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New synthetic strategies for the preparation of heterocyclic and heteropolycyclic compounds

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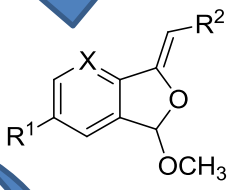
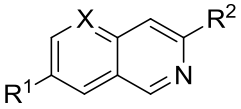
New synthetic strategies for the preparation of heterocyclic and heteropolycyclic compounds

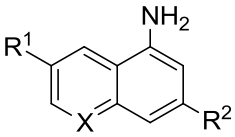
Index

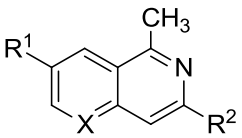
Chapter 1

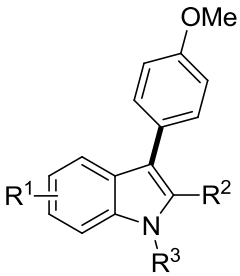
Methodological approaches and aim of the work

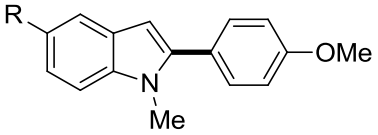


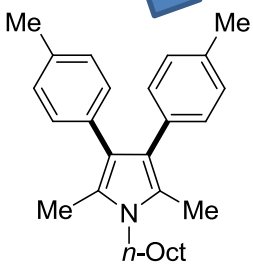












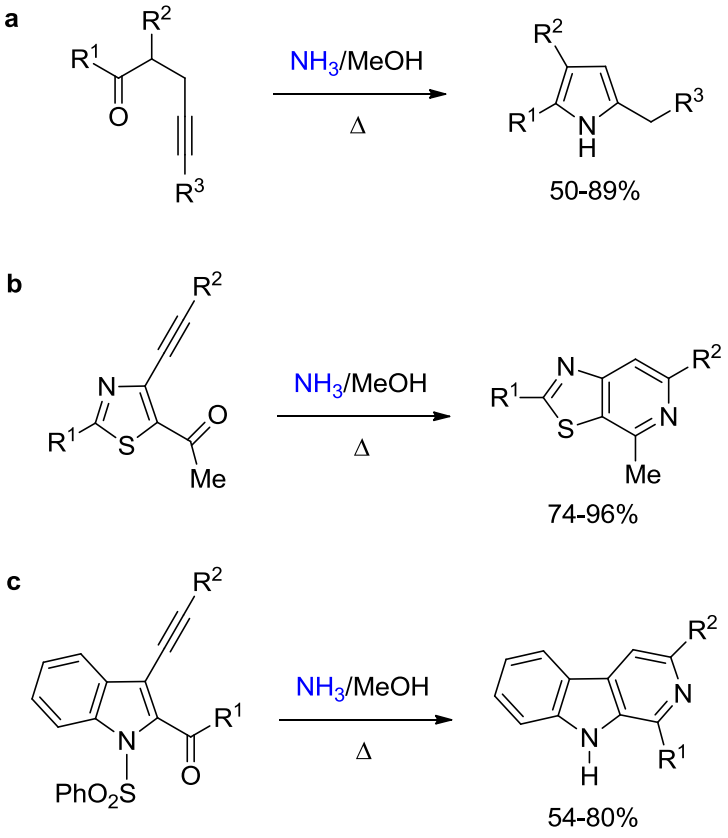
1.1 Domino reactions

A domino reaction
is a process involving two or more bond-forming transformations which takes place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.

In the last decade, the development of new domino[1] strategies for the synthesis of heterocyclic compounds[2] has fascinated many researchers and is a research field in continuous evolution. The possibility of building up simple, as well as complex, heterocycles starting from easily achievable building blocks using a single sequential transformation, is an attractive tool for all synthetic chemists. When a new domino reaction also matches with the atom economy[3] concept of Trost, the advantages of the discovered synthetic strategy are notable. Moreover, the reduction of solvent and energy consumption, waste production and reaction times represent unquestionable advantages from both economical and ecological point of views.

For many years, our research group has been interested in the development of new sequential synthetic strategies for the construction of nitrogen-containing heterocycles starting from alkyne derivatives.[4] In many works, in particular, we devoted our attention on the synthesis of nitrogen containing rings by sequential addition/annulation reactions of γ- and δ-ketoalkynes[5] with ammonia.[6]

For example, 5-*exo-dig* cyclisation of 4-pentynones[6f,g] gave polysubstituted and fused pyrrole derivatives (Scheme 1.1, a), whereas the presence of γ-ketoalkyne moiety in an aromatic framework is responsible for the 6-*endo-dig* cyclisation of 5-acetyl-4-alkynylthiazoles[6d,e] and 2-acyl-3-alkynylindoles[6c] to pyrido[3,4-*d*]thiazoles and pyrido[3,4-*b*]indoles, respectively (Scheme 1.1, b and c).



Scheme 1.1 – Our previous works on cyclisation of γ- and δ-ketoalkynes in the presence of ammonia.

1.2 Multicomponent reactions

A multicomponent reaction
is a process in which three or more reactants are combined in a single chemical step to synthesize molecules that incorporate substantial portions of all the components.

Multicomponent reactions (MCRs) are a powerful tool for the synthesis of complex molecules starting from readily available building blocks in a "well-contrived" one-pot sequential procedure.[7] These approaches allow an overall reduction of the time required to obtain the desired product with an advantageous economy of solvents and energy, and an overall reduction of waste production. The optimal MCR is sufficiently flexible that it can be employed to generate adducts bearing a variety of functional groups and leading to a diverse collection of products. MCRs have been widely used for the preparation of heterocyclic structures,[8] as well as key steps in the total synthesis of natural products.[9] Moreover, the enhancing power of microwaves in MCRs has been recently highlighted.[10] In this thesis, two different microwave-assisted multicomponent approaches are reported as a consequence of improvement, simplification and optimisation of domino sequences.

1.3 Microwave-mediated organic synthesis

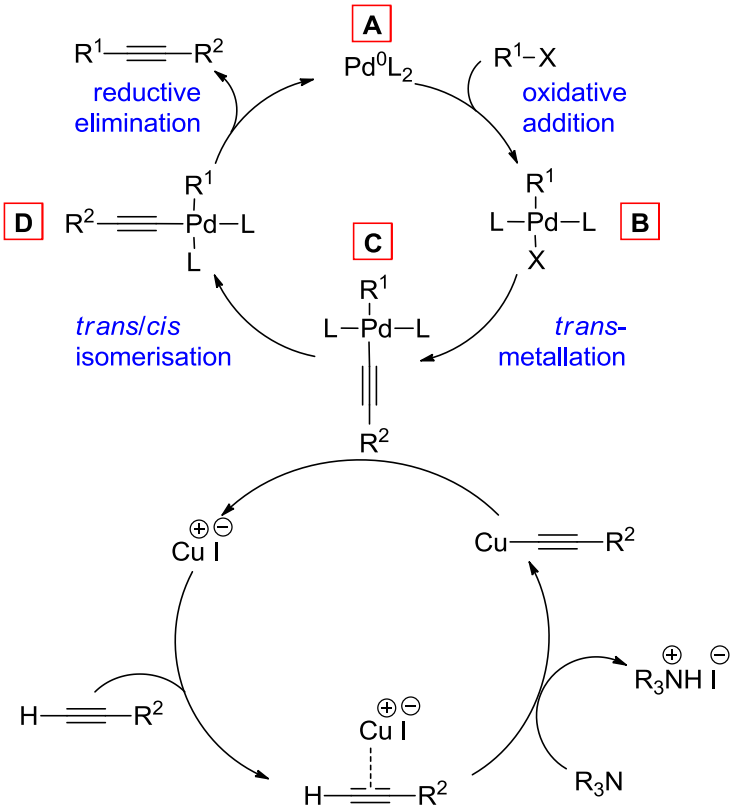
Microwaves
are a highly efficient nonconventional energy source able to improve both yields and selectivity, to reduce reaction times and also to enhance the reactivity of more critical substrates.

Over the last two decades, interest in microwave-mediated organic synthesis[11] has been undergoing continuous growth, as testified by the great number of the works appearing in the literature. Despite the fact that the existence of an authentic 'non-thermal' effect connected to the nature of the electromagnetic waves is still a topic of debate within the scientific community,[12] there is clear evidence that, in a wide range of organic reactions, the use of microwaves reduces reaction times, increases yields and reduces the formation of by-products.[13] Nonthermal microwave effects have been postulated to result from a direct stabilizing interaction of the electric field with specific (polar) molecules in the reaction medium that is not related to a macroscopic temperature effect. Thermal effects (dielectric heating) can result from dipolar polarisation as a consequence of dipole-dipole interactions between polar molecules and the electromagnetic field. They originate in dissipation of energy into heat as an outcome of agitation and intramolecular friction of molecules when dipoles change their mutual orientation at each alternation of the electric field at a very high frequency. This energy dissipation in the core of materials allows a much more regular repartition in temperature when compared to classical heating. Classical thermal phenomena (conduction, convection, radiation, etc.) only play a secondary role in the a posteriori equilibration of temperature.

1.4 Transition-metal catalysis: Pd, Au, Ag

During the second half of the 20th century, transition metals have come to play an important role in organic chemistry and this has led to the development of a large number of transition metal-catalysed reactions for creating organic molecules. Transition metals have a unique ability to activate various functional groups and through this activation they can catalyse the formation of new bonds.

One metal that was early used for catalytic organic transformations was palladium.[14] In particular, the palladium-catalysed sp^2-sp coupling reaction between aryl- or vinyl-halides or triflates and terminal alkynes (with or without the presence of a copper (I) cocatalyst) has become the most important method to prepare aryl- and vinyl-alkynes. This reaction, called Sonogashira (or more precisely, Sonogashira-Hagihara), is the most popular procedure for the alkynylation of vinyl- and aryl-halides. The reaction mechanism is not clearly understood but the most widely accepted mechanism revolves around a palladium cycle and a copper cycle that is less well known (Scheme 1.2).[15] The active palladium catalyst is the 14 electron compound $Pd(0)L_2$ **A** which reacts with the aryl halide or triflate in an oxidative addition to Pd(II) complex **B**. This complex reacts in a rate limiting *trans*-metallation with the copper acetylide produced in the copper cycle to complex **C** expelling the copper halide CuI. Both organic ligands are *trans* oriented and convert to *cis* in a *trans*/*cis* isomerisation to complex **D**. In the final step the product is released in a reductive elimination with regeneration of Pd(0). In this work, all alkyne starting materials were prepared by typical Sonogashira cross-coupling reactions (chapters 2 and 4).



Scheme 1.2 – Sonogashira coupling mechanism.

Moreover, a number of very useful new ways have been discovered to effect the hetero- and carbo-annulation of alkenes, dienes and alkynes to produce a wide range of heterocycles and carbocycles.[16] This chemistry employs only catalytic amounts of palladium and relatively simple starting materials to effect a myriad of valuable synthetic transformations. In this thesis, we explored the potential multiactivity of the palladium (and copper) catalyst, involved in both the Sonogashira coupling step and in the addition/annulation sequence, by two different microwave-assisted multicomponent approaches (chapters 3 and 5). Palladium (or copper) could assist the cyclisation step enhancing the reactivity of triple bond, in particular in the presence of less reactive alkyne derivatives. Although reactions involving palladium should be carried out carefully, palladium reagents and catalysts are not very sensitive to oxygen and moisture, or even to acid. On the other hand, in many reactions catalysed by Pd-phosphine complexes, it is enough to apply precautions to avoid oxidation of the phosphine, and this can be done easily.

Gold salts and complexes are soft and carbophilic Lewis acids with the exclusive ability to activate C-C multiple bonds and C-H bonds of aromatic and heteroaromatic compounds. Gold salts and complexes could exist in two oxidation states (I and III) each of ones could carry out different catalytic activities.[17] In many transformations, gold demonstrate to be more active and more selective than other metal catalysts and, for this reason, is a catalyst of choice in a number of different processes. Moreover, from an environmental and economical point of view, gold catalysts are active in extremely small amount (high TON) and can be used with environmentally-friendly solvents under mild conditions. They are quite robust and generally well tolerate the presence of oxygen and water. Gold is non-toxic, not more expensive than many other transition metals (such as palladium or rhodium) and a rare element but more abundant than platinum, palladium, rhodium and other precious metals.

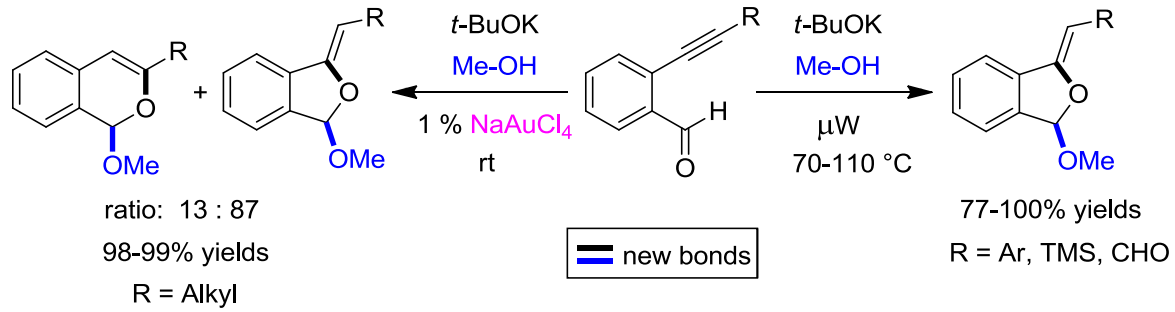
In comparison with other transition metals, silver(I) complexes have long been believed to have low catalytic efficiency, and most commonly, they are used as either co-catalysts or Lewis acids. Only recently have Ag-catalysed reactions emerged as important synthetic methods for a variety of organic transformations.[18] Ag(I) is known to interact with multiple bonds, such as alkenes, alkynes and allenes. The activation of the alkyne, based on the coordination of silver salts to form π-complexes, is advantageously employed in cyclisation reactions by intramolecular nucleophilic attack. This synthetic strategy has been used to prepare a large number of O- and N-heterocycles, and most of these rings are incorporated into a great number of physiologically active natural products. In addition, the use of silver(I) is economic in comparison with some other transition metals.

In this work, the reactivity of less reactive alkyne substrates has been in some cases enhanced by the catalysis of gold (chapter 2) and silver salts (chapter 6).

1.5 Aim and outline of this thesis

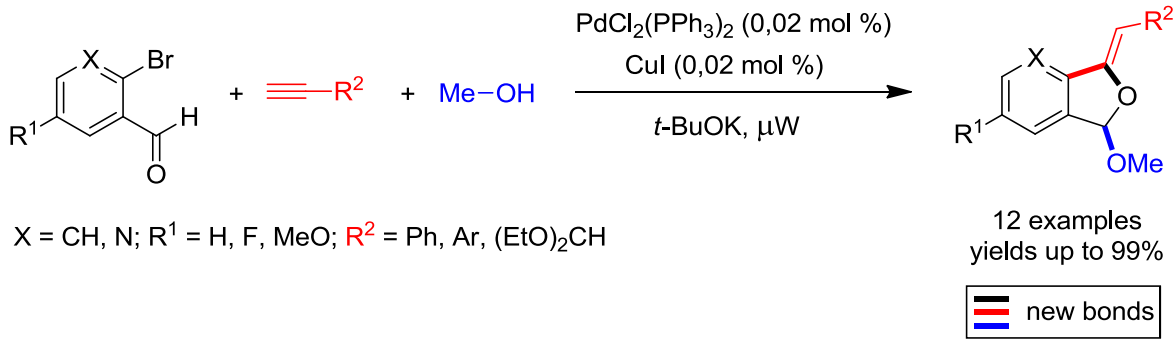
The aim of the project in this doctoral thesis is based on the development of new synthetic strategies for the preparation of heterocyclic and heteropolycyclic compounds of potential interest in biological and pharmacological fields. In particular, we studied new general, flexible and regioselective synthetic approaches to oxygen and nitrogen heterocycles. In this field, the catalysis promoted by transition metals has proven to play a pivotal role to directly construct complicated molecules from readily accessible starting materials, under mild condition, through chemical reactions based on atom-economy.

In the first part of this work, we explored in-depth the base-promoted domino nucleophilic addition/annulation of simple *ortho*-alkynylbenzaldehydes in the presence of alcohols (Scheme 1.3). In particular, we focused our attention on the selective synthesis of the isobenzofuran skeleton and to rationalize the relationship between the nature of the substitution on the alkynyl terminus and the cyclisation mode. The plausible reaction mechanisms involved were discussed. The full details of this study are reported in chapter 2.



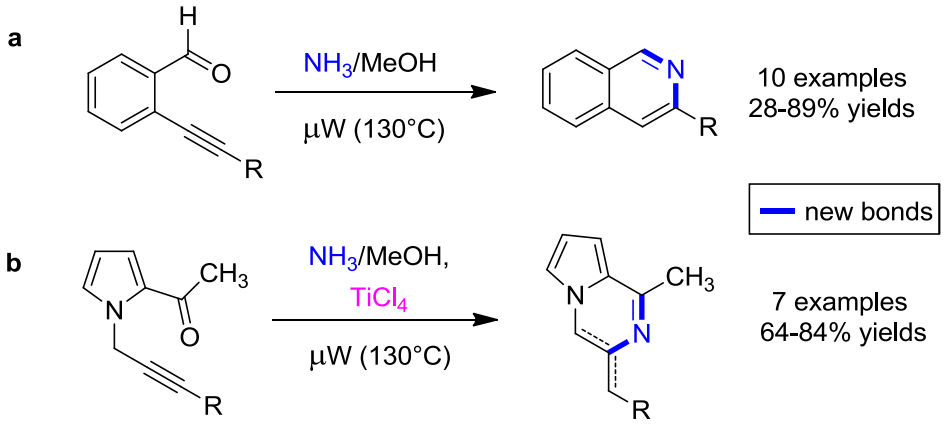
Scheme 1.3 – Chapter 2: synthesis of dihydroisobenzofurans by domino addition/annulation reactions.

The domino approach to dihydroisobenzofuran nucleus has been successfully transformed in a three-component synthesis involving a one-pot coupling/addition/cyclisation sequence promoted by palladium and a base, as reported in scheme 1.4 and defended in chapter 3.



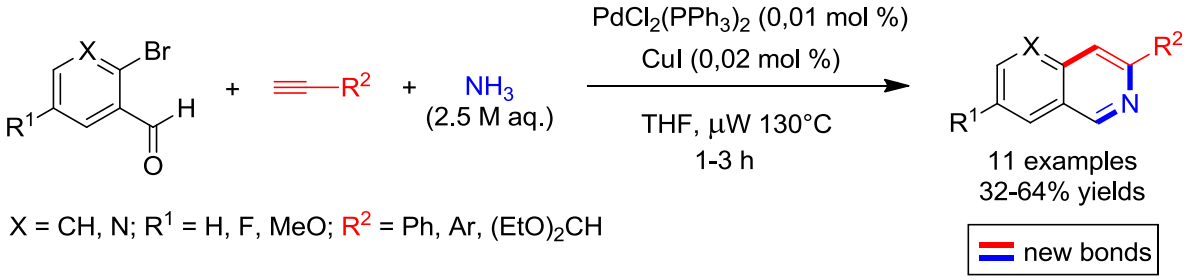
Scheme 1.4 – Chapter 3: multicomponent synthesis of dihydroisobenzofurans.

Furthermore, *ortho*-alkynylbenzaldehydes demonstrated to be suitable building blocks for the synthesis isoquinoline nucleus Also in this case microwaves heating efficiently promoted the domino imination/annulation reaction (Scheme 1.5, a). The approach has been also extended to 2-acetyl-*N*-propargylpyrroles for the synthesis of pyrrolo[1,2-*a*]pyrazine. Nevertheless, as previously observed on analogous 2-acetyl-*N*-propargylindoles,[6a] the reaction run well only in the presence of $TiCl_4$ (Scheme 1.5, b). The full details are reported in chapter 4.



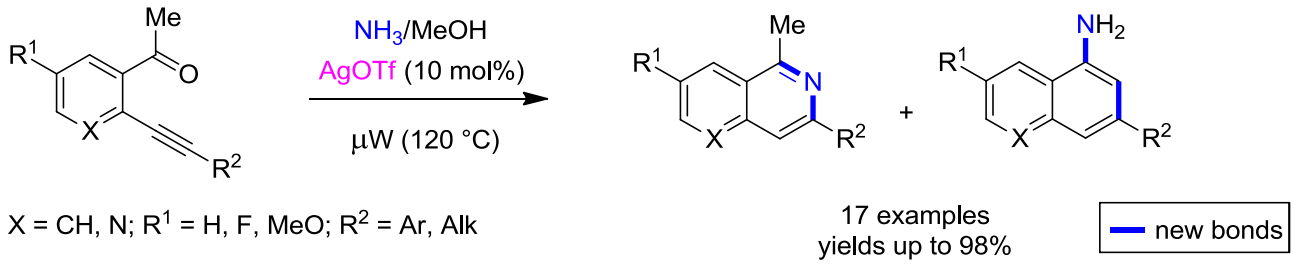
Scheme 1.5 – Chapter 4: synthesis of isoquinoline and pyrrolo[1,2-a]pyrazine by tandem imination/annulation reactions.

Also the domino approach to isoquinolines has been successfully transformed into a valuable microwave-assisted multicomponent process starting from the simple building blocks *ortho*-bromoarylaldehydes, terminal alkynes and aqueous ammonia, as depicted in scheme 1.6 and detailed in chapter 5.



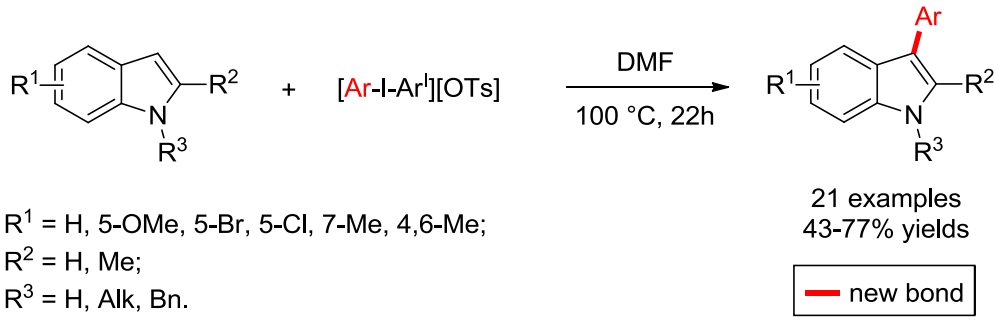
Scheme 1.6 – Chapter 5: multicomponent synthesis of isoquinolines.

We observed that, under our standard domino conditions, the reactions of 2-alkynylacetophenones and 3-acetyl-2-alkynylpyridines in the presence of ammonia gave the corresponding N-heterocycles in very poor results. Starting from these, we exploited the possibility to catalyse the reaction by a transition metal and we found that silver triflate was the catalyst of choice for the synthesis of 1-methylisoquinolines and 5-methyl-1,6-naphthyridines (Scheme 1.7). In most cases the reactions gave mixtures of imino- and carbo-cylisation products with a general preference for the former. Full details are reported in chapter 6.



Scheme 1.7 – Chapter 6: silver-catalysed intramolecular cyclisation of 2-alkynylacetophenones and 3-acetyl-2-alkynylpyridines.

Finally, in chapter 7, direct arylations of indoles and pyrroles with differently substituted diaryliodonium salts are described (Scheme 1.8). These reactions efficiently proceed in the absence of metal catalysts. This work has been realised under the supervision of Prof. L. Ackermann at the Institut für Organische und Biomolekulare Chemie in the Georg-August-Universität Göttingen (Germany), during a part of my PhD course.



R^1 = H, 5-OMe, 5-Br, 5-Cl, 7-Me, 4,6-Me;
R^2 = H, Me;
R^3 = H, Alk, Bn.

Scheme 1.8 – Chapter 7: metal-free direct arylations.

1.6 References and notes

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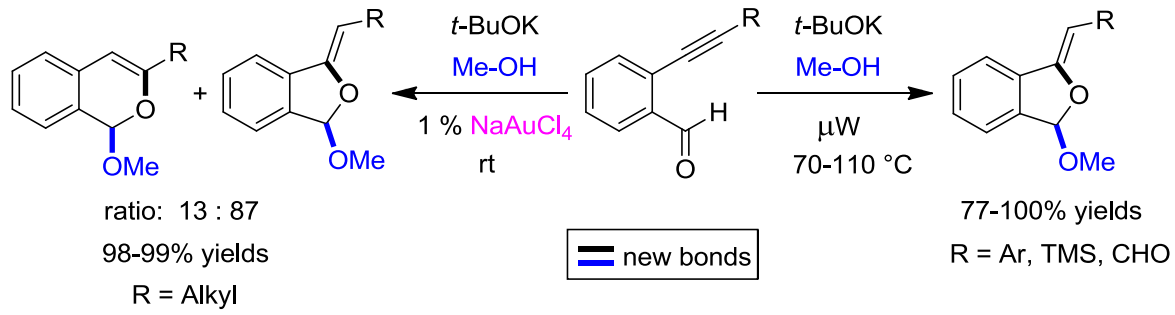
Chapter 2

Selective Base-Promoted Synthesis of Dihydroisobenzofurans by Domino Addition/Annulation Reactions of *ortho*-Alkynylbenzaldehydes



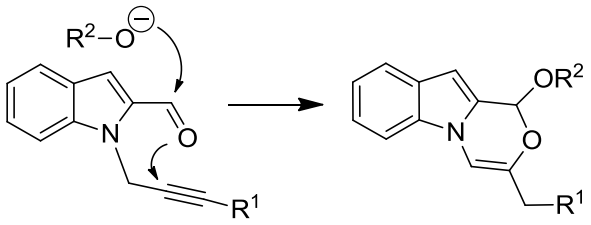
The synthesis of the dihydroisobenzofuran nucleus was achieved by the base-promoted tandem nucleophilic addition/annulation reaction of *ortho*-alkynylbenzaldehydes in the presence of methanol. The reactions of aryl-, trimethylsilyl- and diethoxymethyl-substituted alkynylbenzaldehydes occurred with complete regioselectivity in good to excellent yields under microwaves irradiation. The reactions of alkyl-substituted alkynylbenzaldehydes took place with good yields and high regioselectivity only when performed at room temperature and in the presence of a catalytic amount of a gold(III) salt. The plausible reaction mechanisms involved were discussed. The effect of the substituent at the alkynyl terminus on the cyclisation mode was tentatively rationalised.

Dell'Acqua, M.; Facoetti, D.; Abbiati, G.; Rossi, E.

Synthesis **2010**, *14*, 2367–2378.

2.1 Introduction

In 2005, our research group briefly investigated the synthesis heterocyclic nuclei containing both oxygen and nitrogen, through the study of the reaction of some particular δ-alkynylaldehydes, i.e. 1-propargyl-1*H*-indole-2-carbaldehydes, with different alkoxides generated in situ from the corresponding alcohols (Scheme 2.1).[1] These reactions gave the unusual [1,4]oxazino[4,3-*a*]indoles by a two step sequential path; first, the addition of the nucleophile to the aldehyde resulting in the formation of a transient hemiacetal anion *in situ*; second, the 6-*exo-dig* cyclisation of the hemiacetal anion on the triple bond (or on the central carbon of the allene framework generated by the base-promoted isomerisation of the propargyl moiety), followed by a solvent-mediated protonation/isomerisation.



Scheme 2.1 – Reaction of 1-propargyl-1*H*-indole-2-carbaldehydes with alkoxides.

Taking into account these results, we were intrigued to explore the application of this domino approach to simple γ-alkynylaldehydes, such as *ortho*-alkynylbenzaldehydes, with the aim of finding an alternative route to some interesting oxygen-containing heterocycles, i.e. dihydroisobenzofurans and/or isochromenes. These nuclei are the core of many important biologically active molecules. For example, the dihydroisobenzofuran structure forms the skeleton of BcF,[2] a compound under investigation as a more lipophilic analogue of the anti-HIV d4T[3] (Stavudine) and the methyl 1,5,8-trimethoxy-1*H*-isochromene-3-carboxylate was patented as a potential antitumor agent against breast cancer.[4] Moreover, the structures of isochromane and 1,3-dihydroisobenzofuran are the key structures of a number of diterpenes from the Antarctic sponge *Dendrilla membranosa* called membranolides;[5] in particular, membranolides C and D showed antimycotic and antibiotic activity against *Candida albicans* and Gram-negative bacteria (Figure 2.1).

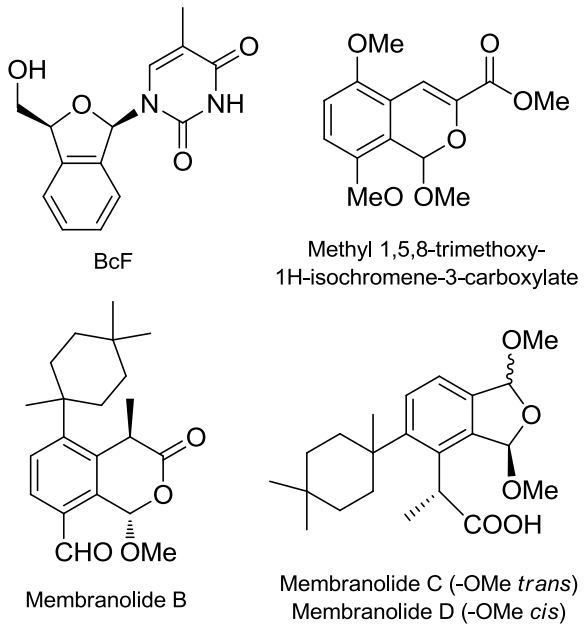
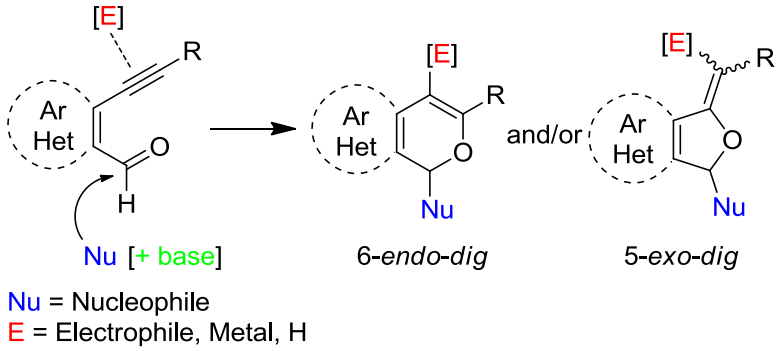


Figure 2.1 – Biologically active isobenzofurans and isochromenes.

The use of *ortho*-alkynylbenzaldehydes and related (hetero)aromatic systems as building blocks for the preparation of dihydroisobenzofuran and isochromene derivatives by sequential inter/intramolecular nucleophilic addition is well documented, and a variety of nucleophiles have been used to do this. Two main conceptually different approaches have been employed: enhancing the strength of the nucleophile with a base[6] and the activation of triple bond with a suitable agent such as an electrophile[7] or a metal catalyst[8] (Scheme 2.2).



Scheme 2.2 – Approaches to dihydroisobenzofuran and isochromene derivatives.

The cyclisation mode (5-*exo-dig* or 6-*endo-dig*) is strongly influenced by several factors, in particular, the nature of the carbonyl group,[7a,b] of the activating agent (base,[6] electrophile[7] or metal catalyst[8]), of the aromatic carbonyl compound[6a,c] (i.e. the presence of one or more nitrogens in the aromatic ring) and of the substituent on triple bond.[6a,8e]

Much work in this field focused on the use of oxygen nucleophiles in the presence of a metal catalyst. Belmont and co-workers have recently developed a silver-catalysed divergent synthesis of furoquinolines and pyranoquinolines starting from 1-alkynyl-2-carbonylquinolines in the presence of primary, secondary, tertiary and benzyl alcohols.[8e] The cyclisation mode is determined by the nature of the silver salt employed as catalyst. It is interesting to note that an inversion of regioselectivity was observed when the same catalyst was used in the presence of an aryl substituent on the triple bond; moreover, only two isolated examples concerning simple alkynylbenzaldehyde derivatives have been reported. Yamamoto and co-workers reported two elegant approaches for the synthesis of isochromenes in the presence of primary and secondary alcohols starting from alkynylbenzaldehydes. The reactions were catalysed by Pd(II)[8b] and Cu(I)[8c] salts, respectively, and the authors claim that these metals performed a dual role of Lewis acid and transition-metal catalyst.

Some different approaches involve the use of an electrophilic reagent that is able to activate/functionalise the triple bond; among them, it is worth noting the multicomponent synthesis of iodinated isochromenes developed by Barluenga's group starting from *ortho*-alkynylarene- and heteroarene-carboxyaldehydes in the presence of IPy_2BF_4 and nucleophiles (in particular oxygen nucleophiles).[7a,b] Moreover, starting from *ortho*-alkynylbenzaldehydes, Larock and co-workers reported a similar approach to isochromenes that takes advantage of milder reaction conditions and from the possibility of using a wide variety of different electrophiles.[7c,d]

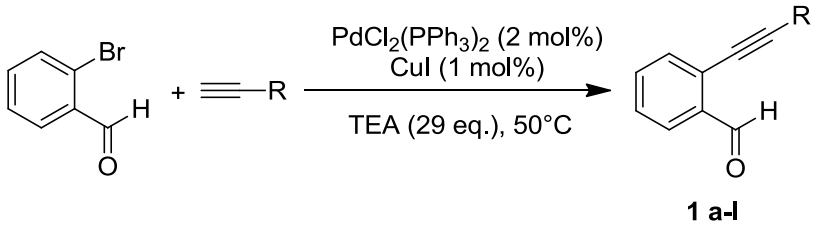
The simple base-promoted approach to these systems was first reported by Belmont and co-workers, starting from 1-alkynyl-2-carbonylquinolines.[6a] Here, the regioselectivity was exclusively determined by the nature of the substituent on the triple bond. In particular, in the presence of TMS, $CH(OEt)_2$ or CH_2OTHP groups, a regiospecific 5-*exo-dig* mode was observed, whereas – interestingly – phenyl substitution result in a 6-*endo-dig* cyclisation mode. It is worth noting that a reverse selectivity was

recently observed by Terada[6d] and Cikotiene[6c] in the base-promoted addition/cyclisation of alcohols on 2-(phenylethynyl)benzaldehyde and 4-amino-6-(phenylethynyl)pyrimidine-5-carbaldehyde, respectively. In particular, in 2009, Terada and co-workers reported the cyclisation of a range of substituted alkynylbenzaldehydes in the presence of isopropanol and a phosphazene base; the reactions worked well when the substituent was either an aryl or an ethoxycarbonyl group, but failed when the substituent was *n*-butyl, TMS or hydrogen.[6d]

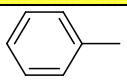
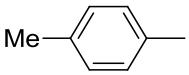
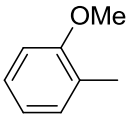
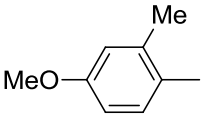
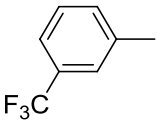
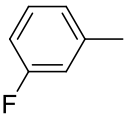
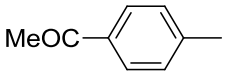
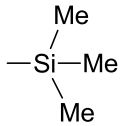
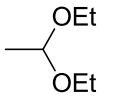
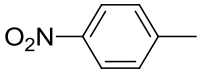
In this contest, we wished to explore *in-depth* the base-promoted domino nucleophilic addition/annulation of simple *ortho*-alkynylbenzaldehydes in the presence of alcohols. In particular, we focused our attention on the selective synthesis of the dihydroisobenzofuran skeleton. Moreover, we analysed the relationship between the nature of the substituent on the alkynyl terminus and the path of the reaction.

2.2 Results and discussion

First, a rational library of starting compounds was prepared. The *ortho*-alkynylbenzaldehydes **1a–l**, variously substituted on triple bond, were synthesised in moderate to excellent yields starting from commercially available *ortho*-bromobenzaldheyde and a selection of terminal acetylenes using typical Sonogashira coupling conditions[9] (Table 2.1).



1 a-l

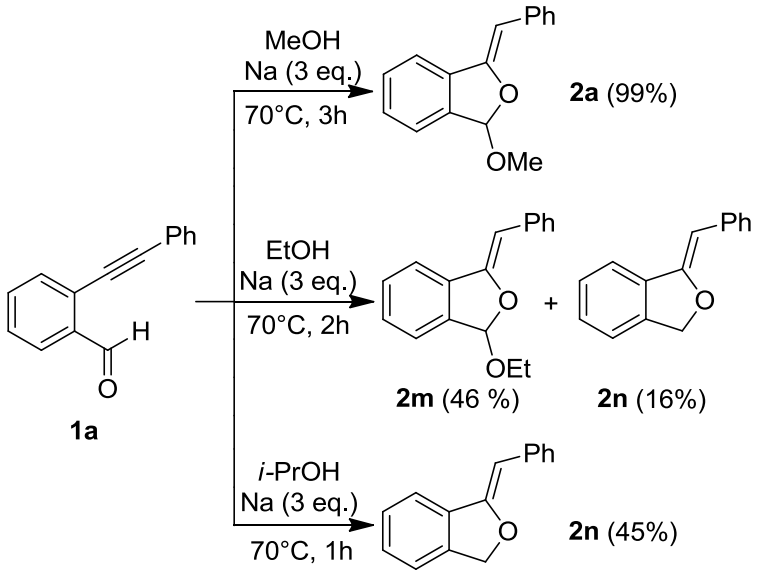
R	t (h)	Product	Yield (%)[a]
	1	**1a**	91
	4	**1b**	78
	7	**1c**	59
	4.5	**1d**	90
	6	**1e**	74
	6	**1f**	87
	2	**1g**	84[b]
	2.5	**1h**	99
	4	**1i**	89
	15	**1j**	80
$CH_3(CH_2)_4$—	4	**1k**	91
$CH_3(CH_2)_7$—	3	**1l**	84

[a] Yields refer to pure isolated product.

[b] Prepared by reaction of 2-ethynylbenzaldehyde (quantitatively obtained by treatment of **1h** with 2 eq. of K_2CO_3 in MeOH at room temp.) with 4-iodoacetophenone under standard Sonogashira conditions.

Table 2.1 – Preparation of *ortho*-alkynylbenzaldehydes **1a–l**.

Aldehyde **1a** was used as a model compound to test the effectiveness of our base-promoted synthetic approach[1] to these new substrates. Thus, sodium was added to the appropriate anhydrous alcohol under a nitrogen atmosphere and, only when the metal was completely dissolved, the *ortho*-alkynylbenzaldehyde **1a** was added and the mixture stirred at 70 °C (Scheme 2.3).



Scheme 2.3 – Base-promoted synthetic approaches.

The reaction with methanol resulted in the selective formation of the (*Z*)-1-benzylidene-3-methoxy-1,3-dihydroisobenzofuran **2a** in high yield. In contrast, under the same conditions, the reaction with ethanol gave the expected dihydroisobenzofuran **2m** in only 46% yield, together with a small amount of the unsubstituted (*Z*)-1-benzylidene-1,3-dihydroisobenzofuran **2n**. Moreover, in the presence of a more hindered alcohol such as isopropanol, **2n** was the only product obtained (Scheme 2.3). The structure and the geometry of compounds **2a**[8a] and **2n**[10] were determined by comparison of their experimental data with those reported in the literature. The formation of by-product **2n** could be explained by a preliminary reduction of aldehyde **1a** to give the (2-(phenylethynyl)benzyl alcohol, followed by a base-promoted intramolecular cyclisation. The benzyl alcohol could arise from a sodium-promoted Bouveault-Blanc-type[11] radical reduction or from a Canizzaro disproportionation reaction.[12] However, only the reductive reaction pathway was observed in the reaction of **1a** with isopropanol; it is interesting to note that after one hour, as expected, the major product detected by ^{1}H NMR in the crude reaction mixture was the (2-(phenylethynyl)benzyl alcohol.

With the aim of avoiding the formation of **2n**, the reaction conditions were modified by changing the amount and nature of the base, the reaction temperature, and the energy source; the use of two radical traps was also investigated. The results are shown in Table 2.2.

Entry	Alcohol	Base/ Additive	Energy	t (min)	T (°C)	2m (yield%)[a]	2n (yield%)[a]
1	EtOH	Na (3 eq.)/ TEMPO	Oil bath	60	70	29	30
2	EtOH	Na (3 eq.)/ BQ	Oil bath	60	70	38[b]	20[b]
3	EtOH	Na (1.5 eq.)	Oil bath	240	50	41	14
4	EtOH	Na (3 eq.)	μW	15	100	25[b]	59[b]
5	EtOH	*t*-BuOK (1 eq.)	Oil bath	120	70	33[b]	18[b]
6	EtOH	*t*-BuOK (3 eq.)	μW	20	100	50	15
7	EtOH	*t*-BuOK (3 eq.)	μW	30	80	59	8
8	*i*-PrOH	*t*-BuOK (3 eq.)	μW	30	80	–	40

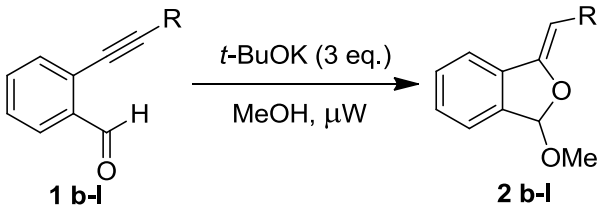
[a] Yields refer to pure isolated product.

[b] Yields calculated from ^{1}H NMR analysis of the crude material.

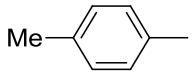
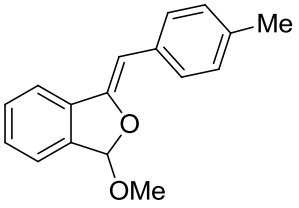
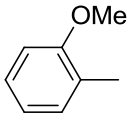
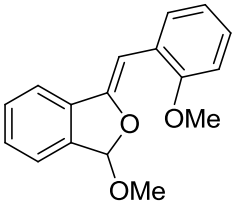
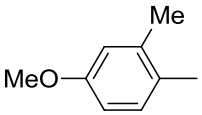
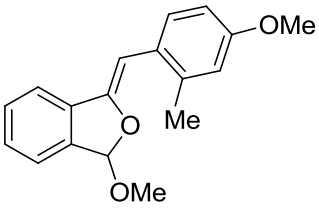
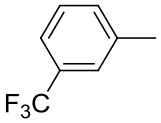
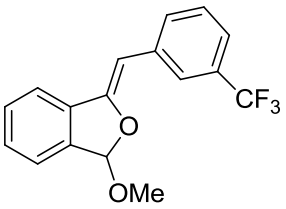
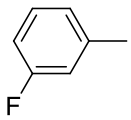
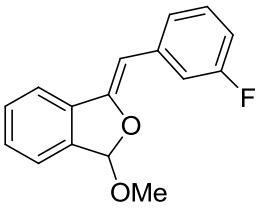
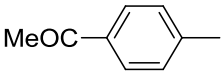
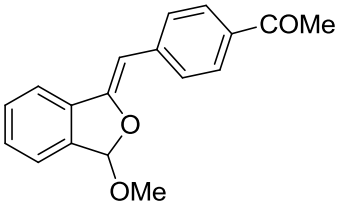
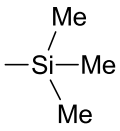
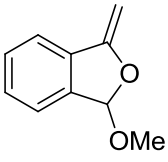
Table 2.2 – Optimisation of the reaction of **1a** with higher alcohols.

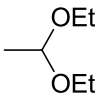
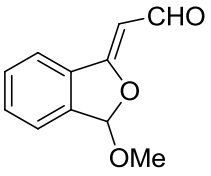
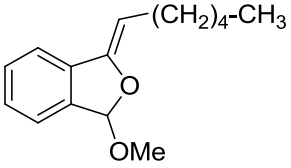
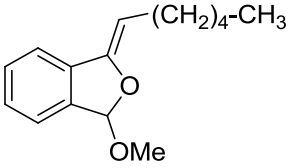
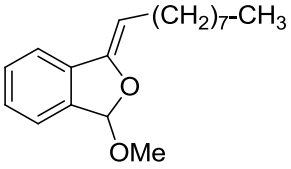
All attempts to restrict the involvement of radical species by using radical inhibitor additives such as TEMPO and 1,4-benzoquinone (BQ) were unsuccessful (Table 2.2, entries 1 and 2). Use of less sodium gave almost the same result, but the reaction required longer reaction times (Table 2.2, entry 3). Use of microwave irradiation as an energy source[13] gave a moderate improvement in conversion yield but led to a less favourable ratio between amount of **2m** and **2n** formed (Table 2.2, entry 4). To avoid the formation of radical species, a preformed base was also tested (Table 2.2, entries 5-7). The most chemoselective and effective conditions found involved the use of 3 eq. of potassium *tert*-butoxide (*t*-BuOK) and microwave heating at 80 °C (Table 2.2, entry 7). Unfortunately, even under these optimised conditions, the reaction with isopropanol failed completely; under these conditions, **2n** was isolated in 40 % yield along with a mixture of other unidentified by-products (Table 2.2, entry 8).

On the basis of these preliminary results, we focused our study on the base-promoted addition/annulation reactions of aldehydes **1** with methanol using the new reaction conditions tested for ethanol (i.e. *t*-BuOK *vs.* Na and microwaves *vs.* conventional heating). The results of the addition/annulation reactions of aldehydes **1b-l** with methanol and potassium *tert*-butoxide under microwave heating are depicted in Table 2.3.



1 b-l 2 b-l

Entry	1	R	T (°C)	t (min)	2 (yield %)[a]
1	**1b**		110	30	 **2b** (100) [b]
2	**1c**		110	75	 **2c** (82)
3	**1d**		110	150	 **2d** (84)
4	**1e**		110	30	 **2e** (96)
5	**1f**		110	30	 (100) **2f**
6	**1g**		110	30	 **2g** (77)
7	**1h**		70	10	 **2h** (93)

8	**1i**		110	30		**2i** (100)
9	**1k**	$CH_3(CH_2)_4$—	70	180		**2k** (-)[c]
10	**1k**	$CH_3(CH_2)_4$—	130	45		**2k** (-)[d]
11	**1l**	$CH_3(CH_2)_7$—	150	30		**2l** (-)[e]

[a] Yields refer to pure products after simple work-up of the reactions.

[b] Under conventional heating at 110°C the reaction gave **2b** in 98% yield in 3 h.

[c] The starting material was almost quantitatively recovered.

[d] Complex mixture with a small amount of starting material (detected by ^{1}H NMR of the crude material).

[e] Complex mixture. Main product isochromene **3l** (detected by ^{1}H NMR of the crude material).

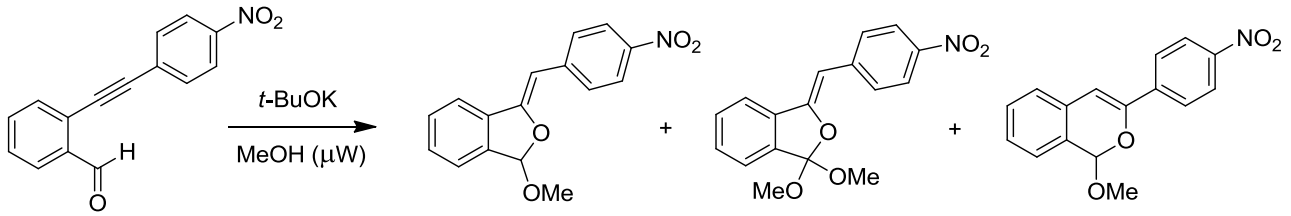
Table 2.3 – Addition/annulation reactions of aldehyde **1b-l**.

In most cases, the reactions proceeded with complete regio- and stereo-specificity,[14] leading to the formation of the corresponding (*Z*)-dihydroisobenzofurans[15] in high yields (Table 2.3, entries 1-8). The presence of common electron-donating (Table 2.3, entries 1-3) and electron-withdrawing groups (Table 2.3, entries 4-6) on the aryl substituent were well tolerated, even when they were in the sterically demanding *ortho*-position (Table 2.3, entries 2 and 3). The presence of a trimethylsilyl group on the triple bond affected neither the yield nor the selectivity of the reaction, leading to the direct formation of the desilylated dihydroisobenzofuran **2h** in reduced time and at lower temperature[16] (Table 2.3, entry 7). When the triple bond was substituted with an acetal moiety, the reaction directly gave the hydrolysis product **2i** in quantitative yield (Table 2.3, entry 8). A different behaviour was observed when aldehydes bearing a simple aliphatic chain on the alkyne terminus were used. The reaction of 2-(hept-1-ynyl)benzaldehyde **1k** at 70°C failed (Table 2.3, entry 9) and the starting material was recovered in almost quantitative yield. At 130 °C, a more complex mixture of compounds containing the starting material was obtained (Table 2.3, entry 10), whereas when the superior homologue **1l** was heated at 150 °C, a mixture of products with traces of isochromene **3l** were identified, along with decomposition compounds (identified by ^{1}H NMR analysis of the crude reaction ; Table 2.3, entry 11).

The aldehyde **1j** showed a particular behaviour, as depicted in Table 2.4. When the reaction was performed under standard conditions, a mixture of 5-*exo-dig* **2j** and 6-*endo-dig* **3j** cyclisation products were formed in a ratio of 13:7 (Table 2.4, entry 1). At room temperature, the reaction was six times slower and the formation of the 6-*endo-dig* product was slightly favoured, leading to a 3:2 mixture of **2j** and **3j** (Table 2.4, entry 2). By increasing the reaction temperature, a moderate increase in the amount

of **2j** was observed, along with the appearance of a small amount of the dimethyl orthoester **2'j**, arising from a base-promoted double substitution on the carbonyl carbon[17] (Table 2.4, entry 3).

To avoid the formation of **2'j**, the amount of base was reduced to 1.1 eq.: under these conditions, the desired product **2j** was obtained in 78 % yield along with only a small amount of by-products **2'j** and **3j** (Table 2.4, entry 4).



1j **2j** **2'j** **3j**

Entry	*t*-BuOK (eq.)	t (min)	T (°C)	Yield (%)[a]	Ratio (%)[b]		
					2j	2'j	3j
1	3	30	110 (μW)	98	65	–	35
2	3	180	rt	100	58[c]	–	42[d]
3	3	10	150 (μW)	100	72	20	8
4	1.1	10	150 (μW)	100	78	10	12

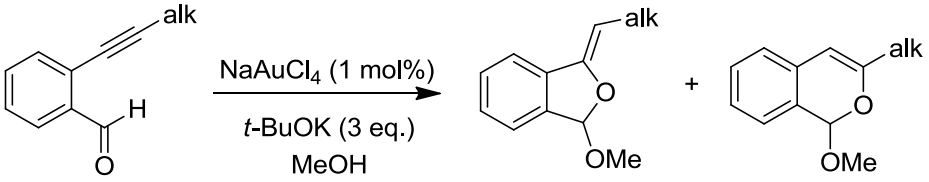
[a] Yields refer to the mixture of products after simple work-up of the crude material.

[b] Ratios were determined by ^{1}H NMR spectra of the crude material.

[c] Isolated yield: 53%. [d] Isolated yield: 40%.

Table 2.4 – Reactions of aldehyde **1j**.

To overcome the unsatisfactory results obtained with the aldehydes **1k** and **1l**, we enhanced the reactivity of the triple bond with a suitable metal catalyst.[18] Amongst the metals tested,[19] the best results were obtained with gold,[20] in particular with an Au(III) salt, whose properties as an alkynophilic Lewis acid are well known.[21] The reactions were carried out in methanol in the presence of 3 eq. of potassium *tert*-butoxide at different temperatures, as summarised in Table 2.5.



1k,l **2k,l** **3k,l**

Entry	1	t (h)	T (°C)	Yield (%)[a]	Ratio (%)[b]	
					2	3
1	**1l**	0.75	110 (μW)	98	**2l** (64)	**3l** (36)
2	**1l**	2.5	70 (μW)	99	**2l** (69)	**3l** (31)
3	**1l**	24	rt	99	**2l** (87)[c]	**3l** (13)
4	**1k**	24	rt	98	**2k** (87)[d]	**3k** (13)

[a] Yields refer to the mixture of products after simple work-up of the crude material.

[b] Ratios were determined by ^{1}H NMR spectra of the crude material.

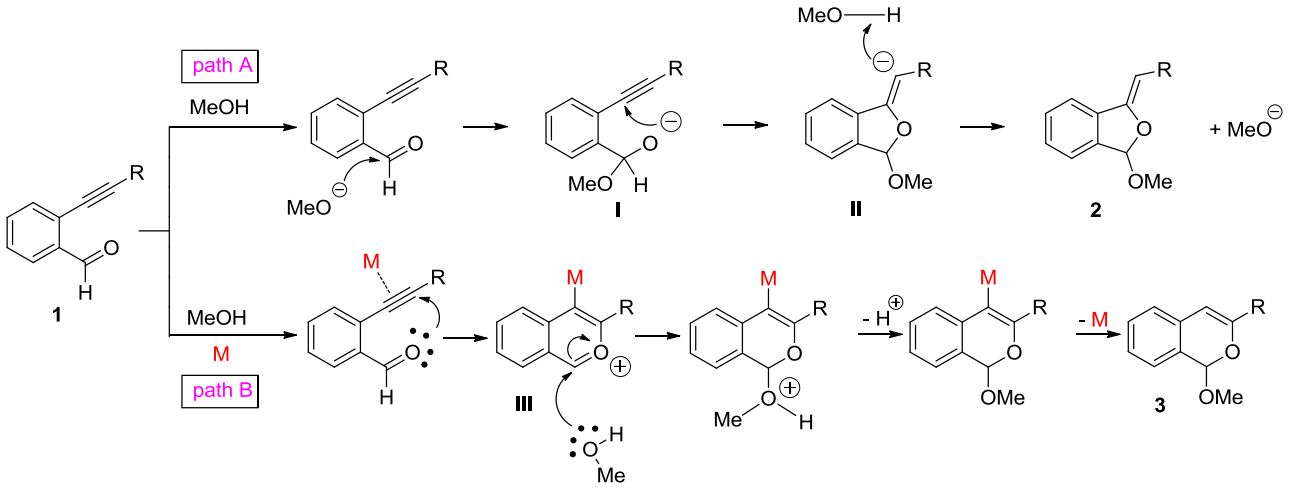
[c] Isolated yield: 83%. [d] Isolated yield: 80%.

Table 2.5 – Gold(III)-catalysed reactions of aldehydes **1k** and **1l**.

Under microwave irradiation at 110 °C, the gold(III)-catalysed reaction of aldehyde **1l** gave a mixture of dihydroisobenzofuran **2l** and isochromene **3l** in a ratio of 16:9 (Table 2.5, entry 1). By decreasing the reaction temperature to 70 °C, a slight increase in the amount of 5-*exo-dig* isomer formed was observed (Table 2.5, entry 2). These results prompted us to perform the reaction at room temperature; under these conditions, **2l** and **2k** were isolated in high yields after more prolonged reaction times (Table 2.5, entries 3 and 4).

According to the literature,[1,6c] the suggested mechanism for the base-triggered nucleophilic addition/annulation sequence involves four steps: a) potassium *tert*-butoxide promoted formation of the strong nucleophilic methoxide anion; b) addition of the methoxide to the aldehyde leading to the formation of a transient hemiacetal anion **I**; c) 5-*exo-dig* cyclisation by attack of the hemiacetal anion on the triple bond to give the anion **II**; d) solvent-assisted protonation to give the dihydroisobenzofuran nucleus (Scheme 2.4, path A).

On the other hand, when the reaction was performed with weaker nucleophiles, such as alcohols, but in the presence of a metal catalyst capable of increasing the electrophilicity of triple bonds – i.e. carbophilic Lewis acids such as gold or silver – the reaction followed a different path: the metal-activated alkyne forms a π-complex that is liable to nucleophilic attach directly from the oxygen of the carbonyl to give a highly reactive benzopyrylium intermediate **III** (auric[22] or silver[8e] ate complex) through a 6-*endo-dig* cyclisation reaction. The nucleophile can then attack the benzopyrylium intermediate and lead to catalyst recycling by protodemetallation (Scheme 2.4, path B) with formation of the isochromene derivative **3**. As suggested by several authors, the driving force for path B, is the formation of the aromatic benzopyrylium intermediate **III**, stabilised by resonance.



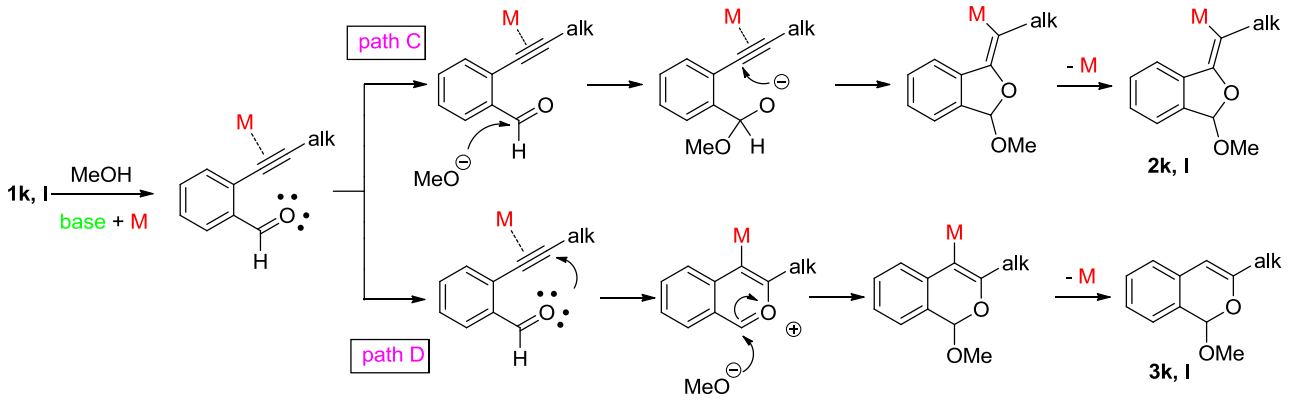
Scheme 2.4 – Mechanism insights.

Although the Csp-carbon proximate to the carbonyl group (Cα) has a larger electron density with respect to the distal carbons (Cβ) - as can be established by the analysis of the relative ^{13}C NMR chemical shifts[23] - the almost exclusive intramolecular nucleophilic attack at Cα in the base-promoted cyclisation clearly suggests that the reaction is not primarily governed by simple electronic factors. In our opinion, steric aspects related to the dimensions of the hemiacetal anion and of the substituent at the alkynyl terminus could both affect path A. Several theoretical studies indicate that the favoured path of approach of a nucleophile to a triple bond is at an obtuse angle of 120-127°.[24] Furthermore, the formation of the 5-*exo* cyclisation product **2** is also preferential and high yielding when the alkyne terminus bears an aromatic ring (see Table 2.3, entries 1-6) or a group that is potentially able to stabilise

the α-anion of the intermediate **II** (see Table 2.3, entry 8).[10, 25] Interestingly, the electronic properties of the aromatic ring do not seem to strongly influence the reaction yield and selectivity.[26]

When the alkyne is substituted with an alkyl framework (**1k,l**), the stabilisation of the α-anion of the intermediate **II** cannot occur. Moreover, the Cα of **1k** and **1l** have larger electron densities with respect to the Cα of alkynylaldehydes substituted with aromatic frameworks. This is verifiable by comparison of the relative ^{13}C-NMR chemical shifts: when the alkyne is substituted with an aryl group the chemical shift of the Cα lies at nearly 85 ppm, whereas in the presence of an aliphatic chain the chemical shift slide to nearly 76 ppm.[22]

These two reasons probably explain the failure of simple base-promoted reactions of alkyl alkynes (Table 2.3, entries 9 and 10). However, when the reaction of **1k** or **1l** was carried out in the presence of a suitable alkynophilic metal catalyst (see Table 2.5), a competition between the two mechanisms is observed (Scheme 2.5): the metal activates the triple bond, which can then undergo intramolecular nucleophilic attack by the strong hemiacetal anion (Scheme 2.5, path C) or by the weaker aldehyde oxygen (Scheme 2.5, path D). Under these reaction conditions, the formation of dihydroisobenzofurans seems to be kinetically governed and favoured by long reaction times at low temperatures (Table 2.5, entries 3 and 4); in contrast, the formation of isochromenes is probably a thermodynamically controlled process and thus promoted by higher temperatures (Table 2.5, entries 1 and 2).



Scheme 2.5 – Mechanism insights.

The anomalous behaviour of aldehyde **1j** under basic conditions is still not completely clarified. Probably, with respect to the other benzaldehydes, the strong electron-withdrawing character of the nitro group perturbs the electronic density of the triple bond, thus enhancing its reactivity to the detriment of selectivity. This is in agreement with the ^{13}C NMR chemical shifts of triple bond carbons observed for **2j** (Cα: δ = 90.2 ppm and Cβ: δ = 94.0 ppm); the greater reactivity of **2j** was also confirmed by the observation that the reaction also proceeded - though with poor selectivity - at room temperature in a reasonable reaction time (see Table 2.4, entry 2).

2.3 Conclusion

In conclusion, the present study confirmed once again the versatility of nucleophilic addition/annulation domino reactions of acetylenic compounds bearing a proximate nucleophile in the synthesis of heterocyclic systems. The regiospecificity of the uncatalysed microwave-assisted/base-promoted reactions of aryl-, TMS- and diethoxymethyl-substituted alkynylbenzaldehydes and the high regioselectivity of gold-catalysed/base-promoted reactions of alkyl substituted alkynylbenzaldehydes represent valuable alternatives for the effective synthesis of dihydroisobenzofurans.

2.4 Experimental section

General details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F254 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 with a FT-IR spectrophotometer using KBr tablets for solids and NaCl disks for oils. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$, at 200 or 500 MHz, with residual chloroform as the internal reference (δH = 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 (δC = 77.3 ppm). The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. 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. Microwave-assisted reactions were performed with a MILESTONE microSYNT multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with a fiber optic sensor.

General Procedure for the synthesis of 2-alkynylbenzaldehydes 1a–l. Under a nitrogen atmosphere, to a solution of *ortho*-bromobenzaldehyde (2.50 mmol) in TEA (10 mL), the appropriate alkyne (2.55 mmol) and *trans*-dichlorobis(triphenylphosphine)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 until no more starting product was detectable by TLC analysis (eluent: 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 2.1).

2-(Phenylethynyl)benzaldehyde (1a). 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.[27]

2-(*p*-Tolylethynyl)benzaldehyde (1b). 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.[29]

2-((2-Methoxyphenyl)ethynyl)benzaldehyde (1c). 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}. ^{1}H 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 (1d). 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}. ^{1}H 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-((3-(Trifluoromethyl)phenyl)ethynyl)benzaldehyde (1e). 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 (1f). 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 (1g). 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}. ^{1}H 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-((Trimethylsilyl)ethynyl)benzaldehyde (1h). Eluent for chromatography: hexane/EtOAc (99:1). Yield 501 mg (99 %). 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.[30]

2-(3,3-Diethoxyprop-1-ynyl)benzaldehyde (1i). 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]

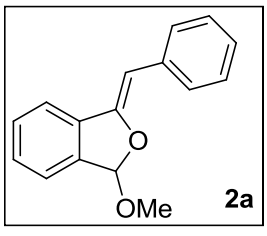
2-[(4-Nitrophenyl)ethynyl]benzaldehyde (1j). Eluent for chromatography: hexane/EtOAc (98:2). Yield 502 mg (80 %). Yellow solid. Mp 136–138 °C. IR (KBr): ν_{max} = 1697, 1588, 1513, 1341, 856, 763 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.51–7.69 (m, 5H, arom.), 7.99 (d, J = 7.2 Hz, 1H, arom.), 8.26 (d, J = 9.2 Hz, 2H, arom.), 10.60 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 90.2, 94.0, 124.0, 125.4, 128.2, 129.4, 129.9, 132.7, 133.8, 134.1, 136.4, 147.7, 191.1 ppm. These data are in good agreement with literature values.[32]

2-(Hept-1-ynyl)benzaldehyde (1k). 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, 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.[33]

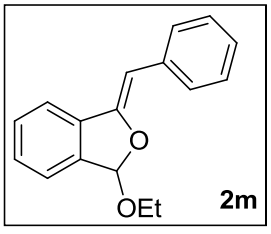
2-(Dec-1-ynyl)benzaldehyde (1l). Eluent for chromatography: hexane/EtOAc (99:1). Yield 509 mg (84 %). Yellow oil. IR (neat): ν_{max} = 2927, 2855, 2230, 1698, 1595, 762 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (m, 3H, CH_3), 1.28–1.70 (m, 12H, CH_2), 2.47 (t, J = 7.0 Hz, 2 H, C_{sp}–CH_2), 7.38 (m, 1H, arom.), 7.50 (m, 2H, arom.), 7.88 (d, J = 7.3 Hz, 1H, arom.), 10.54 (s, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 14.3, 19.8, 22.9, 28.7, 29.2, 29.3, 29.4, 32.1, 76.6, 98.5, 127.1, 128.1, 128.2, 133.5, 133.9, 136.2, 192.4 ppm. These data are in good agreement with literature values.[34]

General Procedure for the sodium-promoted/thermal cyclisation of 2-alkynylbenzaldehyde 1a. In a 25 mL round-bottom flask, Na (1.46 mmol) was dissolved in the appropriate anhydrous alcohol (2 mL) under a nitrogen atmosphere. When the Na was completely dissolved, the 2-alkynylbenzaldehyde **1a** (0.49 mmol) was added. The mixture was stirred at 70 °C until no more starting material was detectable by TLC (eluent: CH_2Cl_2/hexane 8:2). The reaction mixture was poured into sat. $NaHCO_3$ (40 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were collected, dried over Na_2SO_4 and the solvent was removed at reduced pressure. In the reaction with MeOH, the crude product was sufficiently pure and did not require further purification steps. In the reactions with EtOH and *i*-PrOH, the crude material was purified by flash column chromatography over silica gel.

(*Z*)-1-Benzylidene-3-methoxy-1,3-dihydroisobenzo-furan (2a). Yield 115 mg (99 %). Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.51 (s, 3H, CH_3), 6.01 (s, 1H, C_{sp2}–H), 6.57 (s, 1 H, C_{sp3}–H), 7.18–7.76 (m, 7H, arom.), 7.81 (d, J = 7.7 Hz, 2H, arom.) ppm. These data are in good agreement with literature values.[8a,e]

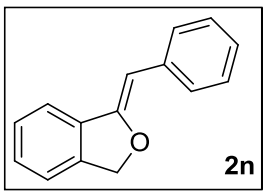


(*Z*)-1-Benzylidene-3-ethoxy-1,3-dihydroisobenzo-furan (2m). Eluent for chromatography: hexane/EtOAc (99:1). Yield 56 mg (46%). White waxy solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.32 (t, J = 7.3 Hz, 3H, CH_3), 3.84 (m, 2H, CH_2), 6.00 (s, 1H, C_{sp2}–H), 6.62 (s, 1H, C_{sp3}–H), 7.15–7.61 (m, 7H, arom.), 7.80 (d, J = 7.2 Hz ,2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.5, 63.6, 98.2, 107.1, 119.9, 123.3, 126.0, 128.5, 128.6, 129.1, 130.0, 135.8, 136.2, 137.7, 153.3 ppm. ESI-MS m/z (%): 253 $[M + 1]^+$ (52), 207 $[M - OCH_2CH_3]^+$ (100). Calcd for



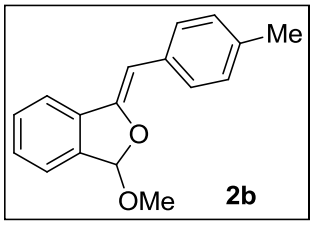
$C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.84; H, 6.40.

(*Z*)-1-Benzylidene-1,3-dihydroisobenzofuran (2n). Eluent for chromatography: hexane/EtOAc (99:1). Yield 16 mg (16 %). White solid. Mp 51-53 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.53 (s, 2H, CH_2), 5.96 (s, 1H, Csp_2–H), 7.14 (t, J = 7.3 Hz ,1H, arom.) 7.30–7.40 (m, 5H, arom.), 7.59 (m, 1H, arom.) 7.74 (d, J = 7.3 Hz ,2H, arom.) ppm. These data are in good agreement with literature values.[10,24]

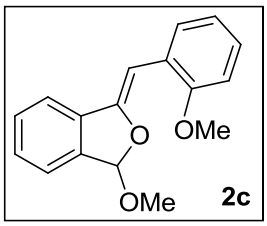


General Procedure for the base-promoted/microwave-assisted cyclisation of 2-alkynylbenzaldehydes 1b-j. A well stirred solution of the appropriate *o*-alkynylbenzaldehyde **1b–j** (100 mg) and *t*-BuOK (molar ratio **1**/*t*-BuOK = 1:3) in anhydrous methanol (4 mL) was heated at 70–110 °C in a sealed tube for 10–150 min in a multimode microwave oven until no more starting material was detectable by TLC. Then, the reaction mixture was diluted with sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to yield 1,3-dihydroisobenzofurans **2** (for temperatures and times, see Table 2.3). The products obtained in this way were sufficiently pure and did not need further purification.

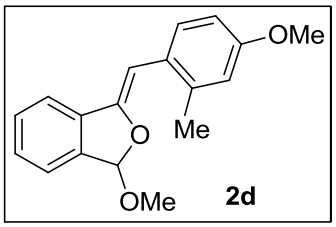
(*Z*)-1-Methoxy-3-(4-methylbenzylidene)-1,3-dihydro-isobenzofuran (2b). Yield 114 mg (100%). Yellow oil. IR (neat): ν_{max} = 3022, 2923, 1661, 1467, 1373, 1115, 1089, 835, 759 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.36 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 5.98 (s, 1H, C_{sp2}–H), 6.56 (s, 1H, C_{sp3}–H), 7.17 (d, J = 8.1 Hz, 2H, arom.), 7.32–7.59 (m, 4H, arom.), 7.68 (d, J = 8.1 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.5, 54.4, 98.5, 107.5, 119.9, 123.3, 128.5, 129.0, 129.4, 130.1, 133.2, 135.9, 136.0, 136.9, 152.6 ppm. ESI-MS m/z (%): 253 $[M + 1]^+$ (100), 222 $[M - OCH_3]^+$ (28). Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.66; H, 6.42.



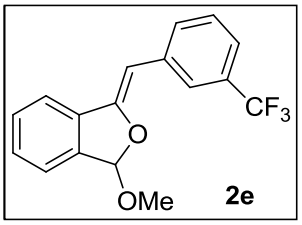
(*Z*)-1-Methoxy-3-(2-methoxybenzylidene)-1,3-dihydroisobenzofuran (2c). Yield 93 mg (82%). Yellow oil. IR (neat): ν_{max} = 3070, 2934, 1694, 1598, 1490, 1464, 1109, 1015, 835, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.48 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 6.48 (s, 1H, C_{sp2}–H), 6.57 (s, 1H, C_{sp3}–H), 6.89 (d, J = 8.1 Hz, 1H, arom.), 7.01–7.47 (m, 5H, arom.), 7.65 (d, J = 8.1 Hz, 1H, arom.), 8.29 (dd, J = 7.7, 1.5 Hz, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 54.4, 55.8, 91.6, 107.5, 110.5, 120.3, 120.9, 123.2, 124.9, 127.2, 128.9, 129.7, 130.1, 136.2, 136.9, 153.3, 156.2 ppm. ESI-MS m/z (%): 269 $[M + 1]^+$ (100), 237 $[M - OCH_3]^+$ (67). Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.88; H, 6.05.



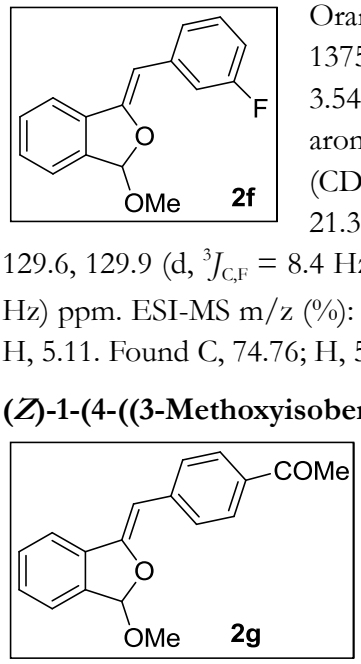
(*Z*)-1-Methoxy-3-(4-methoxy-2-methylbenzylidene)-1,3-dihydroisobenzofuran (2d). Yield 95 mg (84%). Yellow oil. IR (neat): ν_{max} = 3063, 2932, 1695, 1605, 1500, 1466, 1051, 835, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.41 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.08 (s, 1H, C_{sp2}–H), 6.54 (s, 1H, C_{sp3}–H), 6.74–6.84 (m, 2H, arom.), 7.32–7.61 (m, 4H, arom.), 8.14 (d, J = 8.4 Hz, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 54.5, 55.4, 55.5, 94.8, 107.4, 111.6, 115.9, 119.8, 123.4, 127.1, 128.9, 130.1, 130.2, 136.1, 136.8, 137.1, 151.9, 157.9 ppm. ESI-MS m/z (%): 283 $[M + 1]^+$ (20), 251 $[M - OCH_3]^+$ (100). Calcd for $C_{18}H_{18}O_3$: C, 76.57; H 6.43. Found: C, 76.39; H, 6.46.



(*Z*)-1-Methoxy-3-[3-(trifluoromethyl)benzylidene]-1,3-dihydroisobenzofuran (2e). Yield 107 mg, (96%). Yellow solid. Mp 47–48 °C. IR (KBr): ν_{max} = 3049, 2916, 1663, 1335, 755, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.56 (s, 3H, CH_3), 6.02 (s, 1H, C_{sp2}–H), 6.56 (s, 1H, C_{sp3}–H), 7.42–7.62 (m, 6H, arom.), 7.90 (d, J = 6.9 Hz, 1H, arom.), 8.07 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 55.1, 97.1, 108.1, 120.2, 122.4 (q, $^3J_{C,F}$ = 3.8 Hz), 123.4, 124.7 (q, $^1J_{C,F}$ = 272.0 Hz), 125.0 (q, $^3J_{C,F}$ = 3.8 Hz), 128.9, 129.7, 130.3, 130.9 (q, $^2J_{C,F}$ = 32.0 Hz), 131.2, 135.3, 136.9, 137.5, 154.6 ppm. ESI-MS m/z (%): 307 [M + 1]$^+$ (50). Calcd for $C_{17}H_{13}O_2F_3$: C, 66.67; H, 4.28. Found: C, 66.59; H, 4.29.

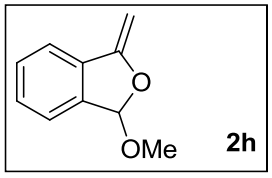


(*Z*)-1-(3-Fluorobenzylidene)-3-methoxy-1,3-dihydro-isobenzofuran (2f). Yield 114 mg (100%). Orange oil. IR (neat): ν_{max} = 3052, 2933, 1662, 1612, 1578, 1487, 1468, 1444, 1375, 1203, 1148, 1117, 960, 944, 758, 686. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.54 (s, 3H, CH_3), 5.98 (s, 1H, C_{sp2}–H), 6.57 (s, 1H, C_{sp3}–H), 6.83–6.93 (m, 1H, arom.), 7.24–7.51 (m, 5H, arom.), 7.56–7.65 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 54.8, 97.5 (d, $^4J_{C,F}$ = 2.7 Hz), 107.9, 112.9 (d, $^2J_{C,F}$ = 21.3 Hz), 114.9 (d, $^2J_{C,F}$ = 22.9 Hz), 120.2, 123.41, 124.3 (d, $^4J_{C,F}$ = 2.7 Hz), 129.6, 129.9 (d, $^3J_{C,F}$ = 8.4 Hz), 130.3, 135.5, 137.4, 138.3 (d, $^3J_{C,F}$ = 8.8 Hz), 154.2, 163.3 (d, $^1J_{C,F}$ = 244 Hz) ppm. ESI-MS m/z (%): 257 [M + 1]$^+$ (100), 225 [M – OCH_3]$^+$ (56). Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H, 5.11. Found C, 74.76; H, 5.15.

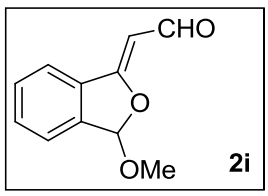


(*Z*)-1-(4-((3-Methoxyisobenzofuran-1(*3H*)-ylidene)-methyl)phenyl)ethanone (2g). Yield 87 mg (77%). Pale-yellow solid. Mp 107–110 °C. IR (KBr): ν_{max} = 3086, 2918, 1679, 1654, 1599, 1467, 1382, 1269, 1090, 944, 848, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.60 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 6.03 (s, 1H, C_{sp2}–H), 6.58 (s, 1H, C_{sp3}–H), 7.42–7.63 (m, 4H, arom.), 7.81–7.85 (d, J = 8.4 Hz, 2H, arom.), 7.93–7.97 (d, J = 8.4 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 26.7, 54.9, 97.6, 108.1, 120.4, 123.4, 128.3, 128.9, 129.9, 130.3, 134.4, 135.4, 137.5, 141.2, 155.5, 197.8 ppm. ESI-MS m/z (%): 281 [M + 1]$^+$ (100), 249 [M – OCH_3]$^+$ (22). Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.09; H, 5.75.

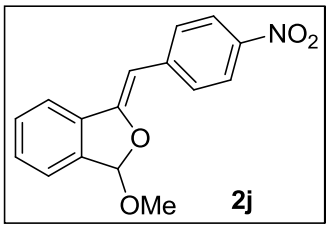
1-Methoxy-3-methylene-1,3-dihydroisobenzofuran (2h). Yield 75 mg (93%). Yellow oil. IR (neat): ν_{max} = 3079, 2934, 1668, 1467, 1377, 1210, 1100, 982, 766, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.45 (s, 3H, CH_3), 4.60 (d, J = 2.2 Hz, 1H, C_{sp2}–H), 4.63 (d, J = 2.2 Hz, 1 H, C_{sp2}–H), 6.36 (s, 1H, C_{sp3}–H), 7.38–7.54 (m, 4H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 56.8, 66.9, 103.3, 123.6, 125.7, 127.5, 131.1, 134.5, 144.9, 168.7 ppm. APCI-MS m/z (%): 163 [M + 1]$^+$ (100). Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.89; H, 6.25.



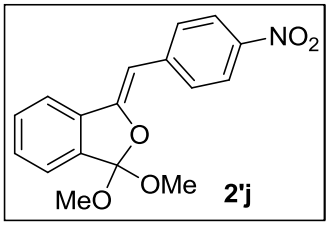
(*Z*)-2-(3-Methoxyisobenzofuran-1(*3H*)-ylidene)acetaldehyde (2i). Yield 82 mg (100%). Brown solid. Mp 99-102 °C. IR (KBr): ν_{max} = 3056, 1670, 1640, 1376, 1090, 1009, 939, 765 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.57 (s, 3H, CH_3), 5.75 (d, J = 8.4 Hz, 1H, C_{sp2}–H), 6.53 (s, 1H, C_{sp3}–H), 7.49–7.66 (m, 4H, arom.), 10.21 (d, J = 8.4 Hz, 1H, CHO) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 56.1, 99.7, 109.3, 122.5, 123.6, 130.9, 132.8, 133.1, 139.1, 169.2, 189.5 ppm. ESI-MS m/z (%): 191 [M + 1]$^+$ (40). Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.42; H, 5.28.



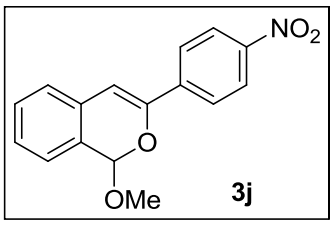
(*Z*)-1-Methoxy-3-(4-nitrobenzylidene)-1,3-dihydro-isobenzofuran (2j). Refer to the reaction conditions reported in Table 2.4, entry 2. Eluent for chromatography: cyclohexane/EtOAc/TEA (93:7:0.6). Yield 60 mg (53 %). Yellow solid. Mp 142–145 °C. IR (KBr): ν_{max} = 1654, 1589, 1510, 1385, 1337, 1088, 958, 855, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.56 (s, 3H, CH_3), 6.05 (s, 1H, C_{sp2}–H), 6.60 (s, 1H, C_{sp3}–H), 7.46–7.66 (m, 4H, arom.), 7.87 (d, J = 9.1 Hz, 2H, arom.), 8.20 (d, J = 9.1 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 55.2, 96.7, 108.5, 120.6, 123.5, 124.1, 128.5, 130.4, 130.5, 135.0, 137.8, 143.2, 145.2, 156.8 ppm. ESI-MS m/z (%): 284 $[M + 1]^+$ (100), 252 $[M - OCH_3]^+$ (33). Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N 4.94. Found: C, 67.86;, H, 4.62; N, 4.95.



(*Z*)-1,1-Dimethoxy-3-(4-nitrobenzylidene)-1,3-dihydroisobenzofuran (2'j). Refer to the reaction conditions reported in Table 2.4, entry 3. Eluent for chromatography: hexane/CH_2Cl_2 (65:35). Yellow solid. Mp 128–130 °C. IR (KBr): ν_{max} = 2921, 1656, 1589, 1508, 1334, 1466, 1307, 1132, 1111, 1089, 900, 855, 769 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.40 (s, 6H, CH_3), 6.07 (s, 1H, C_{sp2}–H), 7.44–7.64 (m, 4 H, arom.), 7.87 (d, J = 9.2 Hz, 2 H, arom.), 8.21 (d, J = 9.2 Hz, 2 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 52.0, 97.2, 120.5, 123.2, 124.2, 125.4, 128.8, 130.7, 131.1, 135.0, 135.3, 142.7, 145.5, 153.8 ppm. ESI-MS m/z (%): 314 $[M + 1]^+$ (34), 282 $[M - OCH_3]^+$ (100). Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.19; H, 4.81; N, 4.45.

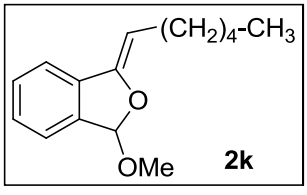


1-Methoxy-3-(4-nitrophenyl)-*1H*-isochromene (3j). Refer to the reaction conditions reported in Table 2.4, entry 2. Eluent for chromatography: cyclohexane/EtOAc/TEA (93:7:0.6). Yield 48 mg (40 %). Yellow solid. Mp 93–95 °C. IR (KBr): ν_{max} = 2929, 1645, 1591, 1503, 1385, 1347, 1067, 975, 854, 757 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz): δ = 3.21 (s, 3H, CH_3), 6.03 (s, 1H, C–H), 6.18 (s, 1H, C–H), 6.80–7.14 (m, 5 H, arom.), 7.22 (d, J = 7.7 Hz, 1 H, arom.), 7.75 (d, J = 8.9 Hz, 2 H, arom.) ppm. ^{13}C NMR (C_6D_6, 50.3 MHz): δ = 54.6, 101.4, 105.9, 122.6, 123.6, 123.7, 129.4, 129.7, 130.0, 132.6, 140.9, 142.4, 146.5, 155.9 ppm. ESI-MS m/z (%): 284 $[M + 1]^+$ (100), 252 $[M - OCH_3]^+$ (25). Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.74; H, 4.67; N, 4.91.



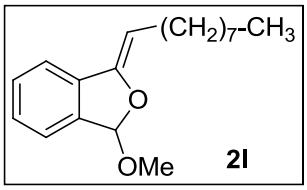
General Procedure for the base-promoted/gold-catalysed cyclisation of 2-alkynylbenzaldehydes 1k and 1l. A solution of the appropriate *o*-alkynylbenzaldehyde **1k** or **1l** (100 mg), *t*-BuOK (molar ratio **1**/*t*-BuOK = 1:3) and $NaAuCl_4 \cdot 2\ H_2O$ (1 mol%) in MeOH (4 mL) was stirred in a sealed tube at room temperature for 24 h. The reaction mixture was poured into sat. $NaHCO_3$ (20 mL), extracted with EtOAc (3 × 10 mL) and the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography over silica gel.

(*Z*)-1-Hexylidene-3-methoxy-1,3-dihydroisobenzo-furan (2k) and 1-Methoxy-3-pentyl-*1H*-isochromene (3k). The minor product **3k** was identified only by ^1H NMR analysis of the crude reaction mixture [selected significant signals in ^1H NMR (C_6D_6, 200 MHz): δ = 3.25 (s, 3 H, CH_3), 5.63 (s, 1H, C–H), 5.81 (s, 1H, C–H)]. The column chromatography of the crude gave only **2k**, whereas **3k** probably decomposed. Eluent for chromatography:



cyclohexane/EtOAc/TEA (99.2:0.2:0.6). Yield 93 mg (80 %). Pale yellow oil. IR (neat): ν_{max} = 2956, 2928, 2856, 1687, 1467, 1371, 1113, 1092, 978, 754 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz): δ = 0.86 (t, J = 7.0 Hz, 3H, CH_2–C<u>H</u>$_3$), 1.22–1.56 (m, 6H, –CH_2–), 2.49 (dt, J = 7.3, 7.3 Hz, 2H, =CH–C<u>H</u>$_2$–), 3.17 (s, 3 H, CH_3), 5.01 (t, J = 7.3 Hz, 1H, =C<u>H</u>–CH_2–), 6.19 (s, 1H, –C<u>H</u>(OCH_3)–O), 6.89–7.17 (m, 4H, arom.) ppm. ^{13}C NMR (C_6D_6, 50.3 MHz): δ = 14.2, 22.8, 25.5, 29.9, 31.8, 53.5, 98.3, 106.3, 119.4, 123.3, 128.1, 129.5, 135.3, 137.9, 153.1 ppm. ESI-MS m/z (%): 233 $[M + 1]^+$ (100), 217 $[M - CH_3]^+$ (25), 201 $[M - OCH_3]^+$ (20).

(*Z*)-1-Methoxy-3-octylidene-1,3-dihydroisobenzo-furan (2l) and 3-Heptyl-1-methoxy-*1H*-isochromene (3l). The minor product **3l** was identified only by the ^1H NMR analysis of the crude reaction mixture [selected significant signals in ^1H NMR (C_6D_6, 200 MHz): δ = 3.27 (s, 3 H, CH_3), 5.65 (s, 1H, C–H), 5.82 (s, 1H, C–H)]. The column chromatography of the crude gave only **2l**, whereas **3l** probably decomposed. Eluent for chromatography: cyclohexane/EtOAc/ TEA (99.2:0.2:0.6). Yield 94 mg (83 %). Yellow oil. IR (neat): ν_{max} = 2955, 2925, 2854, 1687, 1467, 1371, 1113, 1092, 1007, 973, 753 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz): δ = 0.85 (t, J = 7.0 Hz, 3H, CH_2–C<u>H</u>$_3$), 1.27–1.52 (m, 12H, –CH_2–), 2.52 (dt, J = 7.3, 7.3 Hz, 2H, =CH–C<u>H</u>$_2$–), 3.18 (s, 3 H, CH_3), 5.04 (t, J = 7.3 Hz, 1H, =C<u>H</u>–CH_2–), 6.20 (s, 1H, –C<u>H</u>(OCH_3)–O), 6.84–7.20 (m, 4H, arom.) ppm. ^{13}C NMR (C_6D_6, 50.3 MHz): δ = 14.2, 22.9, 25.6, 29.6, 29.7, 29.8, 30.3, 32.2, 53.5, 98.3, 106.3, 119.4, 123.3, 128.1, 129.5, 135.3, 137.9, 153.1 ppm. ESI-MS m/z (%): 275 $[M + 1]^+$ (100).



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[15] These compounds are acid-sensitive. Their stability also depends on the nature of the substituent on the exocyclic double bond. In general, they can be optimally stored for several weeks in a sealed tube, under a nitrogen atmosphere at –20 °C.

[16] The same behaviour was observed by Belmont and co-workers for the related compound 2-[(trimethylsilyl)ethynyl]-quinoline-3-carbaldehyde (see ref. 6a). In that paper, the authors also demonstrated that, under basic conditions, the desilylation occurred before the cyclisation step.

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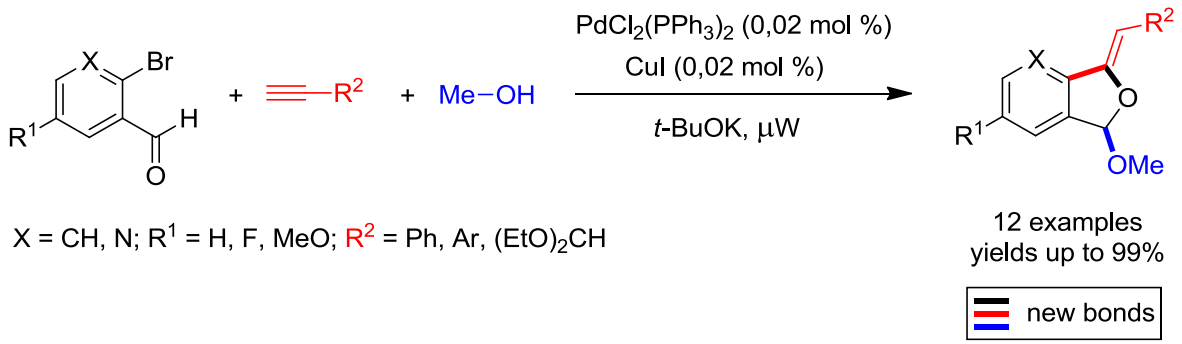
Chapter 3

From Domino to Multicomponent: Synthesis of Dihydroisobenzofurans



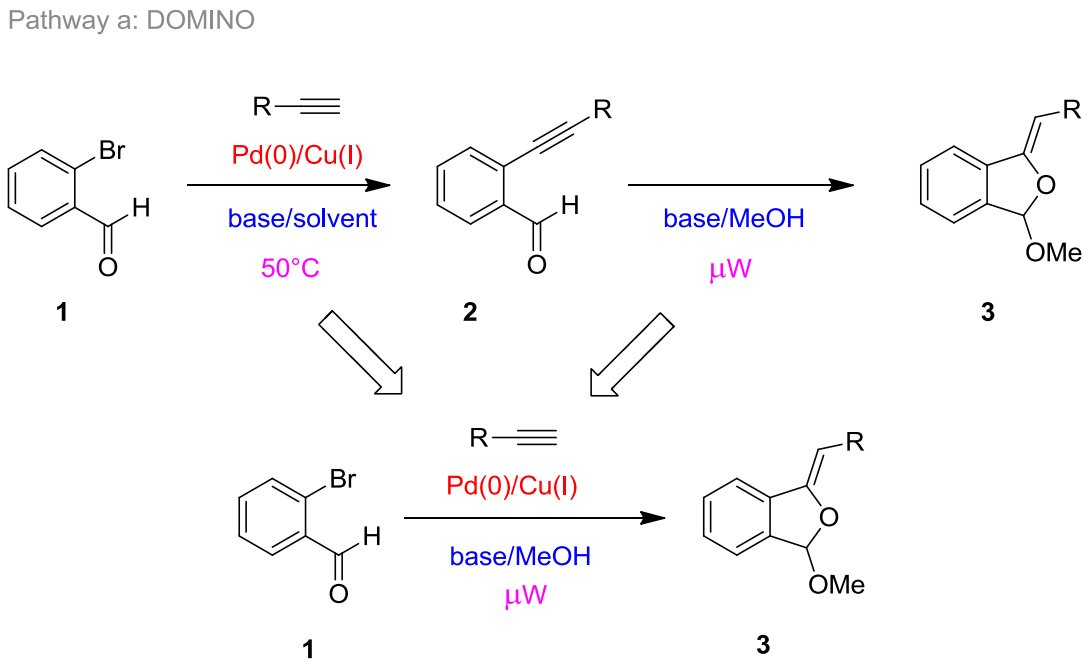
A variety of substituted dihydroisobenzofurans can be easily synthesized in high yield by a microwave-assisted three-component approach starting from *ortho*-bromoarylaldehydes, methanol and terminal alkynes. The reaction occurs through an unprecedented cooperative palladium/base promoted coupling/addition/cyclisation sequence.

Dell'Acqua, M.; Facoetti, D; Abbiati, G.; Rossi, E.

Tetrahedron **2011**, *67*, 1552–1556.

3.1 Introduction

In chapter 2, we reported a selective synthesis of the dihydroisobenzofuran skeleton by a microwave-promoted domino addition/annulation reaction of *ortho*-alkynylbenzaldehydes and methanol in the presence of a suitable base.[1] The overall process involves two steps (Scheme 3.1, pathway a): 1) the palladium-catalysed functionalization of the *ortho*-bromobenzaldehyde **1** with a proper monosubstituted acetylene derivative and 2) the base-promoted microwave-assisted domino addition/annulation reaction of the *ortho*-alkynylbenzaldehyde derivative **2** in the presence of methanol, to give the desired dihydroisobenzofuran **3**.



Scheme 3.1 – Pathways to dihydroisobenzofurans.

We wanted to simplify and optimize this procedure. These two steps of the domino approach have two common requirements: the presence of a base and the needing of an energy source. In the first step, it is presumed that the role of the base is to promote the Sonogashira coupling by abstracting the acetylenic proton from the terminal alkynes,[2] whereas in the second step, the base has the task to generate the methoxide nucleophile. On the other hand, the heat necessary for the Sonogashira coupling reaction could be easily provided by microwave radiation,[3] that, as previously reported, also effectively promote the cyclisation step.[1] Thus a proper choice of the base and reaction temperature could be key factors for the success of the planned strategy. Moreover the reagents featured in each step do not seemed to hamper the multicomponent approach; on contrary, the use of methanol as solvent for the Sonogashira coupling is well known[4] and palladium could also assist the cyclisation step enhancing the reactivity of triple bond, in particular in the presence of less reactive alkyne derivatives.[5]

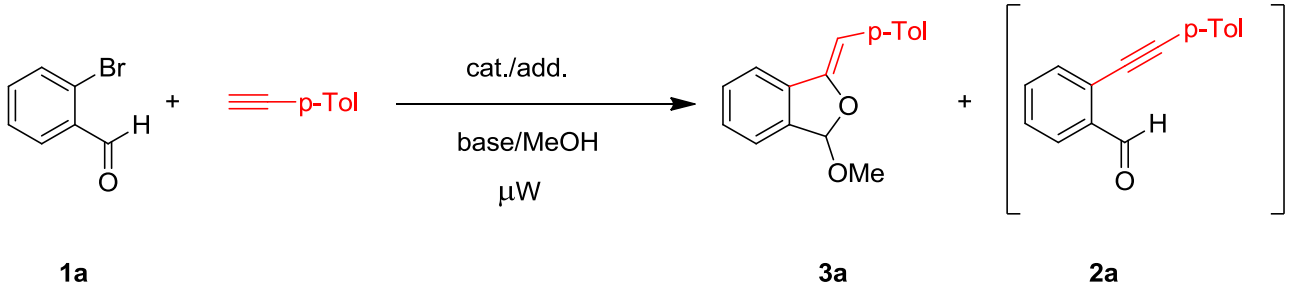
On the basis of these preliminary remarks, we planned a novel microwave-enhanced three-component synthesis of the dihydroisobenzofuran nucleus involving a one-pot coupling/addition/annulation reaction (Scheme 3.1, pathway b) promoted by palladium and base.

In the literature there are some example of MCRs involving a Sonogashira coupling as key-step for the synthesis of different heterocycles such as pyrazoles,[6] isoxazoles,[7] halofurans,[8] substituted and

annulated pyridines,[9] pyrimidines,[10] dihydroisoquinolines,[11] indoles,[12] indolizines,[13] furo[2,3-*b*]pyridones,[14] thiochromen-4-ones,[15] thiopyran-4-ones[16] and tetrahydro-β-carbolines[17] but to the best of our knowledge, this is the first example of a multicomponent synthesis of dihydroisobenzofurans.

3.2 Results and discussion

First, we looked for the optimum reaction conditions. The screening was performed with *ortho*-bromobenzadehyde **1a**, methanol and 1-ethynyl-4-methylbenzene as a model system, and the results are reported in Table 3.1.



1a **3a** **2a**

Entry	Base	Catalyst	Co-catalyst/ ligand	t (h)	T (°C)	3a (yield%)[a]	2a (yield%)[a]
1	K_2CO_3 (5 eq.)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	1	110	75	3
2	K_2CO_3 (5 eq.)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	2	80	63	17
3	*t*-BuOK (3 eq.)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	2	80	80	2
4	*t*-BuOK (3 eq.)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	1	110	63	1
5	*t*-BuOK (1 eq.)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	2	80	30[b]	60[b]
6	**t-BuOK (3 eq.)**	**$PdCl_2(PPh_3)_2$ (2 mol %)**	**CuI (2 mol %)**	**2**	**80**	**82**[c]	**1**
7	*t*-BuOK (3 eq.)	$PdCl_2(PPh_3)_2$ (2 mol %)	CuI (2 mol %)	4	60	70	3
8	*t*-BuOK (3 eq.)	$PdCl_2(PPh_3)_2$ (2 mol %)	-	2	80	67	2
9	*t*-BuOK (3 eq.)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (1 mol %)	2	80	72	1
10	*t*-BuOK (3 eq.)	CuI (10 mol %)	PPh_3 (2 mol %)	4	60	-	-
11	*t*-BuOK (3 eq.)	AgOTf (10 mol %)	PPh_3 (3 mol %)	2	80	-	-
12	*t*-BuOK (3 eq.)	AuI (1 mol %)	dppf (1 mol %)	4	80	trace	-

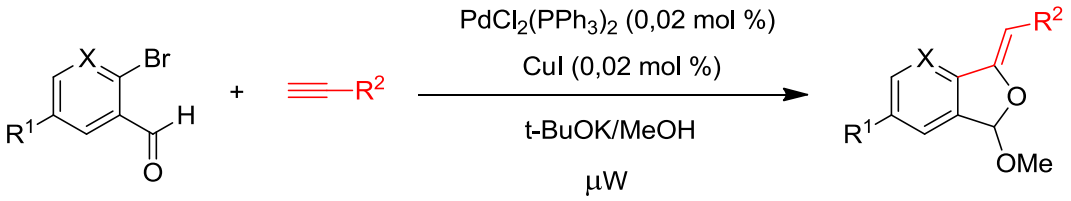
[a] Yields refer to pure isolated product. [b] Yields calculated from ^{1}H NMR spectroscopy of the reaction crude.
[c] Under conventional heating the reaction was complete in 2h and gave **3a** in 71% yield.

Table 3.1 – Optimization of the reaction conditions.

The first experiment was performed under the standard Sonogashira conditions ($Pd(PPh_3)_4$, CuI, and K_2CO_3) but with methanol as solvent and at a higher temperature by microwave irradiation. After 1 h at 110 °C the reaction gave the desired product **3a** in a promising 75% yield, with traces of the simple coupling product **2a** (Table 3.1, entry 1). The reduction of reaction temperature resulted in a worse

yield in a twofold time (Table 3.1, entry 2). In the presence of 3 eq. of a stronger base such as *t*-BuOK, (i.e. using a base analogous to that employed in Cassar reaction condition)[18] the outcome was satisfactory at 80 °C in 2 h (Table 3.1, entry 3), whereas rising the temperature to 110 °C gave poorer results (Table 3.1, entry 4). These results suggested that the use of a stronger base allowed the reaction to work at lower temperature. Next we tried to fine-tune-up the reaction conditions. The reduction of the amount of base to 1 eq. made the reaction sluggish, and the alkyne **2a** was the main product detected in the crude reaction mixture (Table 3.1, entry 5). We were pleasured to find that dichloro bis(triphenyl-phosphine)palladium(II) – cheaper than tetrakis triphenyl-phosphine palladium – gave slightly better results (Table 3.1, entry 6). A further lowering of the temperature to 60 °C gave a worse result in a twofold reaction time (Table 3.1, entry 7). The studies on copper-free Sonogashira coupling (more correctly named Cassar-Heck coupling) are widely reported in the literature,[19] and we were delighted to observe that our multicomponent approach also worked well under these favourable conditions, in spite of a modest reduction of yield (Table 3.1, entry 8). Also, half loading of the catalyst/cocatalyst gave consistent results in the same reaction time (Table 3.1, entry 9). Finally, on the basis of recent studies on palladium-free coupling between terminal alkynes and aryl halides, we tested some alternative metal promoted routes by means of copper iodide,[20] silver triflate[21] or gold iodide[22] in the presence of an appropriate phosphine ligand, but unfortunately all these conditions did not give noteworthy results (Table 3.1, entries 10-12).

With the best conditions in hand, we tested the scope and limitation of the approach by changing the substitution pattern on the triple bond, on the benzaldehyde framework and modifying the nature of the aromatic aldehyde. The reactions proceeded with complete regiospecificity, leading to the formation of the corresponding 5-*exo-dig* heterocycles in high yields (Table 3.2). The (*Z*)-configuration of the exocyclic double bond was established by comparison with literature data and our previous findings.[1]



1 **3**

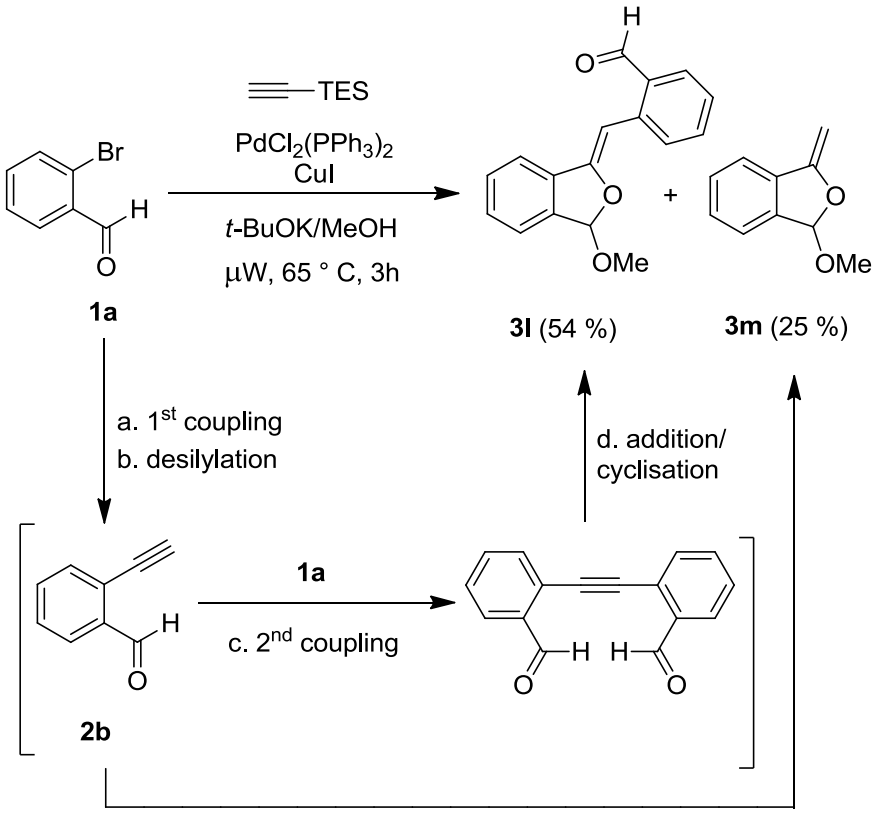
Entry	X	R^1	Aldehyde	R^2	t (h)	T (°C)	Product	Yield (%)[a]
1	CH	–H	**1a**	3-$F_3CC_6H_4$	2	80	**3b**	88
2	CH	–H	**1a**	3-FC_6H_4	2	80	**3c**	92
3	CH	–H	**1a**	4-$MeOC_6H_4$	2	130	**3d**	99
4	CH	–H	**1a**	4-MeO-2-MeC_6H_4	4	130	**3e**	79
5	CH	–H	**1a**	$(EtO)_2CH$	2	80	**3f**	89
6	N	–H	**1b**	4-MeC_6H_4	2	80	**3g**	66
7	N	–H	**1b**	4-MeC_6H_4	2	60	**3g**	78
8	N	–H	**1b**	3-FC_6H_4	2	60	**3h**	85
9	N	–H	**1b**	$(EtO)_2CH$	1	60	**3i**	77
10	CH	–F	**1c**	Ph	2	80	**3j**	98
11	CH	–OMe	**1d**	Ph	2.5	80	**3k**	88

[a] Yields refer to pure isolated product.

Table 3.2 – Scope and limitation of the 3 component approach to dihydroisobenzofuran derivatives.

Electron-poor phenylacetylenes gave excellent yield under standard conditions (Table 3.2, entries 1 and 2), whereas in the presence of an electron-donating group on the aryl moiety (Table 3.2, entry 3) the best result was obtained at 130 °C. When the electron-donating substituent on the aryl framework was in a sterically demanding *ortho*-position, a twofold reaction time was required (Table 3.2, entry 4). When the triple bond was substituted with an acetal moiety the reaction gave the corresponding dihydroisobenzofuran **3f** in very good yield (Table 2, entry 5).[23] The approach was also effective starting from the electron-poor 2-bromonicotinaldehyde **1b** (Table 2, entry 6), but for this more reactive substrate best results were obtained lowering the temperature to 60 °C (Table 3.2, entries 7-9). Finally, the effect of electron-withdrawing and electron-donating groups on the *ortho*-bromobenzaldehyde was briefly investigated (Table 3.2, entries 10 and 11). In the first case the yields are excellent under standard conditions (Table 3.2, entry 10), whereas in the presence of EDG the best result was obtained in a quite longer reaction time (Table 3.2, entry 11). Unfortunately, several attempts to react aliphatic alkynes under the standard MCR conditions completely failed, also in the presence of catalytic amounts of gold salts.[24]

A different result was observed in the reaction of **1a** with triethylsilylacetylene (TES). The main product obtained was **3l** along with a minor amount of the expected desilylated compound **3m**. This is probably due to an early desilylation path occurring after the Sonogashira coupling, followed by a second coupling of terminal acetylene **2b** with **1a**, and a final addition/cyclisation step to give **3l** (Scheme 3.2).



Scheme 3.2 – Reaction of **1a** with triethylsilylacetylene (TES).

According to literature, the reaction mechanism probably involves an earlier Sonogashira coupling (testified by the isolation of the coupling product if the reaction partners were reacted for an insufficient reaction time), followed by a sequential base triggered addition/annulation cascade. The involvement of metal in the activation of the triple bond during the cyclisation step was not investigated but at the moment, it cannot be ruled out. This contribution has been proven on the

related cyclisation of carbonyl groups on alkynes, activated with palladium/copper,[25] gold/silver[26] and also ruthenium or tungsten.[27] Moreover it is worth noting that the 5-*exo-dig* cyclisation observed here with palladium is quite different to the cyclisation observed in similar reactions with different benzylic O-nucleophiles catalysed by gold, which proceeds by a 6-*endo-dig* ring closure.[28]

3.3 Conclusion

In conclusion, we have successfully transformed the previously reported two-step domino approach[1] to dihydroisobenzofurans into an unprecedented high yielding MCR. The strategy demonstrated tolerance to a variety of substituents on both alkynyl and aldehyde partners. Moreover the approach was successfully applied to the preparation of related dihydrofuro[3,4-*b*]pyridines. With respect to the domino approach, this MCR allows a slight improvement on reaction yields together with a considerable reduction in operative steps, reaction times, and consumption of energy, solvent and reagents.

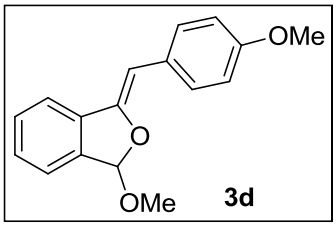
3.4 Experimental section

General details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Catalysts were purchased from Sigma-Aldrich. 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, at 200 or 500 MHz, with the resonance of solvent as the internal reference. ^{13}C NMR spectra were recorded at room temperature at 50.3 or 125.75 MHz, with the resonance of solvent as the internal reference. The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. 2D-NOESY spectra were acquired at 500 MHz in the phase-sensitive TPPI mode with 2K × 256 complex FIDs, spectral width of 5682 Hz, recycling delay of 3 s, 8 scans and a mixing time of 1.3 s. All spectra were transformed and weighted with a 90° shifted sine-bell squared function to 1K × 1K real data points. Microwave assisted reactions were performed in a Microsinth Milestone® multimode labstation, using 12 mL sealed glass vessels. The reaction times specified in Tables 3.1 and 3.2 include "ramp times". The internal temperature was detected with a fiber optic sensor.

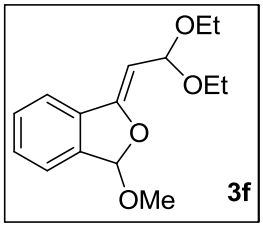
Typical MCR procedure. In a sealed MW test tube, a mixture of the appropriate 2-bromoarylaldehyde **1** (1 mmol), alkyne (1.2 mmol), *t*-BuOK (337 mg, 3 mmol) and $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol) in dry methanol (4 mL) was stirred at r.t. under a nitrogen atmosphere for 10 min, then CuI (3.81 mg, 0.02 mmol) was added. The reactor vessel was sealed and the stirred mixture was heated at the suitable temperature for the proper time in a multimode microwave oven (for times and temperatures see Table 3.2). After cooling, the reaction mixture was poured into sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer, dried over Na_2SO_4, was evaporated under reduced pressure. The reaction crude was purified by flash chromatography over a silica gel column yielding the desired dihydroisobenzofurans **3**.

(*Z*)-1-Methoxy-3-(4-methylbenzylidene)-1,3-dihydro-isobenzofuran (3a), **(*Z*)-1-Methoxy-3-[3-(trifluoromethyl)benzylidene]-1,3-dihydroisobenzofuran (3b)**, **(*Z*)-1-(3-Fluorobenzylidene)-3-methoxy-1,3-dihydro-isobenzofuran (3c)**, **(*Z*)-1-Methoxy-3-(4-methoxy-2-methylbenzylidene)-1,3-dihydroisobenzofuran (3e)** and **1-Methoxy-3-methylene-1,3-dihydroisobenzofuran (3m)** have already been described in the experimental section in chapter 2.

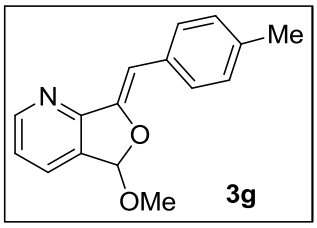
(Z)-1-Methoxy-3-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran (3d). Eluent for chromatography: hexane/EtOAc/TEA (99:1:0.6). Yield 201 mg (75 %). R_f (5% EtOAc/hexane) 0.15. Orange solid. Mp 97–99 °C. IR (KBr): ν_{max} = 2897, 2838, 1693, 1604, 1508, 1467, 1377, 1115, 1088, 844, 763 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.49 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 5.96 (s, 1H, C_{sp2}–H), 6.56 (s, 1H, C_{sp3}–H), 6.91 (d, J = 8.4 Hz, 2H, arom.), 7.35–7.60 (m, 4H, arom.), 7.73 (d, J = 8.4 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 54.3, 55.5, 98.1, 107.5, 114.2, 119.7, 123.3, 128.8, 128.9, 129.8, 130.1, 136.0, 136.9, 151.8, 158.2 ppm. ESI-MS m/z (%): 291 $[M + Na]^+$ (95), 237 $[M - OCH_3]^+$ (100). HRMS (ESI) Calcd for $C_{17}H_{16}O_3Na$(+1): 291.0992. Found: 291.0990.



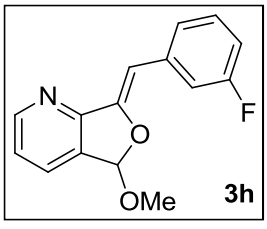
(Z)-1-(2,2-Diethoxyethylidene)-3-methoxy-1,3-dihydroisobenzofuran (3f). Eluent for chromatography: hexane/EtOAc/TEA (90:10:0.6). Yield 235 mg (89 %). R_f (20% EtOAc/hexane) 0.34. Pale yellow oil. IR (neat): ν_{max} = 2975, 2930, 2881, 1689, 1469, 1373, 1116, 1092, 1054, 994, 954, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.25 (t, J = 6.8, 6H, 2 CH_3), 3.42 (s, 3H, CH_3), 3.53–3.80 (m, 4H, 2 CH_2), 5.21 (d, J = 7.6, 1H, CH), 5.61 (d, J = 7.6, 1H, CH), 6.40 (s, 1H, CH), 7.39–7.51 (m, 4H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.5, 54.3, 61.4, 95.7, 97.7, 106.9, 120.6, 123.2, 129.7, 130.0, 134.3, 138.0, 155.0 ppm. ESI-MS m/z (%): 287 $[M + Na]^+$ (100), 219 $[M - OEt]^+$ (25). Calcd for $C_{15}H_{20}O_4$: C, 68.16; H 7.63. Found: C, 68.09; H, 7.65.



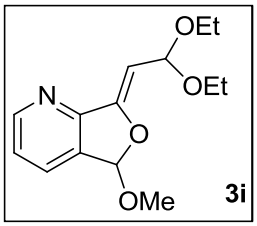
(Z)-5-Methoxy-7-(4-methylbenzylidene)-5,7-dihydrofuro[3,4-b]pyridine (3g). Eluent for chromatography: hexane/EtOAc/TEA (90:10:0.6). Yield 197 mg (78 %). R_f (40% EtOAc/hexane) 0.30. Orange solid. Mp 122-126 °C. IR (KBr): ν_{max} = 2954, 2924, 1667, 1583, 1422, 1378, 1117, 1085, 943, 790 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.36 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 6.49 (s, 1H, CH), 6.56 (s, 1H, CH), 7.17–7.29 (m, 3H, arom.), 7.70–7.80 (m, 3H, arom.), 8.66 (dd, J = 5.1, 1.5, 1H, arom.), ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.5, 54.9, 100.4, 105.8, 122.9, 129.2, 129.4, 130.4, 131.6, 132.6, 136.6, 150.6, 152.2, 154.7 ppm. ESI-MS m/z (%): 254 $[M + 1]^+$ (100). MS-MS m/z (%): 222 $[M - OCH_3]$ (100). HRMS (ESI) Calcd for $C_{16}H_{16}NO_2$(+1): 254.1176. Found: 254.1175.



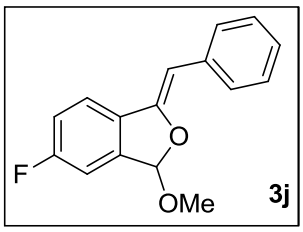
(Z)-7-(3-Fluorobenzylidene)-5-methoxy-5,7-dihydrofuro[3,4-b]pyridine (3h). Eluent for chromatography: hexane/EtOAc/TEA (85:15:0.6). Yield 220 mg (85 %). R_f (40% EtOAc/hexane) 0.26. Orange solid. Mp 89–93 °C. IR (KBr): ν_{max} = 3069, 2939, 1671, 1613, 1579, 1485, 1443, 1423, 1385, 1271, 1146, 1118, 1089, 945, 785, 680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.60 (s, 3H, CH_3), 6.48 (s, 1H, CH), 6.56 (s, 1H, CH), 6.87–6.97 (m, 1H, arom.), 7.26–7.37 (m, 2H, arom.), 7.47 (d, J = 7.7, 1H, arom.), 7.59-7.67 (m, 1H, arom.), 7.79 (dd, J = 7.7, 1.1, 1H, arom), 8.68 (dd, J = 4.8, 1.5, 1H, arom.), ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 55.3, 99.2 (d, $^4J_{C,F}$ = 2.7 Hz), 106.3, 113.5 (d, $^2J_{C,F}$ = 21.7 Hz), 115.5 (d, $^2J_{C,F}$ = 22.5 Hz), 123.4, 124.9 (d, $^4J_{C,F}$ = 2.7 Hz), 129.9 (d, $^3J_{C,F}$ = 8.4 Hz), 130.8, 131.7, 137.7 (d, $^3J_{C,F}$ = 8.4 Hz), 152.1, 152.4, 154.2, 160.8, 165.6 (d, $^1J_{C,F}$ = 244 Hz) ppm. ESI-MS m/z (%): 258 $[M + 1]^+$ (100). MS-MS m/z (%): 226 $[M - OCH_3]$ (100). HRMS (ESI) Calcd for $C_{15}H_{12}NO_2F$(+1): 258.0925. Found: 258.0925.



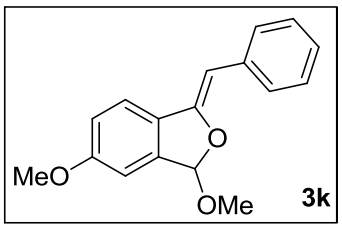
(Z)-7-(2,2-Diethoxyethylidene)-5-methoxy-5,7-dihydrofuro[3,4-b]pyridine (3i). Eluent for chromatography: hexane/EtOAc/TEA (80:20:0.6). Yield 204 mg (77 %). R_f (40% EtOAc/hexane) 0.20. Orange oil. IR (neat): ν_{max} = 2975, 2931, 2897, 1695, 1588, 1424, 1376, 1119, 1093, 1055, 993, 948, 792 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.24 (t, J = 6.9, 6H, 2 CH_3), 3.49 (s, 3H, CH_3), 3.57–3.79 (m, 4H, 2 CH_2), 5.62 (d, J = 7.7, 1H, CH), 5.72 (d, J = 7.7, 1H, CH), 6.39 (s, 1H, CH), 7.25–7.31 (m, 1H, arom.), 7.74 (dd, J = 7.7, 1.1, 1H, arom.), 8.65 (dd, J = 4.8, 1.5, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.5, 55.0, 61.1, 97.2, 97.8, 105.3, 123.7, 131.4, 131.5, 152.3, 153.1, 153.4 ppm. ESI-MS m/z (%): 288 $[M + Na]^+$ (80), 220 $[M - OEt]^+$ (100). Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H 7.22; N, 5.28. Found: C, 63.44; H, 7.23; N, 5,26.



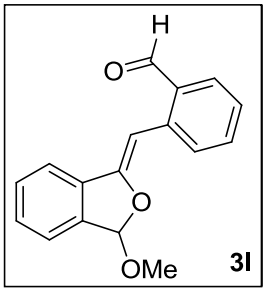
(Z)-1-Benzylidene-5-fluoro-3-methoxy-1,3-dihydroisobenzofuran (3j). Eluent for chromatography: hexane/EtOAc/TEA (99:1:0.6). Yield 250 mg (98 %). R_f (10% EtOAc/hexane) 0.28. Red oil. IR (neat): ν_{max} = 3064, 2935, 1666, 1618, 1595, 1493, 1483, 1449, 1370, 1255, 1142, 1119, 1084, 964, 783, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.52 (s, 3H, CH_3), 5.93 (s,1H, CH), 6.52 (s, 1H, CH), 7.12-7.26 (m, 3H, arom.), 7.32-7.40 (m, 2H, arom.), 7.50-7.57 (m, 1H, arom), 7.74-7.78 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 54.6, 98.3 (d, $^6J_{C,F}$ = 2.3 Hz), 106.9 (d, $^4J_{C,F}$ = 2.7 Hz), 110.5 (d, $^2J_{C,F}$ = 24.0 Hz), 117.9 (d, $^2J_{C,F}$ = 24.0 Hz), 121.6 (d, $^3J_{C,F}$ = 9.1 Hz), 126.2, 128.5, 128.6, 131.8 (d, $^4J_{C,F}$ = 2.7 Hz), 135.9, 139.2 (d, $^3J_{C,F}$ = 8.8 Hz), 152.3, 161.1, 166.1 (d, $^1J_{C,F}$ = 249 Hz) ppm. ESI-MS m/z (%): 257 $[M + 1]^+$ (100). MS-MS m/z (%): 225 $[M - OCH_3]$ (100). Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H 5.11. Found: C, 75.08; H, 5.07.



(Z)-1-Benzylidene-3,5-dimethoxy-1,3-dihydroisobenzofuran (3k). Eluent for chromatography: hexane/EtOAc/TEA (98:2:0.6). Yield 206 mg (77 %). R_f (10% EtOAc/hexane) 0.13. Red solid. Mp 64-67 °C. IR (KBr): ν_{max} = 2915, 2838, 1659, 1612, 1492, 1454, 1369, 1262, 1035, 964, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.51 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.86 (s, 1H, C–H), 6.52 (s, 1H, C–H), 6.94-7.03 (m, 2H, arom.), 7.12–7.21 (m, 1H, arom.), 7.31-7.39 (m, 2H, arom.), 7.49 (d, J = 8.4 Hz, 1H, arom.), 7.75 (dd, J = 8.4, 1.1 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 54.3, 55.9, 96.8, 107.2 (2 signals), 117.8, 121.2, 125.7, 128.3, 128.4 128.6, 136.4, 138.9, 153.3, 161.2 ppm. ESI-MS m/z (%): 269 $[M + 1]^+$ (100). Calcd for $C_{17}H_{16}O_3$: C, 76.10; H 6.01. Found: C, 76.04; H, 6.08.



(Z)-2-((3-Methoxyisobenzofuran-1(3H)-ylidene)methyl)benzaldehyde (3l). Eluent for chromatography: hexane/EtOAc/TEA (95:5:0.6). Yield 71 mg (54 %). R_f (5% EtOAc/hexane) 0.10. Dark yellow oil. IR (neat): ν_{max} = 2933, 2836, 1692, 1647, 1612, 1594, 1484, 1467, 1375, 1205, 1117, 1089, 946, 762 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): δ = 3.22 (s, 3H, CH_3), 6.29 (s, 1H, C–H), 7.04-7.10 (m, 2H, arom.), 7.12–7.21 (m, 1H, arom.), 7.19 (m, 1H, arom.), 7.38 (dt, J = 7.8, 1.5 Hz, 1H, arom.), 7.52 (dd, J = 6.6, 1.4 Hz, 1H, arom.), 7.59 (s, 1H, C–H), 7.63 (dd, J = 7.7, 1.4 Hz, 1H, arom.), 8.57 (dd, J = 8.0, 0.6 Hz, 1H, arom.), 10.2 (s, 1H, CHO) ppm. ^{13}C NMR (C_6D_6, 125.75 MHz): δ = 53.0, 92.7, 107.2, 119.9, 122.3, 125.6, 128.6, 129.2, 129.5, 131.8, 132.2, 132.9, 134.8, 136.8, 134.8, 155.1, 191.8 ppm. ESI-MS m/z (%): 267 $[M + 1]^+$ (100). MS-MS m/z (%): 235 $[M - OCH_3]$ (100). Calcd for $C_{17}H_{14}O_3$: C, 76.68; H 5.30. Found: C, 76.64; H, 5.31.



3.5 References and notes

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[23] It is interesting to note that the previously reported domino addition/annulation of preformed 2-(3,3-diethoxyprop-1-ynyl)benzaldehyde gave directly the corresponding free aldehyde derivative (see ref. 1 and chapter 2, product **2i**).

[24] In the domino approach this drawback has been overcome performing the reaction at room temperature in the presence of a catalytic amount of $NaAuCl_4$ (see ref. 1 and chapter 2, Table 2.5).

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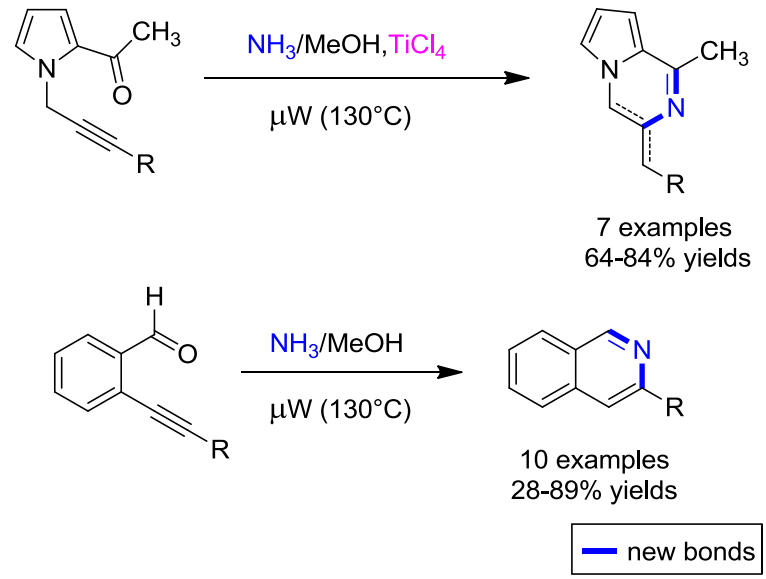
Chapter 4

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



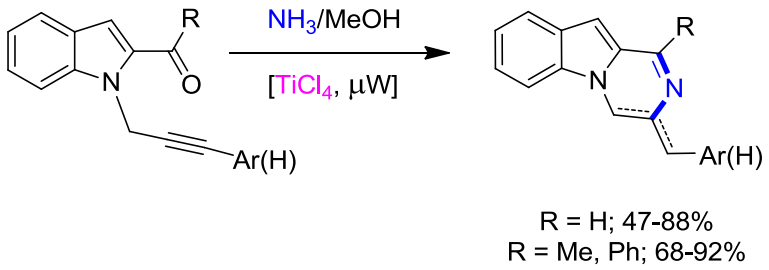
2-Acetyl-*N*-propargyl-pyrroles and *ortho*-alkynylbenzaldehydes demonstrated to be suitable building blocks for the synthesis of pyrrolo[1,2-*a*]pyrazine and isoquinoline nuclei. $TiCl_4$ and/or microwaves heating efficiently promoted the domino imination/annulation reaction. Mechanism and selectivity were discussed on the basis of computational and spectral data.

Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E.

Eur. J. Org. Chem. **2009**, *17*, 2852–2862.

4.1 Introduction

Recently, our research group 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.[1] The reaction worked well with *N*-propargylindole-2-carbaldehydes, but yields and selectivities were unsatisfactory using 2-acetyl-*N*-propargylindoles.[1b] 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 selectivities in the reactions of these less reactive substrates with a widespread reduction of reaction times (Scheme 4.1).[1a]



Scheme 4.1 – Synthesis of the pyrazino[1,2-*a*]indole nucleus.

In this part of the work, we wanted to explore the suitability of this smart 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*-propargyl pyrroles **1** and *ortho*-alkynylbenzaldehydes **2**, respectively. In the literature there are only a few papers dealing with the reactivity of *N*-propargyl-pyrrole-2-carbaldehydes as building blocks for the synthesis of simple and polycyclic pyrrolizine derivatives,[2] 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.[3] 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[4] and dihydroisoquinoline[5] skeletons starting directly from 2-acyl-phenylacetilenes[4a-4f, 5a-5h] or their imine derivatives[4g-4q, 5i-5o] have been reported.

Polycyclic compounds containing a pyrrolo[1,2-*a*]pyrazine moiety are biologically interesting molecules (Figure 4.1). 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.[6] Moreover, pyrrolo[1,2-*a*]quinoxalinones displayed an antiallergic activity,[7] whereas thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrazines[8] and pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazines[9] have been shown to be selective 5-HT_3 receptor agonists. Finally, a few bispyrrolo[1,2-*a*]quinoxalines exhibited an interesting antimalarial activity.[10] 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.[11]

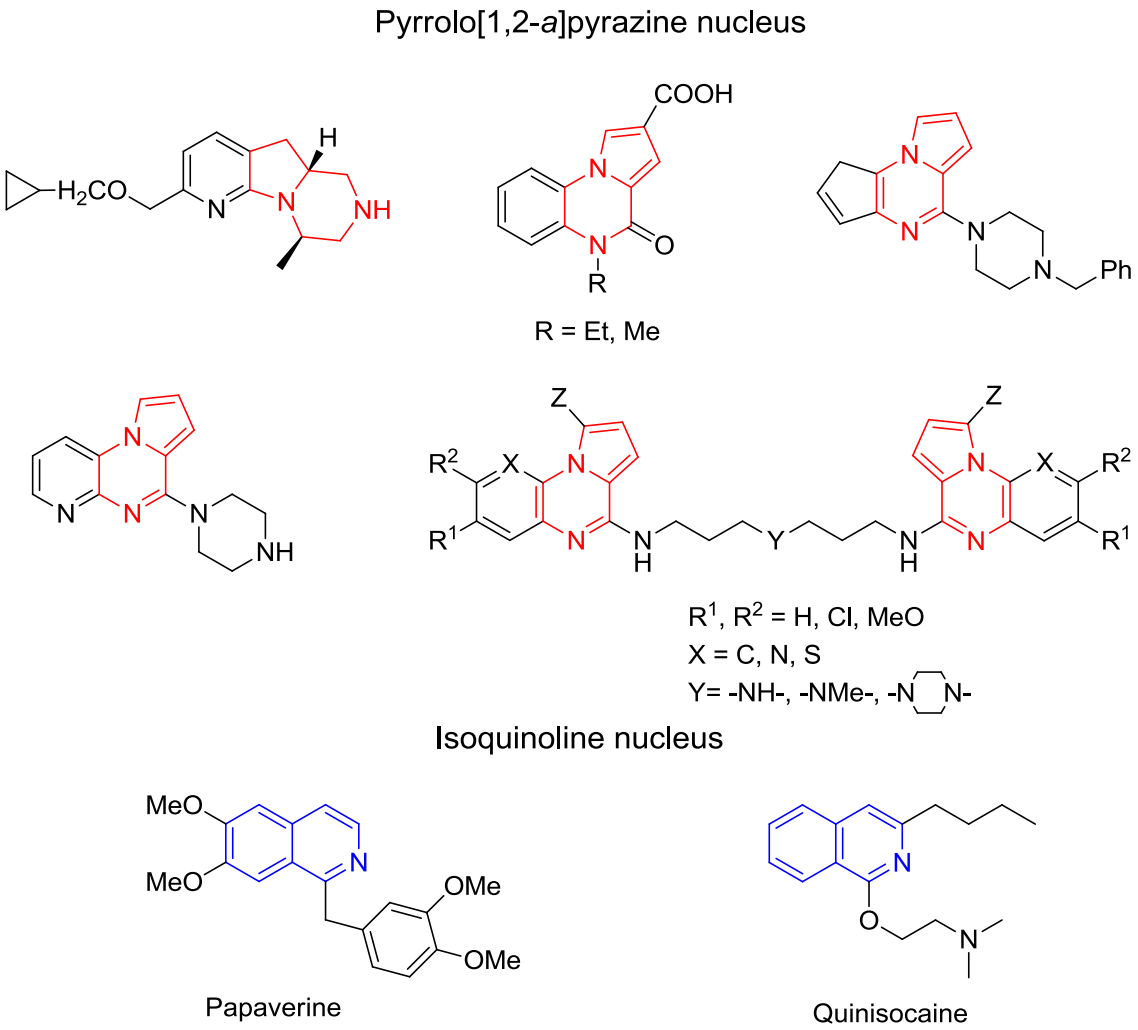
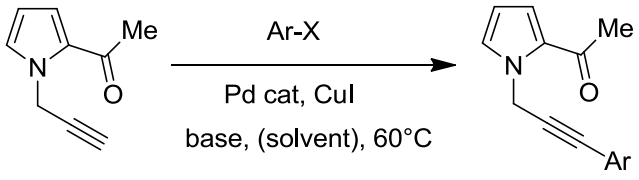


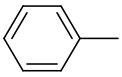
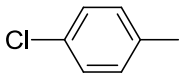
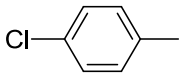
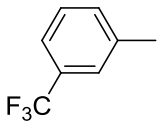
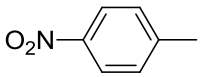
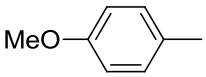
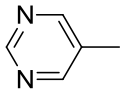
Figure 4.1 – Biologically active compounds.

4.2 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[3] and then functionalised 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 4.1).



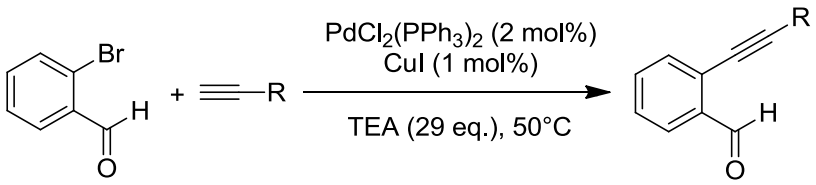
1a **1 b-g**

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

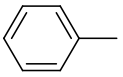
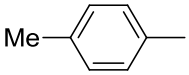
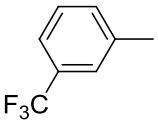
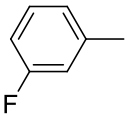
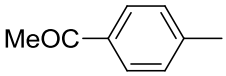
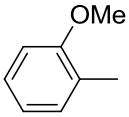
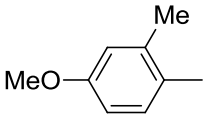
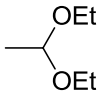
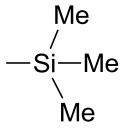
[a] Method A: molar ratio **1a** / Ar–X / K_2CO_3 / $Pd(PPh_3)_4$ / CuI = 1 : 1.01 : 5 : 0.02 : 0.04. DMF (2 mL), 60°C. Method B: molar ratio **1a** / Ar–X / TEA / $PdCl_2(PPh_3)_4$ / CuI = 1 : 1.01 : 29 : 0.02 : 0.01. 60°C.
[b] Yields refer to pure isolated product.

Table 4.1 – Preparation of 2-acetyl-*N*-alkynylpyrroles **1b–g**.

Through a similar approach, we synthesised *ortho*-alkynylbenzaldehydes **2a–k** in moderate to excellent yields starting from commercially available *ortho*-bromobenzaldheyde and selected terminal acetilenes (Table 4.2). Some of them have already been showed in chapter 2.



2 a-k

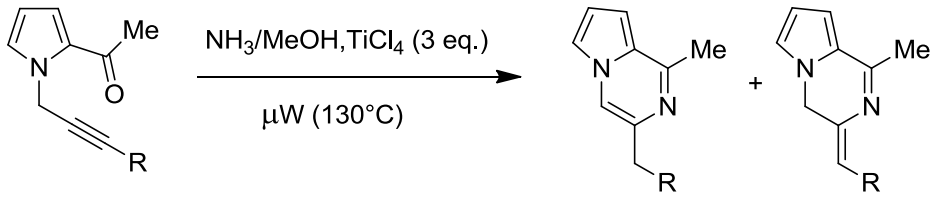
R	t (h)	Product	Yield (%)[a]
	1	**2a**	91
	4	**2b**	78
	6	**2c**	74
	6	**2d**	87
	2	**2e**	84[b]
	7	**2f**	59
	4.5	**2g**	90
$CH_3(CH_2)_4$—	4	**2h**	91
$CH_3(CH_2)_5$—	2	**2i**	91
	4	**2j**	89
	2.5	**2k**	99

[a] Yields refer to pure isolated product.

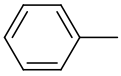
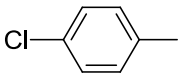
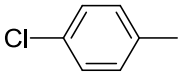
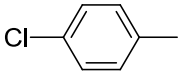
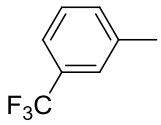
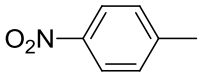
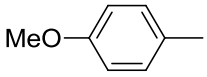
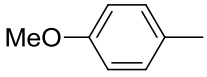
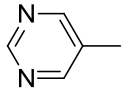
[b] Prepared by the reaction of 2-ethynylbenzaldehyde (quantitatively obtained by treatment of **2k** with 2 equiv. of K_2CO_3 in MeOH at room temp.) with 4-iodoacetophenone under the standard Sonogashira conditions.

Table 4.2 – Preparation of *ortho*-alkynylbenzaldehydes **2a–k**.

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,[1a] we dissolved alkynyl pyrroles **1a–g** in 2M 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 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 4.3.



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

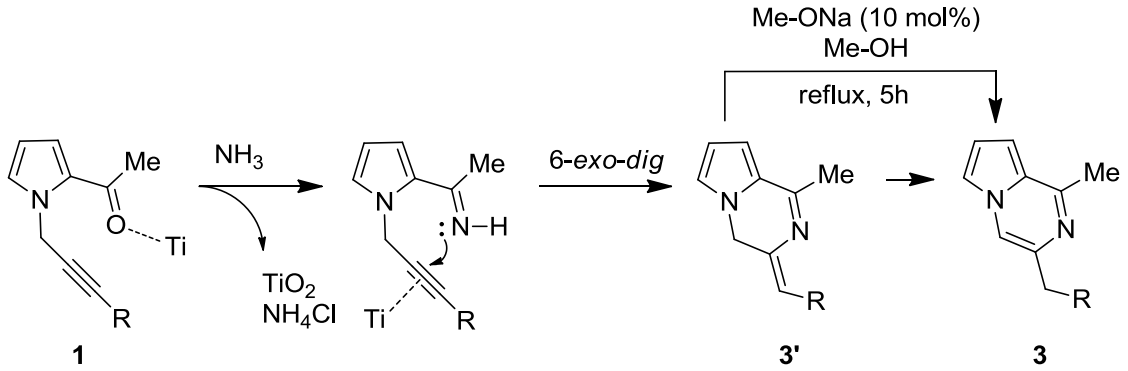
Entry	1	R	t (h)[a]	3 (yield %)[b]	3' (yield %)[b]	1 rec. (yield %)[b]
1	**a**	H	1.5	**3a** (81)	**3'a** (–)	**1a** (–)
2	**b**		6	**3b** (66)	**3'b** (–)	**1b** (–)
3	**c**		1	**3c** (18)	**3'c** (10)	**1c** (50)
4	**c**		6	**3c** (73)	**3'c** (–)	**1c** (–)
5	**c**		13[c]	**3c** (64)	**3'c** (10)	**1c** (–)
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" (ca. 10 °C/min).
[b] Yields refer to pure isolated product.
[c] Conventional heating (silicon oil bath).

Table 4.3 – Imination/annulation of 2-acetyl-*N*-alkynylpyrroles **1a–g.**

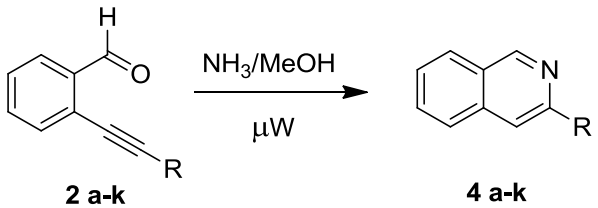
The reaction of 2-acetyl-*N*-propargylpyrrole **1a** gave smoothly the 1,3-dimethylpyrrolo[1,2-*a*]pyrazine **3a** as the sole reaction product in 1.5 h, in good yield (Table 4.3, entry 1). Also, internal alkynes gave preferentially the pyrrolo[1,2-*a*]pyrazine isomers **3** in good yields (Table 4.3, 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 4.3, entries 3 and 8), whereas the reactions were almost complete after 6 h (Table 4.3, entries 4 and 9). With respect to conventional heating however, microwave irradiation increased both the yield and selectivity in a reduced reaction time (Table 4.3, entries 4 and 5). The approach well tolerated the presence of electron-withdrawing groups (EWGs, Table 4.3, entries 4, 6 and 7) and electron-donating groups (EDGs, Table 4.3, entry 9) on the phenyl substituent bonded to the propargyl moiety. Also, a pyrimidine substituent was allowed (Table 4.3, entry 10), but after the standard reaction time, we recovered a considerable amount of dihydro isomer **3'g** and starting material **1g**.

As already reported for the $TiCl_4$-promoted synthesis of pyrazino indoles,[1a] a plausible reaction mechanism involves a Lewis-acid-catalysed formation of the imine intermediate, 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.[12] 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**. 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[13] (Scheme 4.2).

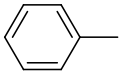
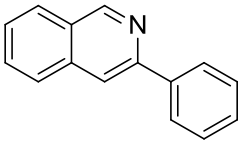
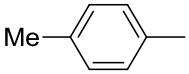
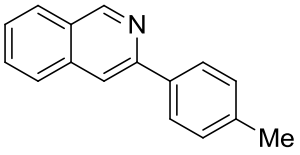
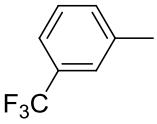
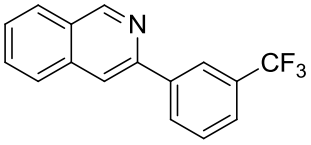
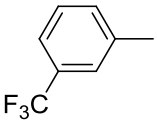
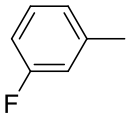
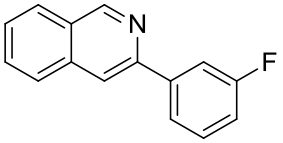
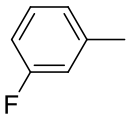
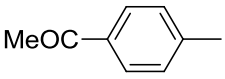
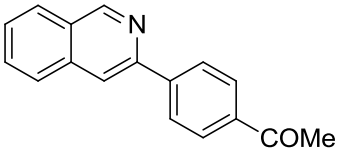
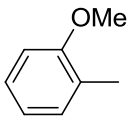
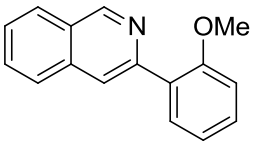
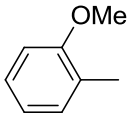
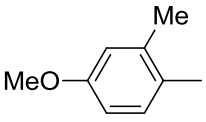
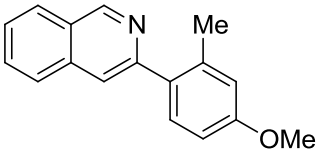


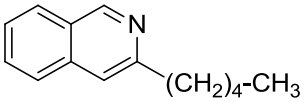
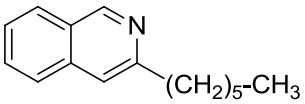
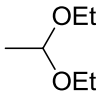
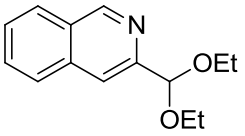
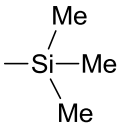
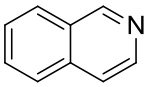
Scheme 4.2 – Mechanism insight.

We then turned our attention to evaluating the reactivity of *ortho*-alkynylbenzaldehydes **2.** The microwave-promoted imination/annulation of **2 a–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 4.4). We note that four examples of the thermal annulation of *ortho*-alkynyl-benzaldehydes in the presence of ammonia were reported eight years ago by Sakamoto et al.[4d] Nevertheless, our investigation represents a more comprehensive study showing that microwave heating gives comparable or better yields in reduced reaction times (Table 4.4) than does conventional heating.



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" (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.

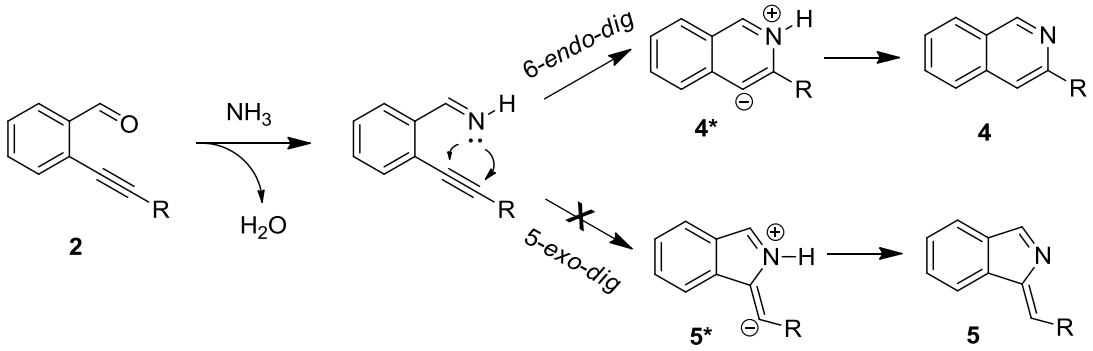
[d] $TiCl_4$ (3 equiv.).

[e] Conventional heating (silicon oil bath).

Table 4.4 – Imination/annulation of *ortho*-alkynylbenzaldehydes **2 a–k**.

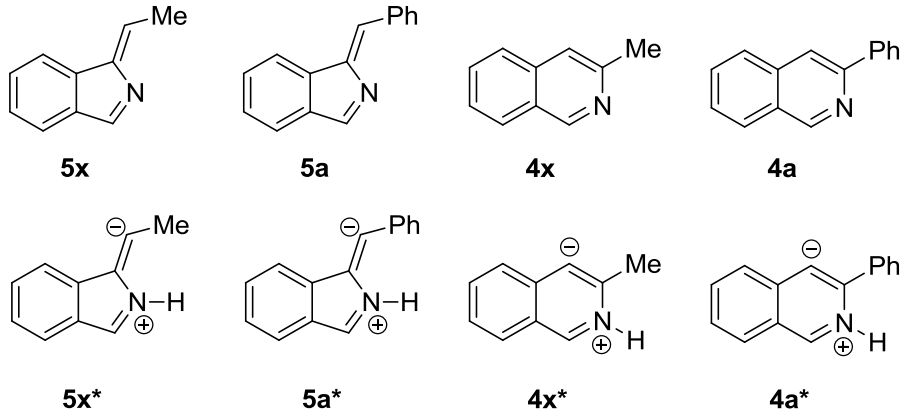
Aldehydes **2a–j** reacted smoothly and quickly to give the corresponding 3-substituted isoquinolines in modest to good yields (Table 4.4, entries 1–13). The presence of EWGs on the aryl moiety gave rise to low reaction yields (Table 4.4, entries 3–7), even after a prolonged reaction time under conventional heating conditions (Table 4.4, entry 6). We note that even $TiCl_4$ did not improve the reaction yield of these less reactive substrates (Table 4.4, entry 4). Also, the presence of the bulky methoxy group in the *ortho*-position of the aryl moiety gave unsatisfactory results (Table 4.4, entry 8), even after a prolonged reaction time at a lower temperature (Table 4.4, 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 4.4, entries 10-12). When the triple bond was substituted with an acetal moiety the reaction gave the corresponding isoquinoline **4j** in 50% yields (Table 4.4, 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% yields**.** We note that this approach represents a valuable alternative to the synthesis of this useful derivative.[14] On the other hand, starting from 2-((trimethylsilyl)ethynyl)benzaldehyde **2k**, the simple desililated isoquinoline **4k** was easily obtained in moderate yields (Table 4.4, entry 14).

According to the literature,[4d,15] the suggested mechanism involves the intermediacy of an imine that undergoes a regioselective 6-*endo* cyclisation followed by a solvent-promoted proton shift (Scheme 4.3). We never isolated or detected the product derived from a 5-*exo-dig* cyclisation mode in the reaction crude. The regiospecificity achieved[16] 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 4.3). 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***.[17]



Scheme 4.3 – Mechanism insights.

We confirmed these statements by theoretical calculations performed on the model compounds 3-methylisoquinoline **4x**, 3-phenylisoquinoline **4a**, 1-ethyleneisoindole **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.[18] 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 4.5.



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

Table 4.5 – Selected Δ*E* (kcal/mol) among isolated and hypothetical isomers and their intermediates.

As expected, both the isoquinolines **4x** and **4a** are thermodynamically favoured with respect to the corresponding isoindoles **5x** and **5a** (Table 4.5, 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 4.5, entries 3 and 4). These theoretical results seems to confirm that, from a thermodynamic point of view, the stabilisation of the α-anion by the aryl substituent in **5a*** is less significant than that of the aromatic stabilisation effect of conjugated bicyclic rings **4a***.[17]

The low yield observed for **2e** is probably due to the steric hindrance of the *ortho*-methoxy group on the reaction (Table 4, entry 7).[4k] On the other hand, against an almost quantitative conversion of starting materials **2c–e** (Table 4, entries 3-5), 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 triple bond;[19] a rough 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 4.2).

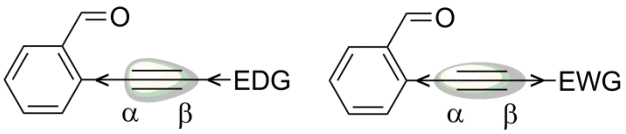


Figure 4.2 – Qualitative estimation of the influence of the Cβ substituent on triple bond polarization.

To gain additional insight into this hypothesis, we analysed the chemical shifts of the *sp*-hybridised carbons[20] 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 4.3.

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[21] and for this reason, we did not evaluate the chemical shift of alkynyl-benzaldehydes bearing an *ortho*-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 4.3, (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 **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 4.3, (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).

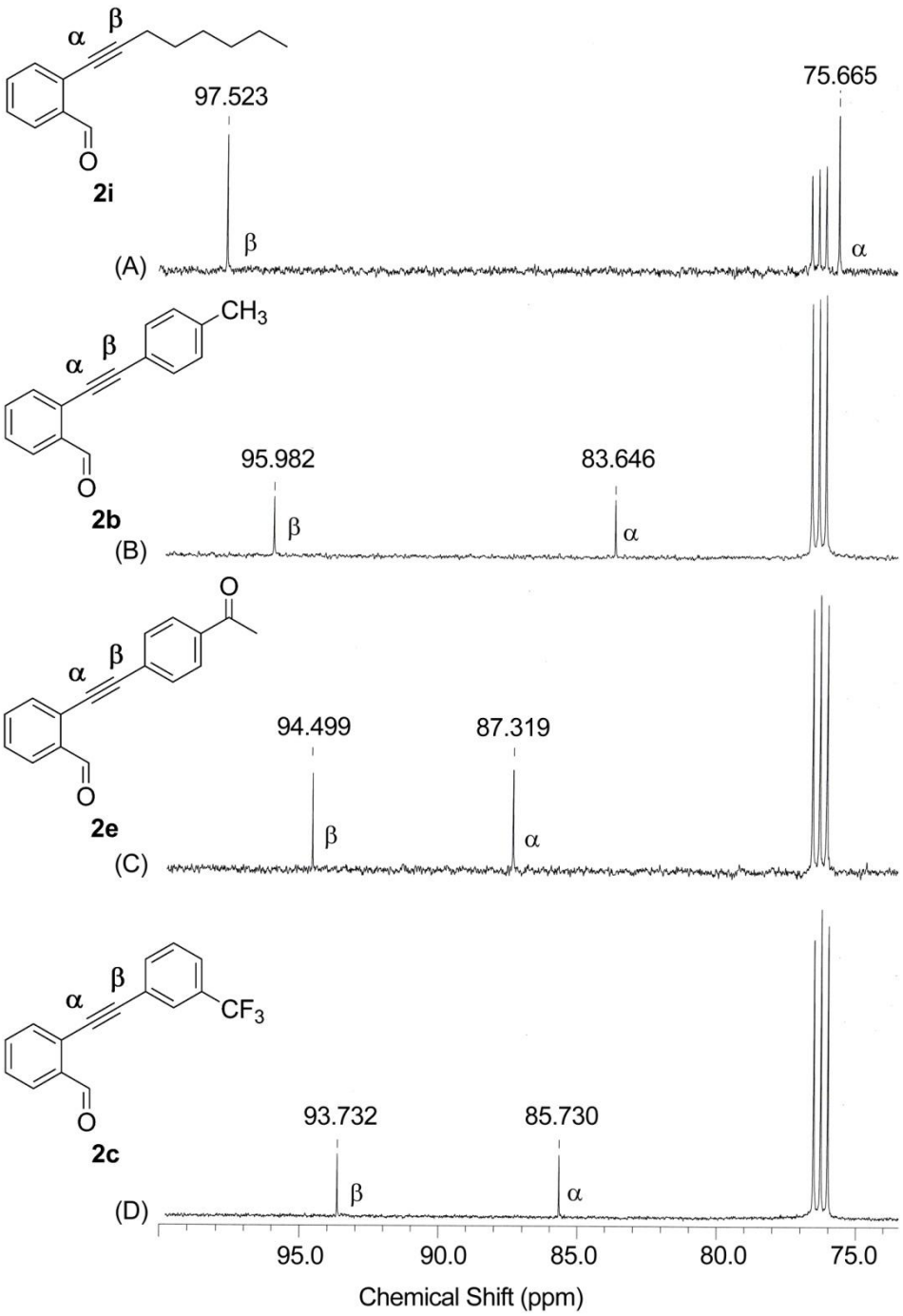


Figure 4.3 – Experimental ^{13}C NMR spectra of compounds **2b**, **2c**, **2e** and **2i**.

4.3 Conclusion

In conclusion, we proved that the microwave-promoted domino imination/annulation 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.

4.4 Experimental section

General details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F_{254} thin-layer plates were employed for thin layer chromatography (TLC). Silica gel 40−63 micron/60 Å was employed for flash column chromatography. Melting points were measured with a Perkin-Elmer DSC 6 calorimeter at a heating rate of 5 °C/min and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer FT-IR 16 PC spectrophotometer using KBr tablets for solids and NaCl disks for oils. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$, at 200 or 500 MHz (with a Varian-Gemini 200 or a Brucker 500 Avance spectrometer), 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. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions. The ammonia in methanol 2M solution was purchased from standard chemical suppliers. Microwave assisted reactions were performed in a Microsinth Milestone® multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with an optical fibre sensor. "EtOAc" means ethyl acetate and "TEA" means triethylamine.

General procedure for the synthesis of 2-acetyl-1-propargylpyrrole (1a).[3] 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 tetrabutylammoniumbromide (0.29 g, 0.9 mmol) in toluene (20 mL), aqueous sodium hydroxide (a 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 over sodium sulfate and the solvent was removed at reduced pressure. The resulting crude material 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. 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 4.1).

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. 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 4.1).

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}. ^{1}H 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 (2.55 mmol) and *trans*-dichlorobis(triphenylphosphine)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 until no more starting product was detectable by TLC analysis (eluent: 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 4.2).

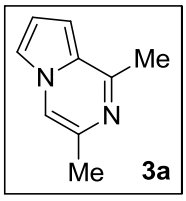
2-(Phenylethynyl)benzaldehyde (2a), **2-(*p*-Tolylethynyl)benzaldehyde (2b)**, **2-((3-(Trifluoromethyl)phenyl)ethynyl)benzaldehyde (2c)**, **2-((3-Fluorophenyl)ethynyl)benzaldehyde (2d)**, **2-((4-Acetylphenyl)ethynyl)benzaldehyde (2e)**, **2-((2-Methoxyphenyl)ethynyl)benzaldehyde (2f)**, **2-((4-Methoxy-2-methylphenyl)ethynyl)benzaldehyde (2g)**, **2-(Hept-1-ynyl)benzaldehyde (2h)**, **2-(3,3-Diethoxyprop-1-ynyl)benzaldehyde (2j)** and **2-((Trimethylsilyl)ethynyl)benzaldehyde (2k)** have already been described in the experimental section in chapter 2.

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.[22]

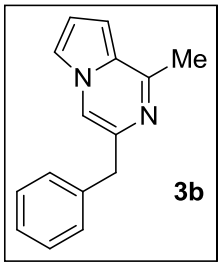
General procedure for microwave-assisted $TiCl_4$-catalysed cyclisation of 2-acetyl-1-alkynylpyrroles 1a–g. In a sealed MW test tube, to a solution of the appropriate pyrrole **1** (0.326 mmol) in dry ammonia in methanol (2M solution, 3.26 mL, 6.52 mmol) $TiCl_4$ (0.185 g, 0.107 mL, 0.978 mmol) was carefully 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 satured 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 4.3).

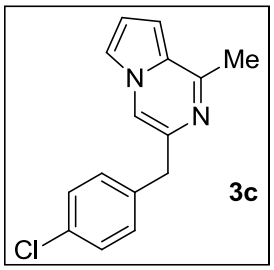
1,3-Dimethylpyrrolo(1,2-*a*)pyrazine (3a). Eluent for chromatography: hexane/EtOAc (95:5). Yield 39 mg (81 %). Brown wax. IR (neat): ν_{max} = 1722, 1650,1527, 1407 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.37 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.70 (d, J = 4.4 Hz, 1H, arom.), 6.76 (dd, J = 4.4, 2.5 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.[23]



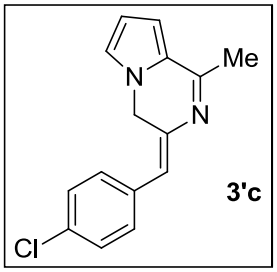
3-Benzyl-1-methyl-pyrrolo(1,2-*a*)pyrazine (3b). Eluent for chromatography: hexane/EtOAc (95:5). Yield 48 mg (66 %). Brown oil. IR (neat): ν_{max} = 1618, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.66 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 6.69–6.77 (m, 2H, arom.), 7.23–7.36 (m, 7H, arom.) ppm. ^{13}C 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.



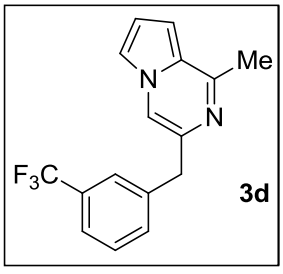
3-(4-Chloro-benzyl)-1-methyl-pyrrolo(1,2-*a*)pyrazine (3c). Eluent for chromatography: hexane/EtOAc (95:5). Yield 61 mg (73 %). Brown oil. IR (neat): ν_{max} = 1621, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.64 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 6.69–7.20 (m, 2H, arom.), 7.21–7.35 (m, 6H, arom.) 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.



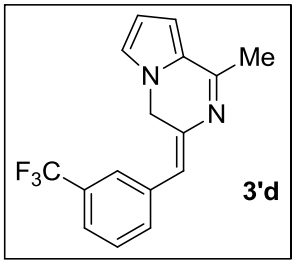
3-(1-(4-Chloro-phenyl)-meth-(*Z*)-ylidene)-1-methyl-3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'c). Eluent for chromatography: hexane/EtOAc (95:5). Yield 9 mg (10 %). Brown oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 5.96 (s, 1H, C_{sp2}–H), 6.22 (dd, J = 3.7, 2.6 Hz, 1H, 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 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**.



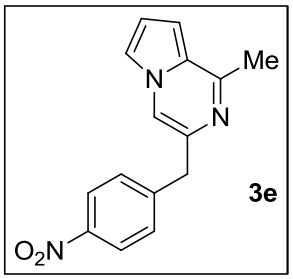
1-Methyl-3-(3-trifluoromethyl-benzyl)-pyrrolo(1,2-*a*)pyrazine (3d). Eluent for chromatography: hexane/EtOAc (93:7). Yield 62 mg (65 %). Brown oil. IR (neat): ν_{max} = 1622, 1597, 1521 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.65 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 6.71–6.79 (m, 2H, arom.), 7.29–7.30 (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, $^3J_{C–F}$



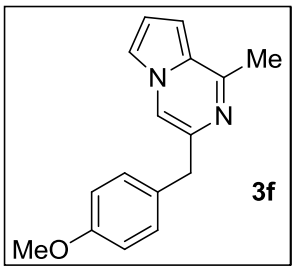
= 3.8 Hz), 127.2, 129.1, 131.0 (q, $^2J_{C–F}$ = 32 Hz), 132.8, 137.4, 140.4, 153.3 ppm. ESI-MS m/z (%): 291 $[M + 1]^+$ (100), 145 (5). Calcd for $C_{16}H_{13}F_3N_2$ (290.28): C, 66.20; H, 4.51; N, 9.65. Found: C, 66.10; H, 4.47; N, 9.69.

1-Methtyl-3-(1-(3-trifluoromethyl-phenyl)-meth-(*Z*)-ylidene)-3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'd). 

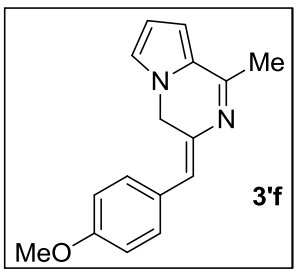
Eluent for chromatography: hexane/EtOAc (93:7). Yield 16 mg (18 %). Brown oil. IR (neat): ν_{max} = 1661, 1564, 1558 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 4.74 (d, 2H, CH_2, J = 1.5 Hz), 6.03 (s, 1H, C_{sp2}–H), 6.24 (dd, J = 4.0, 2.6 Hz, 1H, arom.), 6.56 (dd, J = 4.0, 1.5 Hz, 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 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-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.

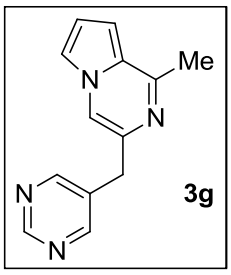
3-(4-Methoxy-benzyl)-1-methyl-pyrrolo(1,2-*a*)pyrazine (3f). 

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.

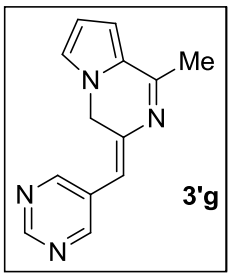
3-(1-(4-Methoxy-phenyl)-meth-(*Z*)-ylidene)-1-methyl-3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'f). 

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.

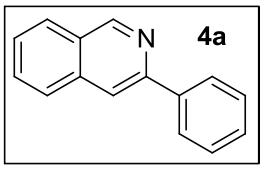


1-Methyl-3-(1-pyrimidin-5-yl-meth-(*Z*)-ylidene)--3,4-dihydro-pyrrolo(1,2-*a*)pyrazine (3'g). Eluent for chromatography: hexane/EtOAc (8:2). Yield 29 mg (40 %). Brown solid. Mp 100–102 °C. IR (KBr): ν_{max} = 1622, 1572, 1560, 1547 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 3H, CH_3), 4.79 (s, 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.

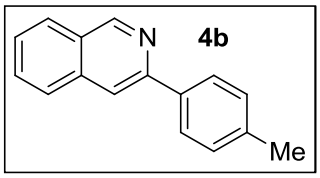


General procedure for the microwave assisted cyclisations of *o*-alkynylbenzaldehydes 2a–k. A stirred solution of the appropriate *o*-alkynylbenzaldehyde **2a–k** (0.5 mmol) in dry ammonia in methanol (2M, 5 mL) was heated at 130 °C in a sealed tube for 15–60 min in a multimode microwave oven, until 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 column yielding the isoquinolines **4** (for temperatures, times and yields, see Table 4.4).

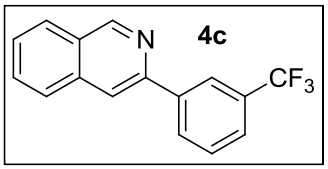
3-Phenylisoquinoline (4a). Eluent for chromatography: hexane/EtOAc (95:5). Yield 60 mg (58 %). Brown solid. Mp 100–102 °C (lit. 101–101.5 °C).[4e] ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.38–7.79 (m, 4H, arom.), 7.70 (dt, J = 6.6, 1.5 Hz, 1H, arom.), 7.88 (d, J = 8.4 Hz, 1H, arom.), 8.00 (d, J = 8.4 Hz, 1H, 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.[4e]



3-*p*-Tolylisoquinoline (4b). Eluent for chromatography: hexane/EtOAc (95:5). Yield 78 mg (71 %). Brown solid. Mp 74–76 °C (lit. 74–75 °C).[4e] ^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.[4e]

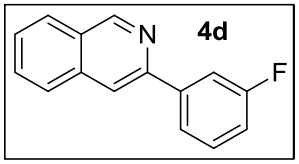


3-(3-(Trifluoromethyl)phenyl)isoquinoline (4c). Eluent for chromatography: hexane/EtOAc (95:5). Yield 38 mg (28 %). Light brown solid. Mp 64–67. IR (KBr): ν_{max} = 1625, 1325, 1178, 1109, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.58–7.77 (m, 4H, arom.), 7.90 (d, J = 8.2 Hz, 1H, arom.), 8.01 (d,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

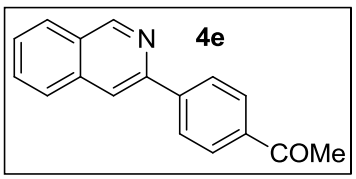


124.0 (q, $^3J_{C–F}$ = 3.8 Hz), 124.5 (q, $^1J_{C–F}$ = 272.0 Hz), 125.3 (q, $^3J_{C–F}$ = 3.8 Hz), 127.2, 127.8, 127.9, 128.3, 129.5, 130.3, 131.0, 131.4 (q, $^2J_{C–F}$ = 32.4 Hz), 136.7, 140.6, 149.8, 152.9 ppm. ESI-MS m/z (%): 274 [M + 1]$^+$ (100). Calcd for $C_{16}H_{10}NF_3$ (273.25): C, 70.33;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

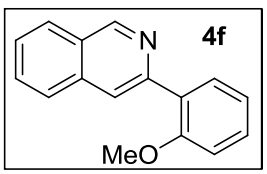
3-(3-Fluorophenyl)isoquinoline (4d). Eluent for chromatography: hexane/EtOAc (95:5). Yield 42 mg (38 %). Brown solid. Mp 105–109. IR (KBr): ν_{max} = 1624, 1573, 1494, 1452, 1158, 875, 792, 746, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.11 (tdd, J = 8.3, 2.5, 0.8 Hz, 1H, arom.), 7.46 (td, J = 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, $^2J_{C–F}$ = 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 [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.



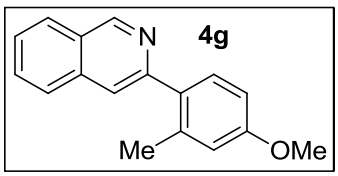
3-(4-Acethylphenyl)isoquinoline (4e). Eluent for chromatography: hexane/EtOAc (85:15). Yield 31 mg (25 %). Orange solid. Mp 150-152. IR (KBr): ν_{max} = 2956, 2924, 2853, 1670, 1599, 1353, 1263, 855, 832, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.67 (s, 3H, CH_3), 7.63 (ddd, J = 8.1, 6.7, 1.2 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.

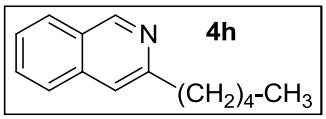


3-(4-Methoxy-2-methylphenyl)isoquinoline (4g). Eluent for chromatography: hexane/EtOAc (95:5). Yield 95 mg (76 %). Red oil. IR (neat): ν_{max} = 1625, 1607, 1580, 1504, 1451, 1295, 1275, 1241, 1162, 1055, 752 cm^{-1}. ^{1}H NMR (C_6D_6, 200 MHz): δ = 2.48 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 6.78 (dd, 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 (%):



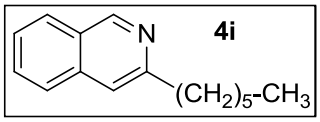
250 $[M + 1]^+$ (100). Calcd for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.79; H, 6.00; N, 5.68.

3-Pentylisoquinoline (4h). Eluent for chromatography: hexane/EtOAc (95:5). Yield 87 mg (87 %).



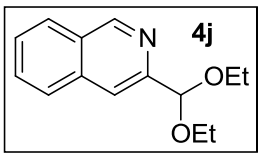
Yellow oil. IR (neat): ν_{max} = 2955, 2928, 2857, 1630, 1591, 1456, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, J = 7.0 Hz, 3H, CH_3), 1.26–1.42 (m, 4H, CH_2), 1.74–1.89 (m, 2H, CH_2), 2.92 (t, J = 7.3 Hz, 2H, CH_2), 7.45 (s, 1H, arom.) 7.50 (ddd, J = 8.1, 7.0, 1.5 Hz, 1H, arom.), 7.62 (ddd, 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 %).



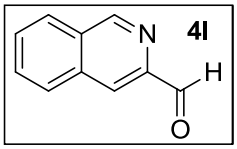
Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (t, J = 7.0 Hz, 3H, CH_3), 1.23–1.46 (m, 6H, CH_2), 1.81 (m, 2H, CH_2), 2.93 (t, J = 7.3 Hz, 2H, CH_2), 7.46 (s, 1H, arom.) 7.51 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H, arom.), 7.63 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H, arom.), 7.74 (d, J = 8.2 Hz, 1H, arom.), 7.92 (d, J = 8.1 Hz, 1H, arom.) 9.20 (s, 1H, arom.) ppm. These data are in good agreement with literature values.[4d]

3-(Diethoxymethyl)isoquinoline (4j).[24] 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 the reaction had cooled to room temp., satured 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. Mp 45–47 (lit. 49.6–50 °C).[14c] ^1H 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.[14c]



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 default options.[25] 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.[18] 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.

4.5 References and notes

[1] a) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola, S. *J. Org. Chem.* **2005**, *70*, 4088–4095; b) Abbiati, G.; Arcadi, A.; Beccalli, E.; Rossi, E. *Tetrahedron Lett.* **2003**, *44*, 5331–5334.

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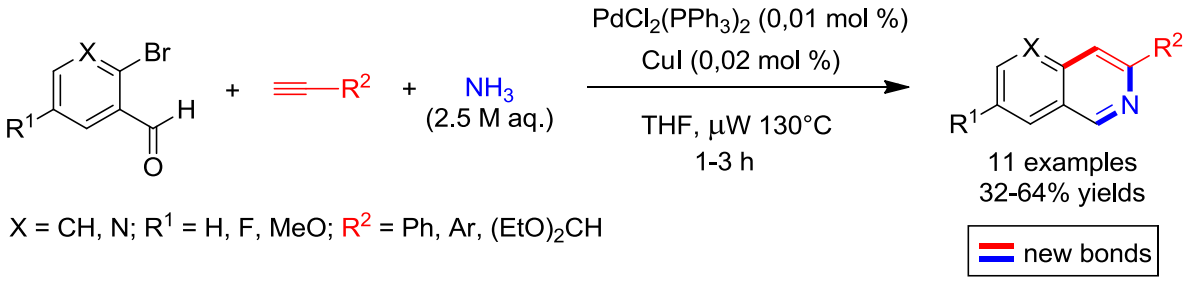
Chapter 5

Pd-Catalysed/Microwave Enhanced Three-Component Synthesis of Isoquinolines with Aqueous Ammonia



X = CH, N; R^1 = H, F, MeO; R^2 = Ph, Ar, $(EtO)_2CH$

A variety of substituted isoquinoline derivatives can be synthesized in moderate yield by a Pd-catalysed/MW-assisted MCR starting from *ortho*-bromoarylaldehydes, terminal alkynes and aqueous ammonia.

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Synlett **2010**, *17*, 2672–2676.

5.1 Introduction

In the literature there are some valuable approaches to isoquinoline[1] and dihydroisoquinoline[2] nuclei starting from 2-acyl-phenylacetylenes[1a-f, 2a-i] or from their imine derivatives.[1g-q, 2j-o] Some of them are MCRs leading to the dihydroisoquinoline skeleton.[2a-h] Conversely, multicomponent strategies to obtain isoquinolines are still scarce.[1f, 3]

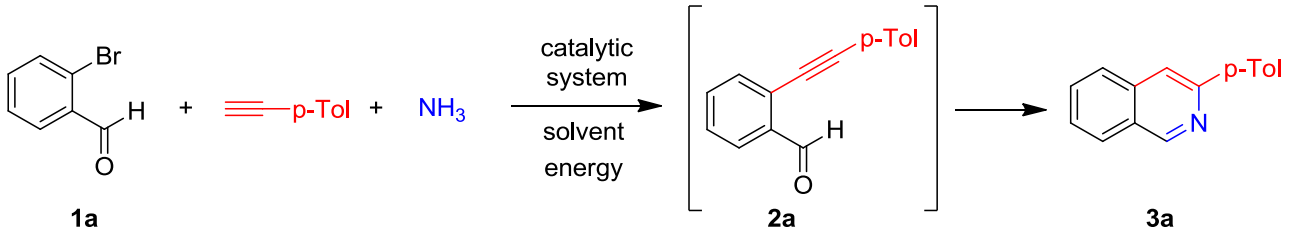
In chapter 4, we described a selective path to the isoquinoline skeleton by a MW-promoted domino imination-annulation cascade of *ortho*-alkynylbenzaldehydes prepared by a Pd-catalysed coupling reaction between *ortho*-bromobenzaldehyde and various alkyne.[4]

We were intrigued to further simplify and optimise our approach to isoquinolines, so we directed our efforts at improving the synthesis of isoquinolines by transforming the domino approach into a valuable multicomponent process starting from simple building-blocks.

In this chapter we present a one-pot three-component approach to isoquinolines directly starting from simple *ortho*-bromobenzaldehyde, terminal alkynes and ammonia in the presence of a suitable catalytic system. The most interesting features of this approach are: a) the double role of ammonia: base for the Sonogashira coupling and amino-partner for imination/cyclisation step; b) the potential multi-activity of the metal catalyst, involved in the Sonogashira coupling step and in the imination/cyclisation sequence. The suitability of ammonia as base in the Sonogashira coupling has been well-described by Mori and co-workers,[5] whereas the ability of some late transition metals to activate the triple bond during the cyclisation step has been proven on related cyclisation of carbonyl groups on alkynes in the presence of palladium/copper,[6] gold/silver[7] and also ruthenium or tungsten.[8]

5.2 Results and discussion

We screened the optimal reaction conditions with *ortho*-bromobenzadehyde **1a**, ammonia solutions and 1-ethynyl-4-methylbenzene as model system. The results are depicted in Table 5.1.



1a **2a** **3a**

Entry	NH_3, solvent	Catalyst	Co-catalyst/ additive	Energy T (°C)	t (h)[a]	3a (yield%)[b]	2a (yield%)[b]
1	2.3 M in DMF[c]	$PdCl_2(PPh_3)_2$ (2 mol %)	CuI (2 mol %)	µW 50	4	trace	-
2	2.3 M in DMF	$PdCl_2(PPh_3)_2$ (2 mol %)	CuI (2 mol %)	µW 80	0.5	10	-
3	2.3 M in DMF	$PdCl_2(PPh_3)_2$ (2 mol %)	CuI (2 mol %)	µW 130	2	26	trace
4	2.0 M in MeOH[d]	$PdCl_2(PPh_3)_2$ (2 mol %)	CuI (2 mol %)	µW 130	1	39	-
5	2.5 M in H_2O[e]	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	Oil bath 100	16	30	-
6	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	Oil bath 100	8	50	-
7	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	µW 100	4	50	-
8	2.5 M in **H_2O/THF** (3 : 1)	**$PdCl_2(PPh_3)_2$** (1 mol %)	**CuI** (2 mol %)	**µW 130**	**1**	**58**	**-**
9	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	µW 130	0.5	48	10
10	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	µW 160	0.34	48	-
11	5 M in H_2O[f]/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	µW 130	1	47	-
12	1.25 M in H_2O[g]/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	µW 130	2.5	44	20
13	2.5 M in H_2O/DMF (3 : 1)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (2 mol %)	µW 130	1	46	-
14	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (2 mol %)	-	µW 130	1	39	11
15	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (2 mol %)	Ag_2O (2 mol %)	µW 130	1	25	20
16	2.5 M in H_2O/THF (3 : 1)	$PdCl_2(PPh_3)_2$ (2 mol %)	KOH 5 eq.	µW 130	1.5	30	15

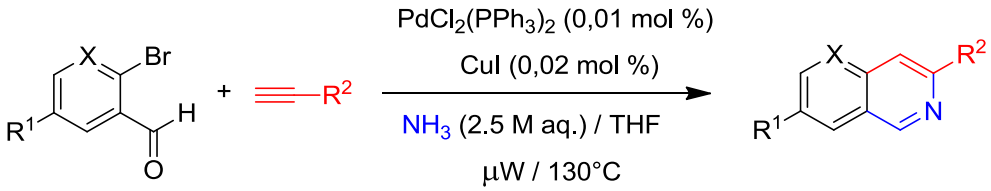
[a] Not including 10 min "ramp time" (ca. 10 °C/min).
[b] Yields refer to pure isolated product.
[c] Molar ratio **1**/NH_3 = 1:10
[d] Molar ratio **1**/NH_3 = 1:16
[e] Molar ratio **1**/NH_3 = 1:7.5
[f] Molar ratio **1**/NH_3 = 1:15
[g] Molar ratio **1**/NH_3 = 1:3.75

Table 5.1 – Screening of optimal reaction conditions.

In first instance, we ran the reaction under typical Sonogashira cross-coupling conditions [$PdCl_2(PPh_3)_2$, CuI, 50 °C], under microwave irradiation and in the presence of a solution of ammonia in DMF. After 4 h the reaction gave only traces of the desired product **3a**, beside a complex mixture of unidentified products (Table 5.1, entry 1). At higher temperatures, a modest rise in yields was observed (Table 5.1, entries 2 and 3). When the reaction was performed in ammonia in methanol, the desired product was obtained in a encouraging 39% yield in 1 h. Next, we move our attention to the use of aqueous solution of ammonia.

This readily available and inexpensive reagent has been successfully used in some example of Sonogashira coupling reactions[5] and the possibility to use it in our MCR could be a further improvement of the method. Nevertheless, probably due to the low water solubility of the reagents, the reaction was sluggish, the yield was still low, and the work-up was troublesome (Table 5.1, entry 5). In the presence of THF as co-solvent and under conventional heating at 100 °C for 8 h the reaction yield jumped to 50 % (Table 5.1, entry 6), whereas under microwave irradiation at the same temperature the reaction gave the same yield in an half time (Table 5.1, entry 7). By increasing the temperature of microwave oven to 130 °C the desired product was obtained in a satisfying 58 % yield in 1 h only (Table 5.1, entry 8). A further reduction of time gave worse results, and a little amount of the *ortho*-alkynylbenzaldehyde **2a** intermediate was isolated (Table 5.1, entry 9). Likewise, a rise in temperature to 160 °C resulted in lower yields (Table 5.1, entry 10). The concentration of ammonia solution was found to be critical in Sonogashira coupling reaction with aqueous ammonia.[5] According to this, an increasing as well as a reduction of the ammonia concentration gave worse results (Table 5.1, entries 11 and 12). We also tried a different water soluble co-solvent such as DMF, but also in this case a slightly lowering of the reaction yield was observed (Table 5.1, entry 13). The studies on copper-free Sonogashira coupling are widely reported in the literature,[9] but when we tested these favourable conditions we observed a reduction of reaction yield (Table 5.1, entry 14). We also tried a different basic co-catalyst such as silver oxide[10] with scarce results (Table 5.1, entry 15). Finally the reaction was performed in the presence of a stronger water soluble base such as KOH so restrict the role of ammonia to simple amino partner for the imination/annulation process, nevertheless the result was still unsatisfactory (Table 5.1, entry 16).

With the best conditions in hand (Table 5.1, entry 8), we briefly investigated the scope and the limitation of the approach by changing the substitution pattern on the alkyne, on the benzaldehyde framework and modifying the nature of the aromatic aldehyde. The reactions proceeded with complete *6-endo-dig* regioselectivity, leading to the formation of the corresponding isoquinolines in moderate yields. It is interesting to note that, although also under the best reaction conditions the yields are not excellent, the overall yields of this multicomponent process are in most cases better than those obtained in the two steps domino sequence.[4] The results are depicted in the Table 5.2.



1 **3**

Entry	X	R^1	Aldehyde	R^2	t (h)[a]	Product	Yield (%)[b]
1	CH	–H	**1a**	Ph	1	**3b**	50
2	CH	–H	**1a**	2-$MeOC_6H_4$	2	**3c**	46
3	CH	–H	**1a**	4-$MeOC_6H_4$	2	**3d**	56
4	CH	–H	**1a**	4-MeO-2-MeC_6H_4	3	**3e**	64
5	CH	–H	**1a**	$(EtO)_2CH$	1	**3f**	42
6	CH	–H	**1a**	3-$F_3CC_6H_4$	1	**3g**	32
7	CH	–H	**1a**	3-FC_6H_4	1	**3h**	33
8	CH	–H	**1a**	C_5H_{11}	3	**3i**	- [c]
9	CH	–H	**1a**	$SiMe_3$	3	**3j**	- [c]
10	CH	–F	**1b**	4-MeC_6H_4	1	**3k**	59
11	CH	–OMe	**1c**	4-MeC_6H_4	2	**3l**	57
12	N	–H	**1d**	4-MeC_6H_4	1	**3m**	35

[a] Not including 10 min "ramp time" (ca. 10 °C/min).
[b] Yields refer to pure isolated product.
[c] Complex mixture of unidentified byproducts.

Table 5.2 – Scope and limitation of the three component approach to isoquinolines.

Electron-rich phenylacetylenes gave the corresponding isoquinolines in good yields (Table 5.2, entries 2-4), also when the substituent is in a sterically demanding *ortho*-position (Table 5.2, entries 2 and 4), but in extended reaction times. The presence of an acetal group on the triple bond is tolerated too (Table 5.2, entry 5). Conversely, in the presence of an electron-withdrawing group on the phenylacetylene, despite a quantitative conversion of **1** in 1 h only, the reaction yields are slightly lower (Table 5.2, entry 6 and 7). Unfortunately the reaction failed in the presence of aliphatic linear alkynes (Table 5.2, entries 8 and 9) giving rise to a complex mixtures of unidentified by-products. Then, the effect of the presence of electron-withdrawing and electron-donating groups on the *ortho*-bromobenzaldehyde was briefly investigated (Table 5.2, entries 10 and 11). In the first trial the reaction yield was satisfying under standard conditions (Table 5.2, entry 10), whereas in the presence of EDG best results were obtained in a twofold reaction time (Table 5.2, entry 11). Finally, starting from the electron poor 2-bromonicotinaldehyde **1d** the approach demonstrated to be a little less effective (Table 5.2, entry 12).

The suggested reaction mechanism involves a well-ordered set of three different events: a) an imination step, b) a Sonogashira coupling (these two steps could also occur simultaneously), c) a final intramolecular annulation reaction. As mentioned above, the ammonia play the double role of base in the cross-coupling and amino partner in the addition/cyclisation sequence. Regarding the role of the metals (Pd and Cu), obviously involved in the cross-coupling between the *ortho*-bromobenzaldehyde and the alkyne, we cannot 'a priori' exclude their involvement as Lewis acids in the imination as well as in the cyclisation steps.[11] This fact could explain the higher overall yields observed in this multicomponent approach, with respect to the domino synthesis.[4]

5.3 Conclusion

In conclusion, we developed an unprecedented multicomponent synthesis of isoquinoline skeleton starting from simple *ortho*-bromoarylaldehydes, alkynes and aqueous ammonia. The strategy tolerate a selection of substituents on both alkynyl and aldehyde partners. Moreover, the approach was briefly tested for the synthesis of related 1,6-naphthyridines. With respect to the reported domino approach,[4] this MCR allow a general increase of the overall yields and a reduction of operative steps, reaction times, energy and solvent consumption. Moreover, the possibility to use of aqueous ammonia represents a remarkable improvement of the approach.

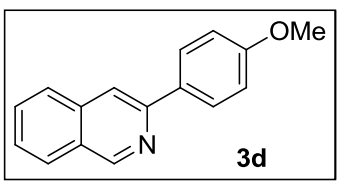
5.4 Experimental section

General details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Catalysts were purchased from Sigma-Aldrich. 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, at 200 or 300 MHz, with the resonance of solvent as the internal reference. ^{13}C NMR spectra were recorded at room temperature at 50.3 or 75.45 MHz, with the resonance of solvent as the internal reference. The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. 2D-NOESY spectra were acquired at 500 MHz in the phase-sensitive TPPI mode with 2K × 256 complex FIDs, spectral width of 5682 Hz, recycling delay of 3 s, 8 scans and a mixing time of 1.3 s. All spectra were transformed and weighted with a 90° shifted sine-bell squared function to 1K × 1K real data points. Microwave assisted reactions were performed in a Microsinth Milestone® multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with a fiber optic sensor.

Typical MCR procedure. In a sealed MW test tube, to a solution of the appropriate 2-bromoarylaldehyde **1** (1 mmol) in THF (1 ml), alkyne (1.2 mmol) and *trans*-dichlorobis(triphenylphosphine)-palladium (7.02 mg, 0.01 mmol) were added. The solution was stirred at room temp. for 10 min., then NH_3 (2.5 M aqueous, 3 ml) and CuI (3.81 mg, 0.02 mmol) were added. The stirred reaction mixture was heated at 130 °C (max power setting = 500 W) in a multimode microwave oven for the proper time (see Table 5.2). The reaction mixture was diluted with H_2O (70 ml) and extracted with EtOAc (3 × 70 ml). The organic layer dried over Na_2SO_4, was evaporated to dryness and the crude material was purified by flash chromatography over a silica gel column yielding the desired isoquinolines **3**.

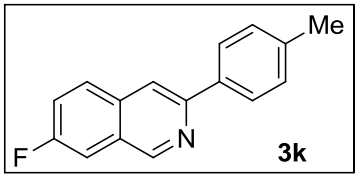
3-*p*-Tolylisoquinoline (3a), **3-Phenylisoquinoline (3b)**, **3-(2-Methoxyphenyl)isoquinoline (3c)**, **3-(4-Methoxy-2-methylphenyl)isoquinoline (3e)**, **3-(Diethoxymethyl)isoquinoline (3f)**, **3-(3-(Trifluoromethyl)phenyl)isoquinoline (3g)** and **3-(3-Fluorophenyl)isoquinoline (3h)** have already been described in the experimental section in chapter 4.

3-(4-Methoxyphenyl)isoquinoline (3d). Eluent for chromatography: hexane/EtOAc (96:4). Yield 132 mg (56 %). Brown solid. Mp 85-87 °C. IR (KBr): ν_{max} = 1626, 1606, 1584, 1512, 1447, 1292, 1249, 1179, 1024, 834 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.88 (s, 3 H, CH_3), 7.04 (d, J = 8.8 Hz, 2 H, arom.), 7.57 (ddd, J = 8.1, 7.0, 1.1 Hz, 1 H, arom.), 7.67 (ddd, J = 8.4, 7.0, 1.5 Hz, 1 H, arom.), 7.85 (d, J = 8.1 Hz, 1 H, arom.), 7.95–7.99 (m, 2 H, arom.), 8.08 (d, J = 8.8 Hz, 2 H, arom.), 9.31 (s, 1 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 55.6

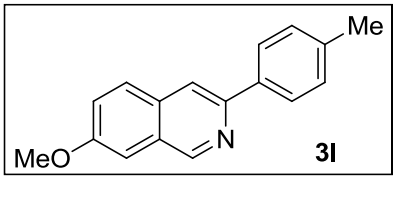


(CH_3), 114.5, 115.5, 126.8 , 126.9, 127.8, 128.4, 130.6, 152.5 (CH arom.), 127.7, 132.6, 137.0, 151.4, 160.5 (C quat.) ppm. ESI-MS m/z (%): 236 $[M + 1]^+$ (100). Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.77; H, 5.60; N, 5.93.

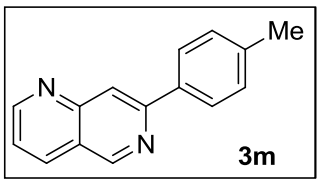
7-Fluoro-3-(p-tolyl)isoquinoline (3k). Eluent for chromatography: hexane/EtOAc (98:2). Yield 140 mg (59 %). Brown solid. Mp 153-155 °C. IR (KBr): ν_{max} = 1631, 1590, 1490, 1136, 823 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3 H, CH_3), 7.32 (d, J = 8.1 Hz, 2 H, arom.), 7.47 (ddd, J = 11.4, 8.8, 2.6 Hz, 1 H, arom.), 7.59 (dd, J = 8.8, 2.6, 1 H, arom.), 7.87 (dd, J = 8.8, 5.5, 1H, arom.), 8.01 (m, 3 H, arom.), 9.28 (s, 1 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 21.6, 110.9 (d, $^2J_{C\text{-}F}$ = 20.7 Hz), 116.9 (d, $^5J_{C\text{-}F}$ = 1.5 Hz), 121.4 (d, $^2J_{C\text{-}F}$ = 25.6 Hz), 127.1, 128.5(d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.8 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.9, 134.1, 136.9, 138.9, 151.5 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 151.9 (d, $^4J_{C\text{-}F}$ = 5.5 Hz), 161.1 (d, $^1J_{C\text{-}F}$ = 249 Hz) ppm. ESI-MS m/z (%): 238 $[M + 1]^+$ (100). Calcd for $C_{16}H_{12}FN$ (237.10): C, 80.99; H, 5.10; N, 5.90. Found: C, 80.91; H, 5.07; N, 5.92.



7-Methoxy-3-(p-tolyl)isoquinoline (3l). Eluent for chromatography: hexane/EtOAc (95:5). Yield 142 mg (57 %). Brown solid. Mp 141-143 °C. IR (KBr): ν_{max} = 1625, 1592, 1514, 1490, 1455, 1230, 1159, 1022, 823 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.42 (s, 3 H, CH_3), 3.95 (s, 3 H, CH_3), 7.23–7.37 (m, 4 H, arom.), 7.74 (d, J = 9.1 Hz, 1 H, arom.), 7.97 (d, J = 4.4 Hz, 2H, arom.), 8.02 (s, 1 H, arom.), 9.22 (s, 1 H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.4, 55.7, 105.1, 116.0, 123.8, 126.8, 128.6, 128.9, 129.7, 132.6, 137.2, 138.2, 149.9, 150.9, 158.5 ppm. APCI-MS m/z (%): 250 $[M + 1]^+$ (75). Calcd for $C_{17}H_{15}NO$ (249.12): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.96; H, 6.08; N, 5.63.



7-(*p*-Tolyl)-1,6-naphthyridine (3m). Eluent for chromatography: hexane/EtOAc (8:2). Yield 77 mg (35 %). Brown solid. Mp 128-130 °C. IR (KBr): ν_{max} = 1611, 1589, 1512, 1464, 1444, 1338, 1120, 945, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.44 (s, 3 H, CH_3), 7.34 (d, J = 7.7 Hz, 2 H, arom.), 7.49 (dd, J = 8.4, 4.4 Hz, 1 H, arom.), 8.08 (d, J = 8.1 Hz, 2 H, arom.), 8.30 (d, J = 8.1 Hz, 2 H, arom.), 9.08 (dd, J = 4.0, 1.5, 1 H, arom.), 9.33 (s, 1 H, arom) ppm. ^{13}C NMR ($CDCl_3$, 75.45 MHz): δ = 21.7, 117.6, 122.4, 122.9, 127.5, 130.1, 135.9, 136.5, 139.6, 151.8, 152.9, 155.4, 155.6 ppm. ESI-MS m/z (%): 221 $[M + 1]^+$ (100). Calcd for $C_{15}H_{12}N_2$ (220.10): C, 81.79; H, 5.49; N, 12.72. Found: C, 81.69; H, 5.43; N, 12.78.



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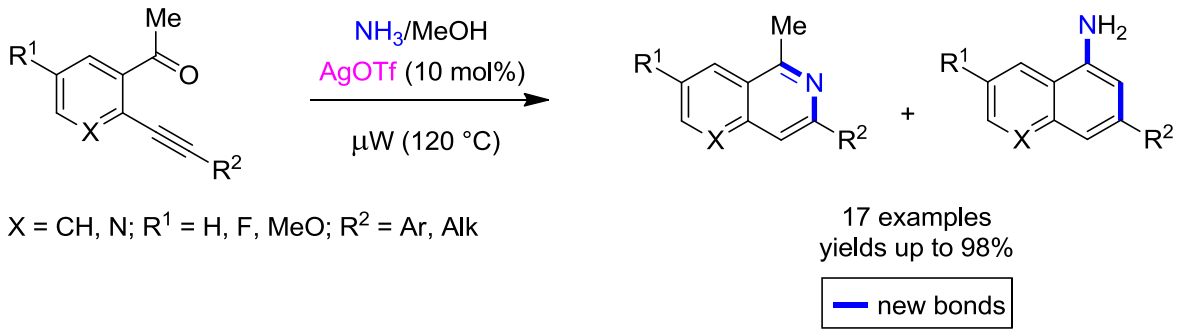
Chapter 6

Silver-Catalysed Intramolecular Cyclisation of 2-Alkynylacetophenones and 3-Acetyl-2-alkynylpyridines in the Presence of Ammonia



A new silver-catalysed/microwave-assisted approach to 2-methylisoquinolines and 5-methyl-1,6-naphthyridines by tandem addition/cyclisation of γ-ketoalkynes with ammonia. A plausible mechanism is proposed and the dual activity of silver salts is supported by NMR experiments.

Dell'Acqua, M.; Abbiati, G.; Arcadi, A.; Rossi, E.

Org. Biomol. Chem. **2011**, *9*, 7836–7848.

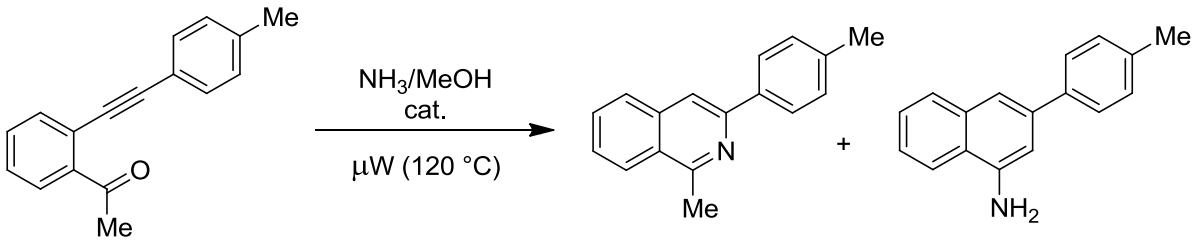
6.1 Introduction

In chapter 4, we showed the sequential imination/annulation reaction of 2-alkynylbenzaldehydes in the presence of ammonia in methanol for the synthesis of isoquinolines.[1] Unexpectedly, when we tried to synthesize 1-methylisoquinolines by reacting 2-alkynylacetophenones with ammonia under our standard domino conditions, the reactions gave very poor results. These outcomes prompted us to investigate the reactions of alkynyl ketones in more depth.

Whereas the use of 2-alkynylbenzaldehydes (and related compounds characterized by the presence of a γ-alkynylaldehyde framework on an (hetero)aromatic scaffold) as starting materials for the preparation of (hetero)cyclic compounds has been widely explored and is in continuous evolution, the reactivity of keto-homologous, 2-alkynylacetophenones, is less investigated.[2] In many articles, 2-alkynylacetophenones are only marginally treated as a digression in more comprehensive works on 2-alkynylbenzaldehydes.[3] In some cases, 2-alkynylacetophenones show a different behaviour with respect to the corresponding 2-alkynylbenzaldehydes, in terms of reaction yield,[4] or product selectivity.[5] It is worth noting that reactions of 2-alkynylacetophenones or their *N*-heterocyclic analogues, 3-acetyl-2-alkynylpyridines, with secondary[6] or branched primary amines[6a] have only few precedents, whereas, to the best of our knowledge, no example of their reaction with ammonia has been reported yet. Thus, in this chapter we report our recent findings on microwave assisted, domino addition/annulation reactions of 2-alkynyl-acetophenones and 3-acetyl-2-alkynylpyridines in the presence of ammonia.[7]

6.2 Results and discussion

We started our study looking for the best conditions to trigger the domino reaction of *o*-(*p*-tolylethynyl)acetophenone **1a**, choosen as model compound, with ammonia (Table 6.1).



1a **2a** **3a**

Entry	t (min)[a]	Catalyst	2a (yield %)[b]	3a (yield %)[b]	1a (rec.) (yield %)[b]	Overall (yield %)[b]	Ratio 2a/3a
1	120	-	11[c]	-	72	11	-
2	120	4Å molecular sieve	4	-	45	4	-
3	30	$TiCl_4$ (3 eq.)	traces[d]	-	-	-	-
4	15	$TiCl_4$[e]	traces[d]	-	-	-	-
5	80	$TiCl_4 \cdot 2$ THF[e]	11	-	18	11	-
6	100	$Pd(OAc)_2$[e]	46	25	-	71	1.8
7	60	$PdCl_2$[e]	23	19	7	42	1.2
8	120	$Cu(OTf)_2$[e]	23	13	8	36	1.8
9	120	CuI[e]	38	20	-	58	1.9
10	120	AgF[e]	15	14	17	29	1.1
11	120	Ag_2O[e]	10	10	18	20	1.0
12	60	$AgSbF_6$[e]	26	17	4	43	1.5
13	60	$AgNO_3$[e]	46	36	9	82	1.3
14	**45**	**AgOTf**[e]	**58**	**40**	-	**98**	1.5
15	120	$NaAuCl_4 \cdot 2H_2O$[e]	11	6	31	17	1.8
16	30	PPh_3AuCl[e]	41	34	10	75	1.2
17	60	PPh_3AuCl (7.5 mol%) AgOTf[e]	27	43	-	70	0.6
18	120	$InCl_3$[e]	5	-	18	5	-
19	120	$In(OTf)_3$[e]	traces[d]	-	-	-	-

[a] Not including 11 min "ramp time" (ca. 10 °C/min).

[b] Yields refer to pure isolated product.

[c] The reaction performed under conventional heating at 110 °C overnight gave only traces of isoquinoline **2a**.

[d] The reaction gave a complex mixture of tarry unidentified by-products.

[e] 10 mol%.

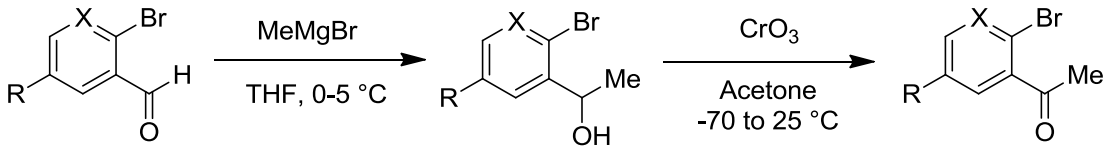
Table 6.1 – Screening of reaction conditions for domino addition/annulation of **1a** with ammonia.

As mentioned above, the uncatalysed reaction of **1a** with 2M ammonia in methanol at 120 °C under microwave heating gave the corresponding isoquinoline **2a** in very low yield (Table 6.1, entry 1). A simple tentative approach to promote the formation of the imine intermediate by the use of molecular sieves did not result in any improvement (Table 6.1, entry 2). On the basis of our previous experiences,[1] we planned to catalyse the reaction with 3 eq. of titanium tetrachloride, but, under these conditions, only traces of the isoquinoline **2a** were identified together with a complex mixture of tarry unidentified by-products (probably derived from a titanium catalysed polymerisation process) (Table 6.1, entry 3). A similar behaviour was observed using a catalytic amount of titanium (Table 6.1, entry 4), whereas the

less acidic complex $TiCl_4 \cdot 2$ THF also gave poor yield after a prolonged reaction time (Table 6.1, entry 5). Due to these disappointing outcomes, we tried some other metal catalysts potentially able to promote both the imine formation as a Lewis acid, and the intermolecular hydroamination step as an alkynophilic catalysts.[8] There are many examples in the literature of this double activity of palladium,[9] copper,[10] silver,[3c] gold[11] and indium[2b,12] salts and complexes in the intramolecular cyclisations involving alkynes bearing a neighboring nucleophile. We were delighted to find that in the presence of $Pd(OAc)_2$ the reaction gave the desired isoquinoline **2a** in a promising 46% yield, as well as a not negligible amount of the isomeric naphtalen-1-amine **3a** (Table 6.1, entry 6). $PdCl_2$ gave poorer results in terms of yield and regioselectivity (Table 6.1, entry 7), whereas $Cu(OTf)_2$ gave a similar ratio **2a**:**3a** but in lower overall yield (Table 6.1, entry 8). In the presence of CuI, yield and selectivity were comparable to those observed using $Pd(OAc)_2$ (Table 6.1, *cf.* entry 9 and 6). Among the five silver-based catalysts tested (Table 6.1, entries 10-14), AgF and Ag_2O gave modest results even after prolonged reaction times (Table 6.1, entries 10 and 11) whereas $AgSbF_6$ was more active and selective, and gave slightly better yield (Table 6.1, entry 12). $AgNO_3$ was a little more effective than palladium, despite the ratio of products being slightly shifted toward the naphtalen-1-amine **3a** (Table 6.1, entry 13). The best result was obtained with AgOTf, which gave an almost quantitative conversion with a quite good regioselectivity (whit respect to the other catalysts tested) in a relatively short reaction time (Table 6.1, entry 14). $NaAuCl_4$ was ineffective (Table 6.1, entry 15), whereas PPh_3AuCl was as active as $AgNO_3$[13] (Table 6.1, entry 16). Surprisingly, in the presence of both PPh_3AuCl and AgOTf a reversed selectivity was observed (Table 6.1, entry 17). Finally, indium salts seemed to be completely unsuited for our purpose (Table 6.1, entries 18 and 19).

It is worth noting that our results with silver salts "fit well" with all other emerging examples in which simple and cheap silver salts seem to be equally or more effective than more expensive gold catalysts.[3c,14]

Afterwards, we investigated the scope and limitations of the approach. Initially, we prepared a library of 2-alkynylacetophenones **1a-m** and 3-acetyl-2-alkynylpyridines **1n-t** by a standard Sonogashira procedure[15] from 2-bromoacetophenones **4a-c** and 2-bromo-3-acetylpyridine **4d** in the presence of a variety of terminal alkynes (Table 6.2). Whereas 2-bromoacetophenone **4a** is a cheap commercially available reagent, the more expensive 2-bromo-3-acetylpyridine **4d** was prepared in two steps in very good yields by a Grignard reaction of 2-bromonicotinaldehyde **5d** with CH_3MgBr,[6b] followed by Jones oxidation[16] (Scheme 6.1). The same procedure was followed to prepare 2-bromo-5-methoxyacetophenone **4b** and 2-bromo-5-fluoroacetophenone **4c** starting from the corresponding aldehydes **5b** and **5c**, respectively (Scheme 6.1).

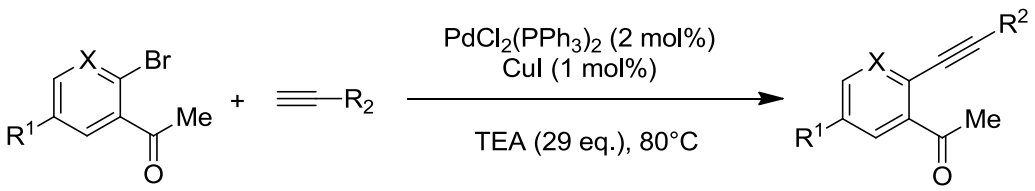


5b: X = CH, R = MeO
5c: X = CH, R = F
5d: X = N, R = H

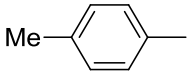
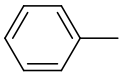
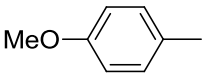
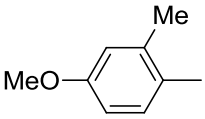
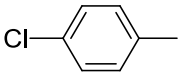
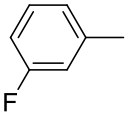
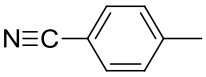
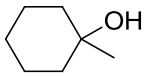
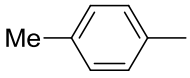
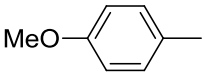
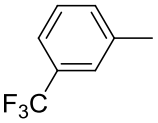
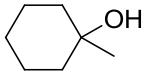
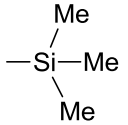
6b: 99 %
6c: 90 %
6d: 96 %

4b: 88 %
4c: 92 %
4d: 91 %

Scheme 6.1 – Preparation of 2-bromo-5-methoxyacetophenone **4b**, 2-bromo-5-fluoroacetophenone **4c** and 2-bromo-3-acetylpyridine **4d**.



1 a-t

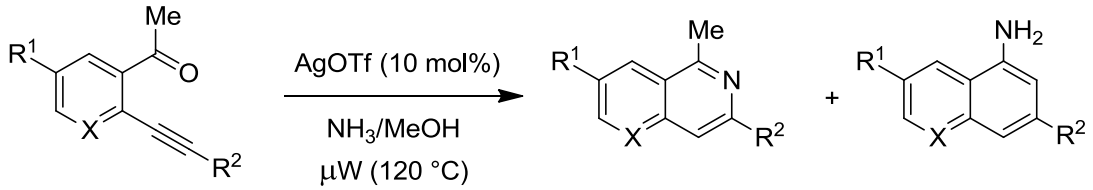
X	R^1	R^2	t (h)	Product	Yield (%)[a]
CH	H		6	**1a**	98
CH	H		2.5	**1b**	66
CH	H		5	**1c**	62
CH	H		5	**1d**	87
CH	H		2	**1e**	38[b]
CH	H		6.5	**1f**	45
CH	H		6.5	**1g**	39
CH	H	$CH_3(CH_2)_4$—	12	**1h**	57
CH	H	$CH_3(CH_2)_5$—	12	**1i**	95
CH	H	$CH_3(CH_2)_7$—	12	**1j**	93
CH	H		2	**1k**	98
CH	MeO	$CH_3(CH_2)_2$—	12	**1l**	63
CH	F	$CH_3(CH_2)_2$—	1	**1m**	94
N	H		1	**1n**	84
N	H		1	**1o**	78
N	H		2	**1p**	84
N	H	$CH_3(CH_2)_4$—	1.5	**1q**	67
N	H	$CH_3(CH_2)_5$—	3	**1r**	76
N	H		1	**1s**	98
N	H		1	**1t**	98

[a] Yields refer to pure isolated product.

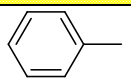
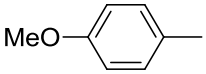
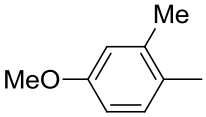
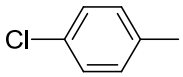
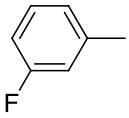
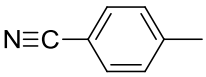
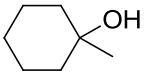
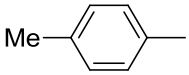
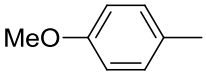
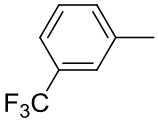
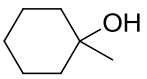
[b] Prepared by reaction of 2-ethynylacetophenone with 4-iodoacetophenone under standard Sonogashira conditions.

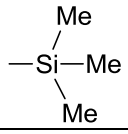
Table 6.2 – Preparation of 2-alkynylacetophenones **1a–m** and 3-acetyl-2-alkynylpyridines **1n–t**.

Then, we tested compounds **1b-t** in the the AgOTf-catalysed domino reaction with ammonia. The obtained results are depicted in Table 6.3.



1 b-t **2 b-t** **3 b-t**

Entry	1,2,3	X	R^1	R^2	t (min)[a]	2 (yield %)[b]	3 (yield %)[b]
1	**b**	CH	H		120	36	44
2	**c**	CH	H		90	32	41
3	**d**	CH	H		90	35	40
4	**e**	CH	H		120	23	39
5	**f**	CH	H		210	traces	traces
6	**g**	CH	H		90	traces	-
7	**h**	CH	H	$CH_3(CH_2)_4$—	90[c]	63	15
8	**i**	CH	H	$CH_3(CH_2)_5$—	90	61	20
9	**j**	CH	H	$CH_3(CH_2)_7$—	90[d]	44	14
10	**k**	CH	H		120	25	-
11	**l**	CH	MeO	$CH_3(CH_2)_2$—	150	71	17
12	**m**	CH	F	$CH_3(CH_2)_2$—	150	55	15
13	**n**	N	H		60	41	25
14	**o**	N	H		30	48	19
15	**p**	N	H		105	-	-
16	**q**	N	H	$CH_3(CH_2)_4$—	60	57	25
17	**r**	N	H	$CH_3(CH_2)_5$—	60	75	-
18	**s**	N	H		60	20	7

19	**t**	N	H		60	(R^2=H) 37[e]	traces[e]

[a] Not including 11 min "ramp time" (ca. 10 °C/min).

[b] Yields refer to pure isolated product.

[c] The reaction performed without catalyst under conventional heating at 110 °C overnight gave only the isoquinoline **2h** in 35% yield.

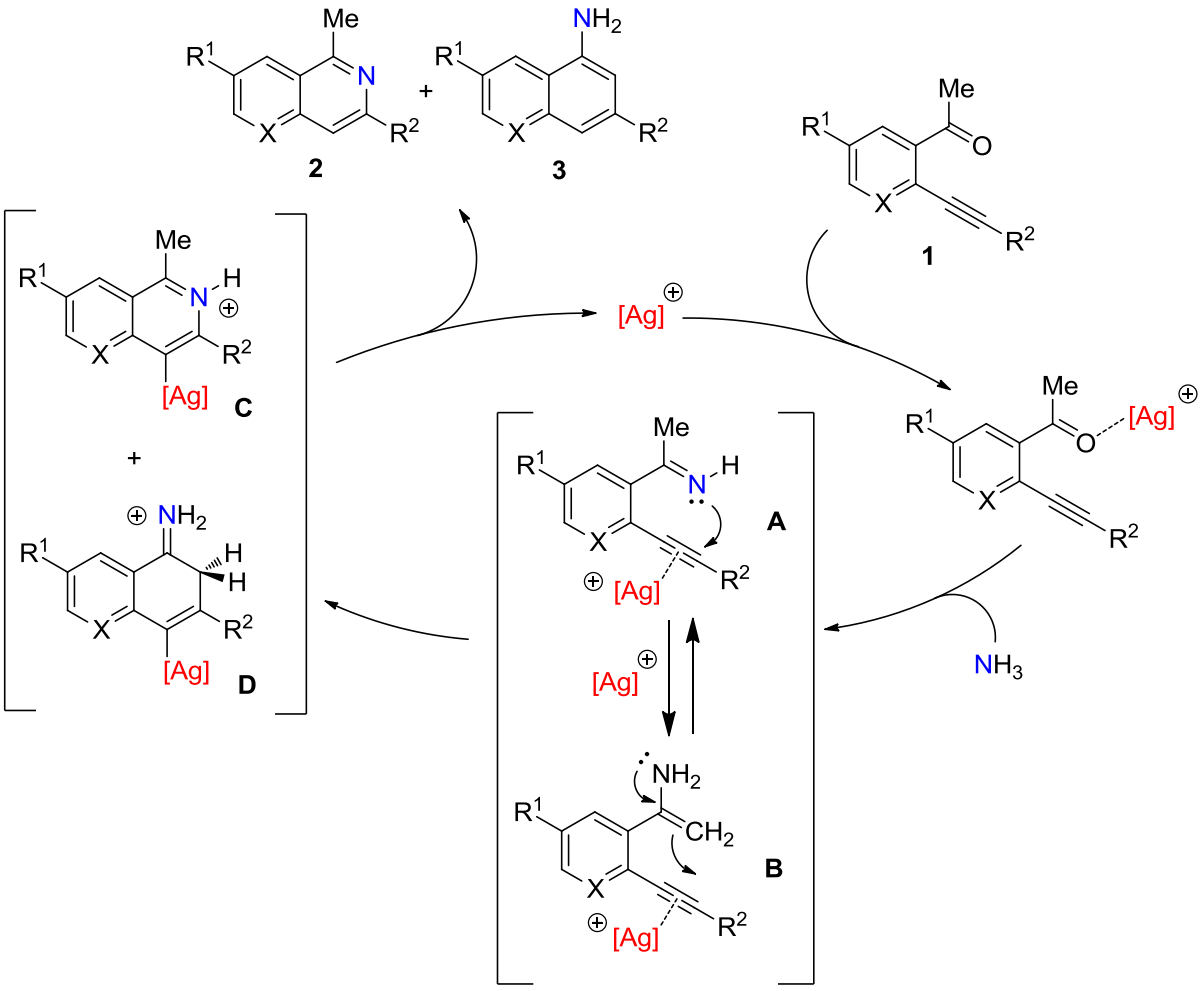
[d] Catalysed with $AgNO_3$ (10 mol%).

[e] Desilylated product.

Table 6.3 – AgOTf-catalysed domino addition/cyclisation reaction of derivatives **1b–t**.

The reactions of acetophenone derivatives substituted on the triple bond with an aryl group, always lead to a mixture of isoquinoline and naphtalenamine isomers in variable ratio (Table 6.3, entries 1-6). Better results were obtained with neutral and electron-donating groups on the aryl moiety (Table 6.3, entries 1-3), whereas electron-withdrawing groups gave lower yields and worse selectivity or inhibited the reaction (Table 6.3, entries 4-6). In the presence of alkyl substituents on the triple bond the reactions run with good yields and a better selectivity toward the isoquinoline isomers (Table 6.3, entries 7-12). The approach also tolerates the presence of bulky substituents on the triple bond such as cyclohexanol, but in this case the yields were moderate (Table 6.3, entry 10). An electronic perturbation on the acetophenone ring does not seem to substantially affect the course of reaction (Table 3, entries 11 -12), although the presence of an electron-withdrawing substituent leads to a slight reduction of yield (Table 6.3, entry 12). In the reactions of the aryl- and alkyl-substituted 3-acetyl-2-alkynylpyridines (Table 6.3, entries 13-19) we observed a general behavior comparable to that of 3-alkynylacetophenones, with an improved selectivity to the 1,6-naphthyridine isomer for the substrates substituted with an aryl moiety on the alkyne (Table 6.3, entries 13-14, *cf.* entry 2 with 14). Finally, the reaction of 3-acetyl-2-(trimethylsilylethynyl)pyridine **1t** gave the desilylated 5-methyl-1,6-naphthyridine in moderate yield (Table 6.3, entry 19). All the obtained products have been identified and fully characterized by NMR spectroscopy, IR and MS.

According to the literature,[3c,14a] the proposed mechanism for the AgOTf-catalysed nucleophilic addition/annulation sequence involves two key steps (Scheme 6.2): in the first step, the nucleophilic attack of ammonia on the carbonyl leads to the formation of imine intermediate **A**, in equilibrium with its enamine tautomer **B**. Although silver triflate is generally considered a Lewis acid with a strong π-philic character,[3c] we believe that it is also able to increase the electrophilic character of the carbonyl carbon atom[8,9] and therefore to promote the nucleophilic attack of ammonia. In a similar way, it is probably able to also coordinate the imine,[8,17] and affect the tautomeric equilibrium imine/enamine thus highlighting the bidentate character of the nucleophile intermediate. The second step involves the intramolecular addition of the N or C-nucleophile on the Ag-activated triple bond.[3c] The cycloisomerisation occurs with selective *6-endo-dig* geometry leading to the corresponding σ-silver complex of isoquinoline **C** and/or naphtalenamine **D**. The final products **2** and/or **3** are then achieved by a solvent mediated protodemetalation that restores the catalyst.



Scheme 6.2 – Proposed reaction mechanism.

To verify the hypothesis that silver can act as a σ-philic Lewis acid and thus is able to enhance the electrophilicity of the carbonyl and to affect the tautomeric processes, some NMR experiments were performed. First, we acquired two ^{13}C NMR spectra of acetophenone in deuterated methanol, in the absence (**A**) and in the presence (**B**) of 1 equiv. of AgOTf (Figure 6.1). It is well-known that one of the most important parameters that determine the chemical shift in nuclear magnetic resonance is the shielding effect, determined by the electron density of the atomic nucleus observed. Therefore, the shift of a signal in response to an interaction with a catalyst, can be related to the change of charge density of the corresponding nucleus. The results showed a slight shift of the C carbonyl signal at higher frequencies (+ 0.227 ppm), indicating a weak interaction between the metal and the carbonyl oxygen with consequent deshielding of carbonyl carbon.[18]

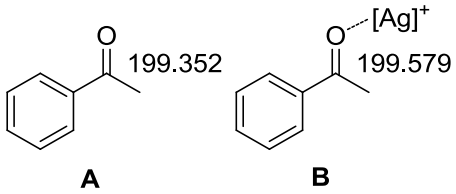
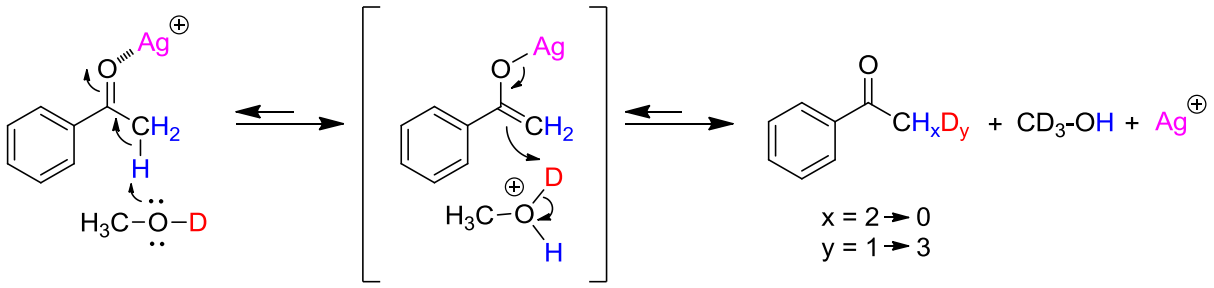


Figure 6.1 – Chemical shift of acetophenone carbonyl with and without the catalyst.

A second dynamic experiment has been performed by recording the ^{1}H NMR spectrum of acetophenone in deuterated methanol at different times with and without the catalyst. The spectra of the sample containing AgOTf (50 mol%) displayed gradual reduction and increasing complexity of the

methyl signal of acetophenone due to progressive deuteration, and the simultaneous rise of the integral for the signal of the OH of solvent (Table 6.4 and Figure 6.2). This behavior was not observed in the control experiment, supporting the hypothesis that the catalyst is able to speed up the tautomeric equilibria.



t (h)	Acetophenone in CD_3OD		Acetophenone + AgOTf (50 mol%) in CD_3OD	
	Integral (ref. to 2 CH arom.)		Integral (ref. to 2 CH arom.)	
	CH_3-CO-Ph	**CD_3OH**	**CH_3-CO-Ph**	**CD_3OH**
0	3.08	1.01	3.30	2.19
16	3.11	1.12	2.94	2.40
21	3.05	1.09	2.81	3.55
44	3.07	1.10	1.92	4.42
65	3.09	1.11	1.30	5.05

Table 6.4 – Dynamic ^{1}H NMR study.

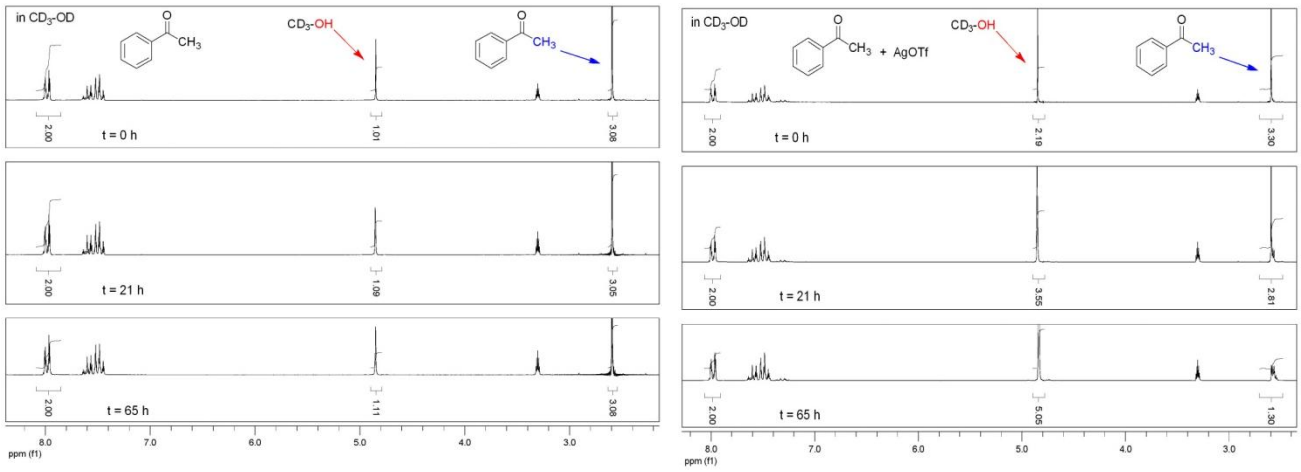


Figure 6.2 – Selected spectra of the dynamic ^{1}H NMR study.

6.3 Conclusion

In conclusion, we found that silver triflate is the catalyst of choice for the microwave-promoted domino nucleophilic addition/annulation reaction of a wide variety of 2-alkynyl-acetophenones and 3-acetyl-2-alkynylpyridines in the presence of ammonia. In most cases the reactions gave mixtures of imino- and carbo-cylisation products with a general preference for the former. A variety of substituted 1-methylisoquinolines and 5-methyl-1,6-naphthyridines can be synthesized by this approach. Simple NMR experiments strongly supported the hypothesis that silver triflate exerts the dual role of σ- and π-philic Lewis acid.

6.4 Experimental section

General details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F_{254} thin-layer plates were employed for thin layer chromatography (TLC). Silica gel 40−63 micron/60 Å was employed for flash column chromatography. Melting points were measured with a Perkin-Elmer DSC 6 calorimeter at a heating rate of 5 °C/min and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer FT-IR 16 PC spectrophotometer using KBr tablets for solids and NaCl disks for oils. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$, at 200, 300 or 500 MHz (with a Varian-Gemini 200 or a Brucker 500 Avance spectrometer), 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, 75.45 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. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions. 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 an optical fibre sensor. "EtOAc" means ethyl acetate and "TEA" means triethylamine.

Compounds **6b-d** are known compounds and were prepared following the method reported in the literature (see ref. 6b).

1-(2-Bromo-5-methoxyphenyl)ethanol (6b). Yellow wax. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.47 (d, 3H, CH_3, *J* = 6.2 Hz), 1.98 (br, 1H, OH), 3.81 (s, 3H, CH_3), 5.19 (q, 1H, CH, *J* = 6.2 Hz), 6.69 (dd, 1H, arom., *J* = 8.8, 3.3 Hz), 7.16 (d, 1H, arom., *J* = 2.9 Hz), 7.40 (dd, 1H, arom., *J* = 8.7, 5.1 Hz) ppm. These data are in good agreement with literature values.[19]

1-(2-Bromo-5-fluorophenyl)ethanol (6c). Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.47 (d, 3H, CH_3, *J* = 6.2 Hz), 2.00 (br, 1H, OH), 5.18 (q, 1H, CH, *J* = 6.4 Hz), 6.85 (ddd, 1H, arom., *J* = 8.8, 7.7, 3.3 Hz), 7.34 (dd, 1H, arom., *J* = 9.5, 2.9 Hz), 7.46 (dd, 1H, arom., *J* = 8.7, 5.1 Hz) ppm. These data are in good agreement with literature values.[20]

1-(2-Bromopyridin-3-yl)ethanol (6d). Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.50 (d, 3H, CH_3, *J* = 6.2 Hz), 1.98 (br, 1H, OH), 5.18 (q, 1H, CH, *J* = 6.2 Hz), 7.30 (dd, 1H, arom., *J* = 7.7, 4.7 Hz), 7.92

(dd, 1H, arom., J = 7.7, 1.8 Hz), 8.26 (dd, 1H, arom., J = 4.7, 1.8 Hz) ppm. These data are in good agreement with literature values.[16, 21]

Compounds **4b-d** are known compounds and were prepared following the method reported in the literature (see ref. 16).

2-Bromo-5-methoxyacetophenone (4b). Colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.63 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 6.85 (dd, 1H, arom., J = 8.8, 2.6 Hz), 6.97 (d, 1H, arom., J = 2.9 Hz), 7.48 (d, 1H, arom., J = 8.8 Hz) ppm. These data are in good agreement with literature values.[22]

2-Bromo-5-fluoroacetophenone (4c). Colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.63 (s, 3H, CH_3), 7.03 (ddd, 1H, arom., J = 8.8, 7.7, 2.9 Hz), 7.18 (dd, 1H, arom., J = 8.4, 2.9 Hz), 7.58 (dd, 1H, arom., J = 8.8, 4.7 Hz) ppm. These data are in good agreement with literature values.[20]

2-Bromo-3-acetylpyridine (4d). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.68 (s, 3H, CH_3), 7.36 (dd, 1H, arom., J = 7.7, 4.7 Hz), 7.76 (dd, 1H, arom., J = 7.7, 2.2 Hz), 8.45 (dd, 1H, arom., J = 4.7, 2.2 Hz) ppm. These data are in good agreement with literature values.[16, 23]

General procedure for the synthesis of 2-alkynylacetophenones 1a-m and 3-acetyl-2-alkynylpyridines 1n-t. Under a nitrogen atmosphere, to a solution of 2-bromoacetophenone or 2-bromo-3-acetylpyridine (5.00 mmol) in TEA (20 mL) the appropriate alkyne (6.00 mmol) and *trans*-dichlorobis(triphenylphosphine)-palladium(II) (0.10 mmol) were added. The reaction was stirred at rt for 15 min, then CuI (0.05 mmol) was added. The reaction mixture was stirred at 80°C (see Table 6.2) 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 times and yields see Table 6.2).

1-(2-(*p*-Tolylethynyl)phenyl)ethanone (1a). Eluent for chromatography: hexane/EtOAc (97:3). Yellow solid. Mp 45-46 °C. IR (KBr): ν_{max} = 2214, 1687 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.38 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.18 (d, 2H, arom., J = 8.1 Hz), 7.34-7.51 (m, 4H, arom.), 7.62 (d, 1H, arom., J = 7.2 Hz), 7.75 (d, 1H, arom., J = 7.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.8, 30.3, 88.2, 95.6, 120.0, 122.2, 128.3, 128.9, 129.5, 131.5, 131.7, 134.0, 139.3, 140.9, 200.7 ppm. ESI-MS m/z (%): 235 $[M + 1]^+$ (100), 102 (13). Calcd for $C_{17}H_{14}O$ (234.29): C, 87.15; H, 6.02. Found: C, 87.11; H, 6.01. These data are in good agreement with literature values.[2a]

1-(2-(Phenylethynyl)phenyl)ethanone (1b). Eluent for chromatography: hexane/EtOAc (98:2). Orange oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.79 (s, 3H, CH_3), 7.33-7.48 (m, 5H, arom.), 7.51-7.57 (m, 2H, arom.), 7.61 (dd, 1H, arom. J = 7.6, 1.1 Hz), 7.74 (dd, 1H, arom. J = 7.8, 1.2 Hz) ppm. These data are in good agreement with literature values. [2a]

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)ethanone (1c). Eluent for chromatography: hexane/EtOAc (98:2). Orange oil. IR (neat): ν_{max} = 2213, 1683 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.79 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 6.89 (d, 2H, arom. J = 9.2 Hz), 7.32-7.52 (m, 4H, arom.), 7.60 (d, 1H, arom., J = 7.9 Hz), 7.74 (d, 1H, arom., J = 7.0 Hz) ppm. These data are in good agreement with literature values. [2a,24]

1-(2-((4-Methoxy-2-methylphenyl)ethynyl)phenyl)ethanone (1d). Eluent for chromatography: hexane/EtOAc (97:3). Orange oil. IR (neat): ν_{max} = 2205, 1688 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.52 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 3.81 (s, 3H, O-CH_3), 6.71 (s, 1H, arom.), 6.76 (d, 1H, arom., J = 7.2 Hz), 7.32-7.50 (m, 3H, arom.), 7.60 (d, 1H, arom., J = 7.2 Hz), 7.75 (d, 1H, arom., J = 8.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.3, 30.2, 55.5, 91.1, 94.6, 111.6, 115.2, 115.4, 122.6, 128.0, 128.8,

131.4, 133.6, 134.1, 140.5, 142.5, 160.2, 200.7 ppm. ESI-MS m/z (%): 265 $[M + 1]^+$ (100). Calcd for $C_{18}H_{16}O_2$ (264.32): C, 81.79; H, 6.10. Found: C, 81.71; H, 6.06.

1-(2-((4-Chlorophenyl)ethynyl)phenyl)ethanone (1e). Eluent for chromatography: hexane/EtOAc (98:2). Orange solid. Mp 61-62 °C. IR (KBr): ν_{max} = 2211, 1672 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.76 (s, 3H, CH_3), 7.31-7.37 (m, 2H, arom.), 7.40-7.52 (m, 4H, arom.), 7.60 (dd, 1H, arom., J = 7.3, 1.5 Hz), 7.74 (dd, 1H, arom., J = 7.3, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 30.0, 89.6, 93.8, 121.6, 121.7, 128.7, 129.0, 129.1, 131.6, 133.0, 134.1, 135.0, 140.8, 200.3 ppm. ESI-MS m/z (%): 255 $[M + 1]^+$ (100). Calcd for $C_{16}H_{11}ClO$ (254.17): C, 75.45; H, 4.35. Found: C, 75.38; H, 4.39.

1-(2-((3-Fluorophenyl)ethynyl)phenyl)ethanone (1f). Eluent for chromatography: hexane/EtOAc (97:3). Yellow oil. IR (neat): ν_{max} = 1689 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.76 (s, 3H, CH_3), 7.06, (m, 1H, arom.), 7.21-7.53 (m, 5H, arom.), 7.62 (dd, 1H, arom. J = 7.3, 1.5), 7.76 (dd, 1H, arom. J = 7.2, 2.0) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 30.0, 89.5, 93.6 (d, $^4J_{C\text{-}F}$ = 3.4), 116.3 (d, $^2J_{C\text{-}F}$ = 21), 118.2 (d, $^2J_{C\text{-}F}$ = 23), 121.4, 125.0 (d, $^3J_{C\text{-}F}$ = 9.5), 127.7 (d, $^4J_{C\text{-}F}$ = 3.1), 128.8, 129.0, 130.3 (d, $^3J_{C\text{-}F}$ = 8.4), 131.6, 134.2, 141,0, 162.7 (d, $^1J_{C\text{-}F}$ = 247), 200.1 ppm. ESI-MS m/z (%): 239 $[M + 1]^+$ (100). Calcd for $C_{16}H_{11}FO$ (238.26): C, 80.66; H, 4.65. Found: C, 80.56; H, 4.62.

4-((2-Acetylphenyl)ethynyl)benzonitrile (1g). Eluent for chromatography: hexane/EtOAc (92:8). Orange solid. Mp 85-86 °C. IR (KBr): ν_{max} = 2226, 1672 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.72 (s, 3H, CH_3), 7.41-7.61 (m, 2H, arom.), 7.63-7.77 (m, 5H, arom.), 7.80 (dd, 1H, arom., J = 6.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 29.7, 92.7, 92.9, 112.1, 118.6, 120.8, 128.1, 129.2, 129.3, 131.7, 132.3, 132.4, 134.4, 140.8, 199.5 ppm. ESI-MS m/z (%): 246 $[M + 1]^+$ (100). Calcd for $C_{17}H_{11}NO$ (245.28): C, 83.25; H, 4.52; N, 5.71. Found: C, 83.42; H, 4.50; N, 5.67.

1-(2-(Hept-1-ynyl)phenyl)ethanone (1h). Eluent for chromatography: hexane/EtOAc (98:2). Yellow oil. IR (neat): ν_{max} = 2232, 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (t, 3H, CH_3, J = 6.9 Hz), 1.25-1.47 (m, 4H, 2 CH_2), 1.58-1.67 (m, 2H, CH_2), 2.45 (t, 2H, CH_2, J = 7.7), 2.72 (s, 3H, CH_3), 7.31-7.50 (m, 3H, arom.), 7.64 (dd, 1H, arom., J = 6.9, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 14.2, 19.9, 22.4, 28.3, 30.3, 31.4, 79.8, 97.1, 122.7, 127.7, 128.5, 131.3, 134.2, 141.2, 201.3 ppm. ESI-MS m/z (%): 215 $[M + 1]^+$ (100). Calcd for $C_{15}H_{18}O$ (214.30): C, 84.07; H, 8.47. Found: C, 83.95; H, 8.41.

1-(2-(Oct-1-ynyl)phenyl)ethanone (1i). Eluent for chromatography: hexane/EtOAc (98:2). Pale yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3H, CH_3, J = 6.5 Hz), 1.25-1.69 (m, 8H, CH_2), 2.45 (t, 2H, CH_2, J = 7.0 Hz), 2.72 (s, 3H, CH_3), 7.27-7.50 (m, 3H, arom.), 7.66 (dd, 1H, arom. J = 7.7, 1.5 Hz) ppm. These data are in good agreement with literature values.[25]

1-(2-(Dec-1-ynyl)phenyl)ethanone (1j). Eluent for chromatography: hexane/EtOAc (99:1). Yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (t, 3H, CH_3, J = 7.0 Hz), 1.20-1.35 (m, 8H, CH_2), 1.44-1.64 (m, 6H, CH_2), 2.43 (t, 2H, CH_2, J = 7.0 Hz), 2.71 (s, 3H, CH_3), 7.31 (t, 1H, arom., J = 7.6 Hz), 7.37 (t, 1H, arom., J = 7.6 Hz), 7.47 (t, 1H, arom., J = 7.6 Hz), 7.65 (t, 1H, arom., J = 7.8 Hz) ppm. These data are in good agreement with literature values.[25b]

1-(2-((1-Hydroxycyclohexyl)ethynyl)phenyl)ethanone (1k). Eluent for chromatography: hexane/EtOAc (85:15). Orange oil. IR (neat): ν_{max} = 2935, 2219, 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.24-1.28 (m, 2H, CH_2), 1.40-2.05 (m, 8H, CH_2), 2.43 (br, 1H, OH), 2.70 (s, 3H, CH_3), 7.31-7.54 (m, 3H, arom.), 7.69 (dd, 1H, arom. J = 6.9, 2.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 23.3, 23.4, 25.2, 25.4, 30.1, 39.8, 39.9, 69.3, 83.3, 99.0, 121.6, 128.4, 128.7, 131.4, 134.4, 140.9, 200.6 ppm. ESI-MS m/z (%): 225 $[M + 1 - OH]^+$ (100). Calcd for $C_{16}H_{18}O_2$ (242.33): C, 79.31; H, 7.49. Found: C, 79.24; H, 7.48.

1-(5-Methoxy-2-(pent-1-ynyl)phenyl)ethanone (1l). Eluent for chromatography: hexane/EtOAc (98:2). Brown oil. IR (neat): ν_{max} = 3306, 2963, 2230, 1682 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.05 (t, 3H, CH_3, J = 7.0 Hz), 1.54-1.69 (m, 2H, CH_2), 2.42 (t, 2H, CH_2, J = 7.0 Hz), 2.74 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 6.95 (dd, 1H, arom. J = 8.4, 2.9 Hz), 7.18 (d, 1H, arom., J = 2.9 Hz), 7.34 (dd, 1H, arom., J = 8.4 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 13.7, 21.8, 22.2, 30.2, 55.6, 79.8, 95.2, 112.8, 115.1, 118.0, 135.5, 142.7, 159.1, 200.9 ppm. ESI-MS m/z (%): 217 $[M + 1]^+$ (100). Calcd for $C_{14}H_{13}O_2$ (216.15): C, 77.75; H, 7.46. Found: C, 77.82; H, 7.47.

1-(5-Fluoro-2-(pent-1-ynyl)phenyl)ethanone (1m). Eluent for chromatography: hexane/EtOAc (98:2). Brown oil. IR (neat): ν_{max} = 2965, 2234, 1686 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.05 (t, 3H, CH_3, J = 7.0 Hz), 1.55-1.69 (m, 2H, CH_2), 2.42 (t, 2H, CH_2, J = 7.0 Hz), 2.77 (s, 3H, CH_3), 7.05-7.14 (m, 1H, arom.), 7.33-7.50 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 13.7, 21.8, 22.1, 30.2, 79.0, 96.7, 115.3 (d, $^2J_{C\text{-}F}$ = 23.2 Hz), 118.5 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 118.9, 136.1 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 143.2 (d, $^3J_{C\text{-}F}$ = 6.5 Hz), 161.9 (d, $^1J_{C\text{-}F}$ = 247 Hz), 199.6 ppm. ESI-MS m/z (%): 205 $[M + 1]^+$ (50), 176 (100). Calcd for $C_{13}H_{13}FO$ (204.24): C, 76.45; H, 6.42. Found: C, 76.38; H, 6.39.

1-(2-(*p*-Tolylethynyl)pyridin-3-yl)ethanone (1n). Eluent for chromatography: hexane/EtOAc (9:1). Brown solid. Mp 50-51 °C. IR (KBr): ν_{max} = 2924, 2215, 1675, 1552 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.38 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 7.19 (d, 2H, arom., J = 8.1 Hz), 7.34 (dd, 1H, arom. J = 7.7, 4.7 Hz), 7.51 (d, 2H, arom., J = 8.1 Hz), 8.06 (dd, 1H, arom. J = 8.0, 1.8 Hz), 8.73 (dd, 1H, arom. J = 4.7, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.8, 30.3, 87.8, 95.7, 118.9, 122.75, 129.6, 132.7, 136.7, 136.8, 140.2, 141.4, 152.5, 199.4 ppm. ESI-MS m/z (%): 236 $[M + 1]^+$ (50), 221 (100). Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.60; H, 5.59; N, 5.92. These data are in good agreement with literature values.[2a]

1-(2-((4-Methoxyphenyl)ethynyl)pyridin-3-yl)ethanone (1o). Eluent for chromatography: hexane/EtOAc (98:2). Brown oil. IR (neat): ν_{max} = 3369, 2964, 2936, 2217, 1682, 1553 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.85 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 6.91 (d, 2H, arom., J = 8.7 Hz), 7.32 (dd, 1H, arom. J = 8.0, 4.7 Hz), 7.56 (d, 2H, arom., J = 8.7 Hz), 8.05 (dd, 1H, arom. J = 8.0, 1.5 Hz), 8.71 (dd, 1H, arom. J = 4.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 30.2, 55.5, 87.5, 95.7, 114.1, 114.5, 122.4, 133.8, 136.5, 136.8, 141.6, 152.3, 160.9, 199.2 ppm. ESI-MS m/z (%): 252 $[M + 1]^+$ (100). Calcd for $C_{16}H_{13}NO_2$ (251.14): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.53; H, 5.19; N, 5.54.

1-(2-((3-(Trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)ethanone (1p). Eluent for chromatography: hexane/EtOAc (8:2). Brown oil. IR (neat): ν_{max} = 3369, 2929, 2220, 1683, 1556 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.82 (s, 3H, CH_3), 7.39 (dd, 1H, arom. J = 8.0, 4.7 Hz), 7.47-7.55 (m, 1H, arom.), 7.65 (d, 1H, arom., J = 8.1 Hz), 7.79 (d, 1H, arom., J = 7.7 Hz), 7.87 (s, 1H, arom.), 8.07 (dd, 1H, arom. J = 8.0, 1.8 Hz), 8.74 (dd, 1H, arom. J = 4.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 29.9, 89.5, 92.8, 123.1, 123.2, 123.8 (q, $^1J_{C\text{-}F}$ = 272 Hz), 126.2 (q, $^3J_{C\text{-}F}$ = 3.81 Hz), 128.9 (q, $^3J_{C\text{-}F}$ = 3.81 Hz), 129.3, 131.5 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 135.2, 136.6, 137.1, 140.6, 152.5, 198.5 ppm. ESI-MS m/z (%): 290 $[M + 1]^+$ (100). Calcd for $C_{16}H_{10}F_3NO$ (289.25): C, 66.44; H, 3.48; N, 4.84. Found: C, 66.38; H, 3.48; N, 4.84.

1-(2-(Hept-1-ynyl)pyridin-3-yl)ethanone (1q). Eluent for chromatography: hexane/EtOAc (8:2). Yellow oil. IR (neat): ν_{max} = 3369, 2932, 2227, 1684, 1423 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3H, CH_3, J = 7.0 Hz), 1.25-1.59 (m, 4H, 2 CH_2), 1.63-1.73 (m, 2H, CH_2), 2.50 (t, 2H, CH_2, J = 7.0 Hz), 2.77 (s, 3H, CH_3), 7.28 (dd, 1H, arom. J = 8.0, 4.7 Hz), 7.97 (dd, 1H, arom. J = 8.0, 1.8 Hz), 8.64 (dd, 1H, arom. J = 4.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 13.9, 19.8, 22.3, 27.9, 30.1, 31.4,

80.1, 97.9, 122.3, 136.3, 137.1, 141.6, 152.1, 199.7 ppm. ESI-MS m/z (%): 216 $[M + 1]^+$ (100). Calcd for $C_{14}H_{17}NO$ (215.29): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.18; H, 7.99; N, 6.48.

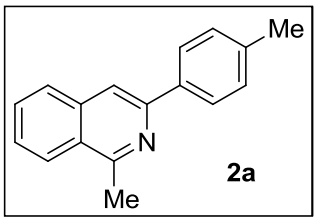
1-(2-(Oct-1-ynyl)pyridin-3-yl)ethanone (1r). Eluent for chromatography: hexane/EtOAc (8:2). Brown oil. IR (neat): ν_{max} = 3369, 2931, 2229, 1686, 1423 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3H, CH_3, J = 7.0 Hz), 1.25-1.49 (m, 6H, 3 CH_2), 1.61-1.70 (m, 2H, CH_2), 2.50 (t, 2H, CH_2, J = 7.0 Hz), 2.77 (s, 3H, CH_3), 7.29 (dd, 1H, arom. J = 8.0, 4.7 Hz), 7.97 (dd, 1H, arom. J = 8.0, 1.8 Hz), 8.65 (dd, 1H, arom. J = 4.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 14.2, 19.9, 22.7, 28.2, 28.9, 30.3, 31.5, 80.1, 97.9, 122.4, 136.4, 136.9, 141.5, 152.2, 199.8 ppm. ESI-MS m/z (%): 230 $[M + 1]^+$ (100). Calcd for $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.44; H, 8.39; N, 6.15.

1-(2-((1-Hydroxycyclohexyl)ethynyl)pyridin-3-yl)ethanone (1s). Eluent for chromatography: hexane/EtOAc (1:1). Brown oil. IR (neat): ν_{max} = 3368, 2935, 2222, 1694, 1424 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.24-2.12 (m, 10H, 5 CH_2), 2.76 (s, 3H, CH_3), 2.81 (s, 1H, OH), 7.32 (dd, 1H, arom. J = 8.0, 4.7 Hz), 7.99 (dd, 1H, arom. J = 8.0, 1.8 Hz), 8.68 (dd, 1H, arom. J = 4.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 23.2, 25.3, 30.1, 39.7, 69.0, 82.8, 99.6, 122.9, 136.4, 137.1, 140.7, 152.1, 199.2 ppm. ESI-MS m/z (%): 244 $[M + 1]^+$ (100). Calcd for $C_{15}H_{17}NO_2$ (243.30): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.98; H, 7.02; N, 5.71.

1-(2-((Trimethylsilyl)ethynyl)pyridin-3-yl)ethanone (1t). Eluent for chromatography: hexane/EtOAc (8.5:1.5). Yellow oil. IR (neat): ν_{max} = 3369, 2961, 2168, 1689, 1417 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.29 (s, 9H, 3 CH_3), 2.81 (s, 3H, CH_3), 7.34 (dd, 1H, arom. J = 8.0, 4.7 Hz), 8.01 (dd, 1H, arom. J = 8.0, 1.8 Hz), 8.69 (dd, 1H, arom. J = 4.7, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = -0.4, 30.2, 102.1, 103.0, 123.2, 136.5, 137.7, 140.7, 152.2, 199.4 ppm. ESI-MS m/z (%): 218 $[M + 1]^+$ (100). Calcd for $C_{12}H_{15}SiNO$ (217.09): C, 66.31; H, 6.96; N, 6.44. Found: C, 66.24; H, 6.97; N, 6.41. These data are in good agreement with literature values.[6b]

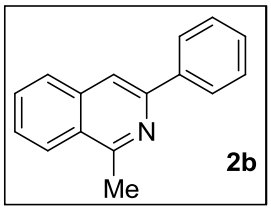
General procedure for microwave-assisted/AgOTf-catalysed cyclisation reaction of 2-alkynylacetophenones 1a-m and 3-acetyl-2-alkynylpyridines 1n-t. In a sealed tube, a well stirred solution of the appropriate 2-alkynylacetophenone (**1a-m**) (0.359 mmol) or 3-acetyl-2-alkynylpyridines (**1 n-t**) and AgOTf (0.009 mg, 0.036 mmol) in dry ammonia in methanol (NH_3/MeOH 2M solution, 3.59 mL, 7.18 mmol), was heated at 120°C in a multimode microwave oven, until no more starting product was detectable by TLC. The reaction mixture was evaporated to dryness and the crude purified by flash chromatography over a silica gel column yielding progressively the 3-substituted-1-methylisoquinoline (**2a-m**) and the 3-substituted-1-naphthalenamine (**3a-m**), or the 1,6-naphthyridine (**2n-t**) and the quinolin-5-amine (**3n-s**), respectively (for times and yields see Table 6.3).

1-Methyl-3-*p*-tolylisoquinoline[7] **(2a).** Eluent for chromatography: hexane/EtOAc (95:5). Brown wax. IR (KBr): ν_{max} = 3056, 2920, 1621 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 7.30 (d, 2H, arom. J = 8.1 Hz), 7.05-7.69 (m, 2H, arom.), 7.86 (t, 2H, arom. J = 7.0 Hz), 8.07 (t, 2H, arom. J = 8.4 Hz), 8.14 (s, 1H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.5, 22.9, 114.9, 125,9, 126.7, 126.8, 127.0, 127.8, 129.7, 130.2, 137.0, 137.3, 138.4, 150.3, 158.7 ppm. ESI-MS m/z (%): 234 $[M + 1]^+$ (100). Calcd for $C_{17}H_{15}N$ (233.31): C, 87.52; H, 6.48; N, 6.00. Found: C, 87.45; H, 6.42; N, 6.03.



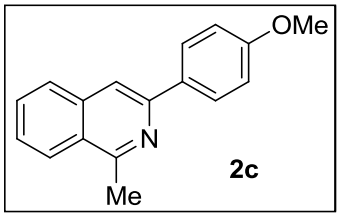
2a

1-Methyl-3-phenylisoquinoline (2b). Eluent for chromatography: hexane/EtOAc (97:3). Brown oil.

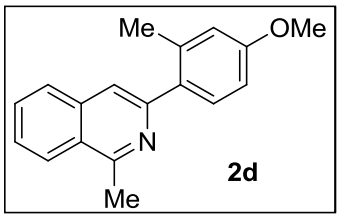


IR (neat): ν_{max} = 3058, 2920, 1622, 1569, 1441, 1029 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.05 (s, 3H, CH_3), 7.39-7.64 (m, 5H, arom.), 7.86 (d, 1H, arom. J = 7.7 Hz), 7.92 (s, 1H, arom.), 8.14 (dd, 3H, arom. J = 8.1, 1.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.9, 115.5, 125.9, 126.8, 127.0, 127.2, 127.8, 128.5, 128.9, 130.3, 137.0, 140.0, 150.2, 158.8 ppm. ESI-MS m/z (%): 220 $[M + 1]^+$ (100). Calcd for $C_{16}H_{13}N$ (219.28): C, 87.64; H, 5.98; N, 6.39. Found: C, 87.76; H, 5.94; N, 6.34.

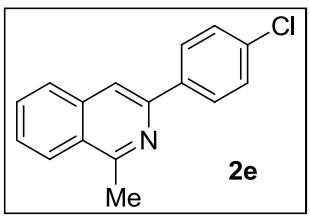
3-(4-Methoxyphenyl)-1-methylisoquinoline (2c). Eluent for chromatography: hexane/EtOAc (96:4). Brown solid. Mp 125-129 °C (dec.). IR (KBr): ν_{max} = 3022, 2924, 1605, 1567, 1513, 1439, 1248, 1175, 1030, 835 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.03 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 7.03 (d, 2H, arom. J = 8.9 Hz), 7.53 (ddd, 1H, arom. J = 8.1, 6.9, 1.3 Hz), 7.65 (ddd, 1H, arom. J = 8.2, 6.9, 1.3 Hz), 7.82 (d, 1H, arom. J = 7.6), 7.84 (s, 1H, arom.), 8.10 (m, 3H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.9, 55.6, 114.3, 114.4, 125.9, 126.4, 126.6, 127.7, 128.4, 130.2, 132.8, 137.1, 150.0, 158.6, 160.2 ppm. ESI-MS m/z (%): 250 $[M + 1]^+$ (100), 235 (8). Calcd for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.84; H, 6.03; N, 5.62.



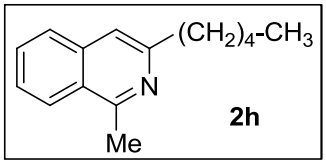
3-(4-Methoxy-2-methylphenyl)-1-methylisoquinoline (2d). Eluent for chromatography: hexane/EtOAc (96:4). Light brown solid. Mp 107-110 °C. IR (KBr): ν_{max} = 2953, 2921, 1707, 1608, 1567, 1505, 1442, 1241, 1162, 1045, 751 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.41 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 6.84 (m, 2H, arom.), 7.45 (d, 1H, arom. J = 9.2 Hz), 7.55-7.71 (m, 3H, arom.), 7.82 (d, 1H, arom. J = 7.8 Hz), 8.15 (d, 1H, arom. J = 7.7 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.1, 22.7, 55.5, 111.5, 116.4, 118.8, 125.8, 126.1, 126.9, 127.6, 130.2, 131.5, 133.9, 136.7, 138.0, 152.5, 158.1, 159.6 ppm. ESI-MS m/z (%): 264 $[M + 1]^+$ (100), 249 (5). Calcd for $C_{18}H_{17}NO$ (263.33): C, 82.10; H, 6.51; N, 5.32. Found: C, 81.97; H, 6.48; N, 5.35.



3-(4-Chlorophenyl)-1-methylisoquinoline (2e). Eluent for chromatography: hexane/EtOAc (98:2). Brown oil. IR (neat): ν_{max} = 3369, 2924, 1622 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.03 (s, 3H, CH_3), 7.47 (d, 2H, arom. J = 8.8 Hz), 7.51-7.71 (m, 2H, arom.), 7.85 (d, 1H, arom. J = 7.3 Hz), 7.89 (s, 1H, arom.), 8.05-8.15 (m, 3H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.8, 115.3, 125.9, 126.9, 127.2, 127.8, 128.4, 129.1, 130.4, 134.6, 136.9, 138.5, 148.9, 158.9 ppm. ESI-MS m/z (%): 254 $[M + 1]^+$ (100). Calcd for $C_{16}H_{12}NCl$ (253.73): C, 75.74; H, 4.77; N, 5.52. Found: C, 75.65; H, 4.75; N, 5.54.

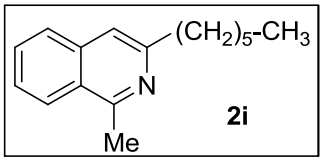


1-Methyl-3-pentylisoquinoline (2h). Eluent for chromatography: hexane/EtOAc (98:2). Yellow oil. IR (neat): ν_{max} = 3067, 2954, 2927, 2857, 1625, 1591, 1569, 1445, 1390, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3H, CH_3, J = 6.9 Hz), 1.28-1.46 (m, 4H, 2 CH_2), 1.79 (qt, 2H, CH_2, J = 7.7 Hz), 2.92 (t, 2H, CH_2, J = 7.7 Hz), 2.94 (s, 3H, CH_3), 7.31 (s, 1H, arom.), 7.40-7.63 (m, 2H, arom.), 7.72 (d, 1H, arom. J = 8.0 Hz), 8.00 (d, 1H, arom. J = 8.4 Hz) ppm. ^{13}C

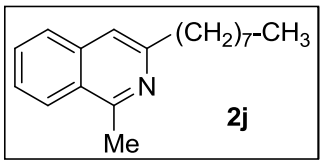


NMR ($CDCl_3$, 200 MHz): δ = 14.3, 22.6, 22.8, 29.9, 31.9, 38.4, 116.7, 125.7, 126.0, 126.2, 127.0, 129.9, 136.9, 154.8, 158.2 ppm. ESI-MS m/z (%): 214 $[M + 1]^+$ (100). Calcd for $C_{15}H_{19}N$ (213.54): C, 84.46; H, 8.98; N, 6.57. Found: C, 84.42; H, 8.97; N, 6.59.

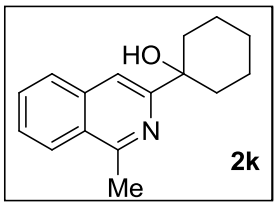
3-Hexyl-1-methylisoquinoline[7] **(2i).** Eluent for chromatography: hexane/EtOAc (96:4). Yellow-green oil. IR (neat): ν_{max} = 2953, 2925, 2855, 1692, 1625, 1590, 1568, 1444, 1390, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (t, 3H, CH_3, J = 7.0 Hz), 1.35 (m, 6H, 3 CH_2), 1.79 (qt, 2H, CH_2, J = 7.6 Hz), 2.88 (t, 2H, CH_2, J = 7.6 Hz), 2.95 (s, 3H, CH_3), 7.32 (s, 1H, arom.), 7.50 (ddd, 1H, arom. J = 8.2, 6.8, 1.5 Hz), 7.61 (ddd, 1H, arom. J = 8.2, 6.8, 1.3 Hz), 7.72 (d, 1H, arom. J = 7.5 Hz), 8.07 (d, 1H, arom. J = 7.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.3, 22.6, 22.9, 29.4, 30.2, 32.0, 38.5, 116.7, 125.8, 126.1, 126.2, 127.0, 129.9, 136.9, 154.9, 158.2 ppm. ESI-MS m/z (%): 228 $[M + 1]^+$ (100). Calcd for $C_{16}H_{21}N$ (227.343): C, 84.53; H, 9.31; N, 6.16. Found: C, 84.41; H, 9.22; N, 6.19.



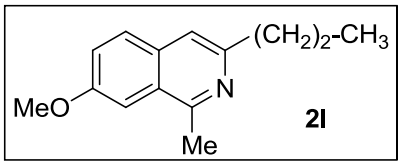
1-Methyl-3-octylisoquinoline (2j). Eluent for chromatography: hexane/EtOAc (98:2). Yellow oil. IR (neat): ν_{max} = 3067, 2953, 2925, 2855, 1626, 1591, 1569, 1446, 1391, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3H, CH_3, J = 6.9 Hz), 1.28-1.46 (m, 10H, 5 CH_2), 1.79 (qt, 2H, CH_2, J = 7.7 Hz), 2.88 (t, 2H, CH_2, J = 7.7 Hz), 2.94 (s, 3H, CH_3), 7.31 (s, 1H, arom.), 7.45-7.65 (m, 2H, arom.), 7.72 (d, 1H, arom. J = 8.0 Hz), 8.06 (d, 1H, arom. J = 8.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.5, 22.6, 23.1, 29.7, 29.8, 29.9, 30.4, 32.3, 38.5, 116.9, 125.9, 126.2, 126.4, 127.2, 130.2, 137.1, 154.9, 158.4 ppm. ESI-MS m/z (%): 256 $[M + 1]^+$ (100). Calcd for $C_{18}H_{25}N$ (255.40): C, 84.65; H, 9.87; N, 5.48. Found: C, 84.72; H, 9.84; N, 5.50.



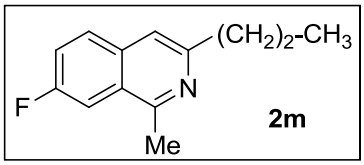
1-(1-Methylisoquinolin-3-yl)cyclohexanol (2k). Eluent for chromatography: hexane/EtOAc (9:1). Violet solid. Mp 89-92 °C. IR (KBr): ν_{max} = 3398, 2920, 2853, 1627, 1591, 1569, 1446, 1415, 1386, 742 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.22-1.41 (m, 2H, CH_2), 1.56-1.99 (m, 8H, 4 CH_2), 2.96 (s, 3H, CH_3), 5.12 (bs, 1H, OH), 7.50-7.65 (m, 3H, arom.), 7.78 (d, 1H, arom. J = 7.7 Hz), 8.01 (dd, 1H, arom. J = 7.7, 1.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.6, 22.7, 26.2, 39.2, 72.7, 113.6, 126.0, 126.7, 126.9, 127.8, 130.4, 137.2, 157.4, 158.8 ppm. ESI-MS m/z (%): 242 $[M + 1]^+$ (100). Calcd for $C_{16}H_{19}NO$ (241.33): C, 79.63; H, 7.94; N, 5.80. Found: C, 79.54; H, 7.97; N, 5.76.



7-Methoxy-1-methyl-3-propylisoquinoline (2l). Eluent for chromatography: hexane/EtOAc (9:1). Brown solid. Mp 99-100 °C. IR (KBr): ν_{max} = 3369, 2958, 2929, 2871, 1597, 1572, 1411, 1227 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.00 (t, 3H, CH_3, J = 6.9 Hz), 1.75-1.86 (m, 2H, CH_2), 2.84 (t, 2H, CH_2, J = 7.7 Hz), 2.91 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 7.26-7.32 (m, 3H, arom.), 7.62 (dd, 1H, arom. J = 9.1, 1.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.0, 22.6, 23.4, 40.2, 55.6, 103.9, 116.5, 122.6, 126.9, 128.5, 132.4, 152.7,156.5, 157.8 ppm. ESI-MS m/z (%): 216 $[M + 1]^+$ (100). Calcd for $C_{14}H_{17}N$ (215.29): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.00; H, 7.98; N, 6.48.

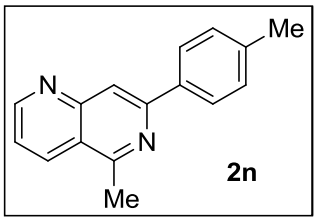


7-Fluoro-1-methyl-3-propylisoquinoline (2m). Eluent for chromatography: hexane/EtOAc (95:5).



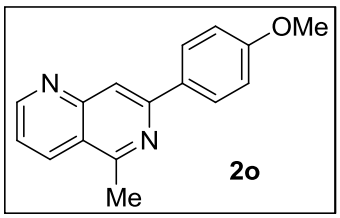
Violet wax. IR (KBr): ν_{max} = 3027, 2954, 2927, 2868, 1593, 1505, 1393, 1184, 878 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.00 (t, 3H, CH_3, J = 7.3 Hz), 1.76-1.87 (m, 2H, CH_2), 2.85 (t, 2H, CH_2, J = 7.7 Hz), 2.89 (s, 3H, CH_3), 7.31 (s, 1H, arom.), 7.35-7.45 (m, 1H, arom.), 7.62-7.76 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.0, 22.5, 23.3, 40.3, 109.2 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 116.4 (d, $^5J_{C\text{-}F}$ = 1.5 Hz), 120.3 (d, $^2J_{C\text{-}F}$ = 25.1 Hz), 126.6 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 129.4 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 133.9, 154.2 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 157.5 (d, $^4J_{C\text{-}F}$ = 5.7 Hz), 160.4 (d, $^1J_{C\text{-}F}$ = 247 Hz) ppm. ESI-MS m/z (%): 204 $[M + 1]^+$ (100). Calcd for $C_{13}H_{14}FN$ (203.26): C, 76.82; H, 6.94; N, 6.89. Found: C, 76.89; H, 6.97; N, 6.83.

5-Methyl-7-*p*-tolyl-1,6-naphthyridine (2n). Eluent for chromatography: hexane/EtOAc (8:2). Brown wax.



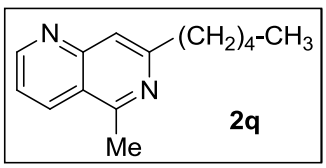
IR (KBr): ν_{max} = 3369, 2920, 1605, 1423 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 7.30 (d, 2H, arom. J = 8.1 Hz), 7.41 (dd, 1H, arom. J = 8.4, 4.4 Hz), 8.08 (d, 2H, arom. J = 8.1 Hz), 8.14 (s, 1H, arom.), 8.37 (dd, 1H, arom. J = 8.4, 1.5 Hz), 9.08 (dd, 1H, arom. J = 4.4, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.4, 22.2, 115.9, 121.6, 121.7, 127.3, 129.7, 133.9, 136.6, 139.1, 152.0, 154.1, 154.5, 159.4 ppm. ESI-MS m/z (%): 235 $[M + 1]^+$ (100). Calcd for $C_{16}H_{14}N_2$ (234.30): C, 82.02; H, 6.02; N, 11.96. Found: C, 81.90; H, 5.96; N, 11.99.

7-(4-Methoxyphenyl)-5-methyl-1,6-naphthyridine (2o). Eluent for chromatography: hexane/EtOAc (8:2). Yellow oil.



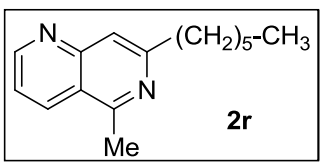
IR (neat): ν_{max} = 3391, 2957, 2935, 1601, 1575, 1515, 1441 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.02 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 7.04 (d, 2H, arom. J = 8.1 Hz), 7.45 (dd, 1H, arom. J = 8.4, 4.4 Hz), 8.11 (s, 1H, arom.), 8.15 (d, 2H, arom. J = 8.1 Hz), 8.42 (dd, 1H, arom. J = 8.4, 1.5 Hz), 9.04 (dd, 1H, arom. J = 4.4, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.2, 55.5, 114.5, 115.2, 121.4, 127.0, 131.9, 133.8, 133.9, 152.1, 153.7, 154.5, 159.3, 160.8 ppm. ESI-MS m/z (%): 251 $[M + 1]^+$ (100). Calcd for $C_{16}H_{14}N_2O$ (250.29): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.63; H, 5.69; N, 11.22.

5-Methyl-7-pentyl-1,6-naphthyridine (2q). Eluent for chromatography: hexane/EtOAc (8:2). Yellow oil.



IR (neat): ν_{max} = 3401, 2954, 2927, 1609, 1568 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (t, 3H, CH_3, J = 6.9 Hz), 1.32-1.42 (m, 4H, 2 CH_2), 1.75-1.83 (m, 2H, CH_2), 2.91 (t, 2H, CH_2, J = 7.0 Hz), 2.91 (s, 3H, CH_3), 7.40 (dd, 1H, arom. J = 8.4, 4.0 Hz), 7.56 (s, 1H, arom.), 8.35 (dd, 1H, arom. J = 8.4, 1.5 Hz), 8.98 (dd, 1H, arom. J = 4.0, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.1, 21.9, 22.7, 29.5, 31.8, 38.5, 118.1, 120.9, 121.2, 133.9, 151.7, 154.3, 158.9, 159.3 ppm. ESI-MS m/z (%): 215 $[M + 1]^+$, (100). Calcd for $C_{14}H_{18}N_2$ (214.30): C, 78.46; H, 8.47; N, 13.07. Found: C, 78.38; H, 8.44; N, 13.11.

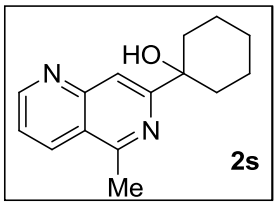
7-Hexyl-5-methyl-1,6-naphthyridine (2r). Eluent for chromatography: hexane/EtOAc (8:2). Red oil.



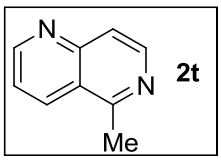
IR (neat): ν_{max} = 3206, 2956, 2926,2856, 1610, 1569, 1379 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (t, 3H, CH_3, J = 6.9 Hz), 1.21-1.87 (m, 8H, 4 CH_2), 2.93 (t, 2H, CH_2, J = 8.0 Hz), 2.93 (s, 3H, CH_3), 7.42 (dd, 1H, arom. J = 8.4, 4.2 Hz), 7.58 (s, 1H, arom.), 8.38 (dd, 1H, arom. J = 8.4, 1.5 Hz), 9.00 (dd, 1H, arom. J = 4.2, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.3, 21.9, 22.8, 29.3, 29.9, 31.9, 38.5, 118.1, 120.9, 121.3, 134.1, 151.6, 154.1, 159.1, 159.3 ppm. ESI-

MS m/z (%): 229 $[M + 1]^+$ (100). Calcd for $C_{15}H_{20}N_2$ (228.33): C, 78.90; H, 8.83; N, 12.27. Found: C, 78.99; H, 8.80; N, 12.23.

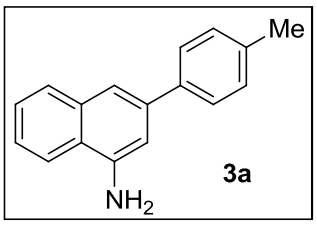
1-(5-Methyl-1,6-naphthyridin-7-yl)cyclohexanol (2s). Eluent for chromatography: hexane/EtOAc (6:4). Brown wax. IR (KBr): ν_{max} = 3399, 3253, 2952, 2927, 2913, 2854, 1609, 1584, 1568, 1448, 1418, 1382 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.67-1.91 (m, 10H, 5 CH_2), 2.96 (s, 3H, CH_3), 4.87 (bs, 1H, OH), 7.46 (dd, 1H, arom. J = 8.4, 4.0 Hz), 7.81 (s, 1H, arom.), 8.40 (dd, 1H, arom. J = 8.4, 1.5 Hz), 9.03 (dd, 1H, arom. J = 4.0, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.9, 22.4, 25.9, 38.8, 72.8, 115.1, 121.5, 121.9, 134.1, 151.8, 154.7, 158.3, 162.9 ppm. ESI-MS m/z (%): 243 $[M + 1]^+$, (100). Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.24; H, 7.54; N, 11.59.



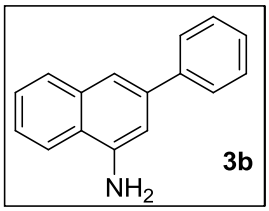
5-Methyl-1,6-naphthyridine (2t). Eluent for chromatography: hexane/EtOAc (8:2). Red oil. IR (neat): ν_{max} = 3212, 2959, 1605 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.96 (s, 3H, CH_3), 7.51 (dd, 1H, arom. J = 8.4, 4.0 Hz), 7.77 (d, 1H, arom. J = 5.9 Hz), 8.43 (dd, 1H, arom. J = 8.4, 1.5 Hz), 8.61 (d, 1H, arom. J = 6.2 Hz), 9.06 (dd, 1H, arom. J = 4.4, 1.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.9, 120.9, 122.2, 122.8, 133.9, 145.8, 151.0, 154.4, 159.7 ppm. ESI-MS m/z (%): 145 $[M + 1]^+$ (100). Calcd for $C_9H_8N_2$ (144.17): C, 74.98; H, 5.59; N, 19.43. Found: C, 75.12; H, 5.59; N, 19.43.



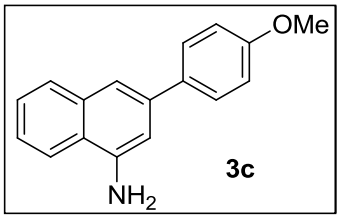
3-*p*-Tolylnaphthalen-1-amine[7] **(3a).** Eluent for chromatography: hexane/EtOAc (95:5). Brown wax. IR (KBr): ν_{max} = 3425, 3024, 2915, 2855 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.43 (s, 3H, CH_3), 4.22 (bs, 2H, NH_2), 7.05 (d, 1H, arom, J = 1.1 Hz), 7.28 (d, 2H, arom, J = 8.4 Hz), 7.44-7.50 (m, 2H, arom), 7.52 (s, 1H, arom), 7.61 (d, 2H, arom, J = 8.1 Hz), 7.79-7.89 (m, 2H, arom) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.4, 109.5, 117.1, 120.9, 123.1, 125.0, 126.5, 127.4, 129.1, 129.7, 134.9, 137.3, 138.7, 139.3, 142.6 ppm. ESI-MS m/z (%): 234 $[M + 1]^+$ (100). Calcd for $C_{17}H_{15}N$ (233.31): C, 87.52; H, 6.48; N, 6.00. Found: C, 87.44; H, 6.43; N, 6.08.



3-Phenylnaphthalen-1-amine (3b). Eluent for chromatography: hexane/EtOAc (97.5:2.5). Brown solid. Mp 79-81 °C. IR (KBr): ν_{max} = 3435, 2925, 2854, 1626, 1454, 1403, 1075, 763 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.26 (bs, 2H, NH_2), 7.07 (d, 1H, arom, J = 1.6 Hz), 7.36-7.42 (m, 1H, arom), 7.47-7.54 (m, 4H, arom), 7.56 (s, 1H, arom), 7.71-7.76 (m, 2H, arom.), 7.84-7.89 (m, 2H, arom) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 109.7, 117.6, 121.1, 123.4, 125.3, 126.7, 127.6, 127.7, 129.1, 129.3, 135.1, 139.6, 141.8, 142.9. ESI-MS m/z (%): 220 $[M + 1]^+$ (100)). Calcd for $C_{16}H_{13}N$ (219.28): C, 87.64; H, 5.98; N, 6.39. Found: C, 87.65; H, 5.99; N, 6.40.

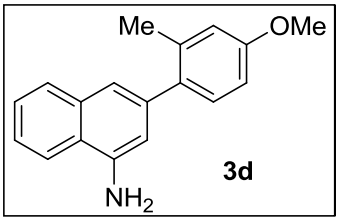


3-(4-Methoxyphenyl)naphthalen-1-amine (3c). Eluent for chromatography: hexane/EtOAc (96:4). Dark purple solid. Mp 125-129 °C (dec.). IR (KBr): ν_{max} = 3435, 2918, 1625, 1510, 1457, 1402, 1239, 1172, 1110, 1022, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.87 (s, 3H, CH_3), 4.37 (bs, 2H, NH_2, exchange with D_2O), 7.00 (m, 3H, arom.), 7.45 (m, 3H, arom.), 7.63 (d, 2H, arom. J = 8.8 Hz), 7.83 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 55.6, 109.4, 114.4, 116.7, 120.9, 122.9, 124.9, 126.5, 128.6, 129.0, 134.2,

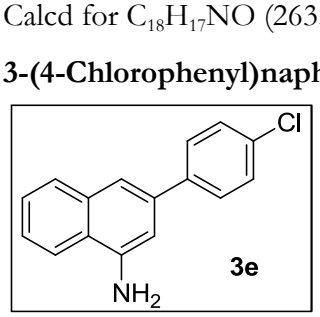


135.0, 139.0, 142.6, 159.4 ppm. ESI-MS m/z (%): 250 $[M + 1]^+$ (100), 235 (6). Calcd for $C_{17}H_{15}N$ (249.31): C, 91.90; H, 6.06; N, 5.62. Found: C, 91.84; H, 6.01; N, 5.68.

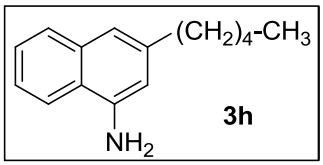
3-(4-Methoxy-2-methylphenyl)naphthalen-1-amine (3d). Eluent for chromatography: hexane/EtOAc (96:4). Brown oil. IR (neat): ν_{max} = 3436, 2916, 1626, 1499, 1454, 1288, 1229, 1160, 1115, 1041, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.31 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.18 (bs, 2H, NH_2, exchange with D_2O), 6.79 (m, 3H, arom.), 7.22 (s, 1H, arom.), 7.47 (m, 3H, arom.), 7.82 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.1, 55.5, 111.2, 112.2, 115.9, 119.6, 120.9, 122.7, 124.9, 126.4, 128.8, 131.1, 134.6, 135.1, 137.2, 140.1, 141.8, 159.0 ppm. ESI-MS m/z (%): 264 $[M + 1]^+$ (100), 249 (7). Calcd for $C_{18}H_{17}NO$ (263.33): C, 82.10; H, 6.51; N, 5.32. Found: C, 82.01; H, 6.49; N, 5.34.



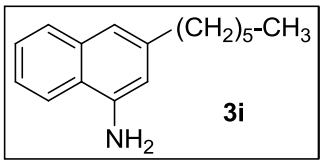
3-(4-Chlorophenyl)naphthalen-1-amine (3e). Eluent for chromatography: hexane/EtOAc (98:2 – 9:1). Brown oil. IR (neat): ν_{max} = 3435, 2923, 1625, 1492, 1090, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.29 (bs, 2H, NH_2), 6.99 (s, 1H, arom.), 7.40-7.48 (m, 4H, arom.), 7.62 (d, 2H, arom, J = 8.4 Hz), 7.80-7.87 (m, 3H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 109.0, 117.3, 120.9, 123.2, 125.4, 126.7, 128.8, 129.0, 129.1, 133.5, 134.9, 138.1, 140.1, 142.9 ppm. ESI-MS m/z (%): 254 $[M + 1]^+$ (100). Calcd for $C_{16}H_{12}NCl$ (253.73): C, 75.74; H, 4.77; N, 5.52. Found: C, 75.61; H, 4.72; N, 5.56.



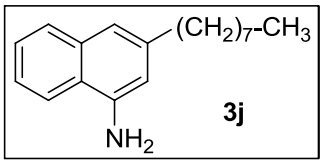
3-Pentylnaphthalen-1-amine (3h). Eluent for chromatography: hexane/EtOAc (98:2 – 97:3). Brown oil. IR (neat): ν_{max} = 3369, 2955, 2924, 2851, 1627, 1598, 1576, 1514, 1463, 1409, 742 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.93 (t, 3H, CH_3, J = 6.9 Hz), 1.29-1.39 (m, 4H, 2 CH_2), 1.69-1.74 (m, 2H, CH_2), 2.70 (t, 2H, CH_2, J = 7.6 Hz), 4.12 (bs, 2H, NH_2), 6.69 (s, 1H, arom), 7.14 (s, 1H, arom), 7.39-7.46 (m, 2H, arom), 7.75-7.80 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 13.3, 21.9, 29.0, 30.2, 35.5, 110.5, 117.1, 119.9, 121.6, 123.3, 125.1, 127.3, 133.9, 140.5, 141.1 ppm. ESI-MS m/z (%): 214 $[M + 1]^+$ (100). Calcd for $C_{15}H_{19}N$ (213.54): C, 84.46; H, 8.98; N, 6.57. Found: C, 84.56; H, 9.02; N, 6.53.



3-Hexylnaphthalen-1-amine[7] **(3i).** Eluent for chromatography: hexane/EtOAc (98:2). Yellow-orange oil. IR (neat): ν_{max} = 3369, 2954, 2926, 2854, 1626, 1597, 1576, 1512, 1460, 1408, 741 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3H, CH_3, J = 6.8 Hz), 1.27-1.41 (m, 6H, 3 CH_2), 1.61-1.76 (m, 2H, CH_2), 2.68 (t, 2H, CH_2, J = 7.6 Hz), 3.82 (bs, 2H, NH_2), 6.66 (s, 1H, arom), 7.12 (s, 1H, arom), 7.35-7.46 (m, 2H, arom), 7.70-7.79 (m, 2H, arom) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.4, 22.9, 29.3, 31.5, 32.0, 36.5, 111.5, 118.0, 120.9, 122.6, 124.2, 126.1, 128.3, 134.9, 141.4, 142.0 ppm. ESI-MS m/z (%): 228 $[M + 1]^+$ (100), 144 (40). Calcd for $C_{16}H_{21}N$ (227.343): C, 84.53; H, 9.31; N, 6.16. Found: C, 84.36; H, 9.28; N, 6.12.

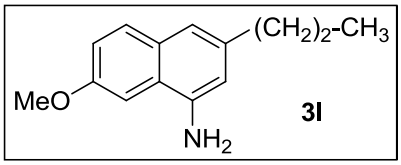


3-Octylnaphthalen-1-amine (3j). Eluent for chromatography: hexane/EtOAc (98:2). Brown oil. IR (neat): ν_{max} = 3369, 2953, 2925, 2855, 1626, 1591, 1569, 1446, 747 cm^{-1}.^1H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (t, 3H, CH_3, J = 6.8 Hz), 1.27-1.40 (m, 10H, 5 CH_2), 1.63-1.71 (m, 2H, CH_2), 2.67 (t, 2H, CH_2, J = 7.6 Hz), 3.40 (bs, 2H, NH_2), 6.68 (s, 1H, arom), 7.12 (s, 1H, arom), 7.37-7.43 (m, 2H, arom), 7.71-7.80 (m, 2H, arom) ppm. ESI-MS m/z (%): 256 $[M + 1]^+$



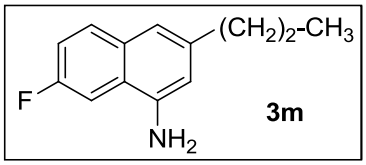
(100). Calcd for $C_{18}H_{25}N$ (255.40): C, 84.65; H, 9.87; N, 5.48. Found: C, 84.74; H, 9.89; N, 5.45.

7-Methoxy-3-propylisoquinolin-1-amine (3l). Eluent for chromatography: hexane/EtOAc (9:1).



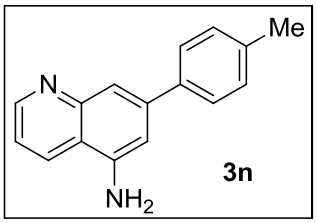
Brown solid. Mp 51-54 °C. IR (KBr): ν_{max} = 3359, 2960, 2928, 2868, 1626, 1604, 1511, 1260, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.96 (t, 3H, CH_3, J = 7.3 Hz), 1.64-1.75 (m, 2H, CH_2), 2.64 (t, 2H, CH_2, J = 7.3 Hz), 3.92 (s, 3H, CH_3), 6.71 (s, 1H, arom.), 7.06-7.15 (m, 3H, arom.), 7.63 (d, 1H, arom. J = 8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.0, 24.5, 38.3, 55.6, 100.3, 112.9, 118.4, 118.6, 123.6, 129.8, 130.3, 138.5, 140.3, 157.1 ppm. ESI-MS m/z (%): 216 $[M + 1]^+$ (100). Calcd for $C_{14}H_{17}N$ (215.29): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.11; H, 7.49; N, 12.99.

7-Fluoro-3-propylisoquinolin-1-amine (3m). Eluent for chromatography: hexane/EtOAc (95:5).



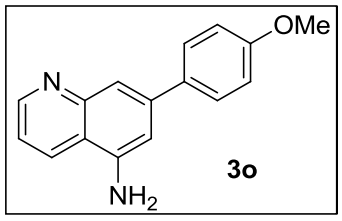
Brown oil. IR (neat): ν_{max} = 3369, 3232, 2958, 2929, 2870, 1624, 1517, 1473, 1193, 852 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.96 (t, 3H, CH_3, J = 7.3 Hz), 1.64-1.79 (m, 2H, CH_2), 2.65 (t, 2H, CH_2, J = 7.3 Hz), 3.99 (bs, 2H, NH_2), 6.68 (s, 1H, arom.), 7.11 (s, 1H, arom.), 7.15-7.25 (m, 1H, arom.), 7.37 (dd, 1H, arom. J = 11, 2.2 Hz), 7.71 (dd, 1H, arom. J = 8.8, 5.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.0, 24.4, 38.4, 104.8 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 112.4, 116.1 (d, $^2J_{C\text{-}F}$ = 24.8 Hz), 118.1, 123.08 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 130.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 131.8, 140.2 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 141.6 (d, $^4J_{C\text{-}F}$ = 5.3 Hz), 160.1 (d, $^1J_{C\text{-}F}$ = 247 Hz) ppm. ESI-MS m/z (%): 204 $[M + 1]^+$ (100). Calcd for $C_{13}H_{14}FN$ (203.26): C, 70.57; H, 6.42; N, 13.72. Found: C, 70.64; H, 6.44; N, 13.71.

7-*p*-Tolylquinolin-5-amine (3n). Eluent for chromatography: hexane/EtOAc (8:2). Brown oil. IR



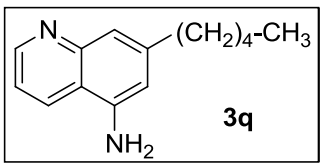
(neat): ν_{max} = 3351, 3214, 2917, 2850, 1612, 1588, 1560, 1503, 1397, 807 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.42 (s, 3H, CH_3), 4.25 (bs, 2H, NH_2), 7.09 (s, 1H, arom.), 7.29 (d, 2H, arom. J = 8.1 Hz), 7.32 (dd, 1H, arom. J = 8.4, 4.4 Hz), 7.63 (d, 2H, arom. J = 8.1 Hz), 7.79 (s, 1H, arom.), 8.17 (dd, 1H, arom. J = 8.4, 1.5 Hz), 8.90 (dd, 1H, arom. J = 4.4, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.3, 109.8, 118.0, 118.1, 119.5, 127.4, 129.6, 129.8, 137.9, 138.0, 142.7, 143.0, 149.7, 150.7 ppm. ESI-MS m/z (%): 235 $[M + 1]^+$ (100). Calcd for $C_{16}H_{14}N_2$ (234.30): C, 82.02; H, 6.02; N, 11.96. Found: C, 81.95; H, 6.00; N, 11.97.

7-(4-Methoxyphenyl)quinolin-5-amine (3o). Eluent for chromatography: hexane/EtOAc (8:2).

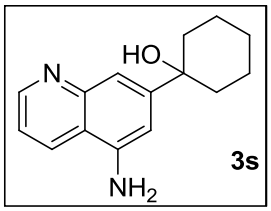


Yellow oil. IR (neat): ν_{max} = 3349, 3214, 2960, 2836, 1608, 1589, 1564, 1505, 1248, 830 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.87 (s, 3H, CH_3), 4.22 (bs, 2H, NH_2), 7.01 (d, 2H, arom. J = 8.1 Hz), 7.06 (s, 1H, arom.), 7.32 (dd, 1H, arom. J = 8.4, 4.4 Hz), 7.67 (d, 2H, arom. J = 8.1 Hz), 7.75 (s, 1H, arom.), 8.16 (dd, 1H, arom. J = 8.4, 1.5 Hz), 8.89 (dd, 1H, arom. J = 4.4, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 55.6, 109.6, 114.6, 117.8, 117.9, 119.4, 128.6, 129.5, 133.4, 142.6, 142.7, 149.8, 150.8, 159.9 ppm. ESI-MS m/z (%): 251 $[M + 1]^+$ (100). Calcd for $C_{16}H_{14}N_2O$ (250.29): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.65; H, 5.69; N, 11.14.

7-Pentylquinolin-5-amine (3q). Eluent for chromatography: hexane/EtOAc (8:2). Green oil. IR (neat): ν_{max} = 3342, 3215, 2929, 1621, 1570 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (t, 3H, CH_3, J = 6.9 Hz), 1.33-1.39 (m, 4H, 2 CH_2), 1.65-1.76 (m, 2H, CH_2), 2.70 (t, 2H, CH_2, J = 7.7 Hz), 4.14 (bs, 2H, NH_2), 6.68 (s, 1H, arom.), 7.26 (dd, 1H, arom. J = 8.4, 4.4 Hz), 7.37 (s, 1H, arom.), 8.11 (dd, 1H, arom. J = 8.4, 1.5 Hz), 8.83 (dd, 1H, arom. J = 4.0, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.1, 22.7, 30.7, 31.7, 36.5, 111.7, 117.5, 118.9, 119 3, 129.4, 142.0, 145.6, 149.6, 150.3 ppm. ESI-MS m/z (%): 215 $[M + 1]^+$ (100). Calcd for $C_{14}H_{18}N_2$ (214.30): C, 78.46; H, 8.47; N, 13.07. Found: C, 78.32; H, 8.51; N, 13.11.



1-(5-Aminoquinolin-7-yl)cyclohexanol (3s). Eluent for chromatography: hexane/EtOAc (6:4). Brown oil. IR (neat): ν_{max} = 3369, 3235, 2927, 2853, 1617, 1590, 1571, 1446, 1407 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.71-1.88 (m, 10H, 5 CH_2), 4.18 (bs, 2H, NH_2), 4.70 (bs, 1H, OH), 7.07 (s, 1H, arom.), 7.31 (dd, 1H, arom. J = 8.4, 4.4 Hz), 7.64 (s, 1H, arom.), 8.13 (dd, 1H, arom. J = 8.4, 1.5 Hz), 8.85 (dd, 1H, arom. J = 4.0, 1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.4, 25.8, 38.8, 73.5, 108.2, 115.8, 117.9, 119.6, 129.5, 142.3, 149.3, 150.5, 151.9 ppm. ESI-MS m/z (%): 243 $[M + 1]^+$ (100). Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.24; H, 7.52; N, 11.51.



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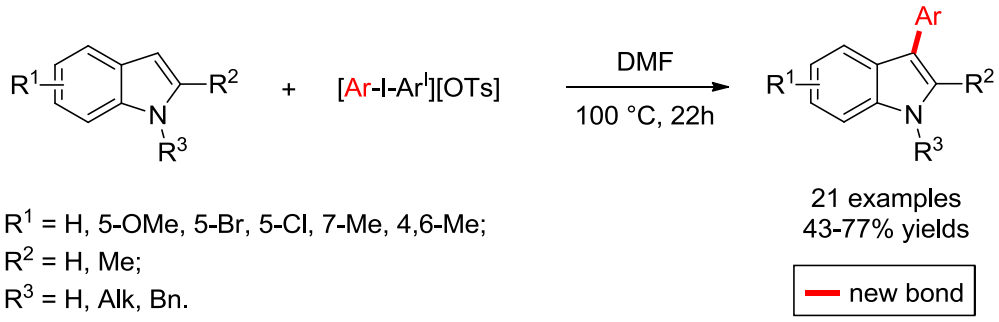
Chapter 7

Metal-Free Direct Arylations of Indoles and Pyrroles with Diaryliodonium Salts



R^1 = H, 5-OMe, 5-Br, 5-Cl, 7-Me, 4,6-Me;
R^2 = H, Me;
R^3 = H, Alk, Bn.

Direct arylations of indoles and pyrroles with differently substituted diaryliodonium salts were shown to efficiently proceed in the absence of metal catalysts. The protocol proved broadly applicable, thereby enabling C-H bond functionalizations of free (NH)- as well as N-substituted indoles and pyrroles.

Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R.

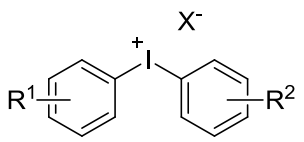
Org. Lett. **2011**, *13*, 2358–2360.

7.1 Introduction

Direct arylations of otherwise unreactive C-H bonds have emerged in recent years as attractive alternatives to traditional cross-coupling reactions with organometallic reagents.[1] Particularly, the direct functionalization of indole derivatives has received significant attention,[2] because this scaffold is omnipresent in biologically active compounds and natural products.[3] Remarkable progress in metal-catalysed direct arylations of electron-rich (hetero)arenes was recently accomplished through the use of diaryliodonium salts as arylating reagents.[2b,4]

7.1.1 Diaryliodonium salts

Hypervalent iodine compounds have recently received considerable attention as mild, nontoxic and selective reagents in organic synthesis. Iodine(III) reagents with two carbon ligands have similar properties to certain transition-metal complexes (metals such as Hg, Pb and Pd), and can be used in C-C bond-forming reactions. As the use of transition metals in organic synthesis suffers from drawbacks like cost, toxicity and threshold values in pharmaceutical products, the interest in this type of iodine (III)-mediated reactions has recently increased considerably.

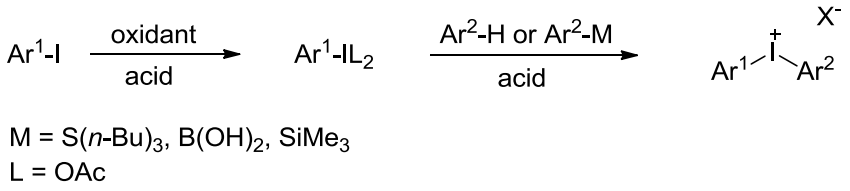


X = Cl, Br, I, OTf, OTs, BF_4 ...

Diaryl-λ-iodanes, also called diaryliodonium salts, are the most well-known compounds in this class. Due to their highly electron-deficient nature and hyperleaving-group ability, they are versatile arylating agents with a variety of nucleophiles, e.g. in α-arylation of carbonyl compounds. They can be employed in copper- and palladium-catalysed cross-coupling reactions, allowing milder reaction conditions than in couplings with aryl halides. Furthermore, diaryliodonium salts are used to generate benzynes, serve as photo-initiators in polymerizations and are also applied as precursors to ^{18}F-labeled radio ligands.

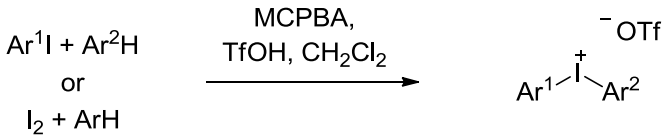
Symmetrical diaryliodonium salts are generally preferable to unsymmetrical salts in arylation reactions because only one of the two aryl groups of the diaryl-iodine (III) reagent is utilized in the arylation. The use of unsymmetrical salts is, however, desirable when the starting materials are complex or expensive; furthermore, the properties of unsymmetrical salts can be varied more easily, which is beneficial in other applications. It's possible to design an unsymmetrical diaryl-iodine (III) reagent containing the desired aryl group and a second aryl unit that would not transfer in the arylation process. Selective aryl transfer has been observed as a the result of poor aryl transfer of a large group (such as mesityl) compared to a less substituted aryl unit. They can have a large diversity of inorganic and organic counterions. In many cases a subsequent anion exchange step is necessary, as the anion influences both the solubility and reactivity of the iodonium salt. Diaryliodonium salts with halide anions are generally sparingly soluble in many organic solvents, whereas triflate and tetrafluoroborate salts have good solubility. Another attractive property with the latter anions is their weak or nonexistent nucleophilicity, which makes them easily applicable in synthesis. It's possible an oxidative anion metatheses in the crude title bromides to produce the respective pure diaryliodonium tetrafluoroborates, triflates and tosylates.[5]

Synthetic routes to diaryliodonium salts generally require several reaction steps that often are time-consuming and moderate-yielding. A typical strategy involves an initial oxidation of an aryl iodide to iodine (III) followed by ligand exchange with an arene or an organometallic reagent to obtain the diaryliodonium salt (Scheme 7.1).[6] The most common two-step synthesis depends on the prior synthesis of iodo-acetates from the starting iodoarenes followed by their acidic coupling.



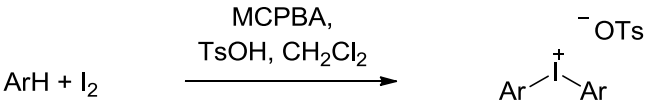
Scheme 7.1 – Synthetic strategy to diaryliodonium salts.

Many strategies have been reported to shorten the synthetic route towards diaryliodonium salts. In order to make these efficient arylating agents more easily available, Olofsson and co-workers have developed a high-yielding, one-pot synthesis of diaryliodonium triflates from arenes and aryl iodides or molecular iodine with MCPBA (Scheme 7.2).[7] New, commercially available cans of MCPBA were found to contain large and variable amounts of H_2O. The MCPBA needs to be dried under vacuum at r.t. for 1 h to obtain reproducible results.



Scheme 7.2 – Synthesis of diaryliodonium triflates.

This procedure is quite general, but fails in the synthesis of symmetric, electron-rich salts. The same research-group has recently found suitable conditions for a one-pot synthesis of electron-rich salts;[8] the best conditions were: molecular iodine (1 eq.), arene (4 eq.), MCPBA (3 eq.) and TsOH (3-4 eq.) in CH_2Cl_2 (Scheme 7.3).



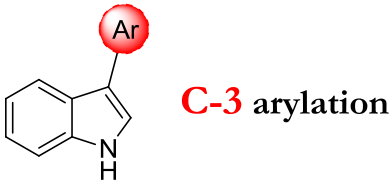
Scheme 7.3 – Synthesis of diaryliodonium tosylates.

Diaryliodonium triflates are more easily applicable than tosylate salts, due to the non-nucleophilic properties of the triflate anion. It's possible an in situ anion exchange of tosylate salt to the corresponding triflate salt (by addition of 2.5 equivalents trifluoromethanesulfonic acid); this in situ anion exchange should be generally applicable to synthesis of electron-rich diaryl-iodonium triflates that are unobtainable by the direct trifluoromethanesulfonic acid mediated reaction.

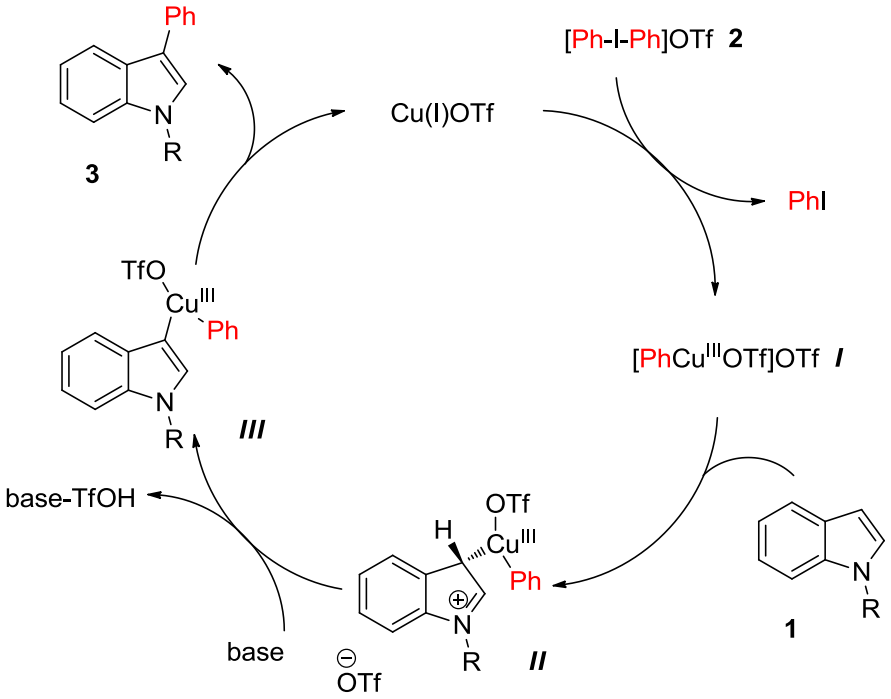
Olofsson and co-workers developed also an efficient, sequential one-pot synthesis of symmetrical and unsymmetrical diaryliodonium tetrafluoroborates.[9] Both electron-deficient and electron-rich salts can be synthesized in a regiospecific manner. An in situ anion exchange with triflic acid gives access also in this case to the corresponding diaryliodonium triflates.

7.1.2 C-3 and C-2 arylation of indole derivatives

It's a real challenge to achieve selective and predictable functionalizations at C-H bonds with heteroaromatic substrates.[10] Site-selectivity can be obtained by applying various reaction conditions that are heteroarene specific. Elegant methodologies for the direct C-3 and C-2 arylation of indole derivatives have already been reported in literature with different reagents.



The "Gaunt's protocol"[11] is a Cu-catalysed method for the C3 arylation of indoles and his conditions are: Indole (1.0 eq.), Diaryliodonium salt (1.3 eq.), $Cu(OTf)_2$ (10 mol%), dtbpy (1.0 eq.) in CH_2Cl_2.



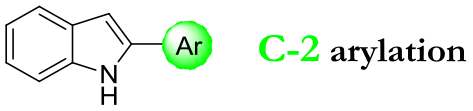
Scheme 7.4 – Proposed Cu catalytic cycle.

The mechanism of the Cu(II)-catalysed C-H bond arylation is proposed to begin with reduction of the Cu(II) catalyst to Cu(I) by the indole (Scheme 7.4). Oxidative addition of the diaryl-iodine(III) reagent to the Cu(I) salt would generate the electrophilic Cu(III)-aryl intermediate ***I*** that can undergo attack at the C3 position of indole to ***II***. Rearomatization via C-H bond cleavage to ***III*** would be followed by reductive elimination, delivering the final product and re-forming the Cu(I) catalyst. Optimization revealed the necessity of dtbpy (2,6-di-*tert*-butylpyridine) as base to capture the TfOH generated in the reaction and to prevent the acid-catalysed dimerization of the indole as deleterious side reaction.

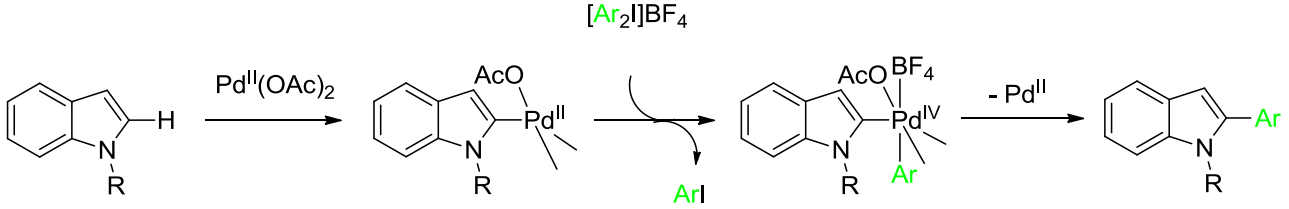
Both free (NH)-indoles and N-alkyl indoles were smoothly converted to the 3-phenylindoles at room temperature. Indoles bearing electron-donating substituents underwent facile arylation and the corresponding indoles with electron-withdrawing groups also delivered the arylated products, albeit at a

higher reaction temperature. This difference in reactivity between electron-rich and electron-deficient indoles supports an electrophilic metalation mechanism for the arylation process.

Gaunt and co-workers, using the same procedure, have developed the first highly *para*-selective arylation of aniline and phenol derivatives.[12]



The "Sanford's protocol"[13] is a Pd-catalysed method for the C2 arylation of indoles and his conditions are: Indole (1.0 eq.), Diaryliodonium salt (2.0 eq.), Pd(II) (5 mol%) in AcOH at room temperature.



Scheme 7.5 – Proposed Pd catalytic cycle.

The key electrophilic palladation step involves the use of an electron-deficient Pd(II) catalyst ($Pd(OAc)_2$ or $IMesPd(OAc)_2$) and the resulting σ-indole Pd(II) complex can undergo subsequent oxidative arylation with the diaryliodonium salt via a Pd(II)/(IV) cycle (Scheme 7.5).

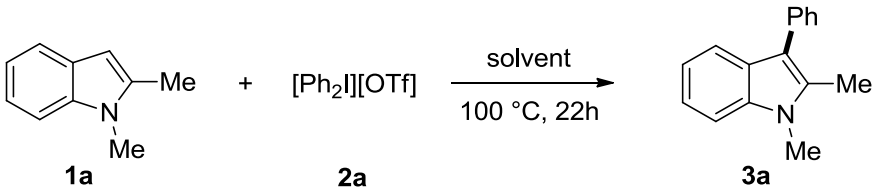
This oxidative approach affords 2-arylindoles in high yields under remarkably mild conditions, this transformation showed no sensitivity to air and moisture and could be conveniently carried out on the benchtop using unpurified solvents. Free indoles exhibited comparable reactivity to N-alkyl indoles and these transformations were also compatible with a diverse variety of electron-donating and -withdrawing substituents.

This Pd-catalysed transformation was applied to the synthesis of a variety of different biaryl products, using directing groups including pyridines, quinolines, pyrrolidines and oxazolidinones.[14]

7.2 Results and discussion

During studies directed toward the development of ruthenium-catalysed[15] C-H bond functionalizations on heteroarenes, Ackermann and co-workers observed that C-H bond arylations of indoles and pyrroles occur in the absence of transition metal catalysts.[16,17] As a consequence of these facts, our research has focused on the metal-free direct arylations of indoles and pyrroles with diaryliodonium salts.

At the outset of our studies, we tested various reaction conditions for the direct functionalization of indole **1a** (0.50 mmol) with diaryliodonium salt **2a** (0.55 mmol) in 2.0 ml of solvent at 100 °C for 22h (Table 7.1).[18] Interestingly, we observed that direct arylations under metal-free reaction conditions proved viable in toluene, NMP, *t*-AmOH, or DMF as the solvent, the latter of which was employed for further optimization studies.

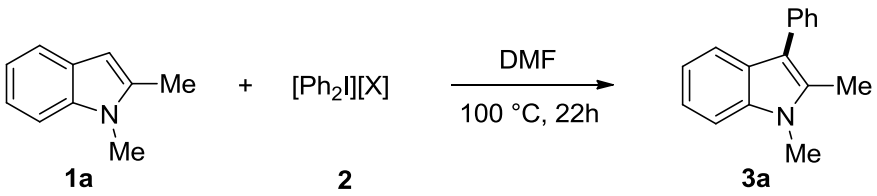


Entry	Solvent	Yield (%)[a]
1	$Br_2CHCHBr_2$	-
2	$Cl_2CHCHCl_2$	3[b]
3	1,4-dioxane	11
4	PEG-400	-
5	PhMe	25
6	AcOH	7[b]
7	*t*-AmOH	39
8	DMA	8[b]
9	NMP	20
10	DMF	38
11	DMF	43[c]

[a] Yields refer to pure isolated product.
[b] GC-conversion with *n*-tridecane as standard.
[c] **1a** (1.00 mmol).

Table 7.1 – Effect of solvents on direct arylation of indole **1a**.

Subsequently, we probed the effect exerted by the counteranions of salts **2**, which showed that satisfactory results could be obtained with diaryliodonium tetrafluoroborates, hexafluorophosphates, trifluoroacetates, or tosylates (Table 7.2, entries 1-6), while the corresponding bromides failed to deliver the desired product **3a** (entry 7).



Entry	X	Yield (%)
1	OTf	38
2	BF_4	40
3	PF_6	58
4	OTfAc	54
5	OTs	47
6	OTs	54[b]
7	Br	-

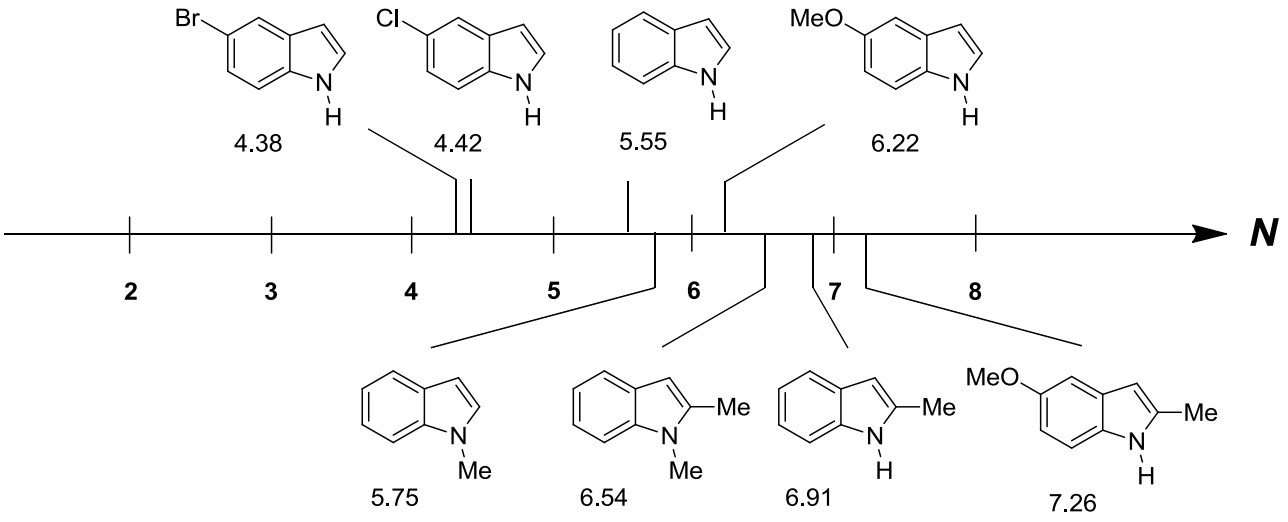
[a] Yields refer to pure isolated product.
[b] **2** (1.00 mmol).

Table 7.2 – Effect of the counteranions.

With optimised reaction conditions in hand, we probed the scope of metal-free direct arylations with differently substituted indoles employing diaryliodonium tosylate **2b**.

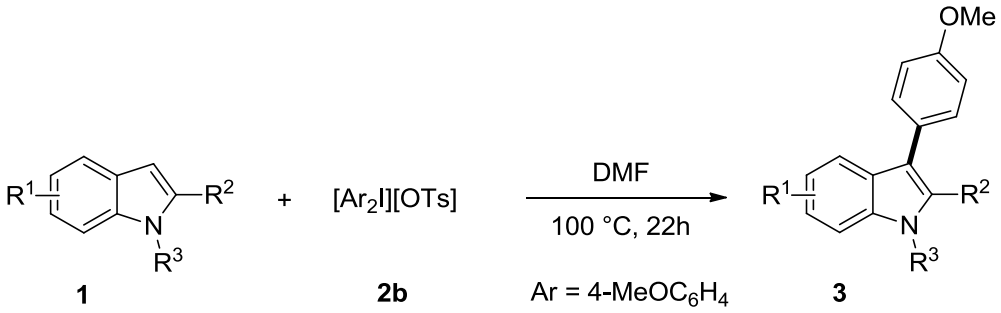
Like pyrroles, indoles are π-excessive heteroarenes which react much faster with electrophiles than most benzene derivatives. Mayr and co-workers investigated the mechanism of the reactions of indoles[19] in order to include them into the comprehensive nucleophilicity scale based on benzhydrylium electrophiles,[20,21] which is useful for designing the use of indoles as nucleophiles in organocatalytic reactions.[22] The nucleophiles are characterized by the nucleophilicity parameter *N*.

Nucleophilicities of Indoles:

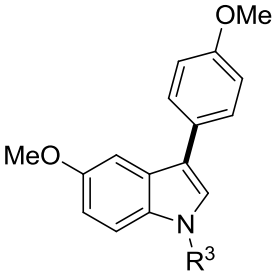


On the basis of these parameters we prepared a library of N-alkyl starting compounds in order to investigate scope and limitation of the approach. Notably, N-alkyl indoles **1** were converted efficiently, as were free (NH)-indoles. The reaction conditions were: indole **1** (0.50 mmol), diaryliodonium salt **2b** (1.00 mmol) in 2.0 ml of DMF at 100 °C for 22h (Scheme 7.6). More hindered 2-substituted indoles **1** reacted with comparable efficacy, thereby yielding products **3h-3l**. Decoration on the aromatic moiety

of indoles **1** was well tolerated, which among others set the stage for the synthesis of chloro-substituted product **3o**.

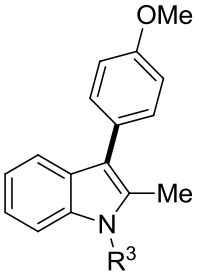


5-OMe derivatives

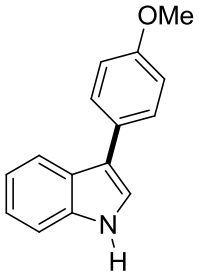


R^3	Product	Yield (%)[a]
Me	**3b**	64
n-Bu	**3c**	65
n-Oct	**3d**	70
n-Dec	**3e**	72
H	**3f**	60

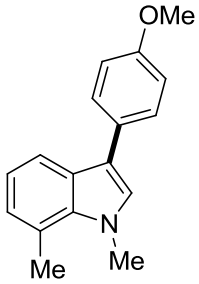
2-Me derivatives



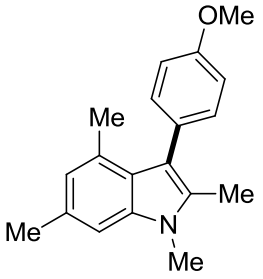
R^3	Product	Yield (%)[a]
Me	**3h**	67 (53)[b]
n-Pr	**3i**	59
n-Bu	**3j**	68
Bn	**3k**	52
H	**3l**	68



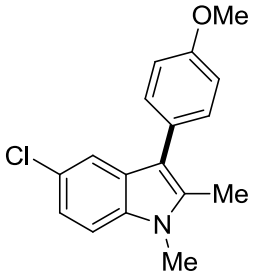
Product	Yield (%)[a]
3g	64



Product	Yield (%)[a]
3m	61



Product	Yield (%)[a]
3n	77



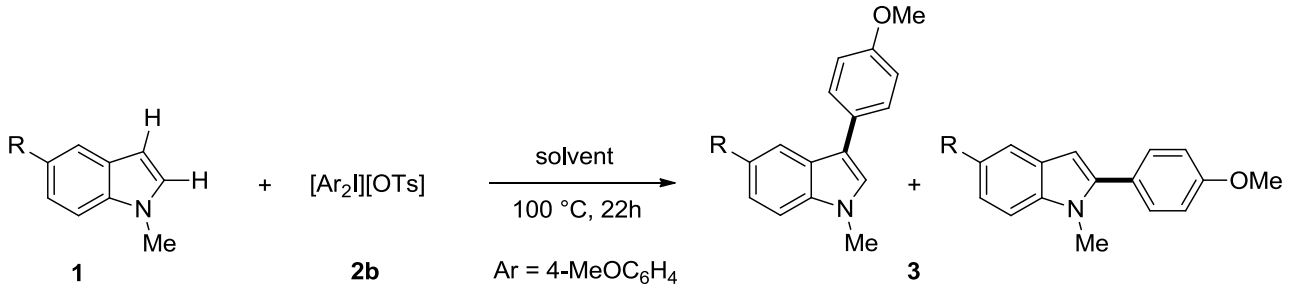
Product	Yield (%)[a]
3o	61

[a] Yields refer to pure isolated product.

[b] **2b** (0.55 mmol).

Scheme 7.6 – Scope of metal-free direct arylations of indoles **1**.

Direct arylations of indoles **1** occurred with excellent site-selectivities to predominantly yield the C-3 arylated products. However, it is noteworthy that small amounts of the C-2 functionalized indoles **3pb** and **3qb** were isolated when using starting materials **1p** and **1q**, respectively (Scheme 7.7). Here, best results were obtained with DMF or toluene as the solvent.[23]

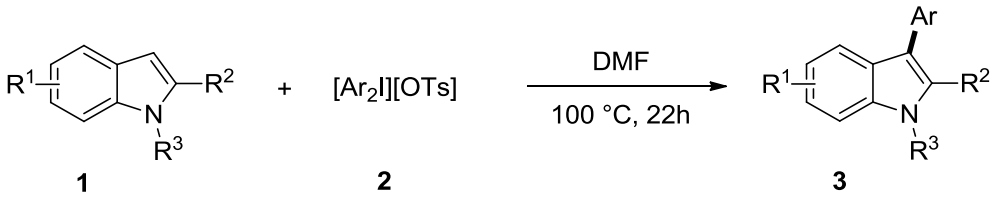


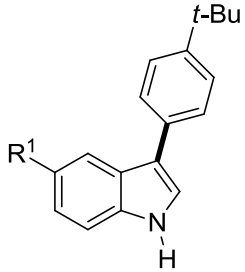
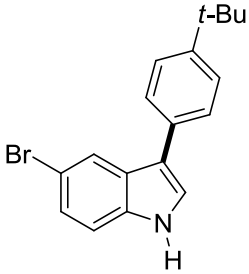
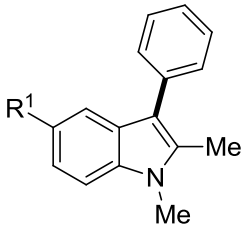
1p	R = H	Solvent	3pa (yield %)	3pb (yield %)
		DMF	56	11
		PhMe	55	12
		1,4-dioxane	43	9
		AcOH	7	-

1q	R = Br	Solvent	3qa (yield %)	3qb (yield %)
		DMF	43	10

Scheme 7.7 – Direct arylations of 2,3-unsubstituted indoles **1p** and **1q**.

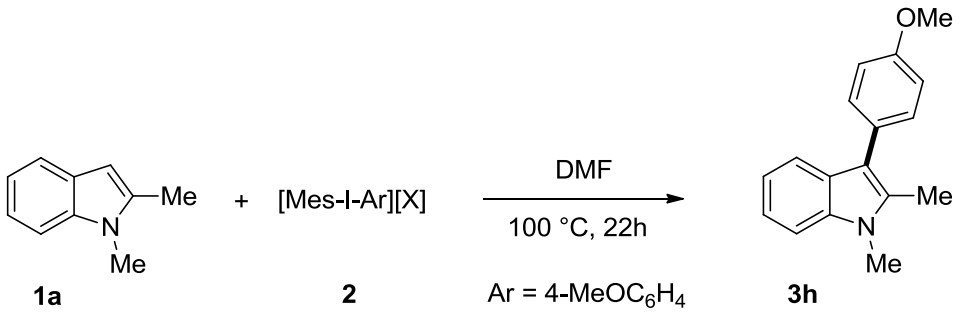
The C-H bond functionalization protocol was not limited to the direct introduction of a 4-anisyl substituent but allowed for the preparation of products **3r-3u** as well (Scheme 7.8).[24,25]



Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
					
3r (R^1 = OMe)	63	**3t**	50	**3a** (R^1 = H)	54
3s (R^1 = H)	62			**3u** (R^1 = Cl)	46

Scheme 7.8 – Scope of direct arylations with [Ar_2I][OTs] **2**.

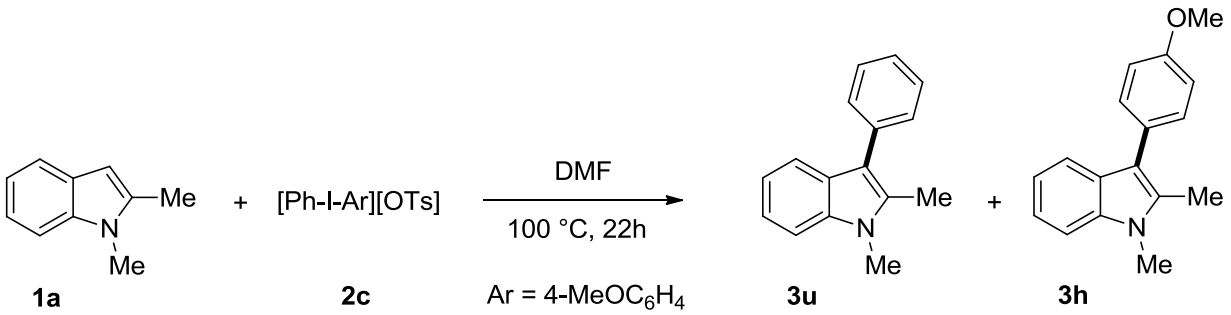
Likewise, unsymmetrically substituted diaryliodonium salts **2** were found to be suitable arylating reagents, which resulted in the preferential transfer of the less sterically hindered aromatic moiety (Scheme 7.9).



X	Yield (%)
OTf	55
BF_4	60

Scheme 7.9 – Direct arylations with unsymmetrically substituted salts **2**.

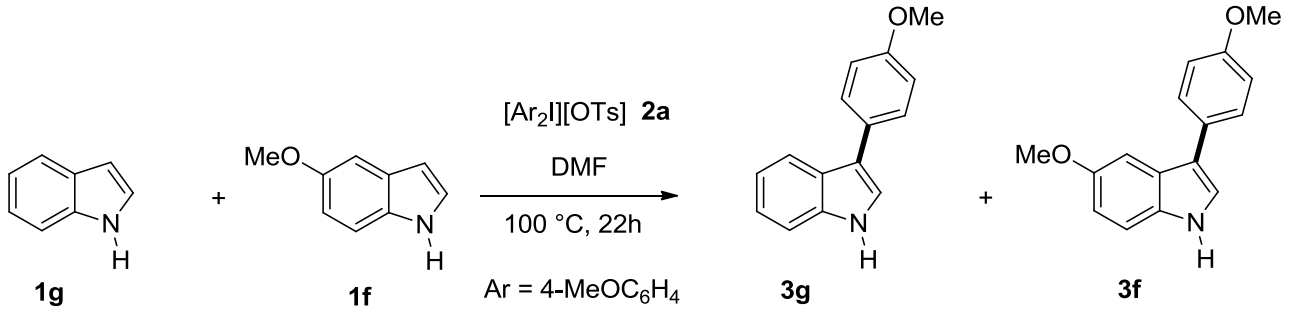
An additional intramolecular competition experiment with iodonium salt **2c** bearing two different aryl substituents with comparable steric demand highlighted that the less electron-rich group is introduced predominantly (Scheme 7.10).



Product	Yield (%)
3u	41
3h	27

Scheme 7.10 – Intramolecular competition experiment with salt **2c**.

Moreover, intermolecular competition experiments with an excess of differently substituted indoles clearly revealed a strong correlation with Mayr's nucleophilicity parameter *N* (Scheme 7.11).

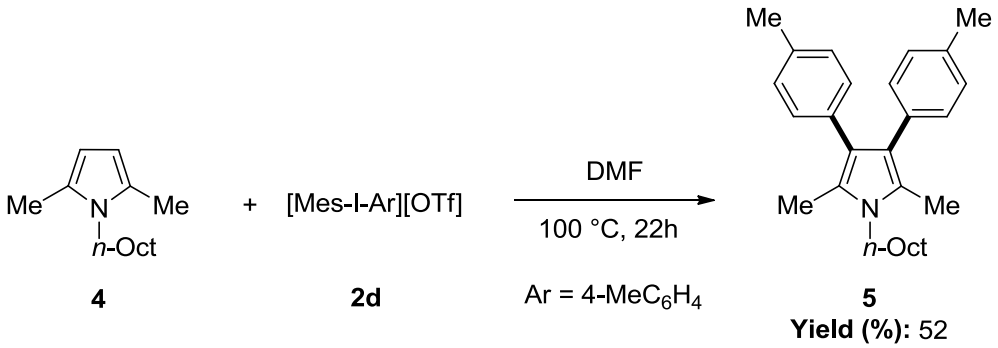


1 (3.0 eq.)	**Product**	**Yield (%)**
1g N = 5.55	**3g**	21
1f N = 6.22	**3f**	39

Scheme 7.11 – Intermolecular competition experiment.

On the basis of these experiments, we finally probed pyrrole **4** as a substrate, which delivered the desired product **5** (Scheme 7.12).

The C-H arylations of pyrrole derivatives involve functionalization at the 2 and 5 positions of pyrroles due to the inherent reactivity of these sites. Alkyl groups were found to have an enormous activating effect on the nucleophilicities of pyrroles (pyrrole: N = 4.63; N-methylpyrrole: N = 5.85; 1,2,5 trimethylpyrrole: N = 8.69).[26]



Scheme 7.12 – Direct arylation of pyrrole **4**.

7.3 Conclusion

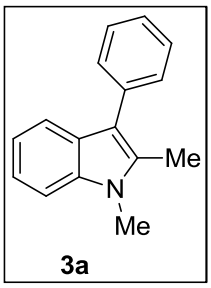
In summary, we have reported on efficient direct arylations of indoles with diaryliodonium salts in the absence of metal catalysts. Importantly, the protocol proved broadly applicable, thereby enabling C-H bond functionalizations of free (NH)- as well as N-substituted indoles and pyrroles.

7.4 Experimental section

General details: All reactions were set up in a M. Braun UNIlab Glove Box and carried out under a N_2 atmosphere using pre-dried glassware. DMF was purified using a MB. Braun SPS-800 solvent purification system and was stored over molecular sieves. *N*-alkyl indoles **1**[27] and iodonium salts **2** [8, 11, 28] were prepared using modified literature procedures. All indole substrates were purified by Kugelrohr distillation prior to their use. Other chemicals were obtained from commercial sources, and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by ^{1}H-NMR and GC. Flash chromatography: Macherey-Nagel silica gel 60 (70-230 mesh). NMR: Spectra were recorded on a Varian-NMR 300 and a Varian-NMR 500 instrument in the solvent indicated; chemical shifts (δ) are provided in ppm. All direct arylation reactions reported herein were performed in new glassware using new stirring bars. Representative starting materials were analysed by ICP-MS, which revealed only trace amounts of transition metals (< 1 ppm Pd, Rh, and Ru; < 10 ppm Cu).

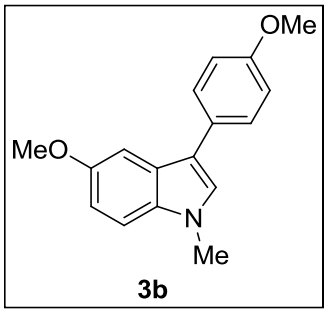
Representative procedure for the metal-free direct arylation. A solution of **1** (0.50 mmol) and **2** (0.55 mmol) in DMF (2 mL) was stirred for 22 h at 100 °C. Water (25 mL) was added at ambient temperature, and the reaction mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica to yield the arylated products **3**.

1,2-Dimethyl-3-phenylindole (3a). Eluent for chromatography: *n*-pentane → *n*-pentane/Et_2O 100:1 → 50:1. Yield 53 mg (47%). Pale rose solid. Mp 111.1–112.7 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.8 Hz, 1H), 7.56-7.43 (m, 4H), 7.38-7.28 (m, 2H), 7.24 (m, 1H), 7.17-7.09 (m, 1H), 3.76 (s, 3H), 2.51 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 136.6 (C_q), 135.8 (C_q), 133.3 (C_q), 129.7 (CH), 128.4 (CH), 126.9 (C_q), 125.6 (CH), 121.1 (CH), 119.6 (CH), 118.7 (CH), 114.0 (C_q), 108.7 (CH), 29.6 (CH_3), 11.0 (CH_3). IR (neat): 3049, 2938, 1599, 1468, 1369, 770, 740, 703 cm^{-1}. MS (EI) m/z (relative intensity): 221 (100) [M^+], 204 (14), 178 (9), 144 (11), 102 (5), 43 (15). HR-MS (EI) m/z calcd for $C_{16}H_{15}N$ 221.1204, found 221.1202. These data are in good agreement with literature values. [13]



3a

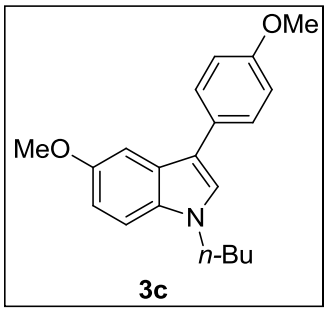
5-Methoxy-3-(4-methoxyphenyl)-1-methylindole (3b). Eluent for chromatography: *n*-pentane/Et_2O 50:1 → 48:1 → 47:1. Yield 85 mg (64 %). Colourless solid. Mp 102.5–104.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (md, J = 8.8 Hz, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.26 (d, J = 8.9 Hz, 1H), 7.13 (s, 1H), 7.02 (md, J = 8.9 Hz, 2H), 6.95 (dd, J = 8.9, 2.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 154.4 (C_q), 132.7 (C_q), 128.4 (C_q), 128.3 (CH), 126.6 (CH), 126.5 (C_q), 115.9 (C_q), 114.3 (CH), 112.1 (CH), 110.2 (CH), 101.6 (CH), 56.0 (CH_3), 55.3 (CH_3), 32.9 (CH_3). IR (neat): 2993, 2952, 2899, 2833, 1541, 1489, 1446, 1205,



3b

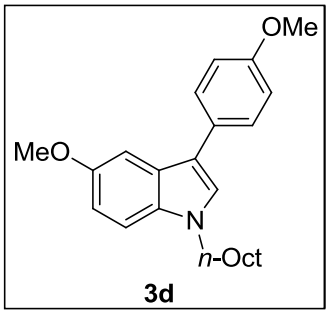
1174, 1029, 838, 788 cm^{-1}. MS (EI) *m/z* (relative intensity): 267 (100) [M^+], 252 (96), 237 (15), 224 (38), 209 (28). HR-MS (EI) *m/z* calcd for $C_{17}H_{17}NO_2$ 267.1259, found 267.1249.

1-*n*-Butyl-5-methoxy-3-(4-methoxyphenyl)indole (3c). Eluent for chromatography: *n*-pentane/Et_2O 50:1 → 48:1 → 47:1. Yield 100 mg (65 %). Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (md, *J* = 8.9 Hz, 2H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.27 (m, 1H), 7.18 (s, 1H), 7.01 (md, *J* = 8.8 Hz, 2H), 6.97-6.88 (m, 1H), 4.12 (t, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 1.90-1.80 (m, 2H), 1.42-1.32 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 154.3 (C_q), 132.0 (C_q), 128.4 (C_q), 128.3 (CH), 126.5 (C_q), 125.6 (CH), 115.8 (C_q), 114.3 (CH), 111.9 (CH), 110.3 (CH), 101.6 (CH), 56.0 (CH_3), 55.3 (CH_3), 46.3 (CH_2), 32.4 (CH_2), 20.2 (CH_2), 13.7 (CH_3). IR (neat): 2931, 1547, 1483, 1451, 1241, 1210, 1173, 1101, 1030, 834, 787 cm^{-1}. MS (EI) *m/z* (relative intensity): 309 (100) [M^+], 294 (44), 266 (84), 252 (32). HR-MS (EI) *m/z* calcd for $C_{20}H_{23}NO_2$ 309.1729, found 309.1731.



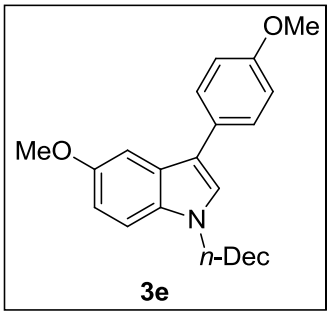
3c

5-Methoxy-3-(4-methoxyphenyl)-1-*n*-octylindole (3d). Eluent for chromatography: *n*-pentane/Et_2O 100:1 → 80:1 → 60:1 → 50:1. Yield 128 mg (70 %). Pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (md, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.26 (m, 1H), 7.18 (s, 1H), 7.01 (md, *J* = 8.8 Hz, 2H), 6.92 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.10 (t, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 1.92-1.78 (m, 2H), 1.41-1.18 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 154.3 (C_q), 132.0 (C_q), 128.5 (C_q), 128.3 (CH), 126.5 (C_q), 125.6 (CH), 115.8 (C_q), 114.3 (CH), 111.9 (CH), 110.4 (CH), 101.6 (CH), 56.0 (CH_3), 55.3 (CH_3), 46.6 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3). IR (neat): 2925, 2853, 1548, 1484, 1451, 1242, 1208, 1173, 1032, 833, 788 cm^{-1}. MS (EI) *m/z* (relative intensity): 365 (100) [M^+], 350 (7), 266 (40), 252 (7). HR-MS (EI) *m/z* calcd for $C_{24}H_{31}NO_2$ 365.2355, found 365.2352.



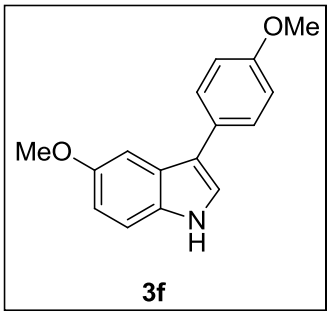
3d

1-*n*-Decyl-5-methoxy-3-(4-methoxyphenyl)indole (3e). Eluent for chromatography: *n*-pentane/Et_2O 60:1 → 55:1 → 50:1. Yield 141 mg (72 %). Pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (md, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.26 (m, 1H), 7.18 (s, 1H), 7.01 (md, *J* = 8.8 Hz, 2H), 6.92 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.10 (t, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 1.94-1.78 (m, 2H), 1.41-1.17 (m, 14H), 0.89 (t, *J* = 6.7 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 154.3 (C_q), 132.0 (C_q), 128.5 (C_q), 128.3 (CH), 126.5 (C_q), 125.6 (CH), 115.8 (C_q), 114.3 (CH), 111.9 (CH), 110.3 (CH), 101.6 (CH), 56.0 (CH_3), 55.3 (CH_3), 46.6 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3). IR (neat): 2924, 2852, 1548, 1484, 1452, 1242, 1208, 1174, 1033, 833, 788 cm^{-1}. MS (EI) *m/z* (relative intensity): 393 (100) [M^+], 378 (9), 266 (43), 252 (8). HR-MS (EI) *m/z* calcd for $C_{26}H_{35}NO_2$ 393.2668, found 393.2666.



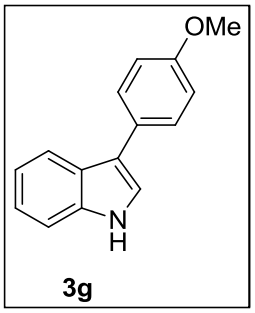
3e

5-Methoxy-3-(4-methoxyphenyl)indole (3f). Eluent for chromatography: *n*-pentane/Et_2O 30:1 → 20:1 → 10:1 → 6:1 → 4:1. Yield 76 mg (60 %). Pale yellow solid. Mp 107.0–109.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.08 (br, s, 1H), 7.56 (md, J = 8.2 Hz, 2H), 7.33 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.01 (md, J = 8.2 Hz, 2H), 6.91 (dd, J = 8.7, 2.4 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 154.6 (C_q), 131.7 (C_q), 128.5 (CH), 128.2 (C_q), 126.3 (C_q), 122.0 (CH), 117.8 (C_q), 114.3 (CH), 112.5 (CH), 112.0 (CH), 101.5 (CH), 55.9 (CH_3), 55.3 (CH_3). IR (neat): 3400, 2837, 1466, 1441, 1240, 1203, 1174, 1104, 1020, 793 cm^{-1}. MS (EI) m/z (relative intensity): 253 (100) [M^+], 238 (88), 210 (41). HR-MS (EI) m/z calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1100. These data are in good agreement with literature values.[29]



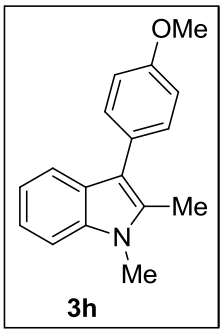
3f

3-(4-Methoxyphenyl)indole (3g). Eluent for chromatography: *n*-pentane/Et_2O 30:1 → 25:1 → 20:1 → 18:1 → 16:1. Yield 72 mg (64 %). Colourless solid. Mp 134.0–136.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.15 (br, s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.62 (md, J = 8.8 Hz, 2H), 7.42 (m, 1H), 7.31-7.17 (m, 3H), 7.03 (md, J = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.1 (C_q), 136.5 (C_q), 128.6 (CH), 128.1 (C_q), 125.9 (C_q), 122.3 (CH), 121.1 (CH), 120.1 (CH), 119.7 (CH), 117.9 (C_q), 114.2 (CH), 111.3 (CH), 55.3 (CH_3). IR (neat): 3399, 3000, 2961, 2927, 2834, 1546, 1499, 1244, 1028, 834, 811, 746 cm^{-1}. MS (EI) m/z (relative intensity): 223 (97) [M^+], 208 (100), 180 (31). HR-MS (EI) m/z calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0990. These data are in good agreement with literature values.[29]



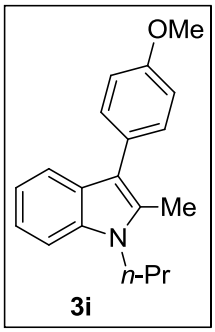
3g

3-(4-Methoxyphenyl)-1,2-dimethylindole (3h). Eluent for chromatography: *n*-pentane → *n*-pentane/Et_2O 100:1 → 70:1 → 50:1. Yield 84 mg (67%). Colorless solid. Mp 149.1–151.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.23-7.16 (m, 1H), 7.13-7.05 (m, 1H), 7.01 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.46 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 136.5 (C_q), 133.0 (C_q), 130.7 (CH), 128.1 (C_q), 127.2 (C_q), 121.0 (CH), 119.5 (CH), 118.6 (CH), 113.9 (CH), 113.6 (C_q), 108.6 (CH), 55.3 (CH_3), 29.6 (CH_3), 11.0 (CH_3). IR (neat): 3036, 2932, 1556, 1464, 1233, 1032, 835, 740, 560 cm^{-1}. MS (EI) m/z (relative intensity) 251 (100) [M^+], 236 (93), 208 (8), 193 (13), 125 (9), 43 (4). HR-MS (EI) m/z calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1312.



3h

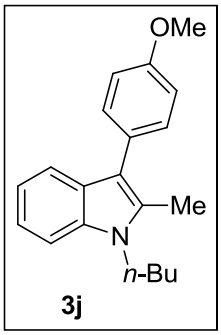
3-(4-Methoxyphenyl)-2-methyl-1-*n*-propylindole (3i). Eluent for chromatography: *n*-pentane → *n*-pentane/Et_2O 200:1 → 100:1. Yield 84 mg (67%). Yellow solid. Mp 77.8–80.7 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.17 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.08 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 4.16-4.00 (t, J = 7.4 Hz 2H), 3.86 (s, 3H), 2.45 (s, 3H), 1.94-1.72 (sext, J = 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 135.9 (C_q), 132.5 (C_q), 130.8 (CH), 128.2 (C_q), 127.3 (C_q), 120.8 (CH), 119.3 (CH), 118.7 (CH), 113.9 (CH), 113.6 (C_q), 108.9 (CH), 55.3 (CH_3), 45.0 (CH_2), 23.5 (CH_2), 11.6 (CH_3), 11.0 (CH_3). IR (neat): 2997, 2916, 1504, 1242, 1171, 826, 732, 563 cm^{-1}. MS (EI) m/z (relative intensity) 279 (100) [M^+], 250



3i

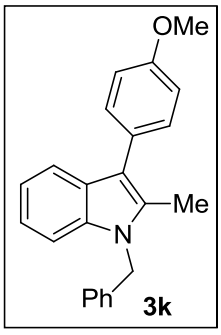
(87), 235 (12), 192 (8), 152 (5), 43 (2). HR-MS (EI) *m/z* calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1631.

1-*n*-Butyl-3-(4-methoxyphenyl)-2-methylindole (3j). Eluent for chromatography: *n*-pentane → *n*-pentane/Et_2O 100:1 → 70:1. Yield 99 mg (68%). Green oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.15-4.08 (t, *J* = 7.5 Hz, 2H), 3.86 (s, 3H), 2.45 (s, 3H), 1.78 (quint, *J* = 7.3 Hz, 2H), 1.43 (sext, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.7 (C_q), 135.9 (C_q), 132.5 (C_q), 130.8 (CH), 128.2 (C_q), 127.3 (C_q), 120.8 (CH), 119.3 (CH), 118.7 (CH), 113.9 (CH), 113.6 (C_q), 108.9 (CH), 55.3 (CH_3), 43.2 (CH_2), 32.4 (CH_2), 20.4 (CH_2), 13.9 (CH_3), 11.0 (CH_3). IR (neat): 3045, 2957, 1559, 1510, 1361, 1241, 1036, 834, 739 cm^{-1}. MS (EI) *m/z* (relative intensity) 293 (100) [M^+], 250 (86), 206 (9), 192 (8), 152 (5), 77 (2). HR-MS (EI) *m/z* calcd for $C_{20}H_{23}NO$ 293.1780, found 293.1785.



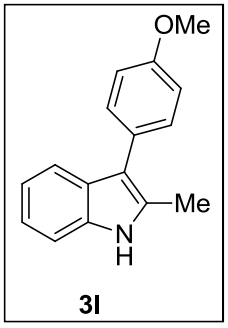
3j

1-Benzyl-3-(4-methoxyphenyl)-2-methylindole (3k). Eluent for chromatography: *n*-hexane → *n*-hexane/*t*-BuOMe 100:1 → 50:1. Yield 85 mg (52%). Colourless solid. Mp 109.8 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.46 (dt, *J* = 8.6, 2.8 Hz, 1H), 7.30-7.25 (m, 4H), 7.20-7.11 (m, 2H), 7.06-7.03 (m, 4H), 5.38 (s, 3H), 3.88 (s, 3H), 2.42 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 157.8 (C_q), 137.8 (C_q), 136.5 (C_q), 132.8 (C_q), 130.8 (CH), 128.8 (CH), 128.0 (C_q), 127.5 (C_q), 127.3 (CH), 126.0 (CH), 121.3 (CH), 119.7 (CH), 118.8 (CH), 114.3 (C_q), 114.0 (CH), 109.1 (CH), 55.3 (CH_3), 46.7 (CH_2), 11.0 (CH_3). IR (neat): 3031, 2933, 2834, 1607, 1508, 1465, 1355, 1243, 1035, 831, 734, 696 cm^{-1}. MS (EI) *m/z* (relative intensity): 327 (96) [M^+], 312 (6), 296 (2), 280 (2), 267 (2), 236 (100), 204 (20), 192 (27), 165 (10), 152 (15), 126 (3), 91 (43). HR-MS (EI) *m/z* calcd for $C_{23}H_{21}NO$ 327.1623, found 327.1629.



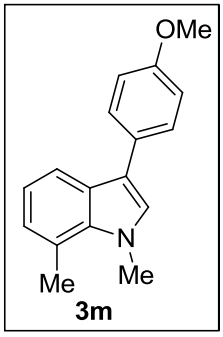
3k

3-(4-Methoxyphenyl)-2-methylindole (3l). Eluent for chromatography: *n*-pentane/Et_2O 30:1 → 20:1 → 19:1 → 18:1 → 17:1. Yield 81 mg (68 %). Pale yellow solid. Mp 124.0–127.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.89 (br, s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.42 (md, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.20-7.05 (m, 2H), 7.01 (md, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.46 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.8 (C_q), 135.1 (C_q), 130.9 (C_q), 130.4 (CH), 128.0 (C_q), 127.8 (C_q), 121.4 (CH), 119.8 (CH), 118.7 (CH), 114.1 (C_q), 113.9 (CH), 110.2 (CH), 55.3 (CH_3), 12.4 (CH_3). IR (neat): 3351, 3052, 3005, 2960, 2909, 1509, 1456, 1235, 1172, 1021, 829, 815, 745 cm^{-1}. MS (EI) *m/z* (relative intensity): 237 (100) [M^+], 222 (95), 194 (22). HR-MS (EI) *m/z* calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1160. The spectral data were in accordance with those reported in literature.[29]



3l

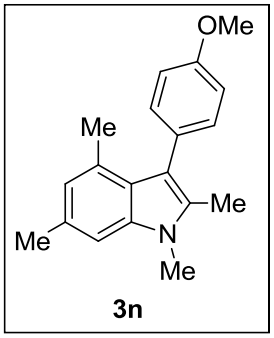
3-(4-Methoxyphenyl)-1,7-dimethylindole (3m). Eluent for chromatography: *n*-hexane → *n*-hexane/*t*-BuOMe 100:1 → 50:1. Yield 77 mg (61 %). Colourless solid. Mp 132.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.9 Hz, 1H), 7.57 (dt, *J* = 8.5, 3.1 Hz, 2H), 7.06-6.95 (m, 5H), 4.10 (s, 3H), 3.86 (s, 3H), 2.80 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 136.0 (C_q), 128.7 (CH), 128.2 (C_q), 127.8 (CH), 127.4 (C_q), 124.5 (CH), 121.4 (C_q), 119.9 (CH), 117.9 (CH), 116.2 (C_q), 114.2 (CH), 55.3 (CH_3), 36.8 (CH_3), 19.8 (CH_3). IR (neat): 2955, 2930, 2834, 1553, 1506, 1458,



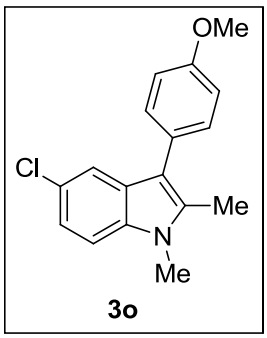
3m

1243, 1177, 1028, 836, 744 cm^{-1}. MS (EI) *m/z* (relative intensity): 251 (98) [M^+], 236 (100), 208 (20), 193 (16), 165 (17), 152 (15), 139 (8), 125 (17). HR-MS (EI) *m/z* calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1312.

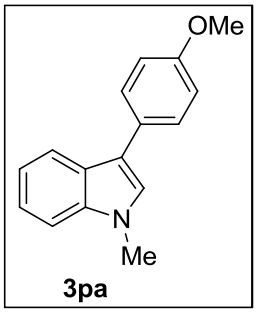
3-(4-Methoxyphenyl)-1,2,4,6-tetramethylindole (3n). Eluent for chromatography: *n*-hexane → *n*-hexane/*t*-BuOMe 100:1 → 50:1. Yield 107 mg (77 %). Colourless solid. Mp 121.8 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.25 (dt, *J* = 8.8, 2.8 Hz, 2H), 6.97 (s, 1H), 6.93 (dt, *J* = 8.8, 2.8 Hz, 2H), 6.66 (s, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 2.46 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 158.1 (C_q), 136.7 (C_q), 133.0 (C_q), 132.5 (CH), 130.4 (C_q), 129.9 (C_q), 129.8 (C_q), 123.9 (C_q), 122.7 (CH), 114.2 (C_q), 112.9 (CH), 106.5 (CH), 55.2 (CH_3), 29.6 (CH_3), 21.6 (CH_3), 20.3 (CH_3), 10.6 (CH_3). IR (neat): 2990, 2959, 1611, 1560, 1372, 1281, 1174, 1026, 833, 657 cm^{-1}. MS (EI) *m/z* (relative intensity): 279 (100) [M^+], 264 (30), 249 (5), 236 (6), 220 (8), 204 (4), 165 (3). HR-MS (EI) *m/z* calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1623.



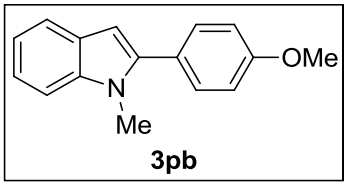
5-Chloro-3-(4-methoxyphenyl)-1,2-dimethylindole (3o). Eluent for chromatography: *n*-pentane/Et_2O 100:1→ 70:1 → 50:1. Yield 87 mg (61%). Colorless solid. Mp 130.1–132.7 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 2.0, 0.4 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.19 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.12 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.69 (s, 3H), 2.43 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.0 (C_q), 134.9 (C_q), 134.4 (C_q), 130.6 (CH), 128.2 (C_q), 127.3 (C_q), 125.2 (C_q), 121.1 (CH), 118.1 (CH), 114.1 (CH), 113.4 (C_q), 109.6 (CH), 55.3 (CH_3), 29.8 (CH_3), 11.0 (CH_3). IR (neat): 3004, 2910, 1507, 1473, 1239, 1031, 793, 584 cm^{-1}. MS (EI) *m/z* (relative intensity) 285 (10) [M^+], 270 (68), 242 (7), 207 (21), 143 (8), 43 (5). HR-MS (EI) *m/z* calcd for $C_{17}H_{16}ClNO$ 285.0920, found 285.0918.



3-(4-Methoxyphenyl)-1-methylindole (3pa). Eluent for chromatography: *n*-pentane/Et_2O 100:1 → 90:1 → 80:1. Yield 67 mg (56 %). Colourless solid. Mp 95.0–97.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.9 Hz, 1H), 7.59 (md, *J* = 8.8 Hz, 2H), 7.37 (m, 1H), 7.28 (m, 1H), 7.23-7.15 (m, 2H), 7.01 (md, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9 (C_q), 137.3 (C_q), 128.4 (CH), 128.2 (C_q), 126.3 (C_q), 125.9 (CH), 121.8 (CH), 119.8 (CH), 119.6 (CH), 116.4 (C_q), 114.2 (CH), 109.4 (CH), 55.3 (CH_3), 32.8 (CH_3). IR (neat): 2990, 1545, 1504, 1470, 1238, 1176, 1028, 812, 743 cm^{-1}. MS (EI) *m/z* (relative intensity): 237 (94) [M^+], 222 (100), 194 (44). HR-MS (EI) *m/z* calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1151. These data are in good agreement with literature values.[27b]

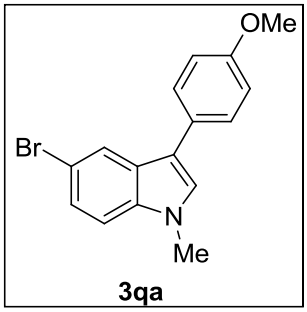


2-(4-Methoxyphenyl)-1-methylindole (3pb). Eluent for chromatography: *n*-pentane/Et_2O 100:1 → 90:1 → 80:1. Yield 13 mg (11 %). Colourless solid. Mp 118.5–119.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.7 Hz, 1H), 7.45 (md, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 1H), 7.13 (m, 1H), 7.02 (md, *J* = 8.8 Hz, 2H), 6.52 (s, 1H), 3.88 (s, 3H), 3.74 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_q), 141.4 (C_q), 138.1 (C_q), 130.6 (CH), 128.0 (C_q), 125.3 (C_q), 121.4 (CH), 120.2 (CH), 119.8 (CH), 113.9 (CH), 109.5 (CH), 101.0 (CH), 55.3



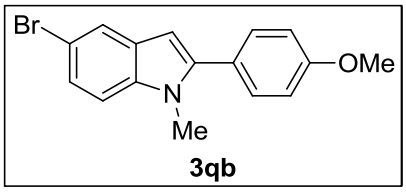
(CH_3), 31.0 (CH_3). IR (neat): 2960, 2929, 2835, 1608, 1496, 1464, 1431, 1237, 1178, 1034, 838, 775, 727 cm^{-1}. MS (EI) *m/z* (relative intensity): 237 (100) [M^+], 222 (63), 194 (15). HR-MS (EI) *m/z* calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1152. These data are in good agreement with literature values.[30]

5-Bromo-3-(4-methoxyphenyl)-1-methylindole (3qa). Eluent for chromatography: *n*-pentane/Et_2O 200:1 → 180:1 → 140:1 → 100:1. Yield 68 mg (43 %). Pale yellow solid. Mp 91.0–93.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 1.9 Hz, 1H), 7.51 (md, *J* = 8.8 Hz, 2H), 7.34 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.23 (t, *J* = 9.1 Hz, 1H), 7.14 (s, 1H), 7.00 (md, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.2 (C_q), 135.9 (C_q), 128.5 (CH), 127.9 (C_q), 127.4 (C_q), 126.9 (CH), 124.7 (CH), 122.3 (CH), 116.2 (C_q), 114.3 (CH), 113.2 (C_q), 110.9 (CH), 55.3 (CH_3), 32.9 (CH_3). IR (neat): 2998, 2952, 2832, 1544, 1503, 1467, 1237, 1176, 1027, 840, 788 cm^{-1}. MS (EI) *m/z* (relative intensity): 315 (100) [M^+], 300 (92), 272 (31), 193 (33), 192 (42). HR-MS (EI) *m/z* calcd for $C_{16}H_{14}BrNO$ 315.0259, found 315.0267.



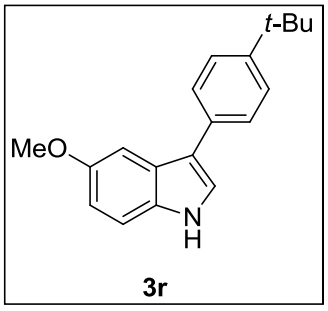
3qa

5-Bromo-2-(4-methoxyphenyl)-1-methylindole (3qb). Eluent for chromatography: *n*-pentane/Et_2O 200:1 → 180:1 → 140:1 → 100:1. Yield 16 mg (10 %). Colourless solid. Mp 120.5–122.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 1.7 Hz, 1H), 7.42 (md, *J* = 8.6 Hz, 2H), 7.36-7.12 (m, 2H), 7.01 (md, *J* = 8.6 Hz, 2H), 6.44 (s, 1H), 3.88 (s, 3H), 3.70 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.7 (C_q), 142.6 (C_q), 136.8 (C_q), 130.6 (CH), 129.6 (C_q), 124.7 (C_q), 124.1 (CH), 122.6 (CH), 114.0 (CH), 112.9 (C_q), 110.9 (CH), 100.5 (CH), 55.4 (CH_3), 31.2 (CH_3). IR (neat): 2962, 2836, 1608, 1492, 1456, 1239, 1048, 831, 782, 767 cm^{-1}. MS (EI) *m/z* (relative intensity): 315 (100) [M^+], 300 (63), 272 (7), 193 (25), 192 (33). HR-MS (EI) *m/z* calcd for $C_{16}H_{14}BrNO$ 315.0259, found 315.0264.



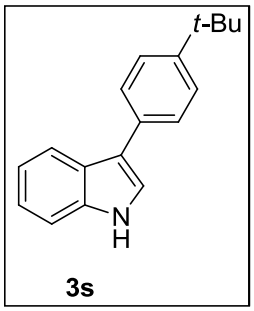
3qb

3-(4-*t*-Butylphenyl)-5-methoxyindole (3r). Eluent for chromatography: *n*-pentane/Et_2O 30:1 → 25:1 → 20:1 → 15:1 → 12:1. Yield 88 mg (63 %). Colourless solid. Mp 142.5–144.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 (br, s, 1H), 7.61 (md, *J* = 8.4 Hz, 2H), 7.50 (md, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.32 (m, 2H), 6.92 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.88 (s, 3H), 1.40 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.5 (C_q), 148.6 (C_q), 132.7 (C_q), 131.7 (C_q), 126.9 (CH), 126.1 (C_q), 125.6 (CH), 122.3 (CH), 117.9 (C_q), 112.6 (CH), 111.9 (CH), 101.6 (CH), 55.9 (CH_3), 34.6 (C_q), 31.5 (CH_3). IR (neat): 3400, 2956, 1478, 1451, 1268, 1208, 1026, 834, 800 cm^{-1}. MS (EI) *m/z* (relative intensity): 279 (77) [M^+], 264 (100), 249 (27). HR-MS (EI) *m/z* calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1620.



3r

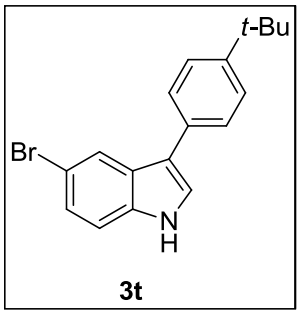
3-(4-*t*-Butylphenyl)indole (3s). Eluent for chromatography: *n*-pentane/Et_2O 30:1 → 25:1 → 20:1 → 15:1. Yield 77 mg (62 %). Colourless solid. Mp 191.0–194.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.16 (br, s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.64 (md, *J* = 8.3 Hz, 2H), 7.50 (md, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.30-7.17 (m, 2H), 1.40 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 148.8 (C_q), 136.6 (C_q), 132.6 (C_q), 127.1 (CH), 125.8 (C_q), 125.6 (CH), 122.3 (CH), 121.5 (CH), 120.1 (CH), 119.9 (CH), 118.2 (C_q), 111.3 (CH), 34.5 (C_q), 31.4 (CH_3). IR



3s

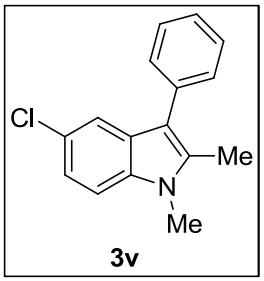
(neat): 3416, 2961, 1455, 1331, 1237, 1096, 1011, 842, 820, 745 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 249 (69) [M^+], 234 (100), 219 (22). HR-MS (EI) *m*/*z* calcd for $C_{18}H_{19}N$ 249.1517, found 249.1511.

5-Bromo-3-(4-*t*-butylphenyl)indole (3t). Eluent for chromatography: *n*-pentane/Et_2O 30:1 → 25:1 → 20:1 → 18:1 → 17:1. Yield 82 mg (50 %). Colourless solid. Mp 156.0–158.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21 (br, s, 1H), 8.06 (m, 1H), 7.57 (md, *J* = 8.4 Hz, 2H), 7.49 (md, *J* = 8.3 Hz, 2H), 7.36-7.26 (m, 3H), 1.39 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.2 (C_q), 135.1 (C_q), 131.7 (C_q), 127.6 (C_q), 127.1 (CH), 125.7 (CH), 125.1 (CH), 122.5 (CH), 122.4 (CH), 118.0 (C_q), 113.5 (C_q), 112.7 (CH), 34.6 (C_q), 31.5 (CH_3). IR (neat): 3406, 2958, 1453, 1287, 1269, 1124, 1101, 879, 835, 796 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 327 (58) [M^+], 312 (100), 297 (5), 233 (45). HR-MS (EI) *m*/*z* calcd for $C_{18}H_{18}BrN$ 327.0623, found 327.0626.



3t

5-Chloro-1,2-dimethyl-3-phenylindole (3v). Eluent for chromatography: *n*-pentane/Et_2O 100:1→ 50:1. Yield 59 mg (46%). Colorless solid. Mp 119.8–121.5 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 2.0 Hz, 1H), 7.52-7.39 (m, 4H), 7.36-7.27 (m, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.13 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.70 (s, 3H), 2.47 (s, 3H).^{13}C-NMR (126 MHz, $CDCl_3$): δ = 135.0 (C_q), 135.0 (C_q), 134.7 (C_q), 129.6 (CH), 128.6 (CH), 128.0 (C_q), 126.0 (CH), 125.4 (C_q), 121.2 (CH), 118.1 (CH), 113.8 (C_q), 109.7 (CH), 29.8 (CH_3), 11.1 (CH_3). IR (neat): 3054, 2920, 1600, 1471, 1368, 1061, 789, 764, 700 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 255 (100) [M^+], 218 (13), 204 (12), 178 (14), 102 (5), 43 (4). HR-MS (EI) *m*/*z* calcd for $C_{16}H_{14}ClN$ 255.0815, found 255.0816.



3v

7.5 References and notes

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[25] Small amounts of the corresponding C-2 arylated products (2-8%) were formed during the preparation of products **3r**-**3t**, as indicated by GC/MS analysis.

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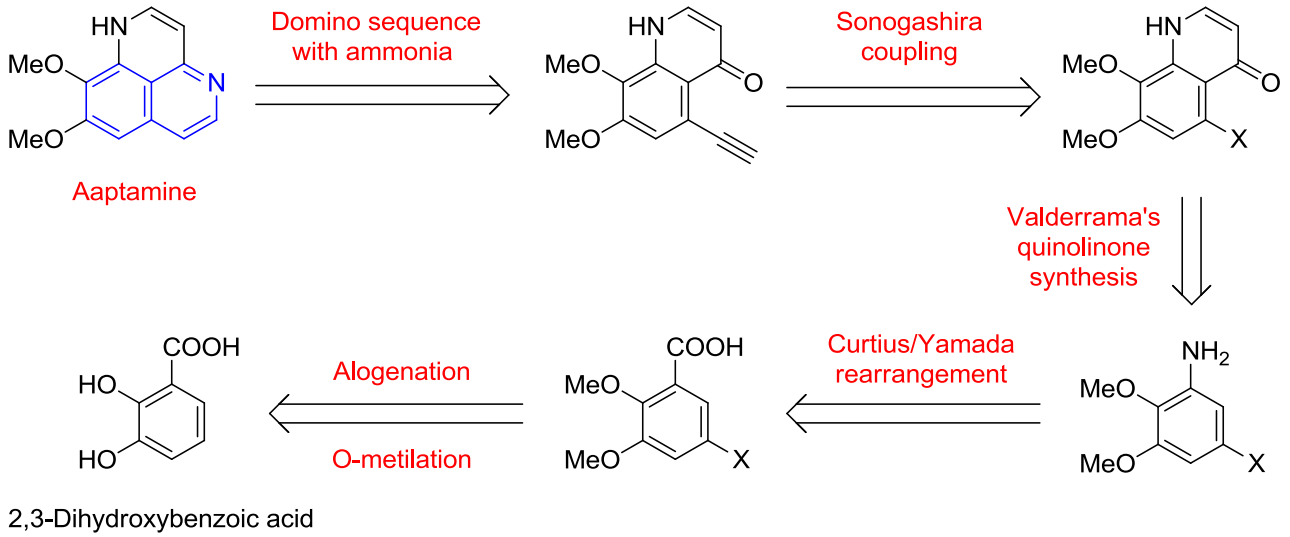
Chapter 8 -Concluding Remarks-

The present PhD thesis showed the versatility of nucleophilic addition/annulation domino reactions of alkyne compounds bearing a proximate nucleophile in the synthesis of heterocyclic systems, such as dihydroisobenzofurans, isoquinolines and naphthyridines. These approaches have been successfully transformed in multicomponent processes involving a one-pot coupling/addition/cyclisation sequence starting from the simple building blocks, such as *ortho*-bromoarylaldehydes, terminal alkynes and methanol or ammonia. In some cases, the reactivity of less reactive alkynyl substrates has been enhanced by the catalysis of alkynophilic transition metals, such as gold and silver. In particular, we reported a new silver-catalysed approach to 2-methylisoquinolines and 5-methyl-1,6-naphtyridines by tandem addition/cyclisation of γ-ketoalkynes with ammonia. The domino approach has been also extended to 2-acetyl-*N*-propargylpyrroles for the synthesis of pyrrolo[1,2-*a*]pyrazine. In this case $TiCl_4$ revealed to be the best promoter. Microwave heating demonstrated to be able to improve the efficiency of both domino and multicomponent processes. Finally, the project developed at the Institut für Organische und Biomolekulare Chemie in the Georg-August-Universität Göttingen (Germany), under the supervision of Prof. L. Ackermann, concerned with the direct arylations of indoles and pyrroles with differently substituted diaryliodonium salts in the absence of metal catalysts. The protocol proved broadly applicable, thereby enabling C-H bond functionalisations of free (NH)- as well as N-substituted indoles and pyrroles.

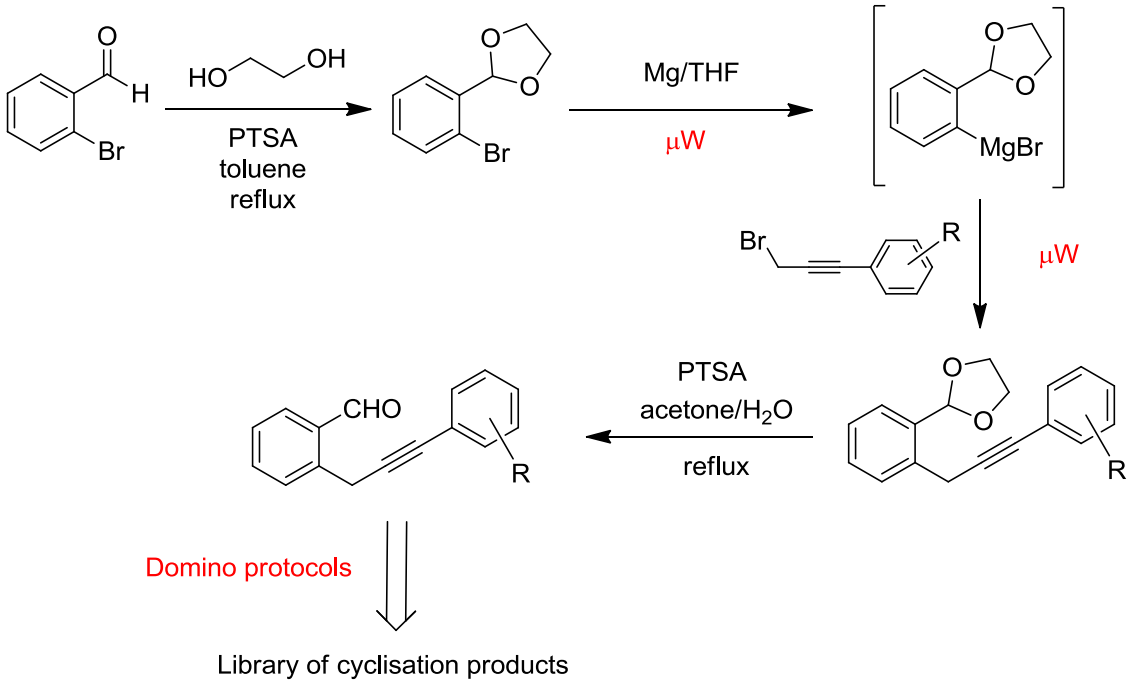
Some possible developments of this work are the application of our domino sequences in new synthetic pathway to some valuable natural products. For example, the domino approach to the isoquinoline nucleus could be the key step in a new total synthesis of the alkaloid Aaptamine.[1] Aaptamine is the ancestor of a series of natural alkaloids known as "aaptamines" characterized by the presence of a benzo[de][1,6]naphthyrydine ring in their framework. Aaptamina has been isolated for the first time in 1981 by Nakamura group[2] from a sponge *Aaptos aaptos* (Schmidt 1864) collected off Okinawa island coast, in Japan. Aaptamines showed a broad range of pharmacological activities. In particular, the ancestor Aaptamine showed in vitro a significant antioxidant activity,[3] a moderate antifungal activity towards *Candida tropicalis*,[4] and an interesting cytotoxic activity towards cancer cells;[1,5] above all, Aaptamine is especially an effective competitive α-adrenoceptor antagonist endowed of potential cardiotonic effects.[6]

In literature there are some different total synthesis[7] of Aaptamine. An alternative retrosynthetic analysis involving our chemistry is depicted in Scheme 8.1. The pyridine-fused ring could be obtained by a domino sequence in presence of ammonia starting from 5-ethynyl-7,8-dimethoxyquinolin-4(1*H*)-one scaffold which could be synthesized by a typical Sonogashira coupling on the corresponding 5-alo-7,8-dimethoxyquinolin-4(1*H*)-one. At the end of our retrosynthetic plan, the starting compound could be the inexpensive and commercially available 2,3-dihydroxybenzoic acid. Preliminary studies are in progress in our research group.



Scheme 8.1 – Our retrosynthetic analysis to Aaptamine.

Another possible development of this work is the synthesis of new propargyl substrates to subject to our domino transformations. Whereas the insertion of an alkynyl group in the benzaldehyde *ortho* position is a widely known reaction, the introduction of a propargyl group in the same position is more difficult, and in the literature only few examples are reported[8] and no general synthetic procedures have so far been described in depth. So, after the optimisation of a new MW-promoted robust method for the synthesis of *ortho*-propargyl benzaldehydes and *ortho*-propargyl acyl-arenes we intend to investigate the reactivity of these new substrates taking advantage of domino protocols reported in this thesis (Scheme 8.2). .



Scheme 8.2 – Reactivity of propargyl-homologous.

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