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Microwave-Promoted Synthesis of *N*-Heterocycles by Tandem Imination/Annulation of γ- and δ-Ketoalkynes in the Presence of Ammonia

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The synthesis of 3-substituted 1-methylpyrrolo[1,2-*a*]pyrazines and 3-substituted isoquinolines was achieved by the intramolecular cyclisation of 2-acetyl-1-propargylpyrroles and 2-alkynylbenzaldehydes, respectively, in the presence of ammonia under microwave heating. The tandem imination/annulation of 2-alkynylbenzaldehydes 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 calculations 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 atom economy[3] concept of Trost, 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, the 5-*exo*-*dig* cyclisation of 4-pentynones[5] gave polysubstituted and fused pyrrole derivatives, whereas the presence of a γ-ketoalkyne moiety in an aromatic framework is responsible for the 6-*endo*-*dig* cyclisation 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 the 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 selectivities were unsatisfactory using 2-acetyl-*N*-propargylindoles.[8b] Moreover, the reaction totally failed with 2-benzoyl-*N*-propargylindoles. These drawbacks were overcome when we found that 3 equiv. of $TiCl_4$ and microwave heating were able to improve both the yield and selectivity in the reactions of these less reactive substrates with a widespread reduction of reaction times.[8a]

The aim of the present work is to explore the suitability of this approach for the construction of some other remarkable heterocyclic targets. In particular, we focused our attention on the synthesis of simple pyrrolo[1,2-*a*]pyrazines and isoquinolines starting from 2-acetyl-*N*-propargylpyrroles and 2-alkynylbenzaldehydes, respectively. In the literature, there are only a few papers dealing with the reactivity of *N*-propargylpyrrole-2-carbaldehydes as building blocks for the synthesis of simple and polycyclic pyrrolizine derivatives,[9] whereas the reactivity of 2-acetyl-*N*-propargylpyrroles 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] skeletons starting directly from 2-acyl-phenylacetylenes[11a–11f,12a–12i] or their imine derivatives[11g–11q,12j–12o] 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-methylpyrido[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 anti-allergic 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 papaver-

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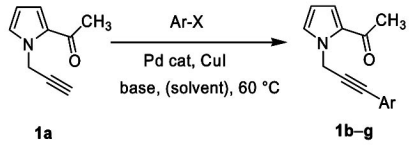
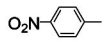
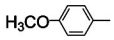
ine and local anaesthetics such as quinisocaine, whereas saturated, functionalized and polycyclic derivatives are known to show different important pharmacological properties.[18]

Results and Discussion

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

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



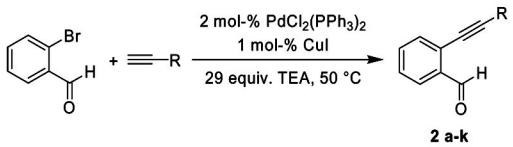
Ar–	X	Method[a]	*t* [h]	Product	% Yield[b]
	I	A	4.5	**1b**	98
	I	A	4	**1c**	74
	I	B	4.5	**1c**	96
	I	A	3	**1d**	87
	I	B	4.5	**1e**	83
	I	A	1	**1f**	95
	Br	A	4	**1g**	83

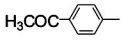
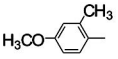
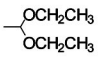
[a] Method A: mole ratio **1a**/Ar-X/K_2CO_3/Pd$(PPh_3)_4$/CuI = 1:1.01:5:0.02:0.04, DMF (2 mL), 60 °C. Method B: mole ratio **1a**/Ar-X/TEA/$PdCl_2(PPh_3)_4$/CuI = 1:1.01:29:0.02:0.01, 60 °C. [b] Yields refer to pure isolated product.

Through a similar approach, we synthesized 2-alkynylbenzaldehydes **2a**–**k** in moderate to excellent yields starting from commercially available 2-bromobenzaldehyde and selected terminal acetylenes (Table 2).

Our initial studies focused on the possibility of obtaining the pyrrolo[1,2-*a*]pyrazine nucleus starting from the *N*-alkynylpyrroles **1a**–**g**. Following the procedure previously optimised for the imination/annulation of 2-acetyl and 2-benzoyl *N*-alkynylindoles,[8a] we dissolved alkynylpyrroles **1a**–**g** in 2 M ammonia in methanol (20 equiv. of NH_3) in a sealed microwave test tube. Three equiv. of $TiCl_4$ 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 dihydropyrrolo[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 2. Preparation of 2-alkynylbenzaldehydes **2a**–**k**.



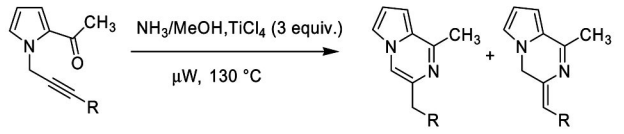
R	*t* [h]	Product	% Yield[a]
	1	**2a**	91
	4	**2b**	78
	6	**2c**	74
	6	**2d**	87
	2	**2e**	84[b]
	7	**2f**	59
	4.5	**2g**	90
$CH_3(CH_2)_4$–	4	**2h**	91
$CH_3(CH_2)_5$–	2	**2i**	91
	4	**2j**	89
	2.5	**2k**	63

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

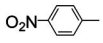
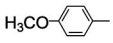
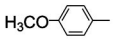
The reaction of 2-acetyl-*N*-propargylpyrrole (**1a**) gave smoothly the 1,3-dimethylpyrrolo[1,2-*a*]pyrazine **3a** as the sole reaction product in 1.5 h in good yield (Table 3, Entry 1). Internal alkynes also gave preferentially the pyrrolo[1,2-*a*]pyrazine isomers **3** in good yields (Table 3, Entries 2, 4, 6, 7 and 9), but the reactions were in general more sluggish. For example, when pyrroles **1c** and **1f** were reacted under standard conditions for 1 h and 2 h, 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 were almost complete after 6 h (Table 3, Entries 4 and 9). With respect to conventional heating, however, microwave irradiation increased both the yield and selectivity in a reduced reaction time (Table 3, Entries 4 and 5). The approach tolerated well the presence of electron-withdrawing groups (EWGs, Table 3, Entries 4, 6 and 7) and electron-donating groups (EDGs, Table 3, Entry 9) on the phenyl substituent bonded to the propargyl moiety. A pyrimidine substituent was also allowed, but after the standard reaction time, we recovered a considerable amount of dihydro isomer **3′g** and starting material **1g** (Table 3, Entry 10).

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 inter-

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

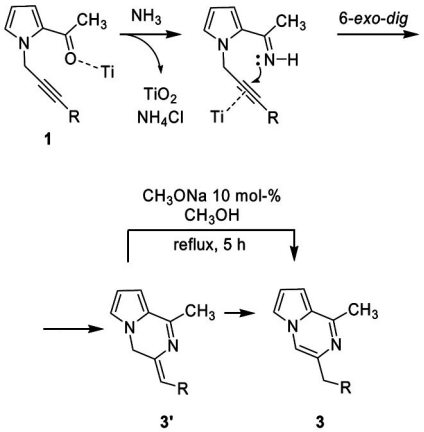


1a–g **3a–g** **3'a–g**

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)	**1g** (20)

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

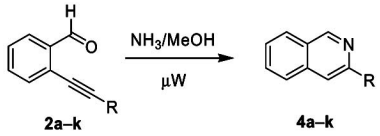
mediate, which undergoes a stereoselective 6-*exo*-*dig* cyclisation on the triple bond activated by $TiCl_4$ or by a catalytically active species generated in situ from $TiCl_4$ and ammonia.[19] The annulation step gives the 3,4-dihydropyrrolo[1,2-*a*]pyrazines **3′**, which can isomerise to the thermodynamically more stable pyrrolo[1,2-*a*]pyrazines **3** (Scheme 1). In confirmation of this, we converted the dihydro isomers **3′**, in almost quantitative yields, to the corresponding fully conjugated isomers **3** under basic conditions by treatment with NaOMe/MeOH (10%) at reflux.[20] (Scheme 1).



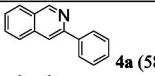
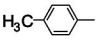
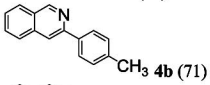
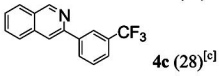
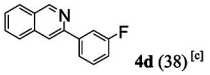
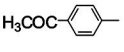
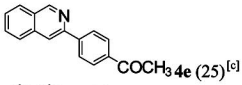
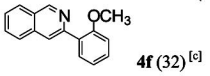
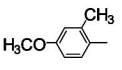
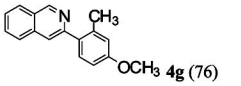
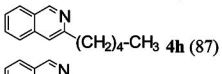
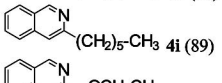
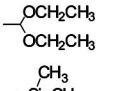
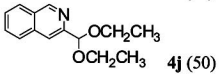
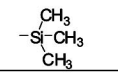
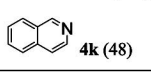
Scheme 1.

We then turned our attention to evaluating the reactivity of 2-alkynylbenzaldehydes **2**. The microwave-promoted imination/annulation of **2a**–**k** in the presence of ammonia proceeded in a regiospecific 6-*endo*-*dig* mode and allowed for the synthesis of isoquinolines **4a**–**k** in moderate to excellent yields (Table 4). Four examples of the thermal annulation of *o*-alkynylbenzaldehydes in the presence of ammonia were reported eight years ago by Sakamoto et al.[11d] Nevertheless, our investigation represents a more comprehensive study showing that microwave heating gives comparable or better yields in reduced reaction times than does conventional heating.

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



2a–k **4a–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)[c]
8	2f		130	30	 **4f** (32)[c]
9	2f		80	190	**4f** (31)[c]
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)

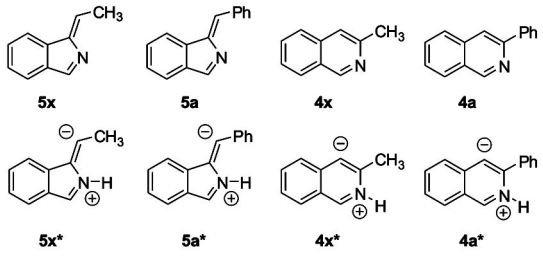
[a] Not including an 11 min "ramp time" (ca. 10 °C/min). [b] Yields refer to pure isolated product. [c] Besides the main product, a complex mixture of unidentified by-products was obtained. [d] $TiCl_4$ (3 equiv.). [e] Conventional heating (silicone oil bath).

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 EWGs 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 6). We note 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% yield (Table 4, Entry 13). We easily converted the acetal moiety into the formyl group by treatment with *p*-toluenesulfonic acid (*p*-TsA, 5 mol-%) in water/acetone (1:1) at reflux giving rise to the intriguing isoquinoline-3-carbaldehyde **4l** in 98% yield. It is worth noting that this approach represents a valuable alternative to the synthesis of this useful derivative.[21] On the other hand, starting from 2-[(trimethylsilyl)ethynyl]benzaldehyde (**2k**), the simple desilylated isoquinoline **4k** was easily obtained in moderate yield (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* cyclisation followed by a solvent-promoted proton shift (Scheme 2). We never isolated or detected in the reaction crude the product derived from a 5-*exo-dig* cyclisation mode. The regiospecificity achieved[22] is probably due to the zwitterionic intermediate **4*** and the resulting isoquinoline **4**, arising from a 6-*endo-dig* mechanism, being more thermodynamically stable than the hypothetical intermediate **5*** and consequent isoindole **5**, derived from a 5-*exo-dig* cyclisation mode (Scheme 2). We never observed the formation of the 5-*exo* cyclisation product **5**, even when the alkyne was substituted with an aromatic ring potentially able to stabilize the α-anion of the zwitterionic intermediate **5***.[23]

We confirmed these statements by theoretical calculations performed on the model compounds 3-methylisoquinoline (**4x**), 3-phenylisoquinoline (**4a**), 1-ethylideneisoindole (**5x**), 1-benzylideneisoindole (**5a**) and the corresponding zwitterionic intermediates **4x***, **4a***, **5x***, and **5a***. We performed the minimisations at the DFT level using the B3LYP functional and the 6-31+G(p) basis set.[24] We performed calculations on isolated molecules in the gas phase and confirmed the character of the minima by the absence of imaginary frequencies. Selected Δ*E* among isolated and hypothetical isomers and intermediates are reported in Table 5.

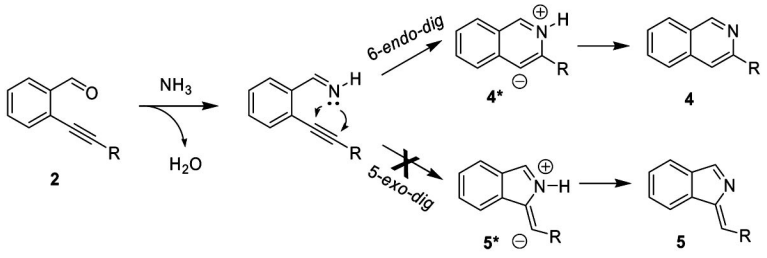
Table 5. Selected Δ*E* [kcal/mol] among isolated and hypothetical isomers and their intermediates.



Entry	Compounds	Δ*E* [kcal/mol]
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 this trend is also preserved for the zwitterionic intermediates; 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). These theoretical results seem to confirm that, from a thermodynamic point of view, the stabilization of the α-anion by the aryl substituent in **5a*** is less significant than the aromatic stabilization effect of conjugated bicyclic rings in **4a***.[23]

The low yield observed for **2f** is probably due to the steric hindrance of the *o*-methoxy group on the reaction (Table 4, Entry 8).[11k] On the other hand, against an almost quantitative conversion of starting materials **2c**–**e** (Table 4, Entries 3–7), the low yields of isoquinolines **4c**–**e** could be explained by the nature of the groups bonded to Cβ and their effect on the polarization of the triple bond;[25] a rough



Scheme 2.

qualitative analysis shows that whereas an EDG is able to decrease the electron density around Cβ and "activate" it towards a nucleophilic attack, an EWG can increase the electron density around Cβ, disfavouring the annulation step and allowing undesired secondary reactions (Figure 1).

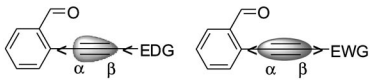


Figure 1. Qualitative estimation of the influence of the Cβ substituent on triple bond polarization.

To gain additional insight into this hypothesis, we analysed the chemical shifts of the *sp*-hybridised carbons[26] of aldehydes **2b**, **2c**, **2e** and **2i** as examples of substrates characterized by the presence of different EDGs and EWGs on Cβ. To ensure consistent conditions, we performed all the NMR experiments on the same 500 MHz NMR spectrometer. We obtained the unambiguous assignment of *sp*-hybridised carbon chemical shifts by means of two-dimensional HMBC and HSQC experiments. The results are depicted in Figure 2.

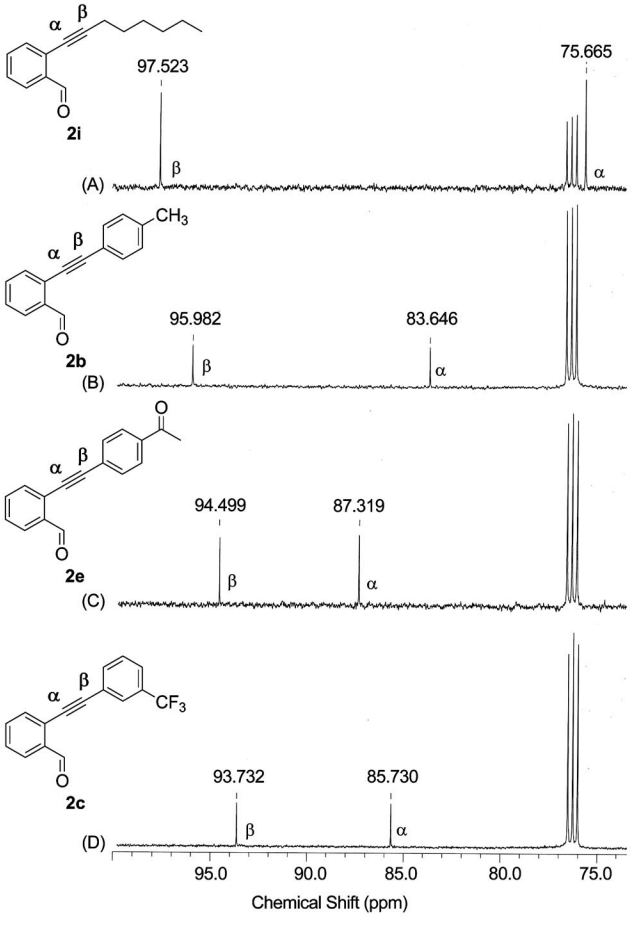


Figure 2. Experimental ^{13}C NMR spectra of **2b**, **2c**, **2e** and **2i**.

It is well-known that one of the most important parameters determining the NMR chemical shift is the shielding effect determined by the electron density around the nucleus of interest. Moreover, the chemical shift may depend also upon the presence of more or less proximate anisotropic groups,[27] and for this reason, we did not evaluate the chemical shift of alkynyl-benzaldehydes bearing an *o*-substituted aryl group on Cβ. Thus, taking into account that both the shielding cone of the triple bond and the substituent on Cα are the same for all substrates **2**, the differences in Cα and Cβ chemical shifts for **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 EDGs caused a deshielding of Cβ [Figure 2, (A) and (B)]; therefore, in **2i** and **2b**, Cβ is more prone to nucleophilic attack. As a result, the imination/annulation reaction of aldehydes **2i** and **2b** gave the corresponding isoquinolines **4i** and **4b** in very good yields (89% and 71%, respectively). On the other hand, the presence of an EWG [Figure 2, (C) and (D)] increased the electron density on Cβ (as indicated by the chemical shift at lower frequencies), so the cyclisation step for these compounds is more awkward, and the yields of **4e** and **4c** are lower (25% and 28%, respectively).

Conclusions

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

Experimental Section

General: All chemicals and solvents were 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 μm/60 Å was employed for flash column chromatography. Melting points are uncorrected. Infrared spectra were recorded with 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 and DEPT sequences were used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. Data for ^1H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet and br. = broad. Coupling constants (*J*) are reported 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 (2 M) 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 in-

ternal 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 an 80% w/w toluene solution) and tetrabutylammonium bromide (0.29 g, 0.9 mmol) in toluene (20 mL), aqueous sodium hydroxide (50% w/v, 3.11 mL) was slowly added at room temperature. The reaction was vigorously stirred for 3 h 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 with sodium sulfate, and the solvent was removed at reduced pressure. The resulting crude material was purified by flash chromatography over a silica gel column (hexane/EtOAc/TEA, 97:2:1) to afford 2.2 g of the desired product **1a** (82% yield). Yellow solid; m.p. 111–114 °C. IR (KBr): $\tilde{\nu}$ = 3258, 2121, 1407, 1239, 1086, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (m, 4 H, C≡C-H and CH_3), 5.20 (d, J = 2.6 Hz, 2 H, CH_2), 6.18 (dd, J = 4.0, 2.9 Hz, 1 H, arom.), 6.98 (dd, J = 4.0, 1.8 Hz, 1 H, arom.), 7.18 (dd, J = 2.9, 1.8 Hz, 1 H, 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 (100) $[M + 1]^+$.

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(triphenylphosphane)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. The reaction mixture was then diluted with aq. HCl (0.1 M, 60 mL) and extracted twice with EtOAc (2 × 50 mL). The organic layer, dried with sodium sulfate, was evaporated to dryness, and the crude material was 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(triphenylphosphane)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. The reaction mixture was then filtered under reduced pressure, and the crude material was purified by flash chromatography over a silica gel column (for reaction times, see Table 1).

1-[1-(3-Phenylprop-2-ynyl)-1*H*-pyrrol-2-yl]ethanone (1b): Eluent for chromatography: hexane/EtOAc (95:5). Method A: Yield 298 mg (98%). Orange solid; m.p. 52–54 °C. IR (KBr): $\tilde{\nu}$ = 1643, 1572 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3 H, CH_3), 5.44 (s, 2 H, CH_2), 6.21 (dd, J = 4.0, 2.6 Hz, 1 H, arom.), 7.01 (dd, J = 4.0, 1.8 Hz, 1 H, arom.), 7.30–7.34 (m, 4 H, arom.), 7.43–7.47 (m, 2 H, 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 (65) $[M + 1]^+$, 182 (7). $C_{15}H_{13}NO$ (223.27): calcd. C 80.69, H 5.87, N 6.27; found C 80.78, H 5.84, N 6.30.

1-{1-[3-(4-Chlorophenyl)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; m.p. 67–68 °C. IR (KBr): $\tilde{\nu}$ = 1645, 1571, 1523 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3 H, CH_3), 5.43 (s, 2 H, CH_2), 6.21 (dd, J = 4.0, 2.9 Hz, 1 H, arom.), 7.00 (dd, J = 4.2, 1.6 Hz, 1 H, arom.), 7.24–7.39 (m, 5 H, 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 (100) $[M + 1]^+$, 216 (13). $C_{15}H_{12}ClNO$ (257.71): calcd. C 69.91, H 4.69, N 5.43; found C 69.76, H 4.64, N 5.46.

1-{1-[3-(3-Trifluoromethylphenyl)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): $\tilde{\nu}$ = 1646, 1529 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3 H, CH_3), 5.44 (s, 2 H, CH_2), 6.21 (dd, J = 4.0, 2.6 Hz, 1 H, arom.), 7.00 (dd, J = 4.0, 1.8 Hz, 1 H, arom.), 7.21–7.23 (m, 1 H, arom.), 7.40–7.44 (m, 1 H, arom.), 7.53–7.60 (m, 2 H, arom.), 7.68 (s, 1 H, 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 (100) $[M + 1]^+$, 250 (7). $C_{16}H_{12}F_3NO$ (291.27): calcd. C 65.98, H 4.15, N 4.81; found C 65.87, H 4.11, N 4.84.

1-{1-[3-(4-Nitrophenyl)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; m.p. 93–95 °C. IR (KBr): $\tilde{\nu}$ = 1635, 1593, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3 H, CH_3), 5.48 (s, 2 H, CH_2), 6.23 (dd, J = 4.0, 2.6 Hz, 1 H, arom.), 7.02 (dd, J = 4.0, 1.8 Hz, 1 H, arom.), 7.19 (dd, J = 2.6, 1.8 Hz, 1 H, arom.), 7.57 (d, J = 9.2 Hz, 2 H, arom.), 8.17 (d, J = 9.2 Hz, 2 H, 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 (20) $[M + 1]^+$, 227 (5). $C_{15}H_{12}N_2O_3$ (268.27): calcd. C 67.16, H 4.51, N 10.44; found C 66.97, H 4.49, N 10.45.

1-{1-[3-(4-Methoxyphenyl)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; m.p. 59–61 °C. IR (KBr): $\tilde{\nu}$ = 1640, 1606 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.44 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 5.41 (s, 2 H, CH_2), 6.19 (dd, J = 4.0, 2.6 Hz, 1 H, arom.), 6.82 (d, J = 8.8 Hz, 2 H, arom.), 6.99 (dd, J = 4.0, 1.8 Hz, 1 H, arom.), 7.31 (t, J = 2.0 Hz, 1 H, arom.), 7.38 (d, J = 8.8 Hz, 2 H, 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 (100) $[M + 1]^+$, 212 (8). $C_{16}H_{15}NO_2$ (253.30): calcd. C 75.87, H 5.97, N 5.53; found C 75.81, H 5.96, N 5.53.

1-[1-(3-Pyrimidin-5-ylprop-2-ynyl)-1*H*-pyrrol-2-yl]ethanone (1g): Eluent for chromatography: hexane/EtOAc (8:2). Method A: Yield 254 mg (83%). Brown solid; m.p. 97–99 °C. IR (KBr): $\tilde{\nu}$ = 1650, 1541, 1529 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.46 (s, 3 H, CH_3), 5.48 (s, 2 H, CH_2), 6.23 (dd, J = 4.0, 2.6 Hz, 1 H, arom.), 7.01 (dd, J = 4.0, 1.8 Hz, 1 H, arom.), 7.15 (t, J = 2.6 Hz, 1 H, arom.), 8.75 (s, 2 H, arom.), 9.12 (s, 1 H, 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 (100) $[M + 1]^+$. $C_{13}H_{11}N_3O$ (225.25): calcd. 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(triphenylphosphane)palladium(II) (0.05 mmol) were added. The reaction was stirred at room temp. for 15 min, and then CuI (0.025 mmol) was added. The reaction mixture was stirred at 50 °C (see Table 2) until no more starting product was detectable by TLC analysis (hexane/EtOAc, 95:5). The solvent was then evaporated under reduced pressure, and the

crude material was 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, 8 H, arom.), 7.95 (dd, J = 7.3, 1.0 Hz, 1 H, arom.), 10.65 (s, 1 H, 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; m.p. 36–38 °C (ref.[28] 38 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.42 (s, 3 H, CH_3), 7.22 (d, J = 8.0 Hz, 2 H, arom.), 7.46 (t, J = 7.6 Hz, 1 H, arom.), 7.49 (d, J = 8.0 Hz, 2 H, arom.), 7.60 (td, J = 7.6, 1.2 Hz, 1 H, arom.), 7.66 (d, J = 7.3 Hz, 1 H, arom.), 7.97 (dd, J = 7.7, 0.8 Hz, 1 H, arom.), 10.68 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 20.8, 83.6, 96.0, 118.6, 126.5 (2 C), 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; m.p. 45–48 °C. IR (KBr): $\tilde{\nu}$ = 2845, 2754, 1696, 1592, 1126 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.53 (t, J = 7.6 Hz, 1 H, arom.), 7.62–7.71 (m, 3 H, arom.), 7.77 (d, J = 7.7 Hz, 1 H, arom.), 7.86 (s, 1 H, arom.), 8.00 (dd, J = 7.8, 0.8 Hz, 1 H, arom.), 10.66 (s, 1 H, 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 (100) [M + 1]$^+$. $C_{16}H_9F_3O$ (274.24): calcd. 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): $\tilde{\nu}$ = 2840, 1697, 1608, 1593, 1579, 1489, 1264, 1207, 1191, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.12 (m, 1 H, arom.), 7.29 (m, 1 H, arom.), 7.38 (m, 2 H, arom.), 7.50 (t, J = 7.5 Hz, 1 H, arom.), 7.62 (td, J = 7.7, 1.2 Hz, 1 H, arom.), 7.68 (d, J = 7.4 Hz, 1 H, arom.), 7.99 (d, J = 7.7 Hz, 1 H, arom.), 10.64 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ = 85.1, 94.1 (d, $^4J_{C,F}$ = 3.3 Hz), 115.7 (d, $^2J_{C,F}$ = 21.1 Hz), 117.7 (d, $^2J_{C,F}$ = 23.0 Hz), 123.5 (d, $^3J_{C,F}$ = 9.3 Hz), 125.5, 126.8, 126.9 (d, $^4J_{C,F}$ = 2.8 Hz), 128.3, 129.5 (d, $^3J_{C,F}$ = 8.7 Hz), 132.6, 133.1, 135.3, 161.7 (d, $^1J_{C,F}$ = 247.2 Hz), 190.7 ppm. ESI-MS: m/z (%) = 225 (100) [M + 1]$^+$. $C_{15}H_9FO$ (224.23): calcd. 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; m.p. 106–108 °C. IR (KBr): $\tilde{\nu}$ = 1683, 1591, 1402, 1364, 1262, 961, 829, 759 cm^{-1}. ^{1}H NMR (C_6D_6, 500 MHz): δ = 2.16 (s, 3 H, CH_3), 6.97 (t, J = 7.6 Hz, 1 H, arom.), 7.04 (td, J = 7.5, 1.4 Hz, 1 H, arom.), 7.41 (d, J = 8.4 Hz, 2 H, arom.), 7.42 (t, J = 7.9 Hz, 1 H, arom.), 7.76 (d, J = 8.3 Hz, 2 H, arom.), 7.97 (dd, J = 7.8, 1.2 Hz, 1 H, arom.), 10.78 (s, 1 H, 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 (61) [M + Na]$^+$, 249 (100) [M + 1]$^+$. $C_{17}H_{12}O_2$ (248.28): calcd. 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; m.p. 77–80 °C. IR (KBr): $\tilde{\nu}$ = 2938, 2859, 2215, 1693, 1590, 1259 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.93 (s, 3 H, CH_3), 6.91–7.01 (m, 2 H, arom.), 7.25–7.68 (m, 5 H, arom.), 7.95 (d, J = 7.7 Hz, 1 H, arom.), 10.74 (s, 1 H, 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 (100) [M + 1]$^+$. $C_{16}H_{12}O_2$ (236.27): calcd. 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; m.p. 72–74 °C. IR (KBr): $\tilde{\nu}$ = 2742, 2839, 2202, 1697, 1594, 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.51 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 6.71–6.80 (m, 2 H, arom.), 7.37–7.65 (m, 4 H, arom.), 7.94 (m, 1 H, arom.), 10.66 (s, 1 H, 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 (100) [M + 1]$^+$. $C_{17}H_{14}O_2$ (250.29): calcd. 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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.93 (t, J = 6.8 Hz, 3 H, CH_3), 1.25–1.71 (m, 6 H, CH_2), 2.47 (t, J = 6.9 Hz, 2 H, C_{sp}-CH_2), 7.33–7.67 (m, 3 H, arom.), 7.90 (m, 1 H, arom.), 10.54 (s, 1 H, 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. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.92 (t, J = 6.9 Hz, 3 H, CH_3), 1.31–1.38 (m, 4 H, CH_2), 1.45–1.51 (m, 2 H, CH_2), 1.65 (qt, J = 7.2 Hz, 2 H, CH_2), 2.49 (t, J = 7.2 Hz, 2 H, C_{sp}-CH_2), 7.38 (ddd, J = 8.0, 6.1, 2.7 Hz, 1 H, arom.), 7.50–7.54 (m, 2 H, arom.), 7.89 (d, J = 7.7 Hz, 1 H, arom.), 10.56 (s, 1 H, 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, J = 7.0 Hz, 6 H, CH_3), 3.60–3.90 (m, 4 H, CH_2), 5.54 (s, 1 H, CH), 7.42–7.63 (m, 3 H, arom.), 7.92 (m, 1 H, arom.), 10.51 (s, 1 H, 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; m.p. 44–48 °C (ref.[32] 50–52 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.27 (s, 9 H, CH_3), 7.39–7.59 (m, 3 H, arom.), 7.90 (m, 1 H, arom.), 10.55 (s, 1 H, CHO) ppm. These data are in good agreement with literature values.[32]

General Procedure for the Microwave-Assisted, $TiCl_4$-Catalyzed Cyclisation of 2-Acetyl-1-alkynylpyrroles 1a–g: In a sealed microwave test tube, to a solution of the appropriate pyrrole **1** (0.326 mmol) in dry ammonia in methanol (2 M, 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 saturated aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 × 50 mL). The organic layer, dried with sodium sulfate, was evaporated to dryness, and the crude material was 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): $\tilde{\nu}$ = 1722, 1650, 1527, 1407 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.37 (s, 3 H, CH_3), 2.64 (s, 3 H, CH_3), 6.70 (d, J = 4.4 Hz, 1 H, arom.), 6.76 (dd, J = 4.4, 2.5 Hz, 1 H, arom.), 7.28 (dd, J = 2.5, 1.2 Hz, 1 H, arom.), 7.53 (s, 1 H, 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 (100) $[M + 1]^+$. $C_9H_{10}N_2$ (146.19): calcd. 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-methylpyrrolo[1,2-*a*]pyrazine (3b): Eluent for chromatography: hexane/EtOAc (95:5). Yield 48 mg (66%). Brown oil. IR (neat): $\tilde{\nu}$ = 1618, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.66 (s, 3 H, CH_3), 4.04 (s, 2 H, CH_2), 6.69–6.77 (m, 2 H, arom.), 7.23–7.36 (m, 7 H, 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 (100) $[M + 1]^+$, 145 (9). $C_{15}H_{14}N_2$ (222.28): calcd. C 81.05, H 6.35, N 12.60; found C 80.87, H 6.28, N 12.64.

3-(4-Chlorobenzyl)-1-methylpyrrolo[1,2-*a*]pyrazine (3c): Eluent for chromatography: hexane/EtOAc (95:5). Yield 61 mg (73%). Brown oil. IR (neat): $\tilde{\nu}$ = 1621, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.64 (s, 3 H, CH_3), 3.98 (s, 2 H, CH_2), 6.69–7.20 (m, 2 H, arom.), 7.21–7.35 (m, 6 H, 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 (100) $[M + 1]^+$, 145 (9). $C_{15}H_{13}ClN_2$ (256.73): calcd. C 70.18, H 5.10, N 10.91; found C 70.00, H 5.03, N 10.94.

3-[1-(4-Chlorophenyl)-(*Z*)-methylidene]-1-methyl-3,4-dihydropyrrolo-[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, 3 H, CH_3), 4.70 (s, 2 H, CH_2), 5.96 (s, 1 H, C_{sp2}-H), 6.22 (dd, J = 3.7, 2.6 Hz, 1 H, arom.), 6.53 (dd, J = 4.0, 1.5 Hz, 1 H, arom.), 6.80 (t, J = 1.5 Hz, 1 H, arom.), 7.32 (d, J = 8.2 Hz, 2 H, arom.), 7.82 (d, J = 8.2 Hz, 2 H, arom.) ppm. We did 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 isomerised into the more stable isomer **3c**.

1-Methyl-3-(3-trifluoromethylbenzyl)pyrrolo[1,2-*a*]pyrazine (3d): Eluent for chromatography: hexane/EtOAc (93:7). Yield 62 mg (65%). Brown oil. IR (neat): $\tilde{\nu}$ = 1622, 1597, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.65 (s, 3 H, CH_3), 4.06 (s, 2 H, CH_2), 6.71–6.79 (m, 2 H, arom.), 7.29–7.30 (m, 1 H, arom.), 7.40–7.57 (m, 5 H, 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 (100) $[M + 1]^+$, 145 (5). $C_{16}H_{13}F_3N_2$ (290.28): calcd. C 66.20, H 4.51, N 9.65; found C 66.10, H 4.47, N 9.69.

1-Methtyl-3-[1-(3-trifluoromethylphenyl)-(*Z*)-methylidene]-3,4-dihydropyrrolo[1,2-*a*]pyrazine (3′d): Eluent for chromatography: hexane/EtOAc (93:7). Yield 16 mg (18%). Brown oil. IR (neat): $\tilde{\nu}$ = 1661, 1564, 1558 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3 H, CH_3), 4.74 (d, J = 1.5 Hz, 2 H, CH_2), 6.03 (s, 1 H, C_{sp2}-H), 6.24 (dd, J = 4.0, 2.6 Hz, 1 H, arom.), 6.56 (dd, J = 4.0, 1.5 Hz, 1 H, arom.), 6.83 (dd, J = 2.6, 1.5 Hz, 1 H, arom.), 7.42–7.45 (m, 2 H, arom.), 8.00–8.04 (m, 1 H, arom.), 8.23 (s, 1 H, arom.) ppm. ESI-MS: *m*/*z* (%) = 291 (100) $[M + 1]^+$. We did 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 isomerised into the more stable isomer **3d**.

3-(4-Nitrobenzyl)-1-methylpyrrolo[1,2-*a*]pyrazine (3e): Eluent for chromatography: hexane/EtOAc (8:2). Yield 82 mg (84%). Brown solid; m.p. 122–124 °C. IR (KBr): $\tilde{\nu}$ = 1603, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.64 (s, 3 H, CH_3), 4.08 (s, 2 H, CH_2), 6.73–6.81 (m, 2 H, arom.), 7.30–7.32 (m, 1 H, arom.), 7.44–7.48 (m, 3 H, 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 (100) $[M + 1]^+$, 222 (5). $C_{15}H_{13}N_3O_2$ (267.28): calcd. C 67.40, H 4.90, N 15.72; found C 67.28, H 4.86, N 15.78.

3-(4-Methoxybenzyl)-1-methylpyrrolo[1,2-*a*]pyrazine (3f): Eluent for chromatography: hexane/EtOAc (95:5). Yield 59 mg (72%). Yellow oil. IR (neat): $\tilde{\nu}$ = 1615, 1584, 1512 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.65 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 3.97 (s, 2 H, CH_2), 6.68–6.76 (m, 2 H, arom.), 6.84–6.91 (m, 2 H, arom.), 7.21–7.26 (m, 3 H, arom.), 7.29 (s, 1 H, 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 (100) $[M + 1]^+$, 145 (15). $C_{16}H_{16}N_2O$ (252.31): calcd. C 76.16, H 6.39, N 11.10; found C 76.06, H 6.32, N 11.12.

3-[1-(4-Methoxyphenyl)-(*Z*)-methylidene]-1-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (3′f): Eluent for chromatography: hexane/EtOAc (95:5). Yield 22 mg (26%). Yellow oil. IR (neat): $\tilde{\nu}$ = 1601, 1558, 1531 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.44 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 4.70 (s, 2 H, CH_2), 5.97 (s, 1 H, C_{sp2}-H), 6.20–6.23 (m, 1 H, arom.), 6.49–6.50 (m, 1 H, arom.), 6.78–6.80 (m, 1 H, arom.), 6.87 (d, J = 8.8 Hz, 2 H, arom.), 7.84 (d, J = 8.8 Hz, 2 H, 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 (100) $[M + 1]^+$, 238 (5), 145 (5). $C_{16}H_{16}N_2O$ (252.31): calcd. C 76.16, H 6.39, N 11.10; found C 75.99, H 6.31, N 11.10.

1-Methyl-3-pyrimidin-5-ylmethylpyrrolo[1,2-*a*]pyrazine (3g): Eluent for chromatography: hexane/EtOAc (8:2). Yield 26 mg (35%). Orange solid; m.p. 87–89 °C. IR (KBr): $\tilde{\nu}$ = 1622, 1564, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.63 (s, 3 H, CH_3), 3.96 (s, 2 H, CH_2), 6.72–6.81 (m, 2 H, arom.), 7.31–7.33 (m, 1 H, arom.), 7.54 (s, 1 H, arom.), 8.72 (s, 2 H, arom.), 9.10 (s, 1 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.7, 35.9, 103.5, 114.6 (2 C), 115.6, 127.1, 133.1, 135.7, 153.7, 157.3, 157.5 ppm. ESI-MS: *m*/*z* (%) = 225 (100) $[M + 1]^+$, 145 (8). $C_{13}H_{12}N_4$ (224.26): calcd. 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-(*Z*)-methylidene]-3,4-dihydropyrrolo-[1,2-*a*]pyrazine (3′g): Eluent for chromatography: hexane/EtOAc (8:2). Yield 29 mg (40%). Brown solid; m.p. 100–102 °C. IR (KBr): $\tilde{\nu}$ = 1622, 1572, 1560, 1547 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3 H, CH_3), 4.79 (s, 2 H, CH_2), 5.89 (s, 1 H, C_{sp2}-H), 6.25 (dd, J = 3.7, 2.6 Hz, 1 H, arom.), 6.59 (dd, J = 3.7, 1.5 Hz, 1 H, arom.), 6.85 (dd, J = 2.2, 1.5 Hz, 1 H, arom.), 9.01 (s, 1 H, arom.), 9.21 (s, 2 H, 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 (2 C), 158.4 ppm. ESI-MS: *m*/*z* (%) = 225 (100) $[M + 1]^+$, 198 (8), 145 (8). $C_{13}H_{12}N_4$ (224.26): calcd. C 69.62, H 5.39, N 24.98; found calcd; found 69.58; H, 5.37; N, 24.96.

General Procedure for the Microwave-Assisted Cyclisation of *o*-Alkynylbenzaldehydes 2a–k: A stirred solution of the appropriate *o*-alkynylbenzaldehyde **2a**–**k** (0.5 mmol) in dry ammonia in methanol (2 M, 5 mL) was heated at 130 °C in a sealed tube for 15–60 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 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; m.p. 100–102 °C (ref.[11e] 101–101.5 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.38–7.79 (m, 4 H, arom.), 7.70 (dt, J = 6.6, 1.5 Hz, 1 H, arom.), 7.88 (d, J = 8.4 Hz, 1 H, arom.), 8.00 (d, J = 8.4 Hz, 1 H, arom.) 8.08 (s, 1 H, arom.), 8.13 (d, J = 7.1 Hz, 2 H, arom.), 9.35 (s, 1 H, 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; m.p. 74–76 °C (ref.[11e] 74–75 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3 H, CH_3), 7.32 (d, J = 7.9 Hz, 2 H, arom.), 7.53 (t, J = 8.0 Hz, 1 H, arom.), 7.68 (s, J = 8.0 Hz, 1 H, arom.), 7.86 (d, J = 8.1 Hz, 1 H, arom.), 7.96 (d, J = 8.2 Hz, 1 H, arom.), 8.05 (m, 3 H, arom.), 9.33 (s, 1 H, 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; m.p. 64–67 °C. IR (KBr): $\tilde{\nu}$ = 1625, 1325, 1178, 1109, 1068 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.58–7.77 (m, 4 H, arom.), 7.90 (d, J = 8.2 Hz, 1 H, arom.), 8.01 (d, J = 8.2 Hz, 1 H, arom.), 8.11 (s, 1 H, arom.), 8.32 (d, J = 7.0 Hz, 1 H, arom.), 8.42 (s, 1 H, arom.), 9.35 (s, 1 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 117.1, 124.0 (q, $^3J_{C,F}$ = 3.8 Hz), 124.5 (q, $^1J_{C,F}$ = 272.0 Hz), 125.3 (q, $^3J_{C,F}$ = 3.8 Hz), 127.2, 127.8, 127.9, 128.3, 129.5, 130.3, 131.0, 131.4 (q, $^2J_{C,F}$ = 32.4 Hz), 136.7, 140.6, 149.8, 152.9 ppm. ESI-MS: m/z (%) = 274 (100) [M + 1]$^+$. $C_{16}H_{10}F_3N$ (273.25): calcd. 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; m.p. 105–109 °C. IR (KBr): $\tilde{\nu}$ = 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, 1 H, arom.), 7.46 (td, J = 8.0, 6.0 Hz, 1 H, arom.), 7.56–7.75 (m, 2 H, arom.), 7.83–7.92 (m, 3 H, arom.), 8.00, (d, J = 8.0 Hz, 1 H, arom.), 8.05 (s, 1 H, arom.), 9.33 (s, 1 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 114.1 (d, $^2J_{C,F}$ = 22.8 Hz), 115.5 (d, $^2J_{C,F}$ = 21.4 Hz), 117, 122.7 (d, $^4J_{C,F}$ = 2.8 Hz), 127.2, 127.6, 127.8, 128.2, 130.4 (d, $^3J_{C,F}$ = 8.2 Hz), 130.9, 136.7, 142.2 (d, $^3J_{C,F}$ = 7.7 Hz), 150.1 (d, $^4J_{C,F}$ = 2.7 Hz), 152.7, 163.6 (d, $^1J_{C,F}$ = 245 Hz) ppm. ESI-MS: m/z (%) = 224 (100) [M + 1]$^+$. $C_{15}H_{10}FN$ (223.25): calcd. 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; m.p. 150–152 °C. IR (KBr): $\tilde{\nu}$ = 2956, 2924, 2853, 1670, 1599, 1353, 1263, 855, 832, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.67 (s, 3 H, CH_3), 7.63 (ddd, J = 8.1, 6.7, 1.2 Hz, 1 H, arom.), 7.73 (ddd, J = 8.4, 7.0, 1.5 Hz, 1 H, arom.), 7.90 (d, J = 8.1 Hz, 1 H, arom.), 8.02 (d, J = 8.4 Hz, 1 H, arom.), 8.09 (d, J = 8.6 Hz, 2 H, arom.), 8.15 (s, 1 H, arom.), 8.25 (d, J = 8.6 Hz, 2 H, arom.), 9.36 (s, 1 H, 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 (100) [M + 1]$^+$. $C_{17}H_{13}NO$ (247.29): calcd. 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): $\tilde{\nu}$ = 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, 3 H, CH_3), 7.05 (dd, J = 8.3, 0.9 Hz, 1 H, arom.), 7.13 (td, J = 7.5, 1.1 Hz, 1 H, arom.), 7.39 (ddd, J = 8.2, 7.4, 1.8 Hz, 1 H, arom.), 7.57 (ddd, J = 8.6, 6.8, 1.4 Hz, 1 H, arom.) 7.68 (ddd, J = 8.2, 6.7, 1.4 Hz, 1 H, arom.), 7.86 (d, J = 8.2 Hz, 1 H, arom.), 7.93 (dd, J = 7.6, 1.8 Hz, 1 H, arom.), 7.98 (d, J = 8.0 Hz, 1 H), 8.21 (s, 1 H, arom.), 9.35 (s, 1 H, 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 (100) [M + 1]$^+$, 221 (19). $C_{16}H_{13}NO$ (235.28): calcd. 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): $\tilde{\nu}$ = 1625, 1607, 1580, 1504, 1451, 1295, 1275, 1241, 1162, 1055, 752 cm^{-1}. ^{1}H NMR (C_6D_6, 200 MHz): δ = 2.48 (s, 3 H, CH_3), 3.36 (s, 3 H, CH_3), 6.78 (dd, J = 8.4, 2.5 Hz, 1 H, arom.), 6.86 (d, J = 2.5 Hz, 1 H, arom.), 7.10 (ddd, J = 8.0, 6.8, 1.3 Hz, 1 H, arom.), 7.21 (ddd, J = 8.2, 6.8, 1.3 Hz, 1 H, arom.), 7.36–7.55 (m, 4 H, arom.), 9.19 (s, 1 H, 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 (100) [M + 1]$^+$. $C_{17}H_{15}NO$ (249.31): calcd. 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): $\tilde{\nu}$ = 2955, 2928, 2857, 1630, 1591, 1456, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.26–1.42 (m, 4 H, CH_2), 1.74–1.89 (m, 2 H, CH_2), 2.92 (t, J = 7.3 Hz, 2 H, CH_2), 7.45 (s, 1 H, arom.) 7.50 (ddd, J = 8.1, 7.0, 1.5 Hz, 1 H, arom.), 7.62 (ddd, J = 8.1, 6.6, 1.5 Hz, 1 H, arom.), 7.74 (d, J = 8.1 Hz, 1 H, arom.), 7.90 (d, J = 8.1 Hz, 1 H, arom.), 9.19 (s, 1 H, 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 (100) [M + 1]$^+$, 143 (10). $C_{14}H_{17}N$ (199.29): calcd. 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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.23–1.46 (m, 6 H, CH_2), 1.81 (m, 2 H, CH_2), 2.93 (t, J = 7.3 Hz, 2 H, CH_2), 7.46 (s, 1 H, arom.) 7.51 (ddd, J = 8.1, 6.8, 1.4 Hz, 1 H, arom.), 7.63 (ddd, J = 8.2, 6.8, 1.4 Hz, 1 H, arom.), 7.74 (d, J = 8.2 Hz, 1 H, arom.), 7.92 (d, J = 8.1 Hz, 1 H, arom.) 9.20 (s, 1 H, 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): $\tilde{\nu}$ = 2975, 2928, 2879, 1694, 1629, 1590, 1441, 1386, 1370, 1345, 1170, 1129, 1107, 1060, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.24 (t, J = 7.1 Hz, 6 H, CH_3), 3.67 (dq, CH_2, J = 9.5, 7.1 Hz, 2 H, ABX_3 system), 3.74 (dq, CH_2, J = 9.5, 7.1 Hz, 2 H, ABX_3 system), 5.69 (s, 1 H, CH), 7.60 (ddd, J = 8.0, 6.9, 1.6 Hz, 1 H, arom.), 7.70 (ddd, J = 8.3, 6.9, 1.6 Hz, 1 H, arom.), 7.87 (dd, J = 8.0, 0.8 Hz, 1 H, arom.), 7.95–8.00 (m, 2 H, arom.), 9.26 (s, 1 H, 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 (64) [M + 1]$^+$, 218 (52), 186 (100), 172 (18), 158 (33). $C_{14}H_{17}NO_2$ (231.29): calcd. 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*-TosA (1.9 mg, 0.01 mmol) in H_2O/acetone (1:1, 1.5 mL) was heated at reflux for 70 min. After the reaction had cooled to room temp., saturated aq. $NaHCO_3$ (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 was evaporated at reduced pressure yielding pure **4k** (31 mg, 98%). Brown solid; m.p. 45–47 °C (ref.[21c] 49.6–50 °C). ^{1}H

NMR ($CDCl_3$, 200 MHz): δ = 7.81 (m, 2 H, arom.), 8.06 (m, 2 H, arom.), 8.40 (s, 1 H, arom.), 9.38 (s, 1 H, arom.), 10.27 (s, 1 H, CHO) ppm. These data are in good agreement with literature values.[21c]

Computational Methods: The structures of **4x**, **4a**, **5x** and **5a** and intermediates **4x***, **4a***, **5x*** and **5a*** were optimised at the DFT level (B3LYP/) with GAUSSIAN03® using the 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 the 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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