m, 2 H, arom.), 7.41–7.45 (m, 2 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.3, 21.4 (CH_3), 19.1, 22.5, 28.6, 31.4 (CH_2), 64.8 (C_{sp^3}-H), 80.5, 87.6 (C≡C), 126.9, 129.4 (C_{sp^2}-H), 138.1, 138.8 (quat. C_{sp^2}) ppm. MS (ESI+): m/z (%) = 217 (40) $[M + H]^+$, 157 (50) $[M - C_4H_9]^+$, 143 (100) $[M - C_5H_{11}]^+$.

3-Propargyl-2-acylindoles **5a**–**g** are new compounds and were prepared as reported in ref.[25] starting from 2 mmol of **8a**,**b**.

1-{3-[1-(4-Methylphenyl)-3-phenylprop-2-ynyl]-1*H*-indol-2-yl}ethanone (5a): Reaction time: 2 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 516 mg, 71%. Yellow solid. M.p. 166–168 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 2920, 2221, 1646, 1527 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 6.24 (s, 1 H, C_{sp^3}-H), 7.03–7.13 (m, 3 H, arom.), 7.25–7.50 (m, 9 H, arom.), 7.84–7.89 (m, 1 H, arom.), 9.00 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3, 29.3 (CH_3), 33.9 (C_{sp^3}-H), 84.6, 89.7 (C≡C), 112.4, 120.9, 123.3, 126.7, 127.6, 128.4, 128.6, 129.5, 131.9 (C_{sp^2}-H), 121.9, 123.6, 127.4, 131.9, 136.6, 136.8, 137.3 (quat. C_{sp^2}), 191.0 (C=O) ppm. MS (ESI–): m/z (%) = 362 (100) $[M - H]^-$. $C_{26}H_{21}NO$ (363.45): calcd. C 85.92, H 5.82, N 3.85; found C 85.73, H 5.71, N 3.91.

1-(3-{1-(4-Methylphenyl)-3-[3-(trifluoromethyl)phenyl]prop-2-ynyl}-1*H*-indol-2-yl)ethanone (5b): Reaction time: 1.5 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 578 mg, 67%. Dark-yellow oil. IR (KBr): $\tilde{\nu}$ = 2921, 2225, 1651, 1529 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 6.28 (s, 1 H, C_{sp^3}-H), 7.04–7.85 (m, 12 H, arom.), 8.94 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3, 29.3 (CH_3), 33.9 (C_{sp^3}-H), 83.0, 91.6 (C≡C), 112.5, 121.0, 123.2, 126.7, 127.5, 129.1, 129.6, 135.1 (C_{sp^2}-H), 121.5, 124.6, 127.3, 131.8, 136.6, 136.9, 137.0 (quat. C_{sp^2}), 124.0 (q, $^1J_{C,F}$ = 272.4 Hz, CF_3), 124.9 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 128.7 (q, $^3J_{C,F}$ = 4.2 Hz, C_{sp^2}-H), 131.1 (q, $^2J_{C,F}$ = 32.8 Hz, quat. C_{sp^2}), 190.9 (C=O) ppm. MS (ESI+): m/z (%) = 432 (100) $[M + H]^+$. $C_{27}H_{20}F_3NO$ (431.45): calcd. C 75.16, H 4.67, N 3.25; found C 74.92, H 4.50, N 3.62.

1-[3-(3-Phenyl-1-thien-2-ylprop-2-ynyl)-1*H*-indol-2-yl]ethanone (5c): Reaction time: 2.5 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 562 mg, 79%. Dark-yellow solid. M.p. 167–169 °C. IR (KBr): $\tilde{\nu}$ = 2921, 1736, 1636, 1517 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.72 (s, 3 H, CH_3), 6.43 (s, 1 H, C_{sp^3}-H), 6.93 (dd, ^3J = 5.1, 3.7 Hz, 1 H, arom.), 7.08–7.49 (m, 10 H, arom.), 7.98 (d, ^3J = 8.0 Hz, 1 H, arom.), 8.96 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 29.2 (CH_3), 30.4 (C_{sp^3}-H), 83.9, 89.0 (C≡C), 112.4, 121.0, 123.1, 124.9, 125.4, 126.7, 127.0, 128.5, 128.6, 131.9 (C_{sp^2}-H), 121.2, 123.3, 127.0, 131.4, 136.4, 144.9 (quat. C_{sp^2}), 190.7 (C=O) ppm. MS (ESI–): m/z (%) = 354 (100) $[M - H]^-$. $C_{23}H_{17}NOS$ (355.45): calcd. C 77.72, H 4.82, N 3.94; found C 77.48, H 4.65, N 3.60.

1-{3-[1-(4-Methoxyphenyl)-3-phenylprop-2-ynyl]-1*H*-indol-2-yl}ethanone (5d): Reaction time: 2.5 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 713 mg, 94%. Yellow solid. M.p. 74–77 °C. IR (KBr): $\tilde{\nu}$ = 2928, 1888, 1650, 1508 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.68 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 6.22 (s, 1 H, C_{sp^3}-H), 6.84 (d, ^3J = 8.8 Hz, 2 H, arom.), 7.07 (m, 1 H, arom.), 7.26–7.48 (m, 7 H, arom.), 7.84 (d, ^3J = 8.5 Hz, 1 H, arom.), 8.96 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 29.3 (CH_3), 33.5 (C_{sp^3}-H), 55.5 (OCH_3), 84.5, 90.0 (C≡C), 112.5, 114.2, 120.9, 123.3, 126.7, 128.4, 128.6, 128.8, 131.9 (C_{sp^2}-H), 122.2, 123.6, 127.3, 131.7, 132.5, 136.7, 158.8 (quat. C_{sp^2}), 191.1 (C=O) ppm. MS (ESI–): m/z (%) = 378 (100) $[M - H]^-$. $C_{26}H_{21}NO_2$ (379.45): calcd. C 82.30, H 5.58, N 3.69; found C 82.21, H 5.56, N 3.48.

1-{3-[1-(4-Methylphenyl)oct-2-ynyl]-1*H*-indol-2-yl}ethanone (5e): Reaction time: 20 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 479 mg, 67%. Dark-yellow oil. IR (KBr): $\tilde{\nu}$ = 2930, 1905, 1651, 1512 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.80–0.83 (m, 5 H, aliph.), 1.31–1.41 (m, 4 H, aliph.), 2.22–2.27 (m, 2 H, aliph.), 2.30 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3), 5.94 (s, 1 H, C_{sp^3}-H), 7.01–7.10 (m, 3 H, arom.), 7.28–7.38 (m, 4 H, arom.), 7.73–7.77 (m, 1 H, arom.), 8.91 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.3, 29.3, 21.2 (CH_3), 19.2, 22.5, 28.8, 31.4 (CH_2), 33.4 (C_{sp^3}-H), 79.9, 84.9 (C≡C), 112.3, 120.5, 123.4, 126.5, 127.5, 129.3 (C_{sp^2}-H), 122.8, 127.4, 131.8, 136.5, 136.6, 137.9 (quat. C_{sp^2}), 191.0 (C=O) ppm. MS (ESI+): m/z (%) = 358 (100) $[M + H]^+$, 315 (20) $[M - CH_3C=O]^+$, 286 (50) $[M - C_5H_{11}]^+$. $C_{25}H_{27}NO$ (357.49): calcd. C 83.99, H 7.61, N 3.92; found C 83.65, H 7.40, N 4.06.

1-(3-{1-(4-Methylphenyl)-2-Phenyl-3-[3-(trifluoromethyl)phenyl]-prop-2-ynyl}-1*H*-indol-2-yl)ethanone (5f): Reaction time: 18 h. Eluent for chromatography: *n*-hexane/EtOAc, 98:2. Yield: 640 mg, 63%. Dark-yellow solid. M.p. 108–111 °C. IR (KBr): $\tilde{\nu}$ = 3072, 2255, 1696 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 4.24 (d, ^2J = 16.1 Hz, 1 H, CH_2), 4.35 (d, ^2J = 16.1 Hz, 1 H, CH_2), 6.39 (s, 1 H, C_{sp^3}-H), 7.04–7.86 (m, 17 H, arom.), 8.87 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3 (CH_3), 33.9 (C_{sp^3}-H), 47.8 (CH_2), 83.1, 91.7 (C≡C), 112.6, 121.1, 123.0, 126.8, 127.5 (2 C), 129.0, 129.1, 129.6, 129.8, 135.1 (C_{sp^2}-H), 122.2, 124.6, 127.2, 131.2, 134.0, 136.8, 136.9, 137.0 (quat. C_{sp^2}), 124.0 (q, $^1J_{C,F}$ = 270.8 Hz CF_3), 124.8 (q, $^3J_{C,F}$ = 3.7 Hz, C_{sp^2}-H), 128.7 (q, $^3J_{C,F}$ = 3.9 Hz, C_{sp^2}-H), 131.1 (q, $^2J_{C,F}$ = 32.6 Hz, quat. C_{sp^2}), 191.2 (C=O) ppm. MS (ESI–): m/z (%) = 506 (100) $[M - H]^-$. $C_{33}H_{24}F_3NO$ (507.54): calcd. C 78.09, H 4.77, N 2.76; found C 77.78, H 4.54, N 2.95.

2-Phenyl-1-[3-(3-phenyl-1-thien-2-ylprop-2-ynyl)-1*H*-indol-2-yl]ethanone (5g): Reaction time: 2.5 h. Eluent for chromatography: *n*-hexane/EtOAc, 97:3. Yield: 509 mg, 59%. Dark-yellow solid. M.p. 105–107 °C. IR (KBr): $\tilde{\nu}$ = 3350, 2877, 1649 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.27 (d, ^2J = 16.1 Hz, 1 H, CH_2) 4.39 (d, ^2J = 16.1 Hz, 1 H, CH_2), 6.56 (s, 1 H, C_{sp^3}-H), 6.91 (dd, ^3J = 4.9, 3.5 Hz, 1 H, arom.), 7.07–7.48 (m, 15 H, arom.), 8.01 (d, ^3J =

8.0 Hz, 1 H, arom.), 8.94 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 30.4 (C_{sp^3}-H), 47.8 (CH_2), 83.8, 89.1 (C≡C), 112.3, 121.1, 123.1, 124.9, 125.4, 126.8, 127.0, 127.5, 128.5 (2 C), 129.1, 129.7, 131.9 (C_{sp^2}-H), 121.9, 123.3, 126.9, 130.8, 133.9, 136.5, 144.9 (quat. C_{sp^2}), 190.8 (C=O) ppm. MS (ESI+): *m*/*z* (%) = 432 (100) $[M + H]^+$. $C_{29}H_{21}NOS$ (431.55): calcd. C 80.71, H 4.90, N 3.25; found C 80.43, H 4.62, N 3.48.

General Procedure for $TiCl_4$-Mediated Synthesis of Pyrido[1,2-*a*]-indoles 6a–d,f: In a 25-mL Schlenk-tube, a solution of the appropriate 2-acyl-*N*-propargylindole **1** (0.55 mmol) and pyrrolidine (0.12 g, 1.65 mmol, 0.14 mL) in dry toluene (4 mL) was stirred under a nitrogen atmosphere. When the starting compound was completely dissolved, a solution of $TiCl_4$ (0.05 g, 0.27 mmol, 0.03 mL) in dry toluene (2 mL) was slowly added by cannula under a nitrogen atmosphere. The reaction was stirred overnight at room temperature and then heated at 80 °C until no more starting product was detectable by TLC. The reaction mixture was poured into cold water (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried with sodium sulfate, and the solvent was removed under reduced pressure. The resulting crude was purified by column flash chromatography over silica gel to yield pyrido[1,2-*a*]indoles **6a**–**d**,**f**.

General Procedure for $GaCl_3$-Mediated Synthesis of Pyrido[1,2-*a*]-indoles 6a–d,f: In a 25-mL Schlenk-tube, a solution of the appropriate 2-acyl-1-propargylindole **1** (0.55 mmol) and pyrrolidine (0.09 g, 1.32 mmol, 0.11 mL) in dry toluene (5 mL) was stirred under a nitrogen atmosphere. When the starting compound was completely dissolved, a solution of $GaCl_3$ (0.26 M in toluene, 2.54 mL, 0.66 mmol) was slowly added by cannula under a nitrogen atmosphere at 0 °C. The reaction was stirred at room temperature and then heated at 100 °C until no more starting product was detectable by TLC. The reaction mixture was poured into cold water (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried with sodium sulfate, and the solvent was removed under reduced pressure. The resulting crude was purified by column flash chromatography over silica gel to yield pyrido[1,2-*a*]indoles **6a**–**d**,**f**.

7-(4-Chlorobenzyl)-9-(pyrrolidin-1-yl)pyrido[1,2-*a*]indole (6a): For $TiCl_4$: heating time: 4 h. Yield: 141 mg, 71%. For $GaCl_3$: heating time: 4 h. Yield: 173 mg, 87%. Eluent for chromatography: *n*-hexane/EtOAc/TEA, 97:2:1. Dark-yellow oil. IR (KBr): $\tilde{\nu}$ = 2945, 2918, 1350, 1030 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (m, 4 H, 2 CH_2 pyrrolidine), 3.61 (m, 4 H, 2 N-CH_2), 3.84 (s, 2 H, Ar-CH_2), 5.62 (s, 1 H, arom.), 6.90 (s, 1 H, arom.), 7.19–7.33 (m, 6 H, arom.), 7.66 (s, 1 H, arom.), 7.74–7.78 (m, 2 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 25.7, 50.3 (CH_2 pyrrolidine), 38.9 (CH_2), 92.8, 100.7, 110.6, 112.9, 119.8, 120.8, 122.2, 128.8, 130.4 (C_{sp^2}-H), 121.7, 128.5, 129.9, 131.7, 132.2, 139.3, 140.8 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 361 (100) $[M + H]^+$. $C_{23}H_{21}ClN_2$ (360.88): calcd. C 76.55, H 5.87, N 7.76; found C 76.34, H 5.71, N 7.47.

7-Methyl-9-(pyrrolidin-1-yl)pyrido[1,2-*a*]indole (6b): For $TiCl_4$: heating time: 4 h. Yield: 84 mg, 61%. For $GaCl_3$: heating time: 4 h. Yield: 77 mg, 56%. Eluent for chromatography: *n*-hexane/EtOAc/TEA, 97:2:1. Yellow solid. M.p. 159–160 °C. IR (KBr): $\tilde{\nu}$ = 3052, 1359 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04 (m, 4 H, 2 CH_2 pyrrolidine), 2.26 (s, 3 H, CH_3), 3.65 (m, 4 H, 2 N-CH_2), 5.73 (s, 1 H, arom.), 6.86 (s, 1 H, arom.), 7.21–7.28 (m, 2 H, arom.), 7.67 (s, 1 H, arom.), 7.73–7.81 (m, 2 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.0 (CH_3), 25.7, 50.3 (CH_2 pyrrolidine), 92.2, 102.2, 110.5, 112.3, 119.5, 120.7, 122.0 (C_{sp^2}-H), 118.5, 128.4, 129.6, 131.7, 140.5 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 251 (100) $[M + H]^+$. $C_{17}H_{18}N_2$ (250.34): calcd. C 81.56, H 7.25, N 11.19; found C 81.37, H 7.21, N 11.03.

9-(Pyrrolidin-1-yl)-7-[3-(trifluoromethyl)benzyl]pyrido[1,2-*a*]indole (6c): For $TiCl_4$: heating time: 8 h. Yield: 91 mg, 42%. For $GaCl_3$: heating time: 4 h. Yield: 119 mg, 55%.Eluent for chromatography: *n*-hexane/EtOAc/TEA, 97:2:1. Dark-yellow oil. IR (KBr): $\tilde{\nu}$ = 2844, 1539, 1332, 1123 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (m, 4 H, 2 CH_2 pyrrolidine), 3.61 (m, 4 H, 2 N-CH_2), 3.88 (s, 2 H, Ar-CH_2), 5.67 (s, 1 H, arom.), 6.88 (s, 1 H, arom.), 7.17–7.76 (m, 9 H, arom.) ppm. ^{13}C NMR (50.3 MHz, C_6D_6): δ = 25.3, 49.8 (CH_2 pyrrolidine), 39.0 (CH_2), 93.5, 99.9, 110.7, 112.7, 120.0, 121.0, 122.4, 129.1, 132.4 (C_{sp^2}-H), 125.0 (q, $^1J_{C,F}$ = 272.4 Hz, CF_3), 123.2 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 125.7 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 126.8, 128.9, 130.2, 131.6, 140.9, 142.3 (quat. C_{sp^2}), 130.8 (q, $^2J_{C,F}$ = 31.6 Hz, quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 395 (100) $[M + H]^+$. $C_{24}H_{21}F_3N_2$ (394.43): calcd. C 73.08, H 5.37, N 7.10; found C 73.21, H 5.28, N 5.28.

7-Benzyl-9-(pyrrolidin-1-yl)pyrido[1,2-*a*]indole (6d): For $TiCl_4$: heating time: 10 h. Yield: 114 mg, 61%. For $GaCl_3$: heating time: 10 h. Yield: 105 mg, 56%. Eluent for chromatography: *n*-hexane/EtOAc/TEA, 97:2:1. Dark-yellow oil. IR (KBr): $\tilde{\nu}$ = 2925, 1602, 1543 cm^{-1}. ^{1}H NMR (200 MHz, C_6D_6): δ = 1.35 (m, 4 H, 2 CH_2 pyrrolidine), 3.14 (m, 4 H, 2 N-CH_2), 3.69 (s, 2 H, Ar-CH_2), 5.57 (s, 1 H, arom.), 6.91 (s, 1 H, arom.), 7.02–7.57 (m, 9 H, arom.), 7.86–7.90 (m, 1 H, arom.) ppm. ^{13}C NMR (50.3 MHz, C_6D_6): δ = 25.3, 49.8 (CH_2 pyrrolidine), 39.6 (CH_2), 93.2, 100.8, 110.8, 112.8, 119.8, 120.9, 122.3, 126.4, 128.6, 129.1 (C_{sp^2}-H), 122.0, 128.9, 130.2, 131.9, 140.8, 141.1 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 327 (100) $[M + H]^+$. $C_{23}H_{22}N_2$ (340.43): calcd. C 84.63, H 6.79, N 8.58; found C 84.57, H 6.71, N 8.39.

7-(4-Chlorobenzyl)-9-(morpholin-1-yl)pyrido[1,2-*a*]indole (6f): For $TiCl_4$: heating time: 6 h. Yield: 122 mg, 59%. For $GaCl_3$: heating time: 4 h. Yield: 135 mg, 65%. Eluent for chromatography: *n*-hexane/EtOAc/TEA, 97:2:1. Dark-yellow oil. IR (KBr): $\tilde{\nu}$ = 2923, 2852, 1384, 1113 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.23 (m, 4 H, 2 N-CH_2), 3.92 (s, 2 H, Ar-CH_2), 3.97 (m, 4 H, 2 O-CH_2), 6.14 (s, 1 H, arom.), 6.63 (s, 1 H, arom.), 7.22–7.37 (m, 6 H, arom.), 7.78–7.82 (m, 2 H, arom.), 7.89 (s, 1 H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 38.3 (CH_2), 51.1, 66.9 (CH_2 morpholine), 91.8, 108.2, 110.6, 117.2, 120.1, 121.0, 123.0, 128.8, 130.3 (C_{sp^2}-H), 119.9, 129.3, 130.6, 132.5, 132.6, 138.9, 143.7 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 376 (100) $[M + H]^+$. $C_{23}H_{21}ClN_2O$ (376.88): calcd. C 73.30, H 5.62, N 7.43; found C 73.43, H 5.76, N 7.46.

General Procedure for the Synthesis of Carbazoles 7a–g: To a solution of 3-propargylindoles **5a**–**g** (0.30 mmol) and pyrrolidine (25 mg, 0.36 mmol, 0.03 μL) in dry acetonitrile (3 mL) was added $InCl_3$ (7 mg, 0.03 mmol). The mixture was stirred at 75 °C until no more starting product was detectable by TLC analysis. After that, the reaction mixture was cooled, and the solvent was removed under reduced pressure. The resulting crude was purified by column flash chromatography over silica gel to yield carbazoles **7a**–**g**.

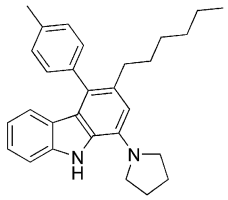
3-Benzyl-4-(4-methylphenyl)-1-(pyrrolidin-1-yl)-9*H*-carbazole (7a): Reaction time: 5 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 97 mg, 78%. Yellow oil. IR (KBr): $\tilde{\nu}$ = 2920, 2244, 1899, 1493 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.05 (m, 4 H, 2 CH_2 pyrrolidine), 2.48 (s, 3 H, CH_3), 3.48 (m, 4 H, 2 N-CH_2), 3.93 (s, 2 H, Ar-CH_2), 6.69–7.59 (m, 14 H, arom.), 8.18 (s, 1 H, NH), ppm. ^{13}C NMR (50.3 MHz, C_6D_6): δ = 21.2 (CH_3), 39.1 (Ar-CH_2), 24.9, 50.3 (CH_2 pyrrolidine), 110.7, 113.4, 119.4, 122.9, 125.1, 125.7, 128.3, 129.1, 129.5, 130.4 (C_{sp^2}-H), 124.8, 129.0, 130.6, 130.8, 135.4, 136.5, 138.0, 140.0, 143.4 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 417 (100) $[M + H]^+$. $C_{30}H_{28}N_2$ (416.56): calcd. C 86.50, H 6.78, N 6.72; found C 86.37, H 6.53, N 6.89.

4-(4-Methylphenyl)-1-(Pyrrolidin-1-yl)-3-[3-(trifluoromethyl)benzyl]-9*H*-carbazole (7b): Reaction time: 2.5 h. Eluent for chromatography: *n*-hexane/EtOAc, 99:1. Yield: 116 mg, 80%. Yellow oil. IR (KBr): $\tilde{\nu}$ = 2963, 1593, 1450, 1330 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.07 (m, 4 H, 2 CH_2 pyrrolidine), 3.51 (m, 4 H, 2 N-CH_2), 2.47 (s, 3 H, CH_3), 3.97 (s, 2 H, Ar-CH_2), 6.67 (s, 1 H, arom.), 6.71–6.69 (m, 2 H, arom.), 7.13–7.41 (m, 10 H, arom.), 8.20 (s, 1 H, NH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.4 (CH_3), 25.1, 50.6 (CH_2 pyrrolidine), 38.9 (Ar-CH_2), 110.5, 112.5, 119.0, 122.4, 125.1, 128.4, 129.4, 130.0, 132.2 (C_{sp^2}-H), 122.3 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, C_{sp^2}-H), 123.4, 123.9 128.3, 129.6, 130.1, 135.0, 136.8, 136.9, 139.6, 143.7, (quat. C_{sp^2}), 124.4 (q, $^1J_{C,F}$ = 272.4 Hz, CF_3), 130.2 (q, $^2J_{C,F}$ = 31.8 Hz, quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 485 (100) $[M + H]^+$. $C_{31}H_{27}F_3N_2$ (484.55): calcd. C 76.84, H 5.62, N 5.78; found C 76.43, H 5.38, N 5.92.

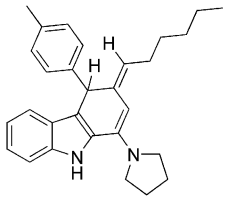
3-Benzyl-1-(pyrrolidin-1-yl)-4-thien-2-yl-9*H*-carbazole (7c): Reaction time: 7 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 102 mg, 83%. Yellow oil. IR (KBr): $\tilde{\nu}$ = 2921, 1641, 1592, 1385 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.05 (m, 4 H, 2 CH_2 pyrrolidine), 3.53 (m, 4 H, 2 N-CH_2), 4.08 (s, 2 H, Ar-CH_2), 6.68 (s, 1 H, arom.), 6.83–7.03 (m, 3 H, arom.), 7.14–7.46 (m, 9 H, arom.), 8.27 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 39.1 (Ar-CH_2), 39.1, 50.6 (CH_2 pyrrolidine), 110.8, 112.4, 119.4, 122.5, 125.5, 125.8, 126.1, 127.5, 127.8, 128.4, 129.1 (C_{sp^2}-H), 119.0, 123.8, 124.8, 129.5, 133.3, 136.3, 139.8, 141.3, 142.9 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 409 (100) $[M + H]^+$. $C_{27}H_{24}N_2S$ (408.56): calcd. C 79.37, H 5.92, N 6.86; found C 79.08, H 5.76, N 6.97.

3-Benzyl-4-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)-9*H*-carbazole (7d): Reaction time: 3 h. Eluent for chromatography: *n*-hexane/EtOAc, 95:5. Yield: 100 mg, 77%. Yellow oil. IR (KBr): $\tilde{\nu}$ = 3380, 2924, 1608, 1507 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.06 (m, 4 H, 2 CH_2 pyrrolidine), 3.50 (m, 4 H, 2 N-CH_2), 3.92 (s, 3 H, OCH_3), 3.96 (s, 2 H, Ar-CH_2), 6.72 (s, 1 H, arom.), 6.76–7.42 (m, 13 H, arom.), 8.18 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 39.0 (Ar-CH_2), 25.3, 50.8 (CH_2 pyrrolidine), 55.6 (OCH_3), 110.8, 113.1, 114.2, 119.2, 122.6, 125.2, 125.7, 128.4, 129.1, 131.6 (C_{sp^2}-H), 123.8, 124.3, 130.3, 130.9, 132.8, 135.1, 135.7, 137.8, 139.9, 143.1 (quat. C_{sp^2}) ppm. MS (ESI–): *m*/*z* (%) = 431 (100) $[M + H]^-$. $C_{30}H_{28}N_2O$ (432.56): calcd. C 83.30, H 6.52, N 6.48; found C 82.96, H 6.45, N 6.62.

3-Hexyl-4-(4-methylphenyl)-1-(pyrrolidin-1-yl)-9*H*-carbazole (7e): Reaction time: 8 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield 87 mg, 71%. Yellow oil. IR (KBr): $\tilde{\nu}$ = 2865, 1548, 1321 cm^{-1}.The ^1H and ^{13}C NMR analysis of the purified compound shows the presence of two isomers **7e** and **7′e** in a 1:3 ratio. ^1H NMR (500 MHz, C_6D_6): δ = 0.91–0.97 (m, 3 H, aliph.), 1.33–1.35 (m, 4 H, aliph.), 1.41–1.47 (m, 2 H, aliph.), 1.76 (m, 4 H, 2 CH_2 pyrrolidine), 1.84–1.90 (m, 2 H, aliph.), 2.35 (s, 3 H, CH_3), 2.93 (t, *J* = 7.8 Hz, 2 H, Ar-CH_2), 3.27 (m, 4 H, 2 N-CH_2), 6.78 (s, 1 H, arom.), 7.06–7.68 (m, 8 H, arom.), 8.23 (s, 1 H, NH) ppm. The presence of isomer **7′e** with an exocyclic bond is detectable by the following characteristic signals: ^1H NMR (500 MHz, C_6D_6): δ = 2.24 (s, CH_3), 2.25 (s, C_{sp^3}–H), 4.55 (t, ^3J = 1.5 Hz, C_{sp^2}–H) ppm. ^{13}C NMR (125.8 MHz, C_6D_6): δ = 13.4, 20.4 (CH_3), 22.0, 28.8, 31.2, 32.2, 32.7, (CH_2), 24.1, 49.8 (CH_2 pyrrolidine) ppm. The signal splitting in the aromatic region evidences the presence of the two isomers: ^{13}C NMR (125.8 MHz, C_6D_6): δ = 109.2, 109.3, 110.0, 111.9, 112.0, 118.4, 120.1, 122.0, 122.3, 124.3, 125.3, 125.4, 128.3, 128.7, 129.7, (C_{sp^2}–H), 124.0, 123.1, 127.1, 127.9, 130.0, 131.9, 134.3, 134.8, 135.6, 135.8, 137.1, 139.4, 142.1 (quat. C_{sp^2}) ppm. Isomer **7′e** shows the characteristic signals: ^{13}C NMR (125.8 MHz, C_6D_6): δ = 13.3, 24.6 (CH_3), 22.1, 27.4, 28.8 (CH_2), 73.5 (C_{sp^3}–H) ppm. MS (ESI+): *m*/*z* (%) = 411 (100) $[M + H]^+$. $C_{29}H_{34}N_2$ (410.59): calcd. C 84.83, H 8.35, N 6.82; found C 84.65, H 8.11, N 6.93.



7e



7′e

4-(4-Methylphenyl)-2-Phenyl-3-[3-(trifluoromethyl)benzyl]-9*H*-carbazol-1-ol (7f): Reaction time: 20 h. Eluent for chromatography: *n*-hexane/EtOAc, 90:10. Yield: 129 mg, 85%. Yellow oil. IR (NaCl): $\tilde{\nu}$ = 2925, 2227, 1738, 1652 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 4.12 (s, 2 H, CH_2), 4.81 (s, 1 H, OH, exchange with D_2O), 6.86–7.74 (m, 17 H, arom.), 8.98 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.7 (CH_3), 35.3 (CH_2), 111.0, 119.2, 122.4, 125.9, 126.8, 128.3, 128.9, 129.1, 130.6 (2 C), 134.1 (C_{sp^2}-H), 120.2, 120.5, 121.9, 123.4, 126.6, 131.9, 134.0, 138.2, 138.7, 139.6, 140.7, 144.1 (quat. C_{sp^2}), 124.4 (q, $^1J_{C,F}$ = 272.4 Hz, CF_3), 124.4 (q, $^3J_{C,F}$ = 3.4 Hz, C_{sp^2}-H), 127.8 (q, $^3J_{C,F}$ = 3.4 Hz, C_{sp^2}-H), 130.8 (q, $^2J_{C,F}$ = 32.2 Hz, quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 508 (100) $[M + H]^+$. $C_{33}H_{24}F_3NO$ (507.54): calcd. C 78.09, H 4.77, N 2.76; found C 77.91, H 4.65, N 2.70.

3-Benzyl-2-phenyl-4-thien-2-yl-9*H*-carbazol-1-ol (7g): Reaction time: 20 h. Eluent for chromatography: *n*-hexane/EtOAc, 99:1. Yield: 101 mg, 78%. Yellow oil. IR (KBr): $\tilde{\nu}$ = 3057, 1618, 1456, 1400 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.14 (s, 2 H, CH_2), 5.01 (s, 1 H, OH, exchange with D_2O), 6.91–7.64 (m, 17 H, arom.), 9.01 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 35.5 (CH_2), 111.0, 119.3, 122.3, 126.0, 126.7, 127.8, 128.0, 128.2, 128.4, 128.9 (2 C), 129.1, 130.7 (C_{sp^2}-H), 112.1, 122.0, 122.7, 123.2, 128.1, 133.8, 136.0, 136.5, 139.7, 140.6, 145.8 (quat. C_{sp^2}) ppm. MS (ESI+): *m*/*z* (%) = 432 (100) $[M + H]^+$. $C_{29}H_{21}NOS$ (431.55): calcd. C 80.71, H 4.90, N 3.25; found C 80.47, H 4.84, N 3.37.

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