Microwaves Promoted Synthesis of *N*-Heterocycles via Tandem Imination/Annulation of (γ)- and (δ)-Ketoalkynes in the Presence of Ammonia.

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Abstract: The synthesis of 3-substituted 1-methyl-pyrrolo[1,2-*a*]pyrazines and 3-substituted isoquinolines was achieved by intramolecular cyclization of 2-acetyl-1-propargyl-pyrroles and 2-alkynyl benzaldehydes respectively, in the presence of ammonia under microwave heating. Tandem imination/annulation of 2-alkynyl benzaldehydes was easily accomplished under standard conditions, while $TiCl_4$ was used to achieve pyrrolo[1,2-*a*]pyrazines. The reaction mechanism and the regioselectivity were discussed on the basis of theoretical calculation and spectroscopic data.

Introduction

The development of new domino[1] approaches for the synthesis of heterocyclic compounds is a research field in continuous evolution.[2] When a new domino reaction also matches with the Trost's atom economy[3] concept, the advantages of the discovered synthetic strategy are notable.

For many years, we have been interested in the development of new domino synthetic strategies for the construction of nitrogen containing heterocycles from alkynes.[4] In particular, we focused our attention on the synthesis of nitrogen containing rings by sequential addition annulation reactions of γ- or δ-ketoalkynes with ammonia. For example, 5-*exo-dig* cyclization of 4-pentynones[5] gave polysubstituted and fused pyrrole derivatives, whereas the presence of γ-ketoalkyne moiety in an

aromatic framework is responsible for the 6-*endo-dig* cyclization of 5-acetyl-4-alkynylthiazoles[6] and 2-acyl-3-alkynylindoles[7] to pyrido[3,4-*c*]thiazoles and pyrido[3,4-*b*]indoles, respectively. More recently we reported an in depth investigation on the synthesis of pyrazino[1,2-*a*]indole nucleus through the sequential imination/annulation of 2-carbonyl-*N*-propargylindoles in the presence of ammonia in methanol.[8] The reaction worked well with *N*-propargylindole-2-carbaldehydes but yields and selectivity were unsatisfactory using 2-acetyl-*N*-propargylindoles.[8b] Moreover, the reaction totally failed reacting 2-benzoyl-*N*-propargylindoles. These drawbacks have been overcome when we found that 3 eq. of $TiCl_4$ and microwave heating were able to improve both yields and selectivity in the reactions of these less reactive substrates together with a widespread reduction of reaction times.[8a]

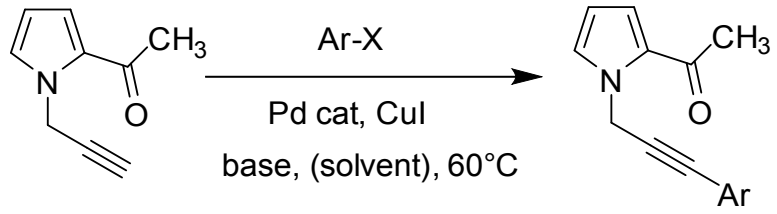
The aim of the present work is to explore the suitability of this smart approach for the construction of some other remarkable heterocyclic targets. In particular we focused our attention to the synthesis of simple pyrrolo[1,2-*a*]pyrazines and isoquinolines starting from 2-acetyl-*N*-propargyl pyrroles **1** and 2-alkynyl-benzaldehydes **2**, respectively. In the literature there are only few papers dealing with the reactivity of *N*-propargyl-pyrrole-2-carbaldehydes as building blocks for the synthesis of simple and polycyclic pyrrolizine derivatives,[9] whereas the reactivity of 2-acetyl-*N*-propargyl pyrroles is nearly unknown and has been only briefly investigated by us in a recent paper regarding a domino approach to 1-substituted pyrrolizin-2-carbaldehydes.[10] On the other hand, a lot of work is reported in the literature regarding the synthetic application of 2-carbonyl-phenylacetylenes. In particular some valuable approaches to isoquinoline[11] and dihydroisoquinoline[12] skeleton starting directly from 2-acyl-phenylacetilenes[11a–f, 12a–h] or from their imine derivatives[11g–q, 12i–n] have been reported.

Polycyclic compounds containing a pyrrolo[1,2-*a*]pyrazine moiety are biologically interesting molecules. For example, some chiral 5,5a,6,7,8,9-hexahydro-9-methyl-pyrido[3',2':4,5]pyrrolo[1,2-*a*]pyrazines showed a potent and selective 5-HT_{2C} receptor agonist activity.[13] Moreover, pyrrolo[1,2-*a*]quinoxalinones displayed an antiallergic activity,[14] whereas thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrazines[15] and pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazines[16] have been shown to be selective 5-HT_3 receptor agonists. Finally, a few bispyrrolo[1,2-*a*]quinoxalines exhibited an interesting antimalarial activity.[17] On the other hand, the isoquinoline nucleus is the core of well-known alkaloids such as papaverine and local anaesthetics such as quinisocaine, whereas saturated, functionalized and polycyclic derivatives are known to show different important pharmacological properties.[18]

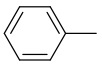
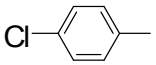
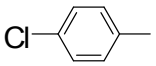
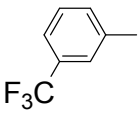
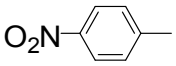
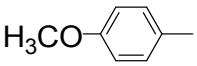
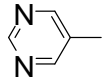
Results and Discussion

First, we prepared a reasonable library of starting compounds. 2-acetyl-*N*-propargylpyrrole **1a** was prepared according to the previously reported procedure[10] and then functionalized on terminal alkyne moiety by means of typical Sonogashira couplings with aryl and heteroaryl halides to give compounds **1b–g** in very good yields (Table 1).

Table 1. Preparation of 2-acetyl-*N*-alkynylpyrroles **1b–g**.



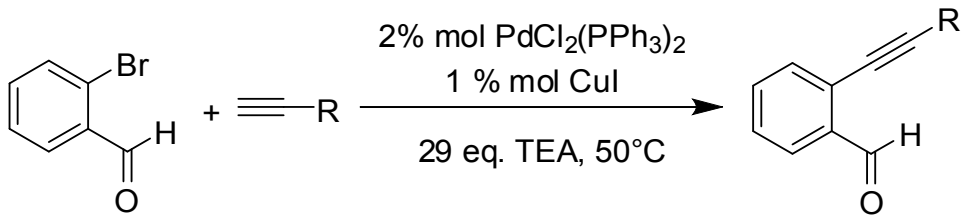
1a **1 b-g**

Ar–	X	Method[a]	t (h)	Prod.	Yield %[b]
	I	A	4.5	**1b**	98
	I	A	4	**1c**	74
	I	B	4.5	**1c**	96
	I	A	3	**1d**	87
	I	B	4.5	**1e**	83
	I	A	1	**1f**	95
	Br	A	4	**1g**	83

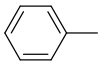
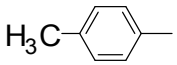
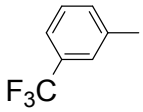
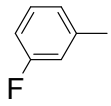
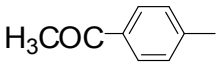
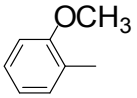
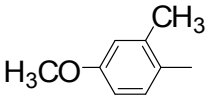
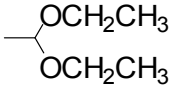
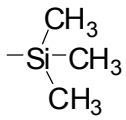
[a] Method A: molar ratio **1a** / Ar–X / K_2CO_3 / $Pd(PPh_3)_4$ / CuI = 1 : 1.01 : 5 : 0.02 : 0.04. DMF (2 mL), 60°C. Method B: molar ratio **1a** / Ar–X / TEA / $PdCl_2(PPh_3)_4$ / CuI = 1 : 1.01 : 29 : 0.02 : 0.01. 60°C.
[b] Yields referred to pure isolated product.

Through a similar approach 2-alkynylbenzaldehydes **2a–k** were synthesized in moderate to excellent yields starting from commercially available 2-bromobenzaldheyde and a choice of terminal acetilenes (Table 2).

Table 2. Preparation of 2-alkynylbenzaldehydes **2a–k**.



2 a-k

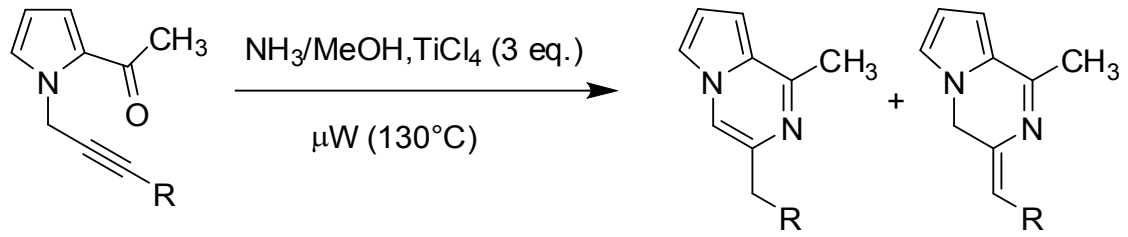
R	t (h)	Product	Yield %[a]
	1	**2a**	91
	4	**2b**	78
	6	**2c**	74
	6	**2d**	87
	2	**2e**	84[b]
	7	**2f**	59
	4.5	**2g**	90
$CH_3(CH_2)_4-$	4	**2h**	91
$CH_3(CH_2)_5-$	2	**2i**	91
	4	**2j**	89
	2.5	**2k**	63

[a] Yields referred to pure isolated product.
[b] Prepared by reaction of 2-ethynylbenzaldehyde (quantitatively obtained by treatment of **2k** with 2 eq. of K_2CO_3 in MeOH at rt) with 4-iodoacetophenone under the standard Sonogashira conditions.

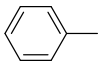
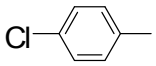
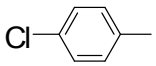
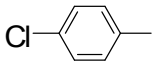
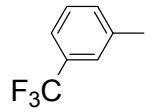
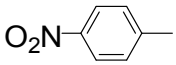
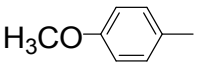
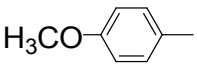
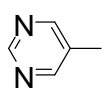
Our initial studies focused on the possibility to obtain the pyrrolo[1,2-*a*]pyrazine nucleus starting from the *N*-alkynylpyrroles **1a–g**. Following the procedure previously optimized for

imination/annulation reactions of 2-acetyl and 2-benzoyl *N*-alkynylindoles,[8a] alkynyl pyrroles **1a–g** were dissolved in 2M ammonia in methanol (20 eq. of NH_3) in a sealed microwave test tube. Three eq. of titanium tetrachloride were slowly added to the solution (caution!) and the reaction mixture was heated in a multi-mode microwave oven at 130°C. The reactions gave the corresponding pyrrolo[1,2-*a*]pyrazines **3**, in some cases beside the isomeric dihydro-pyrrolo[1,2-*a*]pyrazine **3'**. The isomeric products **3** and **3'** were easily separated by flash column chromatography. The results are summarized in Table 3.

Table 3. Imination/annulation reactions of 2-acetyl-*N*-alkynylpyrroles **1a–g.**



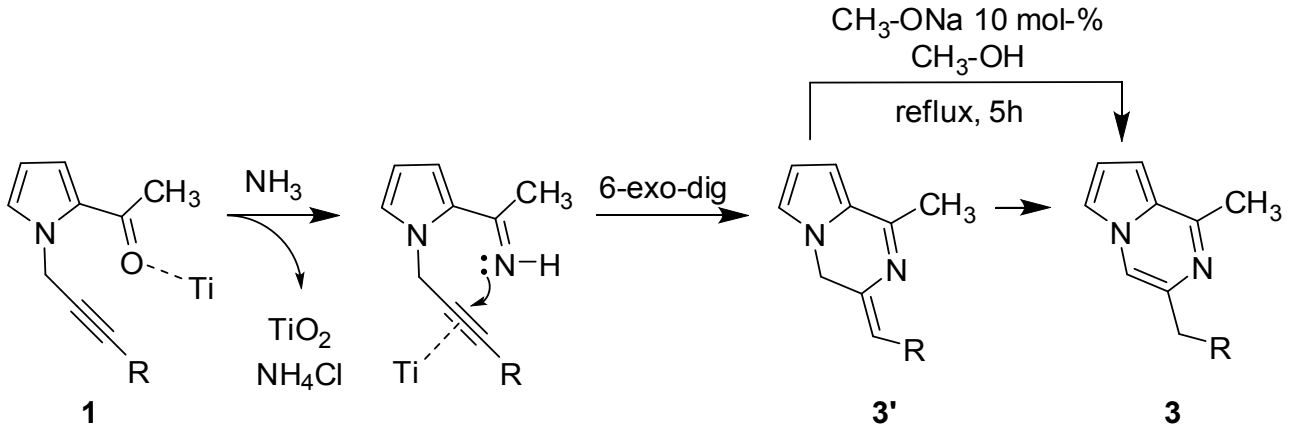
1 a-g **3 a-g** **3' a-g**

Entry	**1**	R	t (h) [a]	**3** (% yield)[b]	**3'** (yield %)[b]	**1** rec. (yield %)[b]
1	**a**	H	1.5	**3a** (81)	**3'a** (–)	**1a** (–)
2	**b**		6	**3b** (66)	**3'b** (–)	**1b** (–)
3	**c**		1	**3c** (18)	**3'c** (10)	**1c** (50)
4	**c**		6	**3c** (73)	**3'c** (–)	**1c** (–)
5	**c**		13[c]	**3c** (64)	**3'c** (10)	**1c** (–)
6	**d**		6	**3d** (65)	**3'd** (18)	**1d** (–)
7	**e**		6	**3e** (84)	**3'e** (–)	**1e** (–)
8	**f**		2	**3f** (38)	**3'f** (26)	**1f** (22)
9	**f**		6	**3f** (72)	**3'f** (–)	**1f** (17)
10	**g**		6	**3g** (35)	**3'g** (40)	**1c** (20)

[a] Not including 11 min "ramp time" (≅ 10 °C/min). [b] Yields referred to pure isolated product. [c] Conventional heating (silicon oil bath).

The reaction of 2-acetyl-*N*-propargylpyrrole **1a** gave smoothly the 1,3-dimethylpyrrolo[1,2-*a*]pyrazine **3a** as the sole reaction product in 1.5h, in good yield (Table 3, entry 1). Also internal alkynes gave preferentially the pyrrolo[1,2-*a*]pyrazine isomers **3** in good yields (Table 3, entries 2, 4, 6, 7, 9) but the reactions are in general more sluggish. For example, when pyrroles **1c** and **1f** were reacted under standard conditions for 1h and 2h respectively, both isomeric products **3** and **3'** were isolated beside a significant amount of starting material (Table 3, entries 3 and 8), whereas the reactions are almost complete after 6h (Table 3, entries 4 and 9). With respect to conventional heating however, microwaves proved again to increase both yields and selectivity in a reduced reaction time (Table 3, cfr. entries 4 and 5). The approach well tolerated the presence of electron-withdrawing groups (EWG) (Table 3, entries 4, 6 and 7) as well as electron-donating groups (EDG) (Table 3, entry 9) on the phenyl substituent bonded to propargyl moiety. Also a pyrimidine substituent was allowed (Table 3, entry 10), but after the standard reaction time a considerable amount of dihydro isomer **3'g** and starting product **1g** were recovered.

As already reported for the $TiCl_4$ promoted synthesis of pyrazino indoles,[8a] a plausible reaction mechanism involves a Lewis acid catalyzed formation of the imine intermediate that undergoes a stereoselective 6-*exo-dig* cyclization on the triple bond activated by $TiCl_4$ or by a catalytically active specie generated in situ from $TiCl_4$ and ammonia.[19] The annulation step give the 3,4-dihydropyrrolo[1,2-*a*]pyrazines **3'** that can isomerise to the thermodynamically more stable pyrrolo[1,2-*a*]pyrazines **3**. In confirmation of this, the dihydro isomers **3'** has been converted, in almost quantitative yields, to the corresponding fully conjugated isomers **3** under basic conditions, by treatment with NaOMe/MeOH 10% at the reflux temperature. [20] (Scheme 1)

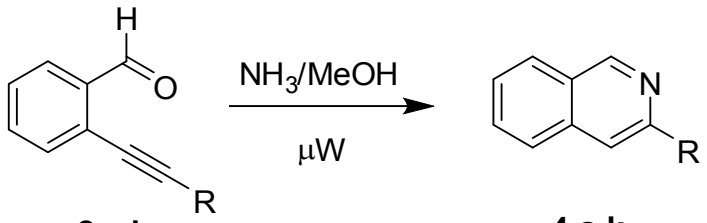


Scheme 1.

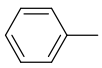
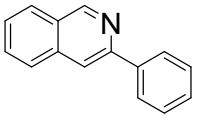
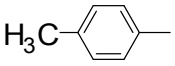
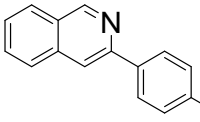
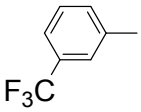
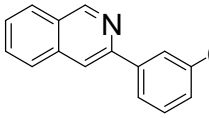
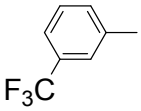
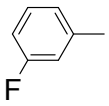
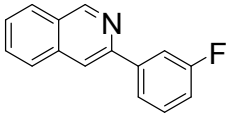
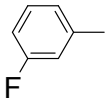
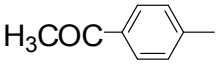
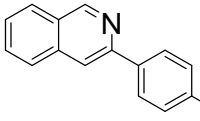
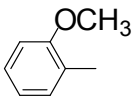
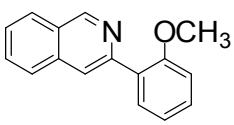
Then, we turned our attention to evaluating the reactivity of 2-alkynylbenzaldehydes **2.** The microwaves promoted imination/annulation reactions of compounds **2 a–k** in the presence of

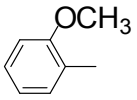
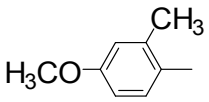
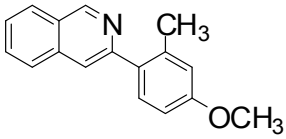
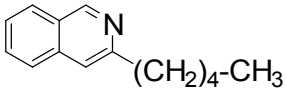
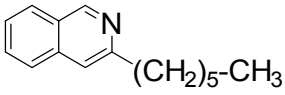
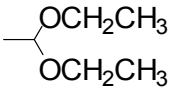
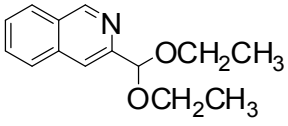
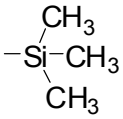
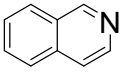
ammonia proceeded in a regiospecific 6-*endo-dig* mode and allows the synthesis of isoquinolines **4a–k** from moderate to excellent yields (Table 4). It is worth noting that four example of thermal annulation of *ortho*-alkynyl-benzaldehydes in the presence of ammonia have been yet reported eight years ago by Sakamoto and coll.[11d] Nevertheless, our investigation represent a more comprehensive study showing that microwaves heating gave comparable or better yields in reduced reaction times (Table 4).

Table 4. Imination/annulation reactions of 2-alkynylbenzaldehydes **2 a–k**.



2 a-k **4 a-k**

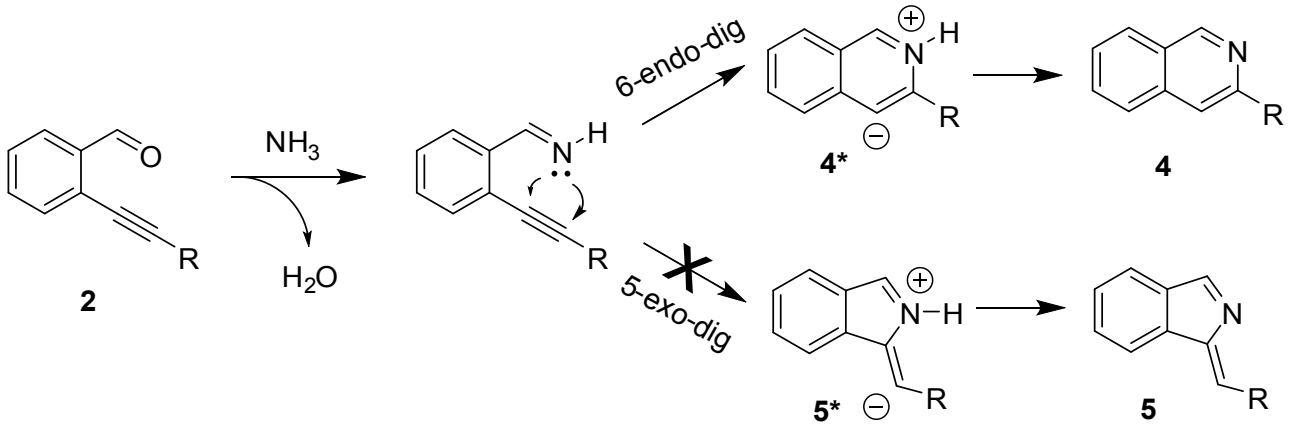
Entry	**2**	R	*T* (°C)	t (min)[a]	**4** (yield %)[b]
1	**2a**		130	30	 **4a** (58)
2	**2b**		130	30	 **4b** (71)
3	**2c**		130	30	 **4c** (28)[c]
4	**2c**		130	30[d]	**4c** (21) [c]
5	**2d**		130	60	 **4d** (38) [c]
6	**2d**		110	180[e]	**4d** (30) [c]
7	**2e**		130	30	 **4e** (25)
8	**2f**		130	30	 **4f** (32) [c]

9	**2f**		80	190	**4f** (31)
10	**2g**		130	30	 **4g** (76)
11	**2h**	$CH_3(CH_2)_4-$	130	30	 **4h** (87)
12	**2i**	$CH_3(CH_2)_5-$	130	15	 **4i** (89)
13	**2j**		130	15	 **4j** (50)
14	**2k**		130	15	 **4k** (48)

[a] Not including 11 min "ramp time" (≅ 10 °C/min). [b] Yields referred to pure isolated product. [c] Beside the main product, a complex mixture of unidentified by-products have been obtained. [d] $TiCl_4$ 3 eq. [e] Conventional heating (silicon oil bath).

Aldehydes **2a–j** reacted smoothly and quickly to give the corresponding 3-substituted isoquinolines in modest to good yields (Table 4, entries 1–13). The presence of EWG on the aryl moiety gave rise to low reaction yields (Table 4, entries 3–7), even after a prolonged reaction time under conventional heating conditions (Table 4, entry 5). It is worth noting that even $TiCl_4$ did not improve the reaction yield of these less reactive substrates (Table 4, entry 4). Also the presence of the bulky methoxy group in the *ortho*-position of the aryl moiety gave unsatisfactory results (Table 4, entry 8), even after a prolonged reaction time at a lower temperature (Table 4, entry 9). On the other hand, the smaller methyl group in the *ortho* position of the aryl moiety, as well as an aliphatic chain directly bonded to alkyne were well tolerated, yielding the corresponding isoquinolines in good yields (Table 4, entries 10-12). When the triple bond was substituted with an acetal moiety the reaction gave the corresponding isoquinoline **4j** in 50% yields (Table 4, entry 13). The acetal moiety was easily converted into the formyl group by treatment with *p*-TSA (5 mol-%) in water/acetone (1:1) at reflux giving rise to the intriguing isoquinoline-3-carbaldehyde **4l** in 98% yields**.** It is worth noting that this approach represent a valuable alternative to the synthesis of this useful derivative.[21] On the other hand, starting from 2-((trimethylsilyl)ethynyl)benzaldehyde **2k** the simple desililated isoquinoline **4k** was easily obtained in moderate yields (Table 4, entry 14).

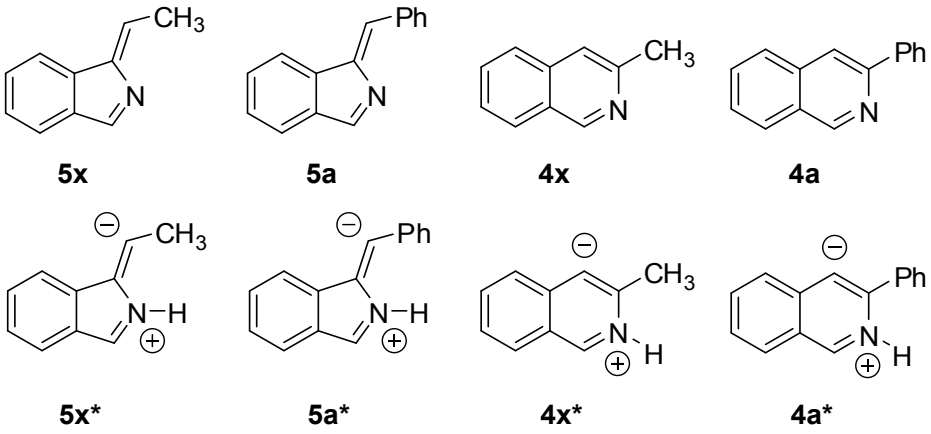
According to the literature,[7, 11d] the suggested mechanism involves the intermediacy of an imine that undergoes a regioselective 6-*endo* cyclization followed by a solvent promoted proton shift (Scheme 2). The product derived from a 5-*exo-dig* cyclization mode was never isolated or detected in the reaction crude. The regiospecificity achieved[22] is probably due to the stabilization of both the zwitterionic intermediate **4*** and the resulting isoquinoline **4** arising from a 6-*endo-dig* mechanism, with respect to the hypothetical intermediate **5*** and consequent isoindole **5** derived from a 5-*exo-dig* cyclization mode (Scheme 2). The formation of the 5-*exo* cyclization product **5** was never observed neither when the alkyne was substituted with an aromatic ring potentially able to stabilize the α-anion of the zwitterionic intermediate **5***.[23]



Scheme 2.

These statements were confirmed by the theoretical calculations performed on the model compounds 3-methyl-isoquinoline **4x** / 3-phenyl-isoquinoline **4a** and 1-ethylene isoindole **5x** / 1-benzylidene-isoindole **5a**, and together on the corresponding zwitterionic intermediates **4x***, **4a***, **5x***, **5a***. The minimisations were performed at the DFT level using the B3LYP functional and the 6-31+G(p) basis-set.[24] Calculations were performed on isolated molecules in the gas phase and the character of minima was confirmed by the absence of imaginary frequencies. Selected ΔE among isolated and hypothetical isomers and intermediate are reported in Table 5.

Table 5. Selected ΔE (kcal/mol) among isolated and hypothetical isomers and their intermediates.



Entry	Compounds	ΔE
1	**5x** – **4x**	20.64
2	**5a** – **4a**	16.82
3	**5x*** – **4x***	13.12
4	**5a*** – **4a***	8.21

As expected both the isoquinolines **4x** and **4a** are thermodynamically favoured with respect to the corresponding isoindoles **5x** and **5a** (Table 5, entries 1 and 2). Moreover the calculation confirmed that also for the zwitterionic intermediates this trend is preserved: both zwitterionic isoquinoline intermediates **4x*** and **4a*** are favoured with respect to the corresponding isoindole zwitterionic intermediates **5x*** and **5a*** (Table 5, entries 3 and 4). This theoretical results seems to confirm that, from a thermodynamic point of view, in these systems the stabilization of α-anion by the aryl substituent in **5a*** is less significant with respect to aromatic stabilization effect of conjugated bicyclic rings **4a***.[23]

The low yield observed in reaction of derivative **2e** is probably due to the negative effect of the steric hindrance of the *ortho*-methoxy group on the reaction (table 4, entry 7).[11k] On the other hand, against an almost quantitative conversion of starting material **2c–e** (Table 4, entries 3-5), the low yields of isoquinolines **4c–e** could be probably explained in view of the nature of the groups bonded to Cβ and their effect on the polarization of triple bond; [25] a rough qualitative analysis point out whereas an EDG is able to decrease the electron density around Cβ, and so to "activate" it towards a nucleophilic attack, an EWG increase the electron density around Cβ disfavouring the annulation step and allowing the setting up of undesired secondary reactions (Figure 1).

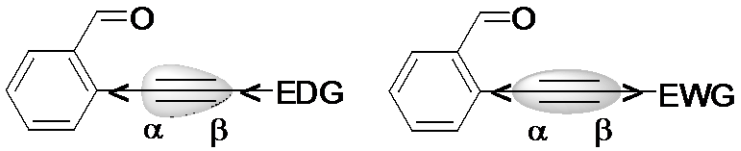


Figure 1. Qualitative estimation of influence of Cβ substituent on triple bond polarization.

To gain additional insight into this hypothesis we analyzed the chemical shifts of the *sp*-carbons[26] of the aldehydes **2b**, **2c**, **2e** and **2i** as examples of substrates characterized by the presence of different EDG and EWG on Cβ. To be sure to evaluate homogeneous data, all the NMR experiments were performed on the same 500 MHz NMR spectrometer. The unambiguous assignment of sp-carbons chemical shift has been obtained by means of two-dimensional HMBC and HSQC experiments. The results are depicted in figure 2.

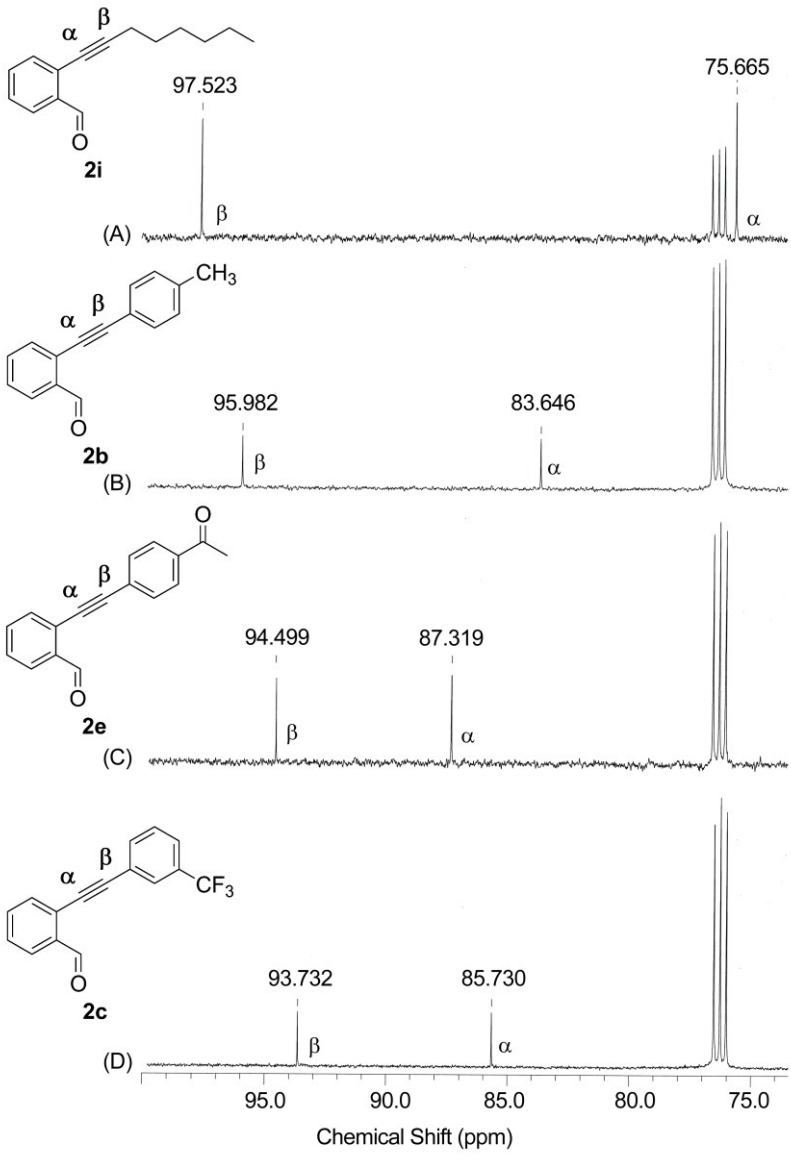


Figure 2. Experimental 13C NMR spectra of compounds **2b**, **2c**, **2e** and **2i**.

It is well known that one of the most important parameter determining the NMR chemical shift is the shielding effect determined by the electron density around the atomic nucleus. Moreover, the chemical shift may depend also by the presence of more or less proximate anisotropic groups[27] and for this reason we do not evaluated the chemical shift of those alkynyl-benzaldehydes bearing an ortho-substituted aryl on Cβ. Thus, taking into account that both the shielding cone of triple bond and the substituent on Cα are the same for all substrates **2**, the differences in Cα and Cβ chemical shift for compounds **2b**, **2c**, **2e** and **2i** are only related to the nature of the substituent bonded to Cβ. In accordance with our hypothesis, ^{13}C NMR spectra showed that EDG cause a deshielding of Cβ (Figure 2, (A) and (B)), therefore in compounds **2i** and **2a** Cβ is more prone to a nucleophilic attack. As result the imination/annulation reaction of aldehydes **2i** and **2a** gave the corresponding isoquinolines **4i** and **4a** in very good yields (89 % and 71% respectively). On the other hand, the presence of a EWG (Figure 2, (C) and (D)) increase the electron density on Cβ (testified by the chemical shift at lower frequencies), so the cyclization step for these compounds is more awkward and the yield of **4e** and **4c** are lower (25 % and 28 % respectively).

Conclusions

In summary we proved once again that the microwaves promoted domino imination/annulation reaction of alkynes bearing a proximate carbonyl group in the presence of ammonia is an useful tool for the synthesis of nitrogen heterocycles as pyrrolo[1,2-*a*]pyrazines and isoquinolines. Current efforts are now directed to improve the synthesis of isoquinolines by transforming the domino approach into a valuable multicomponent process starting from the simple building blocks as 2-bromobenzaldehyde, alkyne and ammonia.

Experimental Section

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/60A was employed for flash column chromatography. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer using KBr tablets for solids and NaCl disks for oils. Proton NMR spectra were recorded at room temperature in $CDCl_3$, at 200 or 500 MHz, with residual chloroform as the internal reference (δ_H = 7.27 ppm). ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ at 50.3 or 125.75 MHz, with the central peak of chloroform as the internal reference (δ_C = 77.3 ppm). The APT or DEPT sequences

were used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. Data for ^{1}H NMR are reported as follows: s = singlet, d =doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet, b = broad. Coupling constants (*J*) are reported as values in hertz. All ^{13}C NMR spectra were recorded with complete proton decoupling. Two-dimensional NMR experiments (NOESY and HMBC) were used, where appropriate, to aid in the assignment of signals in proton and carbon spectra. The ammonia in methanol 2M solution was purchased from standard chemical suppliers. Microwave assisted reactions were performed in a MILESTONE microSYNT multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with a fiber optic sensor. "EtOAc" means ethyl acetate and "TEA" means triethylamine.

General procedure for the synthesis of 2-acetyl-1-propargylpyrrole (1a).[10] To a well-stirred solution of 2-acetylpyrrole (2.00 g, 18.3 mmol), propargyl bromide (2.83 g, 23.8 mmol, corresponding to 3.54 g, 2.65 mL of 80% w/w toluene solution) and tetrabutylammoniumbromide (0.29 g, 0.9 mmol) in toluene (20 mL), a 50% w/v aqueous solution of sodium hydroxide (3.11 mL) was slowly added at room temperature. The reaction was vigorously stirred for 3 hours until no more starting product was detectable by TLC analysis. After that, the reaction mixture was diluted with toluene (15 mL) and washed with water (2 × 30 mL). The organic layer was dried over sodium sulfate and the solvent removed at reduced pressure. The resulting crude was purified by flash chromatography over a silica gel column (eluent: hexane/EtOAc/TEA 97:2:1) to afford 2.2 g of the desired product **1a** (82% yield). Yellow solid. Mp: 111–114 °C. IR (KBr): ν_{max} = 3258, 2121, 1407, 1239, 1086, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (m, 4H, C≡C–H and CH_3), 5.20 (d, *J* = 2.6 Hz, 2H, CH_2), 6.18 (dd, *J* = 4.0, 2.9 Hz, 1H, arom.), 6.98 (dd, *J* = 4.0, 1.8 Hz, 1H, arom.), 7.18 (dd, *J* = 2.9, 1.8 Hz, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.3, 39.0, 74.1, 78.5, 108.8, 120.8, 129.4, 130.2, 188.9 ppm. APCI(+)-MS *m/z* (%): 148 $[M + 1]^+$ (100).

General procedure for the synthesis of 2-acetyl-1-alkynylpyrroles 1b–g (Method A). Under a nitrogen atmosphere, to a solution of **1a** (200 mg, 1.36 mmol) in DMF (2 mL) the appropriate aryl halide (1.37 mmol), potassium carbonate (940 mg, 6.80 mmol), CuI (10.4 mg, 0.054 mmol) and tetrakis(triphenylphosphine)-palladium(0) (31.4 mg, 0.027 mmol) were added. The reaction was stirred at 60°C until no more starting product was detectable by TLC analysis. Then, the reaction mixture was diluted with HCl 0.1 M solution (60 mL) and extracted twice with ethyl acetate (2 × 50 mL). The organic layer, dried over sodium sulfate, was evaporated to dryness and the crude purified by flash chromatography over a silica gel column (for reaction times see table 1).

General procedure for the synthesis of 2-acetyl-1-alkynylpyrroles 1b–g (Method B). Under a nitrogen atmosphere, to a solution of **1a** (214 mg, 1.45 mmol) in TEA (5.8 mL, 4.5 mg, 42,1 mmol) the appropriate aryl halide (1.47 mmol), CuI (2.76 mg, 0.014 mmol) and *trans*-dichlorobis(triphenylphosphine)-palladium(II) (20.4 mg, 0.029 mmol) were added. The reaction was stirred at 60°C until no more starting product was detectable by TLC analysis. Then, the reaction mixture was filtered under reduced pressure and the crude was purified by flash chromatography over a silica gel column (for reaction times see table 1).

1-(1-(3-Phenyl-prop-2-ynyl)-1*H*-pyrrol-2-yl)-ethanone (1b). Eluent for chromatography: hexane/EtOAc (95:5). Method A: Yield 298 mg (98 %). Orange solid. Mp: 52–54 °C. IR (KBr): ν_{max} = 1643, 1572 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 6.21 (dd, J = 4.0, 2.6 Hz, 1H, arom.), 7.01 (dd, J = 4.0, 1.8 Hz, 1H, arom.), 7.30–7.34 (m, 4H, arom.), 7.43–7.47 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.4, 39.9, 83.7, 86.0, 108.7, 120.7, 122.6, 128.5, 128.8, 129.4, 130.3, 132.0, 188.9 ppm. ESI-MS m/z: 224 $[M + 1]^+$ (65), 182 (7). Calcd for $C_{15}H_{13}NO$ (223.27): C, 80.69; H, 5.87; N, 6.27. Found: C, 80.78; H, 5.84; N, 6.30.

1-(1-(3-(4-Chloro-phenyl)-prop-2-ynyl)-1*H*-pyrrol-2-yl)-ethanone (1c). Eluent for chromatography: hexane/EtOAc (95:5). Method A: Yield 259 mg (74 %). Method B: Yield 359 mg (96 %). Orange solid. Mp: 67–68 °C. IR (KBr): ν_{max} = 1645, 1571, 1523 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 6.21 (dd, J = 4.0, 2.9 Hz, 1H, arom.), 7.00 (dd, J = 4.2, 1.6 Hz, 1H, arom.), 7.24–7.39 (m, 5H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.4, 39.7, 84.7, 84.9, 108.8, 120.7, 121.1, 128.9, 129.4, 130.3, 133.3, 134.9, 188.8 ppm. ESI-MS m/z: 258 $[M + 1]^+$ (100), 216 (13). Calcd for $C_{15}H_{12}ClNO$ (257.71): C, 69.91; H, 4.69; N, 5.43. Found: C, 69.76; H, 4.64; N, 5.46.

1-(1-(3-(3-Trifluoromethyl-phenyl)-prop-2-ynyl)-1*H*-pyrrol-2-yl)-ethanone (1d). Eluent for chromatography: hexane/EtOAc (95:5). Method A: Yield 345 mg (87 %). Yellow oil. IR (neat): ν_{max} = 1646, 1529 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 6.21 (dd, J = 4.0, 2.6 Hz, 1H, arom.), 7.00 (dd, J = 4.0, 1.8 Hz, 1H, arom.), 7.21–7.23 (m, 1H, arom.), 7.40–7.44 (m, 1H, arom.), 7.53–7.60 (m, 2H, arom.), 7.68 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.3, 39.6, 84.1, 85.6, 108.9, 120.7, 123.6, 123.9 (q, $^1J_{C–F}$ = 272.4 Hz), 125.3 (q, $^3J_{C–F}$ = 3.8 Hz), 128.8 (q, $^3J_{C–F}$ = 3.8 Hz), 129.1, 129.5, 130.3, 131.1 (q, $^2J_{C–F}$ = 32.8 Hz), 135.1, 188.8 ppm. ESI-MS m/z: 292 $[M + 1]^+$ (100), 250 (7). Calcd for $C_{16}H_{12}F_3NO$ (291.27): C, 65.98; H, 4.15; N, 4.81. Found C, 65.87; H, 4.11; N, 4.84.

1-(1-(3-(4-Nitro-phenyl)-prop-2-ynyl)-1*H*-pyrrol-2-yl)-ethanone (1e). Eluent for chromatography: hexane/EtOAc (85:15). Method B: Yield 323 mg (83 %). Brown solid. Mp: 93–95 °C. IR (KBr): ν_{max} = 1635, 1593, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 6.23 (dd, *J* = 4.0, 2.6 Hz, 1H, arom.), 7.02 (dd, *J* = 4.0, 1.8 Hz, 1H, arom.), 7.19 (dd, *J* = 2.6, 1.8 Hz, 1H, arom.), 7.57 (d, *J* = 9.2 Hz, 2H arom.), 8.17 (d, *J* = 9.2 Hz, 2H arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.4, 39.6, 83.6, 89.4, 109.1, 120.8, 123.7, 129.5, 130.3, 132.8, 147.5, 188.9 ppm (one signal obscured). ESI-MS m/z: 269 $[M + 1]^+$ (20), 227 (5). Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44. Found: C, 66.97; H, 4.49; N, 10.45.

1-(1-(3-(4-Methoxy-phenyl)-prop-2-ynyl)-1*H*-pyrrol-2-yl)-ethanone (1f). Eluent for chromatography: hexane/EtOAc (95:5). Method A: Yield 327 mg (95 %). Light brown solid. Mp: 59–61 °C. IR (KBr): ν_{max} = 1640, 1606 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.44 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.41 (s, 2H, CH_2), 6.19 (dd, *J* = 4.0, 2.6 Hz, 1H, arom.), 6.82 (d, *J* = 8.8 Hz, 2H, arom.), 6.99 (dd, *J* = 4.0, 1.8 Hz, 1H, arom.), 7.31 (t, *J* = 2.0 Hz, 1H, arom.), 7.38 (d, *J* = 8.8 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.4, 39.9, 55.5, 82.3, 86.0, 108.6, 114.2, 114.7, 120.7, 129.4, 130.3, 133.5, 160.1, 188.8 ppm. ESI-MS m/z: 254 $[M + 1]^+$ (100), 212 (8). Calcd for $C_{16}H_{15}NO_2$ (253.30): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.81; H, 5.96; N, 5.53.

1-(1-(3-Pyrimidin-5-yl-prop-2-ynyl)-1*H*-pyrrol-2-yl)-ethanone (1g). Eluent for chromatography: hexane/EtOAc (8:2). Method A: Yield 254 mg (83 %). Brown solid. Mp: 97–99 °C. IR (KBr): ν_{max} = 1650, 1541, 1529 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 6.23 (dd *J* = 4.0, 2.6 Hz, 1H, arom.,), 7.01 (dd, *J* = 4.0, 1.8 Hz, 1H, arom.), 7.15 (t, *J* = 2.6 Hz, 1H, arom.), 8.75 (s, 2H, arom.), 9.12 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 27.4, 39.6, 78.6, 91.4, 109.2, 119.3, 120.8, 129.5, 130.3, 157.3, 159.2, 188.9 ppm. ESI-MS m/z: 226 $[M + 1]^+$ (100). Calcd for $C_{13}H_{11}N_3O$ (225.25): C, 69.32; H, 4.92; N, 18.66. Found: C, 69.22; H, 4.88; N, 18.69.

General Procedure for the synthesis of 2-alkynylbenzaldehydes 2a–j. Under a nitrogen atmosphere, to a solution of 2-bromobenzaldehyde (2.50 mmol) in TEA (10 mL) the appropriate alkyne (2.05 mmol) and *trans*-dichlorobis(triphenylphosphine)-palladium(II) (0.05 mmol) were added. The reaction was stirred at rt for 15 minutes, then CuI (0.025 mmol) was added. The reaction mixture was and stirred at 50 or 80°C (see table 2) until no more starting product was detectable by TLC analysis (eluent: hexane/EtOAc 95 : 5). Then, the solvent was evaporated under reduced pressure and the crude purified by flash chromatography over a silica gel column (for reaction times see table 2).

2-(Phenylethynyl)benzaldehyde (2a). Eluent for chromatography: hexane/EtOAc (99:1). Yield 469 mg (91 %). Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.36–7.67 (m, 8H, arom.), 7.95 (dd, J = 7.3, 1.0 Hz, 1H, arom.), 10.65 (s, 1H, CHO) ppm. These data are in good agreement with literature values.[11k, 12j]

2-(*p*-Tolylethynyl)benzaldehyde (2b). Eluent for chromatography: hexane/EtOAc (99:1). Yield 429 mg (78 %). Yellow solid. Mp 36–38 °C (lit. 38 °C).[28] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.42 (s, 3H, CH_3), 7.22 (d, J = 8.0 Hz, 2H, arom.), 7.46 (t, J = 7.6 Hz, 1H, arom.), 7.49 (d, J = 8.0 Hz, 2H, arom.), 7.60 (td, J = 7.6, 1.2 Hz, 1H, arom.), 7.66 (d, J = 7.3 Hz, 1H, arom.), 7.97 (dd, J = 7.7, 0.8 Hz, 1H, arom.), 10.68 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 20.8, 83.6, 96.0, 118.6, 126.5 (2C), 127.7, 128.6, 130.9, 132.5, 133.1, 135.1, 138.7, 191.1 ppm. These data are in good agreement with literature values.[11e]

2-((3-(Trifluoromethyl)phenyl)ethynyl)benzaldehyde (2c). Eluent for chromatography: hexane/EtOAc (99:1). Yield 505 mg (74 %). Yellow solid. Mp 45–48 °C. IR (KBr): ν_{max} = 2845, 2754, 1696, 1592, 1126 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.53 (t, J = 7.6 Hz, 1H, arom.), 7.62–7.71 (m, 3H, arom.), 7.77 (d, J = 7.7 Hz, 1H, arom.), 7.86 (s, 1H, arom.), 8.00 (dd, J = 7.8, 0.8 Hz, 1H, arom.), 10.66 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 85.7, 93.7, 122.7, 122.9 (q, $^1J_{C–F}$ = 272.6 Hz), 124.9 (q, $^3J_{C–F}$ = 3.8 Hz), 125.2, 126.9, 127.8 (q, $^3J_{C–F}$ = 3.8 Hz), 128.4, 128.5, 130.5 (q, $^2J_{C–F}$ = 32.7 Hz), 132.7, 133.1, 134.1, 135.3, 190.5 ppm. ESI-MS m/z: 275 $[M + 1]^+$ (100). Calcd for $C_{16}H_9OF_3$ (274.24): C, 70.07; H, 3.31. Found: C, 69.92; H, 3.28.

2-((3-Fluorophenyl)ethynyl)benzaldehyde (2d). Eluent for chromatography: hexane/EtOAc (99.5:0.5). Yield 488 mg (87 %). Deep yellow oil. IR (neat): ν_{max} = 2840, 1697, 1608, 1593, 1579, 1489, 1264, 1207, 1191, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.12 (m, 1H, arom.), 7.29 (m, 1H, arom.), 7.38 (m, 2H, arom.), 7.50 (t, J = 7.5 Hz, 1H, arom.), 7.62 (td, J = 7.7, 1.2 Hz, 1H, arom.), 7.68 (d, J = 7.4 Hz, 1H, arom.), 7.99 (d, J = 7.7 Hz, 1H, arom.),10.64 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 85.1, 94.1 (d, $^4J_{C–F}$ = 3.3), 115.7 (d, $^2J_{C–F}$ = 21.1), 117.7 (d, $^2J_{C–F}$ = 23.0), 123.5 (d, $^3J_{C–F}$ = 9.3), 125.5, 126.8, 126.9 (d, $^4J_{C–F}$ = 2.8), 128.3, 129.5 (d, $^3J_{C–F}$ = 8.7), 132.6, 133.1, 135.3, 161.7 (d, $^1J_{C–F}$ = 247.2), 190.7 ppm. ESI-MS m/z: 225 $[M + 1]^+$ (100). Calcd for $C_{15}H_9OF$ (224.23): C, 80.35; H, 4.05. Found: C, 80.29; H, 4.03.

2-((4-Acetylphenyl)ethynyl)benzaldehyde (2e). Obtained by reaction of 2-ethynylbenzaldehyde (150 mg, 1.15 mmol) with 4-iodoacetophenone (340 mg, 1.38 mmol) under the standard

Sonogashira conditions. Eluent for chromatography: hexane/EtOAc (95:5). Yield 240 mg (84 %). Pale yellow solid. Mp 106-108 °C. IR (KBr): ν_{max} = 1683, 1591, 1402, 1364, 1262, 961, 829, 759 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): δ = 2.16 (s, 3H, CH_3), 6.97 (t, J = 7.6 Hz, 1H, arom.), 7.04 (td, J = 7.5, 1.4 Hz, 1H, arom.), 7.41 (d, J = 8.4 Hz, 2H, arom.), 7.42 (t, J = 7.9 Hz, 1H, arom.), 7.76 (d, J = 8.3 Hz, 2H, arom.), 7.97 (dd, J = 7.8, 1.2 Hz, 1H, arom.), 10.78 (s, 1H, CHO) ppm. ^{13}C NMR (C_6D_6, 125.75 MHz): δ = 25.2, 87.4, 94.7, 125.0, 126.0, 127.4, 127.6, 128.2, 131.0, 132.4, 132.5, 135.8, 136.4, 189.2, 194.7 ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 25.9, 87.3, 94.5, 125.3, 126.4, 126.9, 127.7, 128.5, 131.1, 132.7, 133.1, 135.3, 136.1, 190.5, 196.4 ppm. ESI-MS m/z: 271 $[M + Na]^+$ (61), 249 $[M + 1]^+$ (100). Calcd for $C_{17}H_{12}O_2$ (248.28): C, 82.24; H, 4.87. Found: C, 82.29; H, 4.88.

2-((2-Methoxyphenyl)ethynyl)benzaldehyde (2f). Eluent for chromatography: hexane/EtOAc (98:2). Yield 349 mg (59 %). Yellow solid. Mp 77–80 °C. IR (KBr): ν_{max} = 2938, 2859, 2215, 1693, 1590, 1259 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.93 (s, 3H, CH_3), 6.91–7.01 (m, 2H, arom.), 7.25–7.68 (m, 5H, arom.), 7.95 (d, J = 7.7 Hz, 1H, arom.), 10.74 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 56.1, 89.3, 93.3, 110.9, 111.9, 120.8, 127.2, 127.6, 128.6, 130.8, 133.2, 133.5, 133.9, 136.1, 160.7, 192.8 ppm. ESI-MS m/z: 237 $[M + 1]^+$ (100). Calcd for $C_{16}H_{12}O_2$ (236.27): C, 81.34; H, 5.12. Found: C, 81.22; H, 5.10.

2-((4-Methoxy-2-methylphenyl)ethynyl)benzaldehyde (2g). Eluent for chromatography: hexane/EtOAc (99:1). Yield 565 mg (90 %). Yellow solid. Mp 72–74 °C. IR (KBr): ν_{max} = 2742, 2839, 2202, 1697, 1594, 1240 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.51 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.71–6.80 (m, 2H, arom.), 7.37–7.65 (m, 4H, arom.), 7.94 (m, 1H, arom.), 10.66 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.4, 55.5, 87.8, 95.9, 111.7, 114.6, 115.7, 127.4, 127.8, 128.3, 133.3, 133.8, 133.9, 135.7, 142.5, 160.4, 191.9 ppm. ESI-MS m/z: 251 $[M + 1]^+$ (100). Calcd for $C_{17}H_{14}O_2$ (250.29): C, 81.58; H, 5.64. Found: C, 81.50; H, 5.66.

2-(Hept-1-ynyl)benzaldehyde (2h). Eluent for chromatography: hexane/EtOAc (99:1). Yield 456 mg (91 %). Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.93 (t, J = 6.8 Hz, 3H, CH_3,), 1.25–1.71 (m, 6H, CH_2), 2.47 (t, J = 6.9 Hz, 2H, C_{sp}–CH_2,), 7.33–7.67 (m, 3H, arom.), 7.90 (m, 1H, arom.), 10.54 (s, 1H, CHO) ppm. These data are in good agreement with literature values.[29]

2-(Oct-1-ynyl)benzaldehyde (2i). Eluent for chromatography: hexane/EtOAc (99:1). Yield 488 mg (91 %). Yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.92 (t, J = 6.9 Hz, 3H, CH_3,), 1.31–1.38 (m, 4H, CH_2), 1.45–1.51 (m, 2H, CH_2), 1.65 (qt, J = 7.2 Hz, 2H, CH_2), 2.49 (t, J = 7.2 Hz, 2H, C_{sp}–

CH_2,), 7.38 (ddd, J = 8.0, 6.1, 2.7 Hz, 1H, arom.), 7.50–7.54 (m, 2H, arom.), 7.89 (d, J = 7.7 Hz, 1H, arom.), 10.56 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 13.3, 18.9, 21.8, 27.8, 27.9, 30.6, 75.64, 97.5, 126.2, 127.1, 127.3, 132.6, 132.9, 135.3, 191.4 ppm. These data are in good agreement with literature values.[30]

2-(3,3-Diethoxyprop-1-ynyl)benzaldehyde (2j). Eluent for chromatography: hexane/TEA (98:2). Yield 515 mg (89 %). Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.28 (t, 6H, CH_3, J = 7.0), 3.60–3.90 (m, 4H, CH_2), 5.54 (s, 1H, CH), 7.42–7.63 (m, 3H, arom.), 7.92 (m, 1H, arom.), 10.51 (s, 1H, CHO) ppm. These data are in good agreement with literature values.[31]

2-((Trimethylsilyl)ethynyl)benzaldehyde (2k). Eluent for chromatography: hexane/EtOAc (99:1). Yield 319 mg (63 %). Pale yellow solid. Mp 44-48 °C (lit. 50–52 °C). H NMR ($CDCl_3$, 200 MHz): δ = 0.27 (s, 9H, CH_3), 7.39–7.59 (m, 3H, arom.), 7.90 (m, 1H, arom.), 10.55 (s, 1H, CHO) ppm. These data are in good agreement with literature values.[32]

General procedure for microwave-assisted $TiCl_4$-catalyzed cyclization of 2-acetyl-1-alkynylpyrroles 1 a–g. In a sealed microwave test tube, to a solution of the appropriate pyrrole **1** (0.326 mmol) in dry ammonia in methanol (NH_3/MeOH 2M solution, 3.26 mL, 6.52 mmol) $TiCl_4$ (0.185 g, 0.107 mL, 0.978 mmol) was carefully added. The stirred reaction mixture was heated at 130°C in a multimode microwave oven until no more starting product was detectable by TLC. The reaction mixture was diluted with $NaHCO_3$ sat. solution (50 mL) and extracted with twice with ethyl acetate (2 × 50 mL). The organic layer, dried over sodium sulfate, was evaporated to dryness and the crude purified by flash chromatography over a silica gel column yielding progressively 3,4-dihydropyrazino(1,2-*a*)pyrroles **3'** and/or pyrazino(1,2-*a*)pyrroles **3** (for reaction times see table 3).

1,3-Dimethylpyrrolo(1,2-*a*)pyrazine (3a). Eluent for chromatography: hexane/EtOAc (95:5). Yield 39 mg (81 %). Brown wax. IR (neat): ν_{max} = 1722, 1650,1527, 1407 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.37 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.70 (d, J = 4.4 Hz, 1H, arom.), 6.76 (dd, J = 4.4, 2.5 Hz, 1H, arom.), 7.28 (dd, J = 2.5, 1.2 Hz, 1H, arom.), 7.53 (s, 1H, arom) ppm.^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 20.9, 21.7, 102.7, 113.6, 113.9, 114.7, 127.1, 134.8, 152.7, ppm. ESI-MS m/z: 147 $[M + 1]^+$ (100). Calcd for $C_9H_{10}N_2$ (146.19): C, 73.94; H, 6,89; N, 19.16. Found: C, 73.82; H, 6,85; N, 19.19. These data are in good agreement with literature values.[33]

3-Benzyl-1-methyl-pyrrolo(1,2-*a*)pyrazine (3b). Eluent for chromatography: hexane/EtOAc (95:5). Yield 48 mg (66 %). Brown oil. IR (neat): ν_{max} = 1618, 1519 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200

MHz): δ = 2.66 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 6.69–6.77 (m, 2H, arom.), 7.23–7.36 (m, 7H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.9, 41.6, 102.8, 114.2, 114.8, 115.3, 126.8, 127.4, 128.9, 129.7, 138.9, 139.5, 153.1 ppm. ESI-MS m/z: 223 $[M + 1]^+$ (100), 145 (9). Calcd for $C_{15}H_{14}N_2$ (222.28): C, 81.05; H, 6.35; N, 12.60. Found: C, 80.87; H, 6.28; N, 12.64.

3-(4-Chloro-benzyl)-1-methyl-pyrrolo(1,2-*a*)pyrazine (3c). Eluent for chromatography: hexane/EtOAc (95:5). Yield 61 mg (73 %). Brown oil. IR (neat): ν_{max} = 1621, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.64 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 6.69–7.20 (m, 2H, arom.), 7.21–7.35 (m, 6H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.8, 40.7, 102.9, 114.2, 114.6, 115.3, 127.2, 128.9, 130.8, 132.5, 137.9, 138.0, 153.2 ppm. ESI-MS m/z: 257 $[M + 1]^+$ (100), 145 (9). Calcd for $C_{15}H_{13}ClN_2$ (256.73): C, 70.18; H, 5.10; N, 10,91. Found: C, 70.00; H, 5.03; N, 10.94.

3-(1-(4-Chloro-phenyl)-meth-(*Z*)-ylidene)-1-methyl-3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'c). Eluent for chromatography: hexane/EtOAc (95:5). Yield 9 mg (10 %). Brown oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 5.96 (s, 1H, C_{sp2}–H), 6.22 (dd, J = 3.7, 2.6 Hz, 1H, arom.), 6.53 (dd, J = 4.0, 1.5 Hz, 1H, arom.), 6.80 (t, J = 1.5 Hz, 1H, arom.), 7.32 (d, J = 8.2 Hz, 2H, arom.), 7.82 (d, J = 8.2 Hz, 2H, arom.) ppm. We do not obtain a sufficient amount of **3'c** to perform IR, ^{13}C NMR, MS, and elemental analysis. Standing in a $CDCl_3$ solution, **3'c** partially isomerise into the more stable isomer **3c**.

1-Methyl-3-(3-trifluoromethyl-benzyl)-pyrrolo(1,2-*a*)pyrazine (3d). Eluent for chromatography: hexane/EtOAc (93:7). Yield 62 mg (65 %). Brown oil. IR (neat): ν_{max} = 1622, 1597, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.65 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 6.71–6.79 (m, 2H, arom.), 7.29–7.30 (m, 1H, arom.), 7.40–7.57 (m, 5H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.7, 41.0, 103.1, 114.3, 114.7, 115.4, 123.5 (q, $^3J_{C–F}$ = 3.8 Hz), 124.4 (q, $^1J_{C–F}$ = 272 Hz), 126.1 (q, $^3J_{C–F}$ = 3.8 Hz), 127.2, 129.1, 131.0 (q, $^2J_{C–F}$ = 32 Hz), 132.8, 137.4, 140.4, 153.3 ppm. ESI-MS m/z: 291 $[M + 1]^+$ (100), 145 (5). Calcd for $C_{16}H_{13}F_3N_2$ (290.28): C, 66.20; H, 4.51; N, 9.65. Found: C, 66.10; H, 4.47; N, 9.69.

1-Methtyl-3-(1-(3-trifluoromethyl-phenyl)-meth-(*Z*)-ylidene)-3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'd). Eluent for chromatography: hexane/EtOAc (93:7). Yield 16 mg (18 %). Brown oil. IR (neat): ν_{max} = 1661, 1564, 1558 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 4.74 (d, 2H, CH_2, J = 1.5 Hz), 6.03 (s, 1H, C_{sp2}–H), 6.24 (dd, J = 4.0, 2.6 Hz, 1H, arom.), 6.56 (dd, J = 4.0, 1.5 Hz, 1H, arom.), 6.83 (dd, J = 2.6, 1.5 Hz, 1H, arom.), 7.42–7.45 (m, 2H, arom.), 8.00–8.04 (m, 1H, arom.), 8.23 (s, 1H, arom.) ppm. ESI-MS m/z: 291 $[M + 1]^+$ (100). We do not obtain a

sufficient amount of **3'd** to perform ^{13}C NMR, and elemental analysis. Standing in a $CDCl_3$ solution **3'd** partially isomerise into the more stable isomer **3d**.

3-(4-Nitro-benzyl)-1-methyl-pyrrolo(1,2-*a*)pyrazine (3e). Eluent for chromatography: hexane/EtOAc (8:2). Yield 82 mg (84 %). Brown solid. Mp: 122–124 °C. IR (KBr): ν_{max} = 1603, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.64 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 6.73–6.81 (m, 2H, arom.), 7.30–7.32 (m, 1 H, arom.), 7.44–7.48 (m, 3H, arom.), 8.14–8.19 (m, 2 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.8, 41.0, 103.2, 114.5, 114.9, 115.4, 123.9, 127.2, 130.1, 136.6, 146.9, 147.5, 153.5 ppm. ESI-MS m/z: 268 $[M + 1]^+$ (100), 222 (5). Calcd for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.28; H, 4.86; N, 15.78.

3-(4-Methoxy-benzyl)-1-methyl-pyrrolo(1,2-*a*)pyrazine (3f). Eluent for chromatography: hexane/EtOAc (95:5). Yield 59 mg (72 %). Yellow oil. IR (neat): ν_{max} = 1615, 1584, 1512 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.65 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.97 (s, 2H, CH_2), 6.68–6.76 (m, 2H, arom.), 6.84–6.91 (m, 2H, arom.), 7.21–7.26 (m, 3H, arom.), 7.29 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.9, 40.7, 55.7, 102.8, 114.2, 114.4, 114.7, 115.3, 127.4, 130.7, 131.5, 139.3, 153.0, 158.7 ppm. ESI-MS m/z: 253 $[M + 1]^+$ (100), 145 (15). Calcd for $C_{16}H_{16}N_2O$ (252.31): C, 76.16; H, 6.39; N, 11.10. Found: C, 76.06; H, 6.32; N, 11.12.

3-(1-(4-Methoxy-phenyl)-meth-(*Z*)-ylidene)-1-methyl-3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'f). Eluent for chromatography: hexane/EtOAc (95:5). Yield 22 mg (26 %). Yellow oil. IR (neat): ν_{max} = 1601, 1558, 1531 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.44 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2), 5.97 (s, 1H, C_{sp2}–H), 6.20–6.23 (m, 1H, arom.), 6.49–6.50 (m, 1H, arom.), 6.78–6.80 (m, 1H, arom.), 6.87 (d, J = 8.8 Hz, 2H, arom.), 7.84 (d, J = 8.8 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 22.3, 29.9, 47.7, 55.5, 109.6, 110.4, 113.8, 121.6, 124.1, 126.0, 131.8, 136.6, 155.9, 158.8 ppm. ESI-MS m/z: 253 $[M + 1]^+$ (100), 238 (5), 145 (5). Calcd for $C_{16}H_{16}N_2O$ (252.31): C, 76.16; H, 6.39; N, 11.10. Found: C, 75.99; H, 6.31; N, 11.10.

1-Methyl-3-pyrimidin-5-ylmethyl-pyrrolo(1,2-*a*)pyrazine (3g). Eluent for chromatography: hexane/EtOAc (8:2). Yield 26 mg (35 %). Orange solid. Mp: 87–89 °C. IR (KBr): ν_{max} = 1622, 1564, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.63 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 6.72–6.81 (m, 2H, arom.), 7.31–7.33 (m, 1H, arom.), 7.54 (s, 1H, arom.), 8.72 (s, 2H, arom.), 9.10 (s, 1H, arom.) ppm.^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.7, 35.9, 103.5, 114.6 (2C), 115.6, 127.1, 133.1, 135.7, 153.7, 157.3, 157.5. ESI-MS m/z: 225 $[M + 1]^+$ (100), 145 (8). Calcd for $C_{13}H_{12}N_4$ (224.26): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.64; H, 5.35; N, 25.10.

1-Methyl-3-(1-pyrimidin-5-yl-meth-(*Z*)-ylidene)--3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'g). Eluent for chromatography: hexane/EtOAc (8:2). Yield 29 mg (40 %). Brown solid. Mp: 100–102 °C. IR (KBr): ν_{max} = 1622, 1572, 1560, 1547 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 5.89 (s, 1H, C_{sp2}–H), 6.25 (dd, *J* = 3.7, 2.6 Hz, 1H, arom.), 6.59 (dd, *J* = 3.7, 1.5 Hz, 1H, arom.), 6.85 (dd, *J* = 2.2, 1.5 Hz, 1H, arom.), 9.01 (s, 1H, arom.), 9.21 (s, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 22.3, 47.2, 110.3, 111.9, 114.3, 125.2, 125.5, 130.8, 142.9, 156.2, 157.4 (2C), 158.4 ppm. ESI-MS m/z: 225 $[M + 1]^+$ (100), 198 (8), 145 (8). Calcd for $C_{13}H_{12}N_4$ (224.26): C, 69.62; H, 5.39; N, 24.98. Found: , 69.58; H, 5.37; N, 24.96.

General procedure for the microwave assisted cyclizations of *o*-alkynylbenzaldehydes 2a–j. A stirred solution of the appropriate *o*-alkynylbenzaldehyde **2 a–k** (0.5 mmol) in dry ammonia in methanol (NH_3/MeOH 2M solution, 5 mL) was heated at 110–130 °C in a sealed tube for 25–300 min in a multimode microwave oven, until no more starting product was detectable by TLC. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography over silica gel column yielding the isoquinolines **4** (for temperatures, times and yields see table 4).

3-Phenylisoquinoline (4a). Eluent for chromatography: hexane/EtOAc (95:5). Yield 60 mg (58 %). Brown solid. Mp 100–102 °C (lit.[11e] 101–101.5 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.38–7.79 (m, 4H, arom.), 7.70 (dt, *J* = 6.6, 1.5 Hz, 1H, arom.), 7.88 (d, *J* = 8.4 Hz, 1H, arom.), 8.00 (d, *J* = 8.4 Hz, 1H, arom.) 8.08 (s, 1H, arom.), 8.13 (d, *J* = 7.1 Hz, 2H, arom.), 9.35 (s, 1H, arom.) ppm. These data are in good agreement with literature values.[11e]

3-*p*-Tolylisoquinoline (4b). Eluent for chromatography: hexane/EtOAc (95:5). Yield 78 mg (71 %). Brown solid. Mp 74–76 °C (lit.[11e] 74–75 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3H, CH_3), 7.32 (d, *J* = 7.9 Hz, 2H, arom.), 7.53 (t, *J* = 8.0 Hz, 1H, arom.), 7.68 (s, *J* = 8.0 Hz, 1H, arom.), 7.86 (d, *J* = 8.1 Hz, 1H, arom.), 7.96 (d, *J* = 8.2 Hz, 1H, arom.), 8.05 (m, 3H, arom.), 9.33 (s, 1H, arom.) ppm. These data are in good agreement with literature values.[11e]

3-(3-(Trifluoromethyl)phenyl)isoquinoline (4c). Eluent for chromatography: hexane/EtOAc (95:5). Yield 38 mg (28 %). Light brown solid. Mp 64–67. IR (KBr): ν_{max} = 1625, 1325, 1178, 1109, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.58–7.77 (m, 4H, arom.), 7.90 (d, *J* = 8.2 Hz, 1H, arom.), 8.01 (d, *J* = 8.2 Hz, 1H, arom.), 8.11 (s, 1H, arom.), 8.32 (d, *J* = 7.0 Hz, 1H, arom.), 8.42 (s, 1H, arom.), 9.35 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 117.1, 124.0 (q,

$^{3}J_{C–F}$ = 3.8 Hz), 124.5 (q, $^{1}J_{C–F}$ = 272.0 Hz), 125.3 (q, $^{3}J_{C–F}$ = 3.8 Hz), 127.2, 127.8, 127.9, 128.3, 129.5, 130.3, 131.0, 131.4 (q, $^{2}J_{C–F}$ = 32.4 Hz), 136.7, 140.6, 149.8, 152.9 ppm. ESI-MS m/z: 274 $[M + 1]^+$ (100). Calcd for $C_{16}H_{10}NF_3$ (273.25): C, 70.33; H, 3.69; N, 5.13. Found: C, 70.23; H, 3.61; N, 5.16.

3-(3-Fluorophenyl)isoquinoline (4d). Eluent for chromatography: hexane/EtOAc (95:5). Yield 42 mg (38 %). Brown solid. Mp 105–109. IR (KBr): ν_{max} = 1624, 1573, 1494, 1452, 1158, 875, 792, 746, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.11 (tdd, J = 8.3, 2.5, 0.8 Hz, 1H, arom.), 7.46 (td, J = 8.0, 6.0 Hz, 1H, arom.), 7.56–7.75 (m, 2H, arom.), 7.83–7.92 (m, 3H, arom.), 8.00, (d, J = 8.0 Hz, 1H, arom.), 8.05 (s, 1H, arom.), 9.33 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 114.1 (d, $^{2}J_{C–F}$ = 22.8 Hz), 115.5 (d, $^{2}J_{C–F}$ = 21.4 Hz), 117, 122.7 (d, $^{4}J_{C–F}$ = 2.8 Hz), 127.2, 127.6, 127.8, 128.2, 130.4 (d, $^{3}J_{C–F}$ = 8.2 Hz), 130.9, 136.7, 142.2 (d, $^{3}J_{C–F}$ = 7.7 Hz), 150.1 (d, $^{4}J_{C–F}$ = 2.7 Hz), 152.7, 163.6 (d, $^{1}J_{C–F}$ = 245 Hz) ppm. ESI-MS m/z: 224 $[M + 1]^+$ (100). Calcd for $C_{15}H_{10}NF$ (223.25): C, 80.70; H, 4.51; N, 6.27. Found: C, 80.62; H, 4.48; N, 6.29.

3-(4-Acethylphenyl)isoquinoline (4e). Eluent for chromatography: hexane/EtOAc (85:15). Yield 31 mg (25 %). Orange solid. Mp 150-152. IR (KBr): ν_{max} = 2956, 2924, 2853, 1670, 1599, 1353, 1263, 855, 832, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.67 (s, 3H, CH_3), 7.63 (ddd, J = 8.1, 6.7, 1.2 Hz, 1H, arom.), 7.73 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H, arom.), 7.90 (d, J = 8.1 Hz, 1H, arom.), 8.02 (d, J = 8.4 Hz, 1H, arom.), 8.09 (d, J = 8.6 Hz, 2H, arom.), 8.15 (s, 1H, arom.), 8.25 (d, J = 8.6 Hz, 2H, arom.), 9.36 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 26.9, 117.7, 127.2, 127.3, 127.8, 127.9, 128.3, 129.1, 131.0, 136.7, 137.0, 144.1, 150.1, 152.9, 198.1 ppm. ESI-MS m/z: 248 $[M + 1]^+$ (100). Calcd for $C_{17}H_{13}NO$ (247.29): C, 82.57; H, 5.30; N, 5.66. Found: C, 82.69; H, 5.29; N, 5.69.

3-(2-Methoxyphenyl)isoquinoline (4f). Eluent for chromatography: hexane/EtOAc (95:5). Yield 38 mg (32 %). Red oil. IR (neat): ν_{max} = 1626, 1599, 1573, 14932, 1466, 1439, 1278, 1235, 1022, 755, 754, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.91 (s, 3H, CH_3), 7.05 (dd, J = 8.3, 0.9 Hz, 1H, arom.), 7.13 (td, J = 7.5, 1.1 Hz, 1H, arom.), 7.39 (ddd, J = 8.2, 7.4, 1.8 Hz, 1H, arom.), 7.57 (ddd, J = 8.6, 6.8, 1.4 Hz, 1H, arom.) 7.68 (ddd, J = 8.2, 6.7, 1.4 Hz, 1H, arom.), 7.86 (d, J = 8.2 Hz, 1H, arom.), 7.93 (dd, J = 7.6, 1.8 Hz, 1H, arom.), 7.98 (d, J = 8.0 Hz, 1H,), 8.21 (s, 1H, arom.), 9.35 (s, 1H, arom.) ppm. ^{13}C NMR (C_6D_6, 50.3 MHz): δ = 55.1, 111.7, 121.2, 126.6, 127.1, 127.7, 128.2, 129.4, 129.7, 129.8, 132.3, 136.4, 149.7, 152.1, 157.7 ppm (one signal obscured). ESI-MS m/z: 236 $[M + 1]^+$ (100), 221 (19). Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.74; H, 5.58; N, 5.95.

3-(4-Methoxy-2-methylphenyl)isoquinoline (4g). Eluent for chromatography: hexane/EtOAc (95:5). Yield 95 mg (76 %). Red oil. IR (neat): ν_{max} = 1625, 1607, 1580, 1504, 1451, 1295, 1275, 1241, 1162, 1055, 752 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz): δ = 2.48 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 6.78 (dd, *J* = 8.4, 2.5 Hz, 1H, arom.), 6.86 (d, *J* = 2.5 Hz, 1H, arom.), 7.10 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H, arom.), 7.21 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H, arom.), 7.36–7.55 (m, 4H, arom.), 9.19 (s, 1H, arom.) ppm. ^{13}C NMR (C_6D_6, 50.3 MHz): δ = 21.2, 54.7, 111.5, 116.6, 119.7, 126.6, 126.7, 127.3, 127.5, 130.0, 131.9, 133.9, 136.5, 138.2, 151.8, 154.6, 159.9 ppm. ESI-MS m/z: 250 $[M + 1]^+$ (100). Calcd for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.79; H, 6.00; N, 5.68.

3-Pentylisoquinoline (4h). Eluent for chromatography: hexane/EtOAc (95:5). Yield 87 mg (87 %). Yellow oil. IR (neat): ν_{max} = 2955, 2928, 2857, 1630, 1591, 1456, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, *J* = 7.0 Hz, 3H, CH_3), 1.26–1.42 (m, 4H, CH_2), 1.74–1.89 (m, 2H, CH_2), 2.92 (t, *J* = 7.3 Hz, 2H, CH_2), 7.45 (s, 1H, arom.) 7.50 (ddd, *J* = 8.1, 7.0, 1.5 Hz, 1H, arom.), 7.62 (ddd, *J* = 8.1, 6.6, 1.5 Hz, 1H, arom.), 7.74 (d, *J* = 8.1 Hz, 1H, arom.), 7.90 (d, *J* = 8.1 Hz, 1H, arom.), 9.19 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 14.2, 22.8, 29.9, 31.9, 38.3, 118.2, 126.3, 126.4, 127.3, 127.7, 130.4, 136.8, 152.5, 156.1 ppm. ESI-MS m/z: 200 $[M + 1]^+$ (100), 143 (10). Calcd for $C_{14}H_{17}N$ (199.29): C, 84.37; H, 8.60; N, 7.03. Found: C, 84.19; H, 8.53; N, 7.09.

3-Hexylisoquinoline (4i). Eluent for chromatography: hexane/EtOAc (95:5). Yield 95 mg (89 %). Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 1.23–1.46 (m, 6H, CH_2), 1.81 (m, 2H, CH_2), 2.93 (t, *J* = 7.3 Hz, 2H, CH_2), 7.46 (s, 1H, arom.) 7.51 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H, arom.), 7.63 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H, arom.), 7.74 (d, *J* = 8.2 Hz, 1H, arom.), 7.92 (d, *J* = 8.1 Hz, 1H, arom.) 9.20 (s, 1H, arom.) ppm. These data are in good agreement with literature values.[11d]

3-(Diethoxymethyl)isoquinoline (4j).[34] Eluent for chromatography: hexane/TEA (96:4). Yield 56 mg (50 %). Red oil. IR (neat): ν_{max} = 2975, 2928, 2879, 1694, 1629, 1590, 1441, 1386, 1370, 1345, 1170, 1129, 1107, 1060, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.24 (t, *J* = 7.1 Hz, 6H, CH_3,), 3.67 (dq, ABX_3 system, *J* = 9.5, 7.1 Hz, 2H, CH_2,), 3.74 (dq, ABX_3 system, *J* = 9.5, 7.1 Hz, 2H, CH_2), 5.69 (s, 1H, CH), 7.60 (ddd, *J* = 8.0, 6.9, 1.6 Hz, 1H, arom.), 7.70 (ddd, *J* = 8.3, 6.9, 1.6 Hz, 1H, arom.), 7.87 (dd, *J* = 8.0, 0.8 Hz, 1H, arom.), 7.95–8.00 (m, 2H, arom.), 9.26 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.5. 62.2, 102.6, 117.9, 127.3, 127.6, 127.7, 128.6, 130.7, 136.4, 151.7, 152.4 ppm. ESI-MS m/z: 232 $[M + 1]^+$ (64), 218 (52), 186 (100), 172 (18), 158 (33). Calcd for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.60; H, 7.36; N, 6.09.

Isoquinoline-3-carbaldehyde (4l). A mixture of **4j** (46 mg, 0.20 mmol) and *p*-TSA (1.9 mg, 0.01 mmol) in H_2O/acetone (1:1) (1.5 mL) was heated at reflux for 70 min. After this had cooled to room temp., satd. aqueous $NaHCO_3$ (5 mL) was added and the solution was extracted with diethyl ether (4× 5 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4) and the solvent evaporated at reduced pressure yielding pure **4k** (31 mg, 98 %). Brown solid. Mp 45–47 (lit.[21c] 49.6–50 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.81 (m, 2H, arom.), 8.06 (m, 2H, arom.), 8.40 (s, 1H, arom.), 9.38 (s, 1H, arom.), 10.27 (s, 1H, CHO) ppm. These data are in good agreement with literature values.[21c]

Computational Methods

The structures of compounds **4x**, **4a**, **5x** and **5a** intermediates **4x***, **4a***, **5x*** and **5a*** were optimised at DFT level (B3LYP/) with Gaussian03® using default options.[35] The hybrid functional B3LYP was chosen as it generally performs well on organic molecules and the split valence 6-31+G(p) basis set was employed as a good compromise between speed and accuracy.[24] The character of optimised geometries was confirmed by the absence of imaginary frequencies. All calculations were carried out assuming isolated molecules in the gas phase.

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