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ScienceDirect
Tetrahedron 63 (2007) 10320–10329
Tetrahedron

First Suzuki–Miyaura type cross-coupling of *ortho*-azidobromobenzene with arylboronic acids and its application to the synthesis of fused aromatic indole-heterocycles

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Received 23 June 2007; revised 13 July 2007; accepted 18 July 2007
Available online 26 July 2007

Abstract—A short synthesis of some fused indole-heterocycles has been achieved via Pd-catalyzed cross-coupling reactions between azido-2-bromobenzene and arylboronic acids and subsequent thermally induced nitrene insertion. Additionally, 4-amino-α-carboline, a versatile intermediate toward grossularine analogs has also been prepared by Suzuki–Miyaura cross-coupling of 4-pivaloylaminopyridine-3-boronic acid with 2-bromoaniline, followed by simple functional group transformations.

1. Introduction

Indole nucleus is a ubiquitous structural unit of many biologically active alkaloids and pharmaceutical agents. Although the synthesis of functionalized indole derivatives has been well-documented[1] but short, functional group tolerating procedures are always required in organic-pharmaceutical chemistry. Among the diverse synthetic methods intramolecular annulation of nitrene intermediates proved to be an efficient approach for the preparation of indole-heterocycles of biological interest.[2] The recent introduction of organometallic coupling reactions aiming at the formation of aryl–aryl carbon bonds gave a new impetus to develop new approaches.[3] In this field Hajos et al. have worked out a valuable procedure combining the Suzuki–Miyaura cross-coupling reaction[4] implying (hetero)arylhalides and *o*-pivaloylaminobenzene boronic acid with thermally induced intramolecular nitrene insertion (Fig. 1).[5] This approach allowed the synthesis of antiplasmodial alkaloids isocryptolepine,[5a] isoneocryptolepine,[5b] and that of 11*H*-indolo[3,2-*c*]isoquinoline,[5c] indazolo[2,3-*b*]isoquinoline,[5d] 4*H*-pyridazino[4,5-*b*]indol-4-one,[5e] and 1*H*-pyridazino [4,5-*b*]indole[5f] derivatives of biological importance.

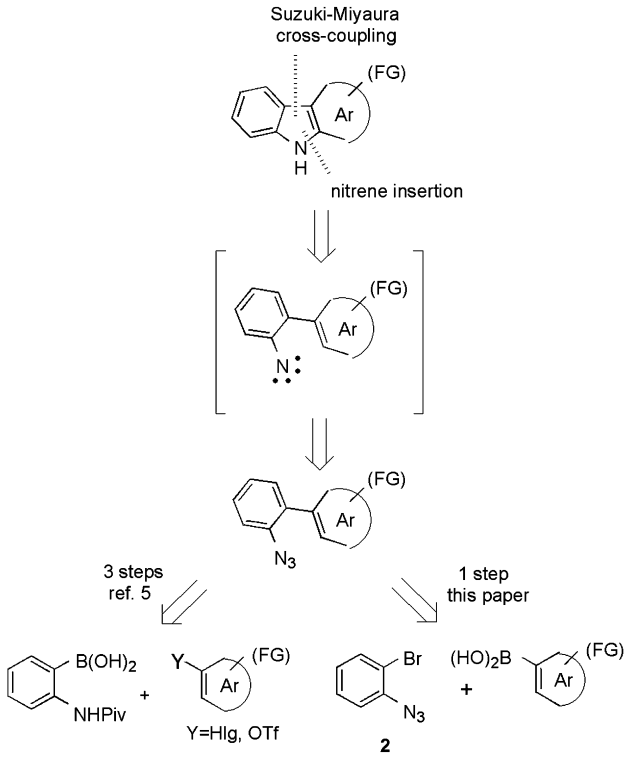

Figure 1. Combined Suzuki–Miyaura cross-coupling—nitrene insertion approach toward fused indole-heterocycles.

Keywords: Indole-heterocycles; Azido-2-bromobenzene; Suzuki–Miyaura cross-coupling; Nitrene insertion.
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doi:10.1016/j.tet.2007.07.068

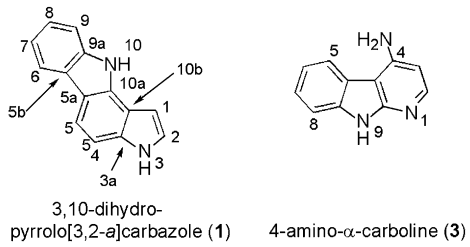


Figure 2. Structures of targeted heterocyclic systems.

Recently, for pharmaceutical purposes we had to prepare some functionalized pyrrolo[3,2-*a*]carbazole derivatives. Although the aimed bis-indole ring system had already been described[6] we searched an alternative phosphine-free pathway based on our before mentioned combination.

Herein, we disclose in detail the synthesis of the pyrrolo[3,2-*a*]carbazole ring system **1** completed with that of some heterocyclic analogs of carbazoles, using for the first time *o*-azido-bromobenzene (**2**), a direct precursor of nitrene in the Suzuki–Miyaura cross-coupling reaction. In addition, we propose a new path based on the classical Suzuki arylation reaction followed by functional group transformations and nitrene insertion for the synthesis of 4-amino-α-carboline skeleton **3** (Fig. 2).

2. Results and discussion

2.1. Synthesis of 3,10-dihydro-pyrrolo[3,2-*a*]carbazole (1)

Initially, we examined the Suzuki–Miyaura cross-coupling reaction between 5-bromoindole (**4**) and 2-(2,2-dimethylpropionylamino)phenyl boronic acid (**5**).[7a] In a mixture of dimethoxyethane and 10% aqueous $NaHCO_3$ solution using tetrakis(triphenylphosphine)palladium, $[Pd(Ph_3P)_4]$ as catalyst coupling reaction smoothly gave diaryl compound **6** in 66% yield. Contrary to expectations removal of the pivaloyl protecting group proved to be troublesome. Neither diluted acid nor base catalyzed hydrolysis afforded the required 2-(1*H*-indol-5-yl)-phenylamine (**7**). To overcome the difficulties of deprotection Pd-catalyzed cross-coupling of **4** was performed with *N*-Boc protected 2-aniline boronic acid **8**[7b] under the same conditions (57%). Higher yield (66%) was obtained when 1*H*-indole-5-boronic acid **9**[7c] was reacted with *N*-Boc protected 2-bromoaniline **10**. Acid catalyzed *N*-Boc deprotection of **11** led to the corresponding aniline derivative **7**, along with varying amount of *tert*-butyl substituted derivative **12**. The formation of such type of side-product results from an intermediate *tert*-butyl cation trapped by the indole nucleus.[8] Unfortunately, the location of the *tert*-butyl group remained uncertain due to the complexity of the NMR spectra (atropisomerism) (Scheme 1).

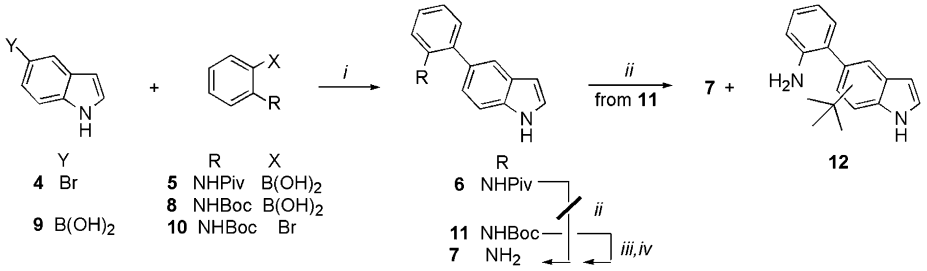
In light of the low yield and the formation of side-products we undertook a more exhaustive study on acid-free deprotection of **11**. Thus, treatment of **11** in boiling toluene in the presence of silica gel smoothly provided amine **7** in 93% yield. Shorter reaction time (30 min) and even higher yield (97%) were achieved by microwave-assisted deprotection using silica gel as solid support.

The key step diazotation of **7**, following the standard procedure, afforded unfortunately a complex mixture of unidentified products. Owing to the acid sensitivity of the indole ring we attempted several modifications (buffered system, low-temperature nitrosation, two-phase reaction, etc.) in vain.

As **7** is presumably too fragile to acid medium we turned our attention to the direct introduction of the nitrene precursor azide group. To this end we envisaged a direct Suzuki–Miyaura cross-coupling between 1-azido-2-bromobenzene (**2**) and 1*H*-indole-5-boronic acid (**9**) enabling a shorter synthetic approach. A survey of the literature showed that Suzuki–Miyaura type couplings had never been reported with free azide function bearing partners. This choice seemed to be risky, even if we hoped in a rapid coupling reaction, faster than the decomposition of nitrene moiety.[9]

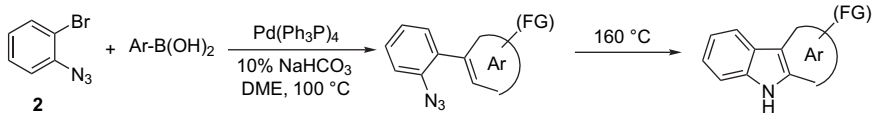
2-Azido-bromobenzene (**2**)[10] was quantitatively prepared from 2-bromoaniline following the standard procedure.

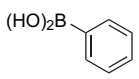
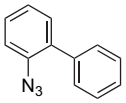
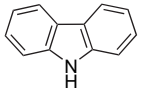
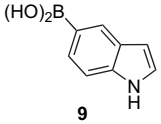
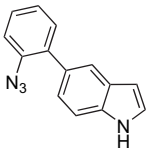
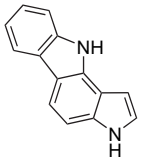
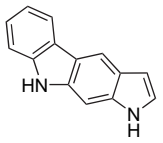
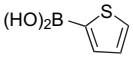
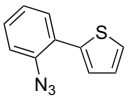
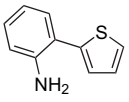
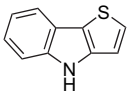
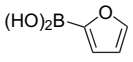
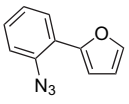
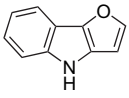
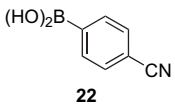
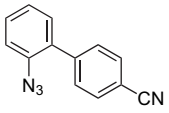
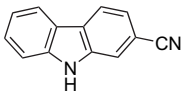
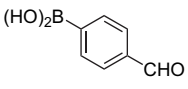
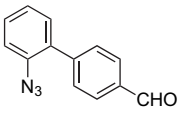
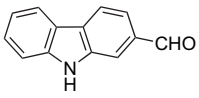
In order to determine the reactivity and thermal stability of **2** a preliminary cross-coupling was carried out under the standard conditions with simple benzene boronic acid (**13**). As expected, the corresponding azido-diaryl compound **14** was isolated in 68% yield by chromatography. The presence of the azide function was evidenced by intense IR absorptions (2114 and 2123 cm^{-1}) and confirmed by NMR spectroscopic methods. Accordingly, it was pleasure to note that cross-coupling of **2** with 1*H*-indole-5-boronic acid (**9**) gave the expected azido-diaryl compound **15** even in higher yield (88%) (Table 1).



Scheme 1. (i) $Pd(Ph_3P)_4$, 10% $NaHCO_{3aq}$, DME, Δ, **6**: 66%, **11**: 57% (**4**+**8**) or 66% (**9**+**10**); (ii) H_2SO_{4aq}, EtOH, Δ, from **6**: **7**:0%, from **11**: **7**:41%+**12**:6%; (iii) SiO_2,toluene, Δ, **7**: 93%; (iv) SiO_2, microwave, **7**: 97%.

Table 1. Synthesis of indole-heterocycles by Suzuki–Miyaura cross-coupling of **2** with arylboronic acids and subsequent nitrene insertion



No.	Ar–B(OH)$_2$	Time	Coupling products (yields)	Time	Heterocycles (yields)
1	 **13**	6 h	 **14** (68%)	0.5 h	 **26** (71%)
2	 **9**	5 h	 **15** (88%)	7 h	 **1** (65%)
					 **16** (0-5%)[a]
3	 **17**	6 h	 **18** (40%)  **19** (3%)	2 h	 **27** (85%)
4	 **20**	3.5 h	 **21** (42%)	4 h	 **28** (55%)
5	 **22**	3 h	 **24** (46%)	4 h	 **29** (70%)
6	 **23**	2 h	 **25** (53%)	4 h	 **30** (51%)

[a] Estimated by ^{1}H NMR from the mother liquor.

Thermal decomposition of **15** at 150 °C and consequent insertion of nitrene intermediate gave the desired 3,10-dihydro-pyrrolo[3,2-*a*]carbazole (**1**) in 65% yield. The sense of nitrene insertion was evidenced by the disappearance of a fine one proton doublet (δ=7.65 ppm, J=1.4 Hz) attributed to H-4 in **15**. In the ^{1}H NMR spectrum of the mother liquor isomer pyrrolo[3,2-*b*]carbazole **16** as minor product could be deduced. Interestingly, this isomer was observed as major product when the nitrene formation was carried out from the corresponding

nitro derivative with triethylphosphite by microwave activation.[11]

2.2. Extension to the preparation of other heterocyclic analogs of carbazole

After some successful couplings we intended to study the scope and limitations of the direct Suzuki arylation with *o*-azidobromobenzene. Under classical conditions coupling of 1-azido-2-bromobenzene (**2**) with 2-thiophene boronic acid (**17**) afforded the corresponding diaryl azide **18** in low yield (40%). From the reaction mixture 2-bromoaniline (2%) and 2-thiophenylaniline (**19**),[12] were isolated by chromatography. Their formation may be explained by hydrolysis of the corresponding iminophosphorane probably resulting from the reaction between the triphenylphosphine ligand and the azide function.

Coupling with 2-furan boronic acid (**20**) smoothly gave the expected bis-aryl derivative **21** without reduced by-products, however, the isolated yield remained modest (42%) due to the instability of **21** during the purification. Cross-coupling of **2** with other functionalized phenyl boronic acids **22** and **23** smoothly afforded the corresponding bis-aryl nitrile **24** and carbaldehyde **25**.

For the thermal decomposition of azides treatment in boiling *o*-dichlorobenzene was generally applied. Thus thermolysis of azides **14**, **18**, and **21** followed by insertion of nitrene intermediate provided carbazole **26**,[13] 4*H*-thieno[3,2-*b*]indole (**27**),[11] and 4*H*-furo[3,2-*b*]indole (**28**)[14] in good or acceptable yields. Similarly, functionalized carbazoles **29** and **30**[11,15] were obtained by thermolysis of the corresponding bis-aryl derivatives **24** and **25**.

2.3. Synthesis of a pyrido[2,3-*b*]indole ring system 3

Pyrido[2,3-*b*]indole (α-carboline) system is a common structural feature of some alkaloids as the cytotoxic grossularines 1 and 2,[16] the neuroprotector mescengricin[17], and cryptotackieine (Fig. 3).[18]

Bibliographic survey evidenced that great attention has been payed to the synthesis of more complex pyrido[2,3-*b*]indoles due to their antiviral,[19] antitumoral[20] or GABA reception modulating activities.[21] 2-Amino-α-carboline found in fried meats or tobacco smoke is reported to take part in the more prevalent carcinogenic and mutagenic heterocyclic arylamines.[22]

From synthetic point of view, among the natural products few total syntheses, only two for the grossularines and one affording cryptotackieine have been reported. In the first total synthesis of grossularines developed by Hibino et al.[23] the imidazo-pyrido[2,3-*b*]indole moiety was obtained by Pd-catalyzed cross-coupling between 3-halogenated indoles and metallated imidazoles, followed by thermal electrocyclisation of the intermediate isocyanate. Aryl appendages on the C-2 carbon were introduced by Pd-catalyzed carbonylation and subsequent treatment by aryllithiums.

Two formal syntheses have passed by the same type of tetracyclic key structure. A linear one by Molina et al.[24] using 3-acetyl-2-aminoindole, while the convergent approach of Achab et al.[25] was based on Pd-catalyzed cross-couplings between functionalized pyridine and aniline derivatives. Recently, Horne and co-workers have reported a nice, three-step biomimetic synthesis of grossularine-1 from β-oxotryptamine.[26]

Substituted or fused α-carbolines have been prepared from various starting materials. Thus, 2-(1*H*)pyrazinones[27] or *N*,*N*′-diaryl-carbodiimides[28] afforded α-carbolines by intramolecular Diels–Alder reaction, followed by aromatization. Thermally induced cyclization–extrusion process from pyridyl-benzotriazoles[29] or 2-amidinylindole-3-carbaldehydes[30] proved to be efficient also. Appropriately substituted indole derivatives led to α-carbolines by intramolecular cyclization between the C-9a and N-1[31] or C-2 and C-3[32] positions. α-Carbolines have also been prepared by a combination of two Pd-catalyzed reactions involving amination of iodobenzene, followed by biaryl coupling reaction.[33]

On the basis of the above mentioned results such a short path using 1-azido-2-bromobenzene (**2**) and *N*-protected 4-aminopyridine-3-boronic acid (**31**) seemed to be suitable for the preparation of pyrido[2,3-*b*]indole **3** skeleton and for further structure–biological activity studies.

Boronic acid **31** was prepared in 70% yield by *n*-BuLi–TMEDA assisted *ortho*-lithiation of *N*-pivaloyl-4-

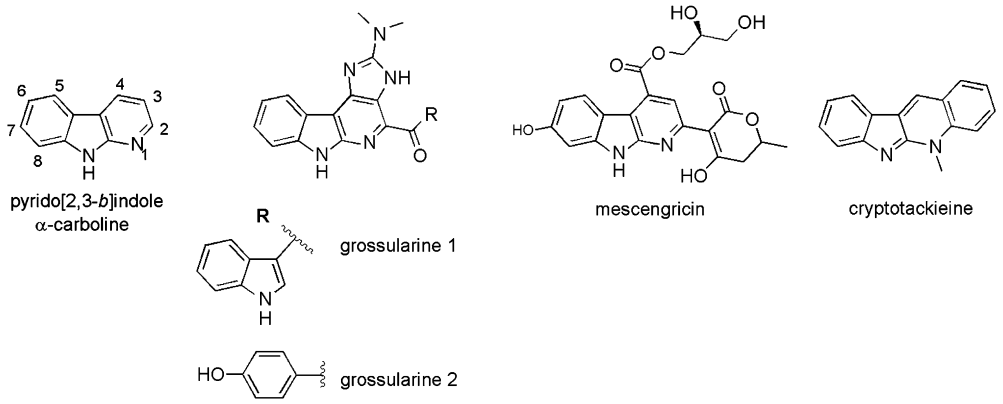
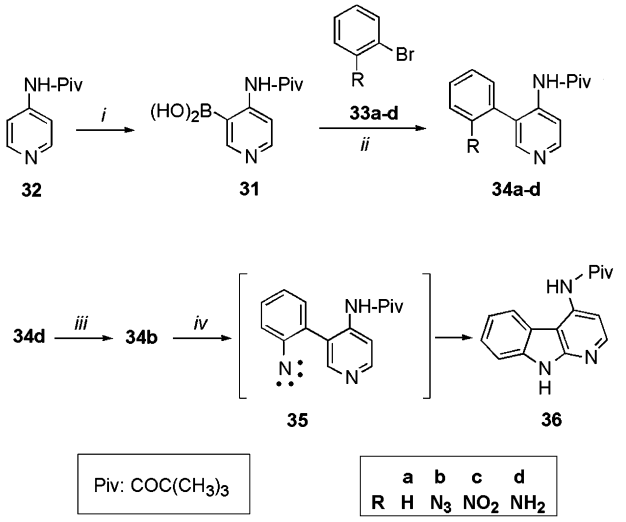


Figure 3. Structures of some α-carboline containing natural products.

aminopyridine **32**, followed by lithium–boron transmetallation.[34] Overall yield proved to be very sensitive to reaction conditions especially to temperature: addition of *n*-BuLi–TMEDA[35] at −78 °C followed by treatment at −10 °C for 2 h seemed to be optimal for lithiation while introduction of boronic acid required slow addition of $(n\text{-BuO})_3B$ at −65 °C and warming up to room temperature overnight. As pyridine boronic acids are frequently suffered from protodeboronation a preliminary coupling of **32** with bromobenzene (**33a**) was tried (Scheme 2). We were pleased to find that Suzuki coupling with bromobenzene (**33a**) smoothly afforded the corresponding bis-aryl derivative **34a** in 69% yield. However, coupling of **32** with 1-azido-2-bromobenzene (**2**) under the classical conditions gave no coupling product **34b**. Despite many efforts like changing catalysts, solvents, and bases or using microwave-assisted activation only deboronated product was isolated. This failure is probably due to the steric hindrance of *ortho* substituents (azide vs. pivaloylamino) around the coupling sites.[36]



Scheme 2. (i) *n*-BuLi, TMEDA, −78 °C, $(BuO)_3B$, THF, 70%; (ii) *o*-R–C_6H_4–Br, $Pd(Ph_3P)_4$, $NaHCO_3$, DME, Δ, **a**: 69%, **b**: 0%, **c**: 76%, **d**: 42%; (iii) (a) $NaNO_2$, HCl_{aq}, 0 °C; (b) NaN_3, 0 °C, **b**: 98%; (iv) dichlorobenzene, Δ.

In view of this unsuccessful coupling we tried a more conventional path using **32** and 2-bromonitrobenzene (**33c**). Under the classical coupling conditions *o*,*o*′-disubstituted diaryl derivative **34c** was smoothly obtained but the trivalent phosphorous compounds (Ph_3P, $(EtO)_3P$) mediated Cadogan type reductive transformation[37] of the nitro group to nitrene **35** remained unsuccessful. Ultimately, we attempted the classical approach to nitrene **35** via the corresponding diazo compound. Cross-coupling between pyridine boronic acid **32** and non-protected *o*-bromoaniline (**33d**) led to the diaryl derivative **34d** in acceptable yield (42%). Transformation of the amine function of **34d** into azide group followed the well-documented pathway in almost quantitative yield. Heated in boiling *o*-dichlorobenzene diaryl azide **34b** was transformed into 4-pivaloylamino-α-carboline (**36**) in 68% yield via the corresponding nitrene **35**.

3. Conclusion

In conclusion, we have accomplished the first Pd-catalyzed cross-couplings between 1-azido-2-bromobenzene (**2**) and diverse arylboronic acids resulting in the corresponding azido-bis-aryl derivatives. Thermal ring closure of latters allowed a short synthesis of some indole annulated aromatic polycycles. This two step Suzuki–Miyaura coupling—nitrene insertion pathway may have wide applications for the synthesis of acid, oxydation, or nitrosation sensitive functionalized indole-heterocycles of biological interest.

During the scope and limitation studies we found that direct coupling of 1-azido-2-bromobenzene (**2**) with 4-pivaloylaminopyridine boronic acid (**31**) failed, probably due to sterical hindrance. However, the aimed 4-amino substituted α-carboline ring system (**3**), a versatile intermediate toward grossularine analogs, was smoothly prepared by Suzuki–Miyaura coupling of **31** with 2-bromoanaline, followed by simple functional group transformations.

4. Experimental

4.1. General

All solvents were of reagent grade and, when necessary, were purified and dried by standard methods. Reactions and products were routinely monitored by thin layer chromatography (TLC) on silica gel (Kieselgel 60 F_{254}, Merck). Column chromatography purifications were performed on CHROMAGEL® Silice 60 ACC 70–200 μm silica gel. Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected.

UV spectra were recorded in methanol solution on a Unicam 8700 apparatus. IR spectra were measured with a Bomen Hartman or on a Spectrum BX/RX (Perkin-Elmer) instrument. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC 300 spectrometer using TMS as internal standard. Couplings expressed as s, sl, d, t, m correspond to singlet, large-singlet, doublet, triplet, and multiplet, respectively. Mass spectra were recorded on a MSQ ThermoFinnigan apparatus using electronspray (ESI) or on a GCT Waters apparatus using electronimpact (EI) ionzation method. Microwave activated reactions were carried out on a Discovery CEM (300 W) apparatus.

4.1.1. General procedure for Suzuki–Miyaura couplings (general method A). A solution of aryl bromide in degassed dimethoxyethane (DME) (5 mL/mmol) was stirred at room temperature with $Pd(Ph_3P)_4$ (3–6 mol %) for 20 min then arylboronic acid (1.2 equiv) and 10% aqueous $NaHCO_3$ or Na_2CO_3 solution (2.4 equiv) were added and the reaction mixture was refluxed under nitrogen. After completion of the reaction (TLC monitoring) DME was partially evaporated under reduced pressure, the mixture was poured on ice-water and extracted with dichloromethane (4×15 mL/mmol). The combined organic layers were dried (Na_2SO_4), filtered over Celite®, evaporated in vacuo, and the residue was purified by column chromatography to give the corresponding diaryl compound.

4.1.2. General procedure of the thermolysis—nitrene insertion (general method B). A solution of aryl azide in *o*-dichlorobenzene (10 mL/mmol) was heated under reflux until the disappearance of the starting material (TLC monitoring). After evaporation of the solvent under reduced pressure the residue was purified by column chromatography to give the corresponding compounds.

4.2. Synthesis of 3,10-dihydro-pyrrolo[3,2-*a*]carbazole (1)

4.2.1. 2,2-Dimethyl-*N*-[2-(1*H*-indol-5-yl)phenyl]propionamide (6). General method A. 5-Bromoindole (**4**): 0.78 g (3.98 mmol); 2-(2,2-dimethylpropionylamino)phenyl boronic acid (**5**): 0.97 g (4.39 mmol); DME: 20 mL; $Pd(Ph_3P)_4$: 0.16 g (0.138 mmol); 10% Na_2CO_3 solution: 4.7 mL (4.4 mmol); time: 3.5 h; purification: column chromatography (eluant: dichloromethane). Yield: 0.771 g (66%); white-yellowish powder; mp: 170–173 °C (ether); IR (KBr) ν=3418, 2947, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11 (s, 9H, $(CH_3)_3$), 1.65 (s, NHCO), 6.62 (d, J=2.2 Hz, 1H, H-3), 7.15 (d, J=8.3 Hz, 1H, H-7), 7.21 (dt, J=7.3, 1.2 Hz, 1H, H-5′), 7.31–7.42 (m, 3H, H-2, H-3′, H-4′), 7.51 (dd, J=8.3, 1.2 Hz, 1H, H-6), 7.65 (d, J=1.2 Hz, 1H, H-4), 7.72 (s, 1H, indole NH), 8.41 (dd, J=7.3, 1.2 Hz, 1H, H-6′) ppm; ^{13}C NMR ($CDCl_3$) δ=27.4 ($(CH_3)_3$), 39.7 (C–$(CH_3)_3$), 102.6 (C-3), 111.6 (C-7), 120.5 (C-4), 121.5 (C-3′), 123.1 (C-4′), 123.7 (C-6), 125.3 (C-2), 127.6 (C-6′), 128.4 (C-5), 129.2 (C-3a), 130.3 (C-5′), 133.2 (C-1′), 135.3 (C-7a), 135.5 (C-2′), 176.5 (CO) ppm.

4.2.2. [2-(1*H*-Indol-5-yl)-phenyl]-carbamic acid *tert*-butylester (11). From **4**: general method A. 5-Bromoindole (**4**): 1.70 g (6.25 mmol); 2-*tert*-butoxycarbonylamino phenyl boronic acid (**8**): 1.60 g (9.93 mmol); DME: 50 mL; $Pd(Ph_3P)_4$: 0.35 g (0.30 mmol); 10% Na_2CO_3 solution: 25 mL (23.6 mmol); time: 3 h; purification: column chromatography (eluant: dichloromethane–hexane 3:2→20:1). Yield: 1.05 g (57%).

From **9**: general method A. 1*H*-indole-5-boronic acid (**9**): 1.30 g (8.07 mmol); 2-bromo-*N*-*tert*-butoxycarbonylaniline (**10**): 1.88 g (6.90 mmol); DME: 40 mL; $Pd(Ph_3P)_4$: 0.35 g (0.30 mmol); 10% Na_2CO_3 solution: 20 mL (19.4 mmol); time: 4.5 h; purification: column chromatography (eluant: dichloromethane–hexane 3:2→20:1). Yield: 1.40 g (66%).

White-yellowish powder; mp: 172–174 °C (ether); IR (KBr) ν=3340, 2966, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (s, 9H, $(CH_3)_3$), 6.61 (d, 1H, J=1.2 Hz, H-3), 6.71 (s, 1H, NHCO), 7.12 (td, J=7.4, 1.1 Hz, 1H, H-5′), 7.15 (dd, J=7.4, 1.1 Hz, 1H, H-6′), 7.25 (m, 2H, H-7, H-2), 7.32 (dt, J=7.4, 1.1 Hz, 1H, H-4′), 7.50 (d, J=8.3 Hz, 1H, H-6), 7.62 (d, J=1.1 Hz, 1H, H-4), 8.18 (d, J=7.4 Hz, 1H, H-6′), 8.52 (s, 1H, indole NH) ppm; ^{13}C NMR ($CDCl_3$) δ=28.3 ($(CH_3)_3$), 80.3 (C–$(CH_3)_3$), 102.7 (C-3), 111.6 (C-7), 119.2 (C-4), 121.4 (C-3′), 122.7 (C-4′), 123.2 (C-6), 125.2 (C-2), 127.7 (C-6′), 128.3 (C-5), 129.7 (C-3a), 130.7 (C-5′), 132.5 (C-1′), 135.2 (C-7a), 135.6 (C-2′), 153.1 (CO) ppm; MS (*m*/*z*, %)=309 (M+1, 12), 308 ($M^{+\bullet}$, 23), 253, 208 (100).

4.2.3. 2-(1*H*-Indol-5-yl)phenylamine (7).

4.2.3.1. By acid catalyzed N-Boc group deprotection. A solution of [2-(1*H*-indol-5-yl)-phenyl]-carbamic acid *tert*-butylester (**11**) (200 mg, 0.65 mmol) in a mixture of 25% H_2SO_4 (10 mL) and ethanol (7 mL) was refluxed until the disappearance of the starting material. The reaction mixture was poured on ice-water, basified with 25% NH_4OH, and extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were dried (Na_2SO_4), evaporated to dryness, and the residue was purified by column chromatography (eluant: dichloromethane) to afford the title product **7** (56 mg, 41%) and its *tert*-butyl substituted derivative **12** (10 mg, 6%). Compound **7**: white-yellowish powder; mp: 120–121 °C (ether); UV (MeOH) λ_{max}=206, 227, 249, 284 nm; IR (KBr) ν=3413, 2943, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.61 (s, 2H, NH_2), 6.51 (t, J=2.1 Hz, 1H, H-3), 6.75 (dd, J=8.0, 0.9 Hz, 1H, H-3′), 6.85 (dt, J=8.0, 0.9 Hz, 1H, H-5′), 7.14 (dt, J=8.0, 0.9 Hz, 1H, H-4′), 7.16 (d, J=2.1 Hz, 1H, H-2), 7.21 (dd, J=8.0, 0.9 Hz, 1H, H-6′), 7.25 (dd, J=8.4, 1.1 Hz, 1H, H-6), 7.35 (d, J=8.4 Hz, 1H, H-7), 7.70 (d, J=1.1 Hz, 1H, H-4), 8.21 (s, 1H, indole NH) ppm; ^{13}C NMR ($CDCl_3$) δ=102.6 (C-3), 111.3 (C-7), 115.4 (C-3′), 118.6 (C-5′), 121.0 (C-4), 123.3 (C-6), 124.8 (C-2), 127.9 (C-4′), 128.1 (C-1′), 129.0 (C-3a), 130.9 (C-6′), 130.9 (C-5), 134.9 (C-7a), 143.7 (C-2′) ppm; MS (EI, *m*/*z*, %)=208 ($M^{+\bullet}$, 100), 180 (14), 152 (8). HREIMS calcd for $C_{14}H_{12}N_2$: 208.1000, found: 208.0976. Compound **12**: amorphous solid; UV (MeOH) λ_{max}=211, 225, 288 nm; IR (KBr) ν=3410, 3366, 3064, 2921, 1621 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.38 and 1.47 (s, 9H, $C(CH_3)_3$), 4.82 (sl, 2H, NH_2), 6.20 (sl, 1H, H-3), 6.72 (dd, J=7.4 Hz, 1H, H-5′), 6.82 (dd, J=7.0 Hz, 1H, H-3′), 7.02–7.15 (m, 3H), 7.18 and 7.42 (d, J=8.3 Hz, 1H, H-3′), 7.47–7.52 (m, 1H), 7.50 and 7.74 (sl, 1H), 10.81 and 10.95 (sl, 1H, indole NH) ppm; ^{13}C NMR ($CDCl_3$) δ=30.1 (30.7), 31.5 (31.8), 96.9, 110.7 (111.5), 115.4 (115.5), 118.6 (120.2), 120.0 (122.3), 121.5 (122.6), 126.1 (126.6), 127.7 (127.8), 128.7 (129.3), 129.6 (130.6), 130.8 (130.9), 134.9 (136.3), 143.6 (143.7), 149.7 (signals in brackets correspond to the atropisomer) ppm; MS (EI, *m*/*z*, %)=264 ($M^{+\bullet}$, 100), 249 (75), 233 (7), 219 (4), 207 (8).

4.2.3.2. By thermal deprotection. A suspension of [2-(1*H*-indol-5-yl)-phenyl]-carbamic acid *tert*-butylester **11** (150 mg, 0.487 mmol) and silica gel (200 mg) in toluene (4 mL) was refluxed under stirring until the disappearance of the starting material (4–5 h). After filtration the silica gel was washed with CH_2Cl_2–MeOH 4:1 (5×15 mL), the combined filtrate was evaporated and the residue was purified by column chromatography (eluant: dichloromethane) to afford **7** (94 mg, 93%), as a pale-yellowish powder.

4.2.3.3. By microwave-assisted deprotection. *N*-Boc protected product **11** (150 mg, 0.487 mmol) evaporated to silica gel (1.0 g) was irradiated with microwave (Discovery CEM 300 W 70% power) by 5 min portions until the disappearance of the starting material. The treatment followed the above mentioned procedure.

4.2.4. 1-Azido-2-bromobenzene (2). To a solution of 2-bromoaniline (2.0 g, 11.6 mmol) in water (50 mL) and concentrated HCl (2 mL) was added dropwise an aqueous (10 mL) solution of sodium nitrite (0.92 g, 13.2 mmol). The reaction

mixture was stirred at 0 °C for 1 h and then sodium azide (0.89 g, 13.2 mmol) dissolved in water (10 mL) was added dropwise. Stirring was maintained at 0 °C for 1 h and then the reaction mixture was allowed to warm up to room temperature. After extraction with dichloromethane (3× 15 mL) the organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. Yield: 2.25 g (98%); brownish oil; IR (KBr) ν=3234, 3061, 2917, 2115, 1576, 1471, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.97 (ddd, J=7.6, 7.7, 0.9 Hz, 1H, H-4), 7.11 (dd, J=8.0, 0.9 Hz, 1H, H-6), 7.30 (ddd, J=7.6, 8.0, 1.0 Hz, 1H, H-5), 7.51 (d, J=7.7, 1.0 Hz, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$) δ=113.8 (C-2), 119.4 (C-6), 125.9 (C-4), 128.5 (C-5), 133.8 (C-3), 138.6 (C-1) ppm; MS (EI, *m*/*z*, %)=169 ($M^{+\bullet}$−28, 77).

4.2.5. 2-Azidobiphenyl (14). General method A. 1-Azido-2-bromobenzene (**2**): 0.500 g (2.5 mmol); benzene boronic acid (**13**): 0.366 g (3.0 mmol); DME: 15 mL; $Pd(Ph_3P)_4$: 0.233 g (0.202 mmol); 10% $NaHCO_3$ solution: 5 mL (6.0 mmol); time: 6 h; purification: column chromatography (eluant: petroleum ether). Yield: 0.329 g (68%); yellow crystals; mp: 45 °C (petroleum ether); UV (MeOH) λ_{max}=206, 236, 256 nm; IR (KBr) ν=3057, 3022, 2916, 2114, 2088, 1577, 1476, 1427, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.21 (t, J=6.6 Hz, 1H, H-4), 7.26 (d, J=6.6 Hz, 1H, H-3), 7.34 (d, J=7.6 Hz, 1H, H-6), 7.39 (dd, J=7.6, 6.6 Hz, 1H, H-5), 7.39 (t, J=7.7 Hz, 1H, H-4′), 7.44 (d, J=7.7 Hz, 2H, H-2′), 7.44 (t, J=7.7 Hz, 2H, H-3′) ppm; ^{13}C NMR ($CDCl_3$) δ=118.7 (C-3), 124.9 (C-4), 127.5 (C-4′), 128.1 (C-2′), 128.7 (C-5), 129.4 (C-3′), 131.2 (C-6), 133.7 (C-2), 137.1 (C-1), 138.1 (C-1′) ppm; MS (EI, *m*/*z*, %)=167 ($M^{+\bullet}$−28, 56).

4.2.6. 5-(2-Azidophenyl)-1*H*-indole (15). General method A. 1-Azido-2-bromobenzene (2): 0.250 g (1.26 mmol); 1*H*-indole-5-boronic acid (9): 0.250 g (1.55 mmol); DME: 13 mL; $Pd(Ph_3P)_4$: 0.175 g (0.152 mmol); 10% Na_2CO_3 solution: 4.0 mL (3.77 mmol); time: 5 h; purification: column chromatography (eluant: heptane–dichloromethane 7:3). Yield: 0.261 g (88%); viscous salmon oil; UV (MeOH) λ_{max}=205, 244 nm; IR (KBr) ν=3452, 2110, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.61 (t, J=2.6 Hz, 1H, H-3), 7.15–7.41 (m, 7H), 7.65 (d, J=1.1 Hz, 1H, H-4), 8.05 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ=103.0 (C-3), 110.5 (C-7), 118.6 (C-3′), 121.5 (C-5′), 123.7 (C-4), 124.8 (C-2), 124.9 (C-6), 127.7 (C-1′), 128.0 (C-4′), 130.0 (C-3a), 131.7 (C-6′), 135.0 (C-7a), 135.1 (C-5), 137.2 (C-2′) ppm; MS (EI, *m*/*z*, %)=234 ($M^{+\bullet}$−28, 77).

4.2.7. 3,10-Dihydro-pyrrolo[3,2-*a*]carbazole (1). General method B. **15**: (330 mg, 1.41 mmol); *o*-dichlorobenzene: 15 mL; time: 7 h; purification: column chromatography (eluant: dichloromethane). Yield: 0.190 g (65%); white powder; mp: 155–158 °C; UV (MeOH) λ_{max}=205, 249, 279, 303, 330 nm; IR (KBr) ν=3408, 3048, 1634, 1460,1387, 1356, 1310, 1229 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.82 (d, 1H, J=2.4 Hz, H-1), 7.15 (t, 1H, J=7.3 Hz, H-7), 7.20 (d, 1H, J=8.1 Hz, H-5), 7.23 (t, 1H, J=8.3 Hz, H-8), 7.39 (dd, 1H, J=2.4, 2.7 Hz, H-2), 7.54 (d, 1H, J=8.1 Hz, H-4), 7.83 (d, 1H, J=8.3 Hz, H-9), 8.05 (d, 1H, J=7.3 Hz, H-6), 11.35 (sl, 1H, NH), 11.55 (sl, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ=99.1 (C-1), 104.4 (C-4), 110.6 (C-5b), 114.6 (C-5*), 114.9 (C-6*), 115.0 (C-8*), 119.2 (C-7), 119.4 (C-5a), 122.6 (C-9), 123.5 (C-2), 124.7 (C-10b), 132.8 (C-10a), 135.1 (C-3a), 138.2 (C-9a) (*interchangeable carbons) ppm; MS (EI, *m*/*z*, %)=206 ($M^{+\bullet}$, 100).

4.3. Synthesis of some heterocyclic analogs of carbazole

4.3.1. 2-(2-Azidophenyl)thiophene (18). General method A. 1-Azido-2-bromobenzene (**2**): 0.514 g (2.6 mmol); thiophene-2-boronic acid (**17**): 0.400 g (3.12 mmol); DME: 30 mL; $Pd(Ph_3P)_4$: 0.240 g (0.208 mmol); 10% $NaHCO_3$ solution: 4.8 mL (5.72 mmol); time: 6 h; purification: column chromatography (eluant: petroleum ether). Yield: 0.214 g (40%); brownish oil; UV (MeOH) λ_{max}=213, 248 nm; IR (KBr) ν=3063, 2918, 2846, 2117, 2090, 1573, 1484, 1443, 1295, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.1 (dd, J=4.8, 3.7 Hz, 1H, H-4), 7.18 (td, J=7.9, 1.1 Hz, 1H, H-5′), 7.25 (dd, J=7.9, 1.1 Hz, 1H, H-3′), 7.32 (td, J=7.9, 1.4 Hz, 1H, H-4′), 7.38 (dd, J=4.8, 1.0 Hz, 1H, H-5), 7.45 (dd, J=3.7, 1.0 Hz, 1H, H-3), 7.55 (dd, J=7.9, 1.4 Hz, 1H, H-6′) ppm; ^{13}C NMR ($CDCl_3$) δ=119.0 (C-3′), 122.6 (C-5′), 122.8 (C-4′), 126.1 (C-1), 126.2 (C-5), 126.8 (C-3), 127.2 (C-4), 128.6 (C-6), 130.1 (C-1′), 139.0 (C-2) ppm; MS (EI, *m*/*z*, %)=173 ($M^{+\bullet}$−28, 67).

4.3.2. 2-(2-Azidophenyl)furan (21). General method A. 1-Azido-2-bromobenzene (**2**): 0.486 g (2.45 mmol); furan-2-boronic acid (**20**): 0.330 g (2.95 mmol); DME: 15 mL; $Pd(Ph_3P)_4$: 0.226 g (0.196 mmol); 10% $NaHCO_3$ solution: 4.9 mL (5.88 mmol); time: 3.5 h; purification: column chromatography (eluant: dichloromethane). Yield: 0.191 g (42%); yellowish oil; UV (MeOH) λ_{max}=202, 250, 256, 287 nm; IR (NaCl) ν=2916, 2846, 2123, 2088, 1564, 1480, 1436, 1375, 1296, 1212, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.50 (dd, J=3.3, 1.7 Hz, 1H, H-4), 7.07 (d, J=3.3 Hz, 1H, H-3), 7.18 (dd, J=7.6, 7.3 Hz, 1H, H-5′), 7.21 (d, J=8.1 Hz, 1H, H-3′), 7.29 (dd, J=8.1, 7.3 Hz, 1H, H-4′), 7.47 (d, J=1.7 Hz, 1H, H-5), 7.84 (d, J=7.6 Hz, 1H, H-6′) ppm; ^{13}C NMR ($CDCl_3$) δ=110.4 (C-5), 111.7 (C-4), 118.8 (C-3′), 122.4 (C-2′), 124.9 (C-5′), 126.8 (C-6′), 128.0 (C-4), 135.0 (C-1′), 141.8 (C-5), 149.6 (C-2) ppm; MS (EI, *m*/*z*, %)=185 ($M^{+\bullet}$, 11), 157 ($M^{+\bullet}$−28, 75); HREIMS calcd for $C_{10}H_7NO_3$: 185.0589, found: 185.0993.

4.3.3. 2′-Azidobiphenyl-4-carbonitrile (24). General method A. 1-Azido-2-bromobenzene (**2**): 0.198 g (1.00 mmol); 4-cyanophenyl boronic acid (**22**): 0.176 g (1.21 mmol); DME: 5 mL; $Pd(Ph_3P)_4$: 0.093 g (0.08 mmol); 10% $NaHCO_3$ solution: 2.0 mL (2.4 mmol); time: 3 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 1:1). Yield: 0.101 g (46%); yellowish crystals; mp: 51–53 °C (petroleum ether); UV (MeOH) λ_{max}=207, 248, 270 nm; IR (KBr) ν=3462, 3366, 3207, 3057, 2916, 2837, 2220, 2123, 2088, 1916, 1797, 1604, 1577, 1507, 1480, 1441, 1397, 1296 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.24 (dd, J=7.6, 6.5 Hz, 1H, H-5′), 7.28 (d, J=7.6 Hz, 1H, H-3′), 7.32 (d, J=7.6 Hz, 1H, H-6′), 7.46 (t, J=7.6, 6.5 Hz, 1H, H-4′), 7.56 (d, J=6.6 Hz, 2H, H-3), 7.71 (d, J=6.6 Hz, 2H, H-2) ppm; ^{13}C NMR ($CDCl_3$) δ=111.1 (C-4), 118.8 (C-3′), 118.8 (CN), 125.1 (C-5′), 129.8 (C-4′), 130.2 (C-3), 130.9 (C-6′), 131.5 (C-1′), 131.8 (C-2), 137.1 (C-2′), 142.8 (C-1) ppm; MS (EI, *m*/*z*, %)=220 ($M^{+\bullet}$, 10), 192 ($M^{+\bullet}$−28, 54); HREIMS calcd for $C_{13}H_8N_4$: 220.0749, found: 220.0774.

4.3.4. 2′-Azidobiphenyl-4-carbaldehyde (25). General method A. 1-Azido-2-bromobenzene (**2**): 0.198 g (1.00 mmol); 4-formylphenyl boronic acid (**23**): 0.180 g (1.20 mmol); DME: 5 mL; $Pd(Ph_3P)_4$: 0.093 g (0.08 mmol); 10% $NaHCO_3$ solution: 2.0 mL (2.4 mmol); time: 2 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 1:1). Yield: 0.118 g (53%); yellowish crystals; mp: <40 °C (petroleum ether); UV (MeOH) λ_{max}=207, 256, 284 nm; IR (KBr) ν=3392, 3339, 2916, 2837, 2740, 2555, 2123, 2088, 1683, 1604, 1577, 1507, 1476, 1445, 1410, 1384, 1296, 1212 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.24 (dd, J=7.1, 6.7 Hz, 1H, H-5′), 7.28 (d, J=6.8 Hz, 1H, H-3′), 7.36 (d, J=6.7 Hz, 1H, H-6′), 7.45 (dd, J=7.1, 6.8 Hz, 1H, H-4′), 7.63 (d, J=7.9 Hz, 2H, H-2), 7.94 (d, J=7.9 Hz, 2H, H-3), 10.06 (s, 1H, CHO) ppm; ^{13}C NMR ($CDCl_3$) δ=118.8 (C-3′), 125.1 (C-5′), 129.4 (C-3), 129.6 (C-4′), 130.1 (C-2), 131.0 (C-6′), 132.2 (C-1), 135.2 (C-4), 137.2 (C-2′), 144.3 (C-1), 191.9 (CHO) ppm; MS (EI, m/z, %)=223 ($M^{+\bullet}$, 12), 195 ($M^{+\bullet}-28$, 44); HREIMS calcd for $C_{13}H_9N_3O$: 223.0796, found: 223.0746.

4.3.5. 9*H*-Carbazole (26). General method B. 2-Azidobiphenyl (**14**): 130 mg (0.666 mmol); *o*-dichlorobenzene: 5 mL; time: 0.5 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 8:2). Yield: 79 mg (71%); yellow powder; mp: 240–243 °C; UV (MeOH) λ_{max}=210, 233, 257, 298 nm; IR (KBr) ν=3410, 3040, 2951, 2916, 2846, 1621, 1599, 1489, 1445, 1392, 1322, 1203, 1137 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.12 (sl, 1H, NH), 7.17 (t, J=7.7 Hz, 2H, H-3), 7.40 (t, J=7.7 Hz, 2H, H-2), 7.51 (d, J=7.7 Hz, 2H, H-1), 8.11 (d, J=7.7 Hz, 2H, H-4) ppm; ^{13}C NMR (DMSO-d_6) δ=111.2 (C-1), 118.9 (C-3), 120.5 (C-4), 122.8 (C-4a), 140.0 (C-8a) ppm; MS (ESI, m/z, %)=168 (M+$H^{+\bullet}$, 12); MS (EI, m/z, %)=167 ($M^{+\bullet}$, 24); HREIMS calcd for $C_{12}H_9N$: 167.0735, found: 167.0731.

4.3.6. 4*H*-Thieno[3,2-*b*]indole (27). General method B. 2-(2-Azidophenyl)thiophene (**18**): 0.104 g (0.47 mmol); *o*-dichlorobenzene: 5 mL; time: 2 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 8:2). Yield: 70 mg (85%); brown powder; mp: 115 °C; UV (MeOH) λ_{max}=192, 194, 204, 229, 244, 302, 312 nm; IR (KBr) ν=3392, 2916, 2493, 2123, 1647, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.05 (d, J=5.1 Hz, 1H, H-3), 7.15 (t, J=7.6 Hz, 1H, H-7), 7.25 (t, J=7.7 Hz, 1H, H-6), 7.35 (d, J=5.1 Hz, 1H, H-2), 7.45 (d, J=7.7 Hz, 1H, H-5), 7.75 (d, J=7.6 Hz, 1H, H-8), 8.02 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ=111.5 (C-3), 111.9 (C-5), 117.9 (C-8b), 118.8 (C-8), 119.8 (C-7), 122.0 (C-8a), 122.8 (C-6), 126.9 (C-2), 141.1 (C-4a), 142.9 (C-3a) ppm; MS (EI, m/z, %)=173 ($M^{+\bullet}$, 21); HREIMS calcd for $C_{10}H_7NS$: 173.0299, found: 173.0292.

4.3.7. 4*H*-Furo[3,2-*b*]indole (28). General method B. 2-(2-Azidophenyl)furan (**21**): 0.100 g (0.54 mmol); *o*-dichlorobenzene: 2 mL; time: 4 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 7:3→5:5). Yield: 46 mg (55%); brown oil; UV (MeOH) λ_{max}=240, 297, 305 nm; IR (KBr) ν=3392, 3310, 3048, 2916, 1463, 1436, 1392, 1309, 1278, 1243, 1155, 1133 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.57 (d, J=2.1 Hz, 1H, H-3), 7.19 (ddd, J=7.6, 6.7, 2.3 Hz, 1H, H-7), 7.20 (td, J=6.7, 2.8 Hz, 1H, H-6), 7.38 (dd, J=6.7, 2.3 Hz, H-5), 7.47 (dd, J=2.1 Hz, 1H, H-2), 7.59 (sl, 1H, NH), 7.72 (dd, J=7.6, 2.8 Hz, H-8) ppm; ^{13}C NMR ($CDCl_3$) δ=99.4 (C-3), 112.2 (C-5), 114.5 (C-8a), 116.2 (C-8), 119.8 (C-7), 121.7 (C-6), 129.9 (C-8b), 138.9 (C-4a), 142.4 (C-3a), 145.8 (C-2) ppm; MS (EI, m/z, %)=158 (M+1, 21), 157 ($M^{+\bullet}$, 12).

4.3.8. 9*H*-Carbazole-2-carbonitrile (29). General method B. 2′-Azidobiphenyl-4-carbonitrile (**24**): 0.130 g (0.59 mmol); *o*-dichlorobenzene: 2.5 mL; time: 4 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 5:5→dichloromethane). Yield: 79 mg (70%); yellowish crystals; mp: 120–122 °C; UV (MeOH) λ_{max}=205, 222, 245, 305, 345 nm; IR (KBr) ν=3515, 3401, 3269, 3048, 2220, 1626, 1608, 1454, 1436, 1322, 1287, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.30 (t, J=7.7 Hz 1H, H-6), 7.46–7.55 (m, 3H, H-7, H-8, H-3), 7.75 (s, 1H, H-1), 8.09 (d, J=8.1 Hz, 1H, H-4), 8.12 (d, J=7.7 Hz, 1H, H-5), 8.51 (sl, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ=107.8 (C-2), 111.1 (C-8), 114.8 (C-1), 120.2 (CN), 120.3 (C-6), 120.9 (C-4), 121.1 (C-5), 122.0 (C-4b), 122.5 (C-3), 126.7 (C-4a), 127.8 (C-7), 138.2 (C-8a), 140.6 (C-9a) ppm; MS (EI, m/z, %)=192 ($M^{+\bullet}$, 19); HREIMS calcd for $C_{13}H_8N_2$: 192.0687, found: 192.0680.

4.3.9. 9*H*-Carbazole-2-carbaldehyde (30). General method B. 2′-Azidobiphenyl-4-carbaldehyde (**25**): 0.160 g (0.717 mmol); *o*-dichlorobenzene: 2.5 mL; time: 4 h; purification: column chromatography (eluant: petroleum ether–dichloromethane 5:5→dichloromethane). Yield: 71 mg (51%); yellow crystals; mp: 150–152 °C; UV (MeOH) λ_{max}=194, 206, 251, 319, 366 nm; IR (KBr) ν=3374, 3330, 3031, 2846, 2740, 2460, 1921, 1877, 1744, 1683, 1665, 1621, 1498, 1441, 1344, 1322, 1274, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.85 (s, 1H, NH), 7.26 (t, J=7.9 Hz, 1H, H-6), 7.50 (t, J=7.9 Hz, 1H, H-7), 7.50 (d, J=7.9 Hz, 1H, H-8), 7.72 (d, J=8.0 Hz, 1H, H-3), 7.97 (s, 1H, H-1), 8.12 (d, J=7.9 Hz, 1H, H-5), 8.18 (d, J=8.0 Hz, 1H, H-4), 10.07 (s, 1H, CHO) ppm; ^{13}C NMR ($CDCl_3$) δ=111.1 (C-7), 111.9 (C-1), 120.15 (C-6), 120.55 (C-4), 121.3 (C-5), 121.5 (C-3), 122.3 (C-4b), 127.8 (C-8), 128.5 (C-4a), 133.9 (C-2), 139.0 (C-9a), 141.2 (C-8a), 192.6 (CHO) ppm; MS (EI, m/z, %)=195 ($M^{+\bullet}$, 17); HREIMS calcd for $C_{13}H_9NO$: 195.0684, found: 195.0688.

4.4. Synthesis of the pyrido[2,3-*b*]indole ring system 3

4.4.1. 4-Pivaloylaminopyridine boronic acid (31). A 2.5 M solution of *n*-BuLi in hexane (17.5 mL, 43.8 mmol) was added dropwise at −78 °C to a mixture of 2,2-dimethyl-*N*-(pyridin-4-yl)propionamide (**32**) (3.0 g, 16.8 mmol) and TMEDA (6.6 mL, 43.8 mmol) suspended in dry THF (70 mL). The reaction mixture was stirred at −78 °C for 15 min and warmed up to −10 °C and maintained at this temperature for 2 h. After formation of the lithium derivative a solution of tributylborate (7.7 g, 33.6 mmol) in dry THF (20 mL) was added dropwise to the cooled (−78 °C) reaction mixture. After 2 h stirring at −78 °C the reaction mixture was allowed to warm up to room temperature during overnight. To the mixture 4% NaOH solution (84 mL) was carefully added and than extracted with ethylacetate (100 mL). After separation the aqueous layer was acidified

to pH=6 by careful addition of 30% HCl at 5 °C. The mixture was extracted with dichloromethane (10×30 mL), the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure. The residue was triturated with ether to obtain a gray-white solid **32** (2.63 g, 70%); mp: >350 °C (ether); IR (KBr) ν=3450, 2956, 2870, 1704, 1616, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, CD_3OD) δ=1.36 (s, 9H, $(CH_3)_3$), 7.40 (s, 1H, H-2), 8.17 (d, J=6.5 Hz, 1H, H-5), 8.31 (sl, 1H, NH), 8.55 (d, J=6.5 Hz, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$, CD_3OD) δ=26.5 (CH_3), 40.4 (C–*C*(CH_3)$_3$), 112.9 (C-5), 121.1 (C-3), 147.5 (C-6), 156.0 (C-2), 156.8 (C-4), 175.4 (CO) ppm; MS (ESI, *m*/*z*, %)=223 (M+1, 65).

4.4.2. 2,2-Dimethyl-*N*-(3-phenylpyridin-4-yl)propionamide (34a). General method A. Bromobenzene (**33a**): 0.152 g (0.965 mmol); 4-pivaloylaminopyridine boronic acid (**31**): 0.300 g (1.35 mmol); DME: 10 mL; $Pd(Ph_3P)_4$: 0.089 g (0.077 mmol); 10% $NaHCO_3$ solution: 1.8 mL (2.12 mmol); time: 10 h; purification: column chromatography (eluant: dichloromethane–methanol 95:5). Yield: 0.171 g (69%); brownish solid; mp: 80 °C; UV (MeOH) λ_{max}=208, 228, 249 nm; IR (KBr) ν=3216, 3145, 3057, 3022, 2960, 1687, 1577, 1502, 1472, 1401 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11 (s, 9H, $(CH_3)_3$), 7.39 (d, J=7.3 Hz, 2H, H-2′), 7.47–7.59 (m, 3H, H-3′, H-4′), 7.71 (sl, NH), 8.43 (s, 1H, H-2), 8.44 (d, J=5.8 Hz, 1H, H-5), 8.53 (d, J=5.8 Hz, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$) δ=27.1 (CH_3), 40.1 (C–*C*(CH_3)$_3$), 113.3 (C-5), 126.2 (C-1′), 128.5 (C-4′), 132.1 (C-3′), 134.1 (C-3), 142.1 (C-4), 150.0 (C-6), 150.2 (C-2), 176.9 (CO) ppm; MS (ESI, *m*/*z*, %)=254 ($M^{+\bullet}$, 25); HREIMS calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 254.1403.

4.4.3. 2,2-Dimethyl-*N*-[3-(2-nitrophenyl)pyridin-4-yl]-propionamide (34c). General method A. 1-Bromo-2-nitrobenzene (**33c**): 0.152 g (0.75 mmol); 4-pivaloylaminopyridine boronic acid (**31**): 0.200 g (0.91 mmol); DME: 8 mL; $Pd(Ph_3P)_4$: 0.069 g (0.06 mmol); 10% $NaHCO_3$ solution: 1.39 mL (1.65 mmol); time: 10 h; purification: column chromatography (eluant: dichloromethane–heptane 8:2). Yield: 0.170 g (76%); yellowish solid; mp: 75 °C; UV (MeOH) λ_{max}=207, 221, 246 nm; IR (KBr) ν=3427, 3331, 3057, 2960, 1696, 1573, 1524, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.06 (s, 9H, $(CH_3)_3$), 7.20 (sl, 1H, NH), 7.42 (td, J=7.5, 1.2 Hz, 0.5H, H-5′*a*), 7.46 (dd, J=7.5, 1.2 Hz, 0.5H, H-′*a*), 7.49 (dd, J=7.8, 1 Hz, 0.5H, H-3′*b*), 7.56 (td, J=7.5, 1.2 Hz, 0.5H, H-4′*a*), 7.68 (td, J=7.8, 1.1 Hz, 0.5H, H-4′*b*), 7.72 (td, J=7.8, 1 Hz, 0.5H, H-5′*b*), 7.79 (dd, J=7.5, 1.2 Hz, 0.5H, H-6′*a*), 8.12 (dd, J=7.8, 1.1 Hz, 0.5H, H-6′*b*), 8.31 (s, 1H, H-2), 8.32 (d, J=5.8 Hz, 1H, H-5), 8.59 (d, J=5.8 Hz, H-6) [*a* and *b* correspond to atropisomers] ppm; ^{13}C NMR ($CDCl_3$) δ=26.9 (CH_3), 39.8 (C–*C*(CH_3)$_3$), 114.0 (C-5), 122.8 (C-3), 128.2 and 128.3 (C-3′), 130.4 (C-6′), 131.7 and 131.9 (C-4′), 132.7 and 133.4 (C-5′), 142.5 (C-4), 148.7 (C-2), 150.0 (C-2′), 151.1 (C-6), 176.5 (CO) ppm; MS (EI, *m*/*z*, %)=299 ($M^{+\bullet}$, 24); HREIMS calcd for $C_{16}H_{17}N_3O_3$: 299.1270, found: 299.1234.

4.4.4. 2,2-Dimethyl-*N*-[3-(2-aminophenyl)pyridin-4-yl]-propionamide (34d). General method A. 2-Bromonaniline (**33d**): 0.129 g (0.75 mmol); 4-pivaloylaminopyridine boronic acid (**31**): 0.200 g (0.91 mmol); DME: 10 mL; $Pd(Ph_3P)_4$: 0.069 g (0.06 mmol); 10% $NaHCO_3$ solution: 1.39 mL (1.65 mmol); time: 8 h; purification: column chromatography (eluant: dichloromethane–heptane 8:2). Yield: 0.102 g (42%); brownish oil; UV (MeOH) λ_{max}=205, 242 nm; IR (KBr) ν=3401, 3330, 3198, 2966, 1692, 1591, 1573, 1498, 1401, 1304 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11 and 1.32 (s, 9H, $(CH_3)_3$), 3.68 (sl, 2H, NH_2), 6.87 (dd, J=6.6 Hz, 1H, H-3′), 6.93 (dd, J=7.25, 6.6 Hz, 1H, H-5′), 7.09 (d, J=7.25 Hz, 1H, H-6′), 7.28 (t, J=6.6 Hz, 1H, H-4′), 7.52 (d, J=5.2 Hz, 0.8H, H-5*a*), 7.62 (sl, 0.4H, NH*b*), 7.99 (sl, 0.6H, NH*a*), 8.34 (d, J=5.4 Hz, 0.4H, H-5*b*), 8.45 (s, 1H, H-2), 8.48 (d, J=5.2 Hz, 0.6H, H-6*a*), 8.55 (d, J=5.4 Hz, 0.4H, H-6*b*) [*a* and *b* correspond to atropisomers] ppm; ^{13}C NMR ($CDCl_3$) δ=27.0 and 27.4 (CH_3), 40.0 (C–*C*(CH_3)$_3$), 113.5 (C-5′), 113.6 and 114.0 (C-5), 115.7 (C-3′), 123.6 (C-3), 130.4 (C-4′), 131.3 (C-6′), 143.0 (C-2′), 143.8 (C-4), 150.6 and 150.5 (C-2), 150.9 (C-6), 177.3 (CO) ppm; MS (EI, *m*/*z*, %)=269 ($M^{+\bullet}$, 11); HREIMS calcd for $C_{16}H_{19}N_3O$: 269.1528, found: 269.1523.

4.4.5. 2,2-Dimethyl-*N*-[3-(2-azidophenyl)pyridin-4-yl]-propionamide (34b). To a solution of 2,2-dimethyl-*N*-[3-(2-aminophenyl)pyridin-4-yl]propionamide (**34d**) (0.100 g, 0.37 mmol) in 5% HCl (2.5 mL) was added dropwise at 0 °C a solution of sodium nitrite (0.028 g, 0.41 mmol) in water (0.5 mL). The reaction mixture was stirred at 0 °C for 1 h and then sodium azide (0.026 g, 0.41 mmol) dissolved in water (0.5 mL) was added dropwise and stirring continued for 1 h. After careful treatment with 5% sodium hydroxide (pH=10) the reaction mixture was extracted with dichloromethane (4×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. Yield: 0.116 g (98%); pink powder; mp: 110 °C; UV (MeOH) λ_{max}=213, 248 nm; IR (KBr) ν=3418, 2960, 2114, 1692, 1568, 1494, 1397 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11 (s, 9H, $(CH_3)_3$), 7.27–7.60 (m, 4H, H-3′, H-4′, H-5′, H-6′), 8.35 (s, 1H, H-2), 8.37 (d, J=5.8 Hz, 1H, H-5), 8.55 (d, J=5.8 Hz, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$) δ=27.1 (CH_3), 40.0 (C–*C*(CH_3)$_3$), 113.6 (C-5), 118.8 (C-3′), 122.8 (C-2′), 125.7 (C-5′), 125.8 (C-1′), 130.9 (C-6′), 131.1 (C-4′), 138.8 (C-3), 142.5 (C-4), 150.5 (C-2), 150.6 (C-6), 176.7 (CO) ppm; MS (EI, *m*/*z*, %)=295 ($M^{+\bullet}$, 11), 276 (89); HREIMS calcd for $C_{16}H_{17}N_5O$: 295.1419, found: 295.1423.

4.4.6. 2,2-Dimethyl-*N*-(9*H*-pyrido[2,3-*b*]indol-4-yl)propionamide (36). General method B. 2,2-Dimethyl-*N*-[3-(2-azidophenyl) pyridin-4-yl]propionamide (**34b**): 0.230 g, (0.78 mmol); *o*-dichlorobenzene: 5 mL; time: 5 h; purification: column chromatography (eluant: cyclohexane–ethylacetate 5:5). Yield: 0.141 g (68%); yellowish solid; mp: 190–193 °C; UV (MeOH) λ_{max}=216, 248, 299 nm; IR (KBr) ν=3311, 3142, 3069, 2957, 2908, 2844, 1668, 1608, 1588, 1496, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, CD_3OD) δ=1.50 (s, 9H, $(CH_3)_3$), 7.33 (dd, J=7.9, 7.3 Hz, 1H, H-6′), 7.50 (dd, J=8.0, 7.3 Hz, 1H, H-7′), 7.58 (d, J=8.0 Hz, 1H, H-8′), 7.85 (d, J=7.9 Hz, 1H, H-5′), 8.13 (d, J=7.8 Hz, 1H, H-3), 8.34 (d, J=7.8 Hz, 1H, H-2), 8.41 (sl, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, CD_3OD δ=27.4 (CH_3), 40.0 (C–*C*(CH_3)$_3$), 106.2 (C-3), 111.6 (C-8), 118.8 (C-4a), 118.9 (C-4b), 120.0 (C-7), 120.3 (C-5), 126.0 (C-6), 137.9 (C-4), 140.8 (C-8a), 146.2 (C-2), 152.3 (C-9a), 177.3 (CO) ppm; MS (*m*/*z*, %)=268 (M+1, 25), 267 ($M^{+\bullet}$, 45); HREIMS calcd for $C_{16}H_{17}N_3O$: 267.1372, found: 267.1367.

Acknowledgements

Financial support of CNRS and University of Reims is gratefully acknowledged. D.C. thanks the French Ministry of Education and Research for a fellowship. Spectroscopic measurements by C. Petermann (NMR), D. Patigny, and P. Sigaut (MS) are gratefully acknowledged.

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