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Synthesis of 3-benzylisoquinolines by domino imination/cycloisomerisation of 2-propargyl-benzaldehydes†

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An easy entry to uncommon 2-propargylbenzaldehydes was developed. 2-Propargylbenzaldehydes demonstrated to be suitable building blocks for the synthesis of 3-benzyl isoquinolines by microwave promoted domino imination/cycloisomerisation in the presence of ammonium acetate. A small library of 3-benzyl isoquinolines was obtained in good yields under mild reaction conditions. Two alternative plausible reaction mechanisms are proposed.

Introduction

During the past twenty years, many researchers have been fascinated by the development of new domino[1] strategies for the synthesis of heterocyclic compounds,[2] a field of research in constant evolution. A domino reaction is a process involving two or more bond-forming transformations taking place under the same reaction conditions without adding additional reagents and catalysts. The subsequent reactions are a consequence of the functionalities formed in the previous steps. The possibility of building up simple and complex heterocycles starting from easily achievable building blocks by a single sequential transformation is something deeply fascinating for all synthetic chemists.

For many years, we have been interested in the development of new sequential synthetic strategies for the construction of oxygen- or nitrogen-containing heterocycles starting from alkyne derivatives bearing a proximate carbonyl group. In particular, we have employed the addition/cycloisomerisation reactions of 2-alkynylbenzaldehydes (and their related heteroaromatic systems) in the presence of simple oxygen or nitrogen nucleophiles as useful tools to synthesise some interesting compounds such as isoquinolines,[3] dihydroisobenzofurans,[4] and isochromenes.[5]

Moreover, the domino approaches to dihydroisobenzofurans and isoquinolines have also been successfully transformed in two valuable Pd-catalysed multicomponent processes involving a one-pot coupling/addition/cyclisation sequence starting from simple building blocks, *i.e.*, *ortho*-bromoarylaldehydes, terminal alkynes and a nucleophile, methanol[6] or ammonia,[7] respectively.

In order to extend the scope of our research, we have recently explored the reactivity of 2-alkynylacetophenones (keto-homologues of the 2-alkynylbenzaldehydes) and their pyridine analogues. We have found that the imination/annulation reactions of these less reactive substrates with ammonia needed a promoter, and silver triflate proved to be the preferred catalyst for these transformations, yielding the expected N-cyclisation products in addition to variable amounts of the isomeric carboannulation products.[8]

After having obtained these interesting results, we were intrigued by the idea of preparing some 2-propargylbenzaldehydes and to test their reactivity in the domino transformations described above. While the coupling of an alkynyl group in the *ortho* position of an *ortho*-haloarylaldehyde is a simple and well-known Pd-catalysed procedure, the introduction of a propargyl group in the same position is much more challenging, and only a few examples are reported in the literature.[9] The most acknowledged approach was described by Eberbach and co-workers[9a,b] in 2000. The method includes five synthetic steps starting from the 2-bromobenzaldehyde. The first step of the approach involves the protection of the carbonyl group as a cyclic acetal, followed by a coupling reaction between the lithiated acetal derivative and the 3-bromo-1-(trimethylsilyl)-1-propyne. The triple bond is then deprotected by fluoride promoted desilylation, and functionalized by a Sonogashira coupling or by a base promoted nucleophilic substitution with methyl bromide. Finally, the acid promoted deprotection of the aldehyde gives the desired product. This is a useful and

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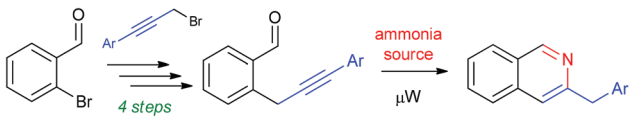
elegant method, and yet it presents some drawbacks: (1) the lithiation reaction is often a troublesome step requiring strictly controlled conditions; (2) the 3-bromo-1-(trimethylsilyl)-1-propyne is a rather expensive starting material; (3) the desilylation of the TMS-protected propargyl intermediate can experience scarce reproducibility (when fluoride promoted) or can give the isomeric allene (when base promoted).

Owing to the lack of general methods for the preparation of 2-propargyl arylaldehydes, the reactivity of these superior homologues of 2-alkynyl benzaldehydes has been less explored. For example, Eberbach and his co-workers have employed the 2-propargylbenzaldehydes as key-intermediates in the synthetic route to 2-propargylaryl nitrones, thus leading the way to the synthesis of the 1,2-dihydro[*c*]benzazepin-3-ones.[9a,b] On the other hand, Yamamoto's research group has documented the synthesis of important frameworks starting from these substrates. In 2010, they discovered an efficient metallic catalyst-free benzannulation with dialkylamines giving rise to various 2-dialkylaminonaphthalenes,[10] and two years later they developed a smart synthetic approach to 2,3-dihydro-*1H*-inden-1-one derivatives through a Ni-catalysed intramolecular hydroacylation of 2-propargylbenzaldehydes.[11]

The 1-oxo-5-ynes are a class of related propargyl-based substrates, bearing a mandatory oxy group in the propargylic position. Liu and co-workers have described a highly stereoselective Au-catalysed synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes from diverse 1-oxo-4-oxy-5-ynes.[12] In 2013, a namesake of Liu (and his co-workers) proposed a new synthetic route to indeno[1,2-*b*]quinolones by reactions of 2-propargylbenzaldehydes with *N*-aryl amines based on an intramolecular aza-Diels–Alder (Povarov) reaction.[13]

In this work, we describe a general and effective approach to 2-propargylbenzaldehydes and their participation in microwave promoted domino addition/cycloisomerisation reactions in the presence of ammonia for the synthesis of 3-benzylisoquinolines (Scheme 1).

The isoquinoline nucleus is the core of various biologically active compounds, such as the alkaloid papaverine and the anaesthetic quinisocaine (Fig. 1). Saturated, functionalized and polycyclic isoquinolines show different important pharmacological properties;[14] moreover, some simple 3-benzyl isoquinolines are also significantly active, and may be useful as lead compounds for developing potential chemotherapeutic agents. For example, some 1- and 3-benzylisoquinolines (*e.g.*, 6,7-dimethoxy-3-veratryl-isoquinoline) and the corresponding quaternary salts have been tested for antimicrobial, antimalarial, cytotoxic, and anti-HIV activities.[15] On top of this, the 3-benzylisoquinoline structure is the skeleton of some patented



Scheme 1 Synthesis of 2-propargylbenzaldehydes and 3-benzylisoquinolines.

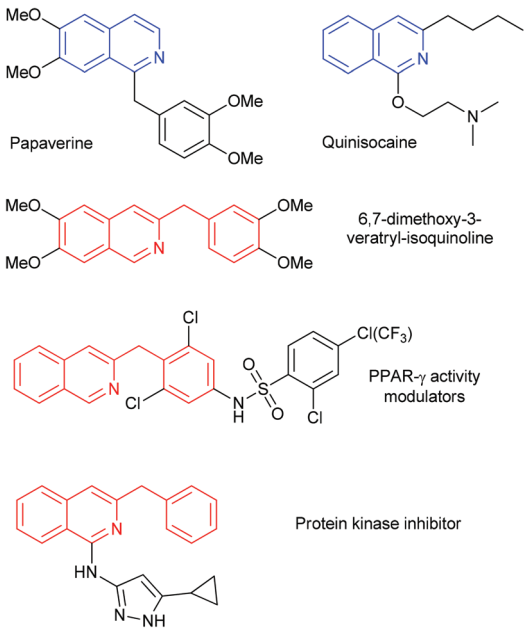


Fig. 1 Some examples of biologically active isoquinolines.

compounds, such as the PPAR-γ activity modulators[16] proposed for the treatment of conditions such as type II diabetes and obesity, and the protein kinase inhibitors[17] proposed for treating cancer, diabetes and Alzheimer's disease (Fig. 1).

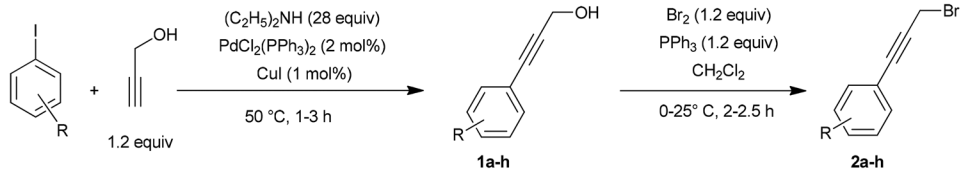
Results and discussion

With Eberbach's seminal work in mind, we developed an alternative strategy, in order to simplify the preparation of the propargylic scaffolds. The peculiar feature of our approach is the preliminary preparation of properly substituted propargyl bromides **2**: this implies avoiding the use of expensive (3-bromoprop-1-yn-1-yl)trimethylsilane and the subsequent desilylation step. Compounds **2a–h** were prepared in two steps: first of all, the cheap and easily available propargyl alcohol was functionalized by reaction with various aryl iodides under standard Sonogashira cross-coupling conditions[18] to give the substituted propargyl alcohols **1a–h**, used in some cases for the subsequent step without the need of a chromatographic purification. The compounds **1a–h** were then reacted with bromine and triphenylphosphine[19] to give the desired substituted propargyl bromides **2a–h** (Table 1).

The Sonogashira coupling did not seem to be strongly influenced by the nature of substituents on the phenyl ring; in fact, the yields of the reactions were in general very good for both electron-rich and electron-poor aryl iodides (entries 1–7). The presence of a group in the *ortho*-position of the aryl moiety was well tolerated too (entries 6–8). Conversely, in the bromination step, the presence of stronger EWGs on the aryl moiety gave low yields (entries 4 and 5).

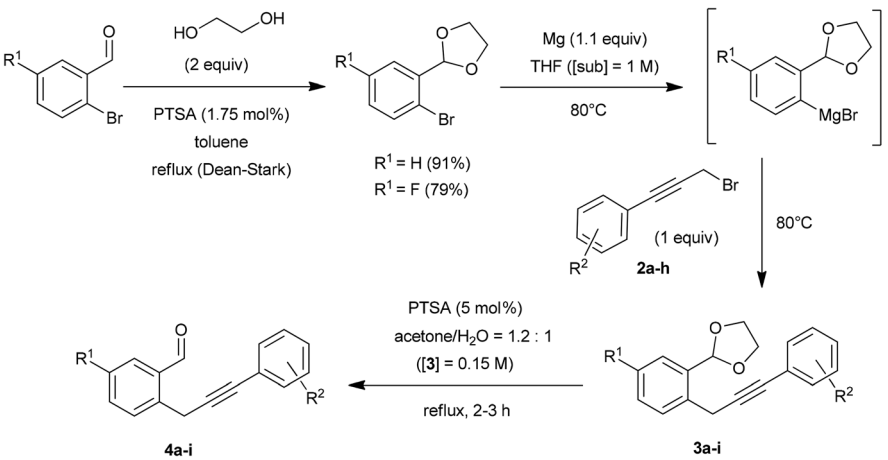
We then optimised the coupling step between the 2-bromobenzaldehyde partner and the substituted propargyl bromides

Table 1 Preparation of propargyl bromides



Entry	**1, 2**	**R**	*t* (h) step 1	**1** Yield[a] (%)	*t* (h) step 2	**2** Yield[a] (%)
1	**a**	H	1.0	99[b]	2.0	81[d]
2	**b**	4-Cl	1.5	99[b]	2.0	90[d]
3	**c**	4-CH_3	2.0	99[b]	2.0	99[d]
4	**d**	4-SO_2CH_3	3.0	77[c]	2.0	57[c]
5	**e**	3-CF_3	2.0	99[b]	2.5	59[d]
6	**f**	2-C_2H_5	3.0	87[c]	2.5	68[c]
7	**g**	2-CH_3, 3-Cl	3.0	99[c]	2.5	81[d]
8	**h**	2-(i-Pr)	2.0	95[c]	2.0	85[c]

[a] Yields refer to pure isolated products. [b] Yields after simple work-up. [c] Yields after column chromatography. [d] Yields after filtration on a short silica pad.



Scheme 2 Optimised sequence for the synthesis of 2-propargylbenzaldehydes **4**.

through a Grignard reaction: this allowed us to skip the annoying lithiation step described in the Eberbach approach. We protected the 2-bromobenzaldehyde and the 5-fluoro-2-bromobenzaldehyde as cyclic acetals by treating them with ethylene glycol and *p*-toluenesulfonic acid in toluene at reflux. Then, a stirred solution of properly protected benzaldehyde in anhydrous tetrahydrofuran and magnesium turnings was heated at 80 °C under a protective nitrogen atmosphere. Once the magnesium was almost completely dissolved, we slowly added the suitable substituted propargyl bromides **2a–h**, and the reaction mixture was heated at 80 °C to give the 2-propargylbenzaldehyde acetals **3a–i**. These intermediates were then hydrolysed to give the corresponding 2-propargylbenzaldehydes **4a–i** by treatment with *p*-toluenesulfonic acid in a mixture of water and acetone at reflux (Scheme 2).

The key step of this procedure is the Grignard coupling reaction between 2-bromobenzaldehyde acetals and substituted propargyl bromides **2** (Table 2). The concentration of aryl bromide was found to be critical,[20] and the best results were obtained using 1 M solution of the aryl bromide in tetrahydrofuran, while using a more diluted solution resulted in worse reproducibility and longer reaction times. The majority of the yields of the reactions ranged from fair to very good with all aryl propargyl bromides, while worse results were obtained in the presence of a methylsulfonyl group on arylalkyne terminus (entry 4), or of a fluorine atom on the benzaldehyde moiety (entry 9). In addition, the presence of a bulky group in the *ortho* position of the aryl iodide resulted in reduced yields (entry 8).

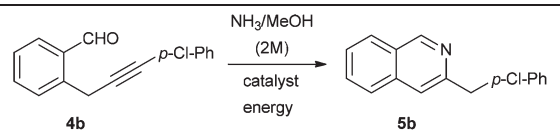
We also explored the Grignard coupling step under microwave heating.[21] Arylmagnesium species can be efficiently generated from magnesium turnings and aryl bromides (or chlorides) under dielectric heating.[20] The reactions performed under dielectric heating were faster and the yields of **3** were comparable to those observed under traditional heating (see footnote entries 1–3 and 5). In the end, however, as the

Table 2 Grignard coupling reactions and deprotection of an aldehyde group

Entry	3, 4	R^1	R^2	t (h) step 1	3 Yield[a] (%)	t (h) step 2	4 Yield[f] (%)
1	**a**	H	H	3.0	61[b]	2.0	85
2	**b**	H	4-Cl	3.0	81[c]	2.0	94
3	**c**	H	4-CH_3	3.0	68[d]	2.0	96
4	**d**	H	4-SO_2CH_3	4.0	32	2.0	82
5	**e**	H	3-CF_3	4.0	76[e]	2.0	78
6	**f**	H	2-C_2H_5	4.0	79	2.0	89
7	**g**	H	2-CH_3, 3-Cl	4.0	77	3.0	89
8	**h**	H	2-(i-Pr)	3.0	38	2.5	82
9	**i**	F	4-Cl	5.5	54	3.0	78

[a] Yields refer to pure isolated products after flash column chromatography on a short silica gel column. [b] Under μW approach: reaction time, 50 min; yield, 70%. [c] Under μW approach: reaction time, 50 min; yield, 65%. [d] Under μW approach: reaction time, 50 min; yield, 64%. [e] Under μW approach: reaction time, 50 min; yield, 56%. [f] Yields refer to the pure isolated product after flash column chromatography.

Table 3 Screening of reaction conditions with methanolic ammonia



4b 5b

Entry	Catalyst (mol%)	Energy – T (°C)	t (min)	5b Yield (%)
1	—	μW – 100	10	36[a]
2	4 Å mol. sieves	μW – 100	20	14[a]
3	AgOTf (10)	μW – 100	10	41[b]
4	AgOTf (10)	Oil bath – 60	360	51[b]
5	AgOTf (10)	μW – 100	10	48[a]
6	$TiCl_4$ (50)	μW – 100	10	34[a]
7	$TiCl_2(Indenyl)_2$ (5)	μW – 100	10	47[a]
8	$InCl_3$ (10)	μW – 100	20	49[a]
9	$NaAuCl_4$ (5)	μW – 80	40	36[a]
10	$AuCl_3$ (5)	μW – 100	50	46[a]
11	$Au(PPh_3)NTf_2$ (3)	μW – 100	10	42[b]

[a] Yields calculated *via* ^{1}H NMR using dimethyl terephthalate (DMT) as an internal standard. [b] Yields refer to pure isolated products.

microwave approach presented some reproducibility problems we decided to choose conventional heating as the standard procedure, because this enabled an easier control of the reaction progress. The dioxolane intermediates **3** were not so stable, in particular at room temperature and in the presence of a slightly acidic solvent (*i.e.*, deuterochloroform); therefore, after a quick ^{1}H NMR and MS characterization, they were directly hydrolysed into the corresponding aldehydes **4** with yields ranging from good to excellent.

Having optimized an effective entry to 2-propargylbenzaldehydes **4**, we then explored the reactivity of these starting materials to synthesise 3-benzylisoquinolines. At first, we screened the optimal reaction conditions on the 2-propargylbenzaldehyde **4b** as a model substrate in the presence of methanolic ammonia[3] (Table 3).

We then ran the reaction under the conditions previously adopted for the addition/cycloisomerisation reactions of 2-alkynylbenzaldehydes (*i.e.*, 20 equiv. of NH_3).[3] This uncatalysed reaction at 100 °C under microwave heating gave the corresponding isoquinoline **5b** in low yield (entry 1). A tentative approach to promote the formation of the imine intermediate by the use of molecular sieves did not result in any improvement (entry 2). Based on our previous experience with 2-alkynylacetophenones,[8] we planned to catalyse the reaction with AgOTf (10 mol%) both under dielectric and conventional heating conditions (entries 3–5). Under conventional heating the reaction yield raised to 51% in 6 h at 60 °C (entry 4), while under microwave heating at 100 °C the reaction gave almost the same yield in only 10 minutes (entry 5). Aiming to improve the yield, we tried some other metal catalysts potentially able to promote the reaction. Following the procedure previously optimised in our laboratory for the imination/annulation of 2-acetyl and 2-benzoyl *N*-propargylindoles[22] and 2-acetyl-*N*-propargylpyrroles,[3] we tried to catalyse the reaction with 0.5 equiv. of titanium tetrachloride, but these conditions gave poor yields (entry 6), while in the presence of a catalytic amount of $TiCl_2(indenyl)_2$ the desired product was obtained in 47% yield (entry 7). Using $InCl_3$ as the catalyst gave comparable yield to the best results obtained in this screening (*cf.* entries 8, 4 and 5). We also tested some gold-based catalysts, well renowned as an alkynophilic Lewis acid, but the results were still unsatisfactory (entries 9–11).[23]

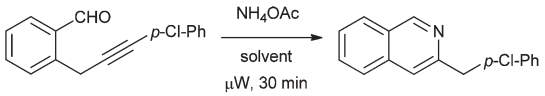
The homogeneous – but not completely satisfactory – results obtained under metal catalysis suggested that the tricky point of the approach was not the activation of the triple bond but, more probably, the nature of the nitrogen partner: this prompted us to try different ammonia sources.

In the existing literature, several ammonium salts are listed as alternative ammonia sources (*e.g.*, $(NH_4)_2CO_3$, NH_4HCO_3, HCO_2NH_4), and NH_4OAc proved to be the most effective among them.[24] Ammonium acetate is the salt of a weak acid (acetic acid) and a weak base (ammonia), and therefore it is easily decomposed by heat to AcOH and NH_3. On top of this, ammonium acetate is a practical choice because it is an inexpensive and easy-to-handle solid. It has been employed only two times in the isoquinoline synthesis, that is in the cyclisation of 2-(1,1-difluoroalkenyl)-benzaldehyde[25] and, more recently, in a Pd-catalysed multicomponent approach starting from 2-bromobenzaldehydes and terminal alkynes.[26] However, the reactivity of the 2-propargylbenzaldehydes with ammonium acetate is unprecedented.

For this reason, we screened the optimal reaction conditions for the synthesis of 3-benzylisoquinolines with ammonium acetate as the ammonia source, and the results are shown in Table 4.

It has been reported that a large excess of NH_4OAc is necessary for an effective ammonia generation,[27] so the first experiment was performed with 20 equiv. of NH_4OAc in ethanol at 120 °C under microwave irradiation. After 30 minutes, the reaction gave the desired product **5b** in a promising 68% yield (entry 1). Then, we tried the reaction in

Table 4 Screening of reaction conditions with ammonium acetate

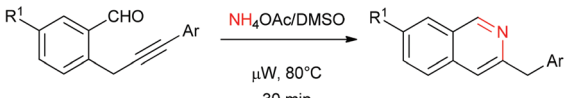


4b **5b**

Entry	NH_4OAc	Solvent	T (°C)	**5b** Yield (%)
1	20 equiv.	EtOH	120	68[a]
2	20 equiv.	DMSO	120	83[a]
3	10 equiv.	DMSO	120	79[a]
4	**20 equiv.**	**DMSO**	**80**	**99**[a]
5	20 equiv.	H_2O	80	—
6	20 equiv.	H_2O–EtOH (3 : 1)	80	—
7	20 equiv.	H_2O–DMSO (3 : 1)	80	—

[a] Yields calculated *via* ^{1}H NMR using dimethyl terephthalate (DMT) as an internal standard.

Table 5 Scope and limitation of the approach



4a-i **5a-i**

Entry	**4, 5**	$\mathbf{R^1}$	Ar	**5** Yield[a] (%)
1	**a**	H	Ph-	78
2	**b**	H	4-Cl-Ph-	93
3	**c**	H	4-CH_3-Ph-	74
4	**d**	H	4-SO_2CH_3-Ph-	67
5	**e**	H	3-CF_3-Ph-	81
6	**f**	H	2-C_2H_5-Ph-	71
7	**g**	H	(2-CH_3, 3-Cl)-Ph-	83
8	**h**	H	2-(i-Pr)-Ph-	76
9	**i**	F	4-Cl-Ph-	71

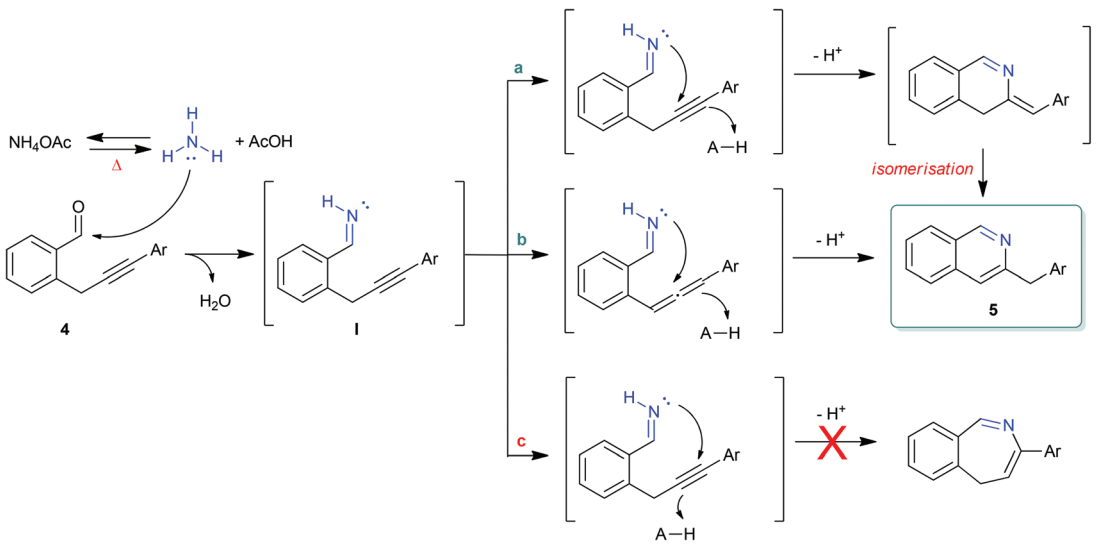
[a] Yields refer to pure isolated products.

DMSO[27b] and we were pleased to observe a good rise in yield (entry 2). The reduction of the amount of ammonium acetate to 10 equiv. gave only a modest reduction of the reaction yield (entry 3). Conversely, an excellent rise in yields was observed when we lowered the temperature (entry 4). Aiming to make the approach more environmentally-friendly, we tried to use water as the solvent (entry 5), but all our attempts were unsuccessful, also in the presence of EtOH or DMSO as co-solvents (entries 6 and 7).

Working under the best available conditions, we investigated the scope and the limitation of the approach. The results are shown in Table 5.

This microwave-enhanced protocol proved to be a general route for the synthesis of an array of isoquinolines in very good yields (entries 1–9). Both electron-donating and electron-withdrawing substituents were allowed on the phenyl group at alkynyl terminus (entries 1–5). The presence of a bulky substituent in the *ortho* position of the arylalkyne moiety did not seem to affect the reaction course (entries 6–8). Moreover, the presence of a fluorine group on the benzaldehyde moiety was also well tolerated (entry 9). All the reactions were clean and complete within 30 minutes, and the final products were easily and quickly purified by flash column chromatography. All the products have been fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, as well as by MS spectrometry.

In accordance with our previous findings,[28] we proposed a tentative reaction mechanism in which two different pathways are feasible (Scheme 3). The first step, the *in situ* formation of an imine intermediate (**I**) by reaction of 2-propargylbenzaldehydes **4** with the ammonia obtained by thermal cleavage of ammonium acetate, is common to both paths. To explain the cycloisomerisation step there are two conceivable pathways: (a) the triple bond undergoes a 6-*exo-dig* cyclisation directly by the imine, and the subsequent isomerisation leads to the formation of the final product **5**; (b) the reaction conditions (heat and ammonia) promote the isomerisation of the triple bond to



Scheme 3 Proposed reaction mechanism.

allene,[29] thus allowing the intramolecular attack of the nucleophile on the central carbon of the allene framework[30] with direct formation of the isoquinoline **5**. On top of this, the regiospecificity observed is probably due to the resonance stabilization of the six-membered cyclisation product with respect to the alterative seven-membered one. As proof of that, the 7-*endo-dig* cyclisation mode is quite uncommon in the literature (c).[31]

Conclusions

We have developed a new, easy and effective access to neglected 2-propargylbenzaldehydes. These building blocks proved to be suitable substrates for domino addition/cycloisomerisation reactions in the presence of a nitrogen nucleophile. The synthesis of the 3-benzylisoquinoline nucleus was achieved in an easy way and in very good yields by a microwave enhanced methodology. Ammonium acetate proved to be the most effective nitrogen source for this purpose. This approach represents a useful, simple and unprecedented alternative access to the 3-benzylisoquinoline skeleton, which is an important framework in a number of different molecules of biological interest.

Experimental

General experimental details

All the reactions that involve the use of reagents sensitive to oxygen or hydrolysis were carried out under an inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under a nitrogen atmosphere. Some solvents, used for reactions sensitive to oxygen and hydrolysis, were distilled and stored under a protected atmosphere of nitrogen, according to the following standard operations: dichloromethane: distilled on $CaCl_2$ and placed on 4 Å sieves into a recycling appliance. Anhydrous THF, DMSO and ethanol are commercially available. The chromatographic column separations were conducted by the flash technique, using silica gel Davisil LC 60 Å (230–400 mesh). For thin-layer chromatography (TLC), silica gel 60 F254 FLUKA thin-layer plates were employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 366 nm). ^{1}H NMR analyses were performed with a Varian-Gemini 200 at 200 MHz at room temperature. The coupling constants (J) are expressed in hertz (Hz) and the chemical shifts (δ) in ppm. The multiplicity of the proton spectra was described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dt (double triplet), dd (double doublet), ddd (double double doublet), m (multiplet). ^{13}C NMR analyses were performed with the same instruments at 50.3 MHz; an APT sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. Infrared spectra were recorded with a Perkin Elmer FT-IR 16 PC spectrometer, using discs of NaCl for liquid samples and KBr tablets for solid samples. The absorbance is reported in wavenumbers (cm^{-1}) with values between 4000 and 400 cm^{-1}. Low resolution MS spectra were recorded with a Fisons MD 800 spectrometer with an electron impact source and a Thermo-Finnigan LCQ-advantage AP electrospray/ion trap equipped instrument, using a syringe pump device to directly inject sample solutions. The values are reported as the mass–charge ratio and the relative intensities of the most significant peaks are shown in brackets. High resolution MS spectra were recorded with an instrument equipped with an electrospray source and an ICR-FTMS analyser. The melting points of the solid products were measured with a Stuart Scientific SMP3 apparatus and are uncorrected. Microwave promoted reactions were performed with a single-mode Personal Chemistry microwave synthesizer "Emrys Creator," using sealed glass vessels. The temperature was detected with an infrared sensor.

General procedure for the synthesis of aryl propargyl alcohols (1a–h)

Under a nitrogen atmosphere, to a solution of the appropriate aryl iodide (6.00 mmol) in DEA (18 mL), propargyl alcohol (403.8 mg, 0.419 mL, 7.20 mmol) and *trans*-dichlorobis(triphenylphosphine)palladium(II) (84.3 mg, 0.120 mmol) were added. The reaction was stirred at room temperature for 15 min, and then CuI (12.0 mg, 0.063 mmol) was added. The reaction mixture was stirred at 50 °C until no starting product was detectable by TLC analysis (eluent: hexane–ethyl acetate = 95 : 5). After cooling to room temperature, the mixture was concentrated under reduced pressure, poured in a HCl 0.1 N aq. solution (60 mL) and extracted with diethyl ether (3 × 40 mL). The organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Unless otherwise stated, the compounds were used without the need for chromatographic purification.

3-Phenylprop-2-yn-1-ol (1a). Reaction time: 1 h. Yield: 785 mg (99%). Brown oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.95 (bs, 1H, OH), 4.50 (s, 2H, CH_2), 7.29–7.33 (m, 3H, H_{Ar}), 7.43–7.45 (m, 2H, H_{Ar}). These data are in good agreement with literature values.[32]

3-(4-Chlorophenyl)prop-2-yn-1-ol (1b). Reaction time: 1.5 h. Yield: 989 mg (99%). Brown solid. Mp 74–77 °C (lit. 76–78 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.20 (bs, 1H, OH), 4.49 (s, 2H, CH_2), 7.28 (d, J = 8.5 Hz, 2H, H_{Ar}), 7.36 (d, J = 8.5 Hz, 2H, H_{Ar}). These data are in good agreement with literature values.[33]

3-(*p*-Tolyl)prop-2-yn-1-ol (1c). Reaction time: 2 h. Yield: 868 mg (99%). Yellow wax. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (bs, 1H, OH), 2.34 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.10 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.33 (d, J = 8.1 Hz, 2H, H_{Ar}). These data are in good agreement with literature values.[34]

3-(4-(Methylsulfonyl)phenyl)prop-2-yn-1-ol (1d). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (5 : 5). Yield: 971 mg (77%). Light brown solid. Mp 81–82 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.41 (bs, 1H, OH), 3.04 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 7.53 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.85 (d, J =

8.1 Hz, 2H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.6 (CH_3), 51.5 (CH_2), 83.9 (C_{sp}), 91.9 (C_{sp}), 127.5 (CH_{Ar}), 128.8 (C_q), 132.6 (CH_{Ar}), 140.0 (C_q). ESI-MS *m/z* (%): 211.2 (45) $[M + H]^+$, 233.1 (60) $[M + Na]^+$, 242 (100) $[M + CH_3OH + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{10}H_{11}O_3S$ 211.0423, found 211.424.

3-(3-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (1e). Reaction time: 2 h. Yield: 1.19 g (99%). Light yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.03 (s, 1H, OH), 4.51 (s, 2H, CH_2), 7.39–7.46 (m, 1H, H_{Ar}), 7.52–7.59 (m, 2H, H_{Ar}), 7.68 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 51.7 (CH_2), 84.4 (C_{sp}), 89.1 (C_{sp}), 123.8 (C_q), 123.9 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3), 125.2 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 128.7 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 129.0 (CH_{Ar}), 131.2 (q, $^2J_{C-F}$ = 33.0 Hz, C_q), 134.9 (CH_{Ar}). ESI-MS *m/z* (%): 223.1 (100) $[M + Na]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{10}H_8F_3O$ 201.0522, found 201.0520.

3-(2-Ethylphenyl)prop-2-yn-1-ol (1f). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (9 : 1). Yield: 836 mg (87%). Light yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.5 Hz, 3H, CH_3), 1.81 (bs, 1H, OH), 2.80 (q, *J* = 7.5 Hz, 2H, CH_2), 4.54 (s, 2H, CH_2), 7.09–7.31 (m, 3H, H_{Ar}), 7.41 (d, *J* = 7.5 Hz, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.0 (CH_3), 27.8 (CH_2), 52.0 (CH_2), 84.6 (C_{sp}), 90.8 (C_{sp}), 121.8 (C_q), 125.8 (CH_{Ar}), 128.1 (CH_{Ar}), 128.9 (CH_{Ar}), 132.6 (CH_{Ar}), 146.5 (C_q). ESI-MS *m/z* (%): 301 (52) $[dimer - H_2 - H_2O + H]^+$, 303 (32) $[dimer - H_2O + H]^+$, 339 (100) $[dimer + H_2O + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{11}H_{13}O$ 161.0961, found 161.0959.

3-(3-Chloro-2-methylphenyl)prop-2-yn-1-ol (1g). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (9 : 1). Yield: 1.07 g (99%). Light brown solid. Mp: 54–59 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.71 (bs, 1H, OH), 2.50 (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 7.06 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.32 (d, *J* = 7.9 Hz, 2H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 18.5 (CH_3), 51.8 (CH_2), 84.2 (C_{sp}), 91.9 (C_{sp}), 124.5 (C_q), 126.7 (CH_{Ar}), 129.7 (CH_{Ar}), 130.9 (CH_{Ar}), 134.9 (C_q), 138.3 (C_q). ESI-MS *m/z* (%): 145.1 (50) $[M - Cl]^+$, 164.8 (100) $[M - H_2O + H]^+$, 180.9 (75) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{10}H_{10}ClO$ 181.0415, found 181.0413.

3-(2-Isopropylphenyl)prop-2-yn-1-ol (1h). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (9 : 1). Yield: 994 mg (95%). Brown oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 7.0 Hz, 6H, CH_3), 3.44 (sept, *J* = 7.0 Hz, 1H, CH), 4.54 (s, 2H, CH_2), 7.08–7.17 (m, 1H, H_{Ar}), 7.26–7.30 (m, 2H, H_{Ar}), 7.41 (d, *J* = 7.3 Hz, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.4 (CH_3), 31.7 (CH), 51.9 (CH_2), 84.6 (C_{sp}), 91.1 (C_{sp}), 121.5 (C_q), 125.2 (CH_{Ar}), 125.7 (CH_{Ar}), 129.1 (CH_{Ar}), 132.8 (CH_{Ar}), 150.8 (C_q). ESI-MS *m/z* (%): 174.2 (10) $[M]^+$, 234.4 (100) $[M + AcOH]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{12}H_{15}O$ 175.1117, found 175.1119.

General procedure for the synthesis of aryl propargyl bromides (2a–h)

Triphenylphosphine (3.93 g, 15.0 mmol) was dissolved in dichloromethane (40 mL). Bromine (2.40 g, 15.0 mmol) was then added dropwise at 0 °C and stirred for 30 min. The appropriate functionalized propargyl alcohols **1a–h** (12.5 mmol) were added at 0 °C and the reaction mixture was stirred until no starting product was detectable by TLC analysis (eluent: hexane–ethyl acetate = 9 : 1). Hexane (130 mL) was added to precipitate the phosphine oxide and the white suspension was passed through a short silica pad (3 cm diameter × 2 cm height) and washed with hexane. The crude product was freed from solvents under reduced pressure. Unless otherwise stated, the compounds were used without the need of chromatographic purification.

(3-Bromoprop-1-yn-1-yl)benzene (2a). Reaction time: 2 h. Yield: 1.97 g (81%). Light yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.17 (s, 2H, CH_2), 7.31–7.36 (m, 3H, H_{Ar}), 7.43–7.48 (m, 2H, H_{Ar}). These data are in good agreement with literature values.[35]

1-(3-Bromoprop-1-yn-1-yl)-4-chlorobenzene (2b). Reaction time: 2 h. Yield: 2.58 g (90%). Colourless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.14 (s, 2H, CH_2), 7.29 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.37 (d, *J* = 8.6 Hz, 2H, H_{Ar}). These data are in good agreement with literature values.[36]

1-(3-Bromoprop-1-yn-1-yl)-4-methylbenzene (2c). Reaction time: 2 h. Yield: 2.59 g (99%). Light yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 7.12 (d, *J* = 7.8 Hz, 2H, H_{Ar}) 7.34 (d, *J* = 7.8 Hz, 2H, H_{Ar}). These data are in good agreement with literature values.[37]

1-(3-Bromoprop-1-yn-1-yl)-4-methylsulfonylbenzene (2d). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (6 : 4). Yield: 1.94 g (57%). Brown solid. Mp: 98–102 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.05 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 7.60 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.88 (d, *J* = 8.6 Hz, 2H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.4 (CH_2), 44.6 (CH_3), 84.8 (C_{sp}), 88.4 (C_{sp}), 127.6 (CH_{Ar}), 128.2 (C_q), 132.8 (CH_{Ar}), 140.6 (C_q). ESI-MS *m/z* (%): 217.3 (100) $[M - Br + Na]^+$, 273.2/275.1 (18) $[M + H]^+$, 295.0/297.1 (31) $[M + Na]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{10}H_{10}BrO_2S$ 272.9579, found 272.9581.

1-(3-Bromoprop-1-yn-1-yl)-3-(trifluoromethyl)benzene (2e). Reaction time: 2.5 h. Yield: 1.94 g (59%). Dark yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.15 (s, 2H, CH_2), 7.39–7.50 (m, 1H, H_{Ar}), 7.54–7.65 (m, 2H, H_{Ar}), 7.70 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.6 (CH_2), 85.2 (C_{sp}), 86.0 (C_{sp}), 123.4 (C_q), 123.8 (q, $^1J_{C-F}$ = 272.8 Hz, CF_3), 125.6 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 128.9 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 129.1 (CH_{Ar}), 131.3 (q, $^2J_{C-F}$ = 33.0 Hz, C_q), 135.1 (CH_{Ar}). ESI-MS *m/z* (%): 206.4 (100) $[M - Br + Na]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{10}H_7BrF_3$ 262.9678, found 262.9681.

1-(3-Bromoprop-1-yn-1-yl)-2-ethylbenzene (2f). Reaction time: 2.5 h. Eluent for chromatography: hexane–EtOAc (9 : 1). Yield: 1.90 g (68%). Light yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.6 Hz, 3H, CH_3), 2.80 (q, *J* = 7.6 Hz, 2H, CH_2), 4.21 (s, 2H, CH_2), 7.07–7.34 (m, 3H, H_{Ar}), 7.41 (dd, *J* = 7.4, 1.1 Hz, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.1 (CH_3), 15.7 (CH_2), 27.8 (CH_2), 86.0 (C_{sp}), 87.7 (C_{sp}), 121.5 (C_q), 125.8 (CH_{Ar}), 128.2 (CH_{Ar}), 129.3 (CH_{Ar}), 132.7 (CH_{Ar}), 147.0 (C_q). ESI-MS *m/z* (%): 143.1 (75) $[M - Br]^+$, 447 (100) $[dimer + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{11}H_{12}Br$ 223.0117, found 223.0120.

1-(3-Bromoprop-1-yn-1-yl)-3-chloro-2-methylbenzene (2g). Reaction time: 2.5 h. Yield: 2.47 g (81%). Yellow solid. Mp:

60–65 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 7.07 (t, J = 7.6 Hz, 1H, H_{Ar}), 7.32 (d, J = 7.6 Hz, 2H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.1 (CH_2), 18.4 (CH_3), 85.3 (C_{sp}), 88.7 (C_{sp}), 124.1 (C_q), 126.7 (CH_{Ar}), 130.0 (CH_{Ar}), 130.9 (CH_{Ar}), 135.0 (C_q), 138.7 (C_q). ESI-MS m/z (%): 649.5 (100) [trimer − Br + H]$^+$. HRMS ESI [M + H]$^+$ calcd for $C_{10}H_9BrCl$ 242.9571, found 242.9576.

1-(3-Bromoprop-1-yn-1-yl)-2-isopropylbenzene (2h). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (9 : 1). Yield: 2.52 g (85%). Light brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (d, J = 7.0 Hz, 6H, CH_3), 3.41 (sept, J = 7.0 Hz, 1H, CH), 4.21 (s, 2H, CH_2), 7.09–7.17 (m, 1H, H_{Ar}), 7.26–7.32 (m, 2H, H_{Ar}), 7.40 (d, J = 7.3 Hz, 1H, H_{Ar}).^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.8 (CH_2), 23.3 (CH_3), 31.8 (CH), 86.0 (C_{sp}), 87.9 (C_{sp}), 121.1 (C_q), 125.2 (CH_{Ar}), 125.7 (CH_{Ar}), 129.4 (CH_{Ar}), 132.8 (CH_{Ar}), 151.3 (C_q). ESI-MS m/z (%): 157.4 (100) [M − Br]$^+$. HRMS ESI [M + H]$^+$ calcd for $C_{12}H_{14}Br$ 237.0273, found 237.0277.

General procedure for the synthesis of 2-(2-bromophenyl)-1,3-dioxolanes

Ethylene glycol (1.80 g, 1.62 mL, 29.0 mmol) and *p*-toluenesulfonic acid·H_2O (50 mg, 0.26 mmol) were added to a solution of 2-bromobenzaldehyde or 2-bromo-5-fluorobenzaldehyde (14.5 mmol) in toluene (40 mL). The mixture was heated at reflux in a Dean–Stark apparatus for 3 hours. After cooling to room temperature, the mixture was washed with a satd aq. $NaHCO_3$ solution (40 mL) and with brine (40 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed at reduced pressure. The residue was purified by flash column chromatography, affording the desired dioxolane derivatives.

2-(2-Bromophenyl)-1,3-dioxolane. Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 3.02 g (91%). Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.05–4.10 (m, 2H, O-CH_2), 4.13–4.18 (m, 2H, O-CH_2), 6.10 (s, 1H, CH), 7.20 (dt, J = 7.3, 1.8 Hz, 1H, H_{Ar}), 7.34 (dt, J = 7.5, 1.4 Hz, 1H, H_{Ar}), 7.58 (dt, J = 7.5, 1.6 Hz, 2H, H_{Ar}). These data are in good agreement with literature values.[38]

2-(2-Bromo-5-fluorophenyl)-1,3-dioxolane. Eluent for chromatography: hexane–EtOAc (9 : 1). Yield: 2.83 g (79%). Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.03–4.10 (m, 2H, O-CH_2), 4.13–4.20 (m, 2H, O-CH_2), 6.04 (s, 1H, CH), 6.95 (tdd, J = 8.5, 3.1, 0.6 Hz, 1H, H_{Ar}), 7.33 (dd, J = 3.1, 9.3 Hz, 1H, H_{Ar}) 7.52 (dd, J = 5.1, 8.7 Hz, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 65.8 (CH_2), 102.2 (d, $^4J_{C-F}$ = 1.1 Hz, CH), 115.3 (d, $^2J_{C-F}$ = 24.4 Hz, CH_{Ar}), 117.0 (d, $^4J_{C-F}$ = 3.0 Hz, C_q), 117.9 (d,^{2} J_{C-F} = 22.9 Hz, CH_{Ar}), 134.5 (d, $^3J_{C-F}$ = 7.6 Hz, CH_{Ar}), 139.2 (d, $^3J_{C-F}$ = 6.9 Hz, C_q), 162.2 (d, $^1J_{C-F}$ = 247 Hz, C–F). ESI-MS m/z (%): 247.2/245.2 (100) [M]$^+$. HRMS ESI [M + H]$^+$ calcd for $C_9H_9BrFO_2$ 246.9764, found 246.9761.

General procedure for the Grignard coupling reaction (3a–i)

Mg turnings were activated by trituration in a mortar. Mg turnings (53 mg, 2.2 mmol) were charged in a reaction flask under a nitrogen atmosphere. An appropriate amount of 1,3-dioxolane derivative (2.0 mmol) was dissolved in THF (2 mL) and added to Mg turnings. The mixture was stirred for 1 h at 80 °C under a nitrogen atmosphere until the Mg was almost completely dissolved. Then the propargyl bromides (**2a–h**) (2.0 mmol) were added and the reaction was stirred at 80 °C until no starting product was detectable by TLC analysis. After cooling to rt, the reaction mixture was poured in a saturated ammonium chloride solution (30 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were washed with brine (40 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude was quickly purified by flash chromatography on a short silica gel column. The dioxolane intermediates were not very stable (in particular at rt or in a slightly acidic solvent such as deuterochloroform), so after ^{1}H NMR and MS characterization they were immediately converted into the corresponding aldehydes.

2-(2-(3-Phenylprop-2-yn-1-yl)phenyl)-1,3-dioxolane (3a). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.32 g (61%). Light brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.01 (s, 2H, CH_2), 4.04–4.10 (m, 2H, O-CH_2), 4.11–4.17 (m, 2H, O-CH_2), 6.07 (s, 1H, CH), 7.22–7.50 (m, 7H, H_{Ar}), 7.53–7.71 (m, 2H, H_{Ar}). These data are in good agreement with literature values.[9a]

2-(2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3b). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.48 g (81%). Light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.99 (s, 2H, CH_2), 4.05–4.09 (m, 2H, O-CH_2), 4.12–4.16 (m, 2H, O-CH_2), 6.05 (s, 1H, CH), 7.24–7.38 (m, 6H, H_{Ar}), 7.61 (m, 2H, H_{Ar}). ESI-MS m/z (%): 299.2 (100) [M + H]$^+$.

2-(2-(3-(*p*-Tolyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3c). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.39 g (68%). Dark yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 4.04–4.10 (m, 2H, O-CH_2), 4.17–4.10 (m, 2H, O-CH_2), 6.07 (s, 1H, CH), 7.06–7.15 (m, 2H, H_{Ar}), 7.27–7.43 (m, 4H, H_{Ar}), 7.52–7.69 (m, 2H, H_{Ar}). ESI-MS m/z (%): 279.3 (100) [M + H]$^+$. These data are in good agreement with literature values.[9a]

2-(2-(3-(4-(Methylsulfonyl)phenyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3d). Reaction time: 4 h. Eluent for chromatography: hexane–EtOAc (7 : 3). Yield: 0.22 g (32%). Light brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.04 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 4.04–4.11 (m, 2H, O-CH_2), 4.11–4.18 (m, 2H, O-CH_2), 6.04 (s, 1H, CH), 7.28–7.48 (m, 3H, H_{Ar}), 7.53–7.65 (m, 3H, H_{Ar}), 7.87 (d, J = 8.5 Hz, 2H, H_{Ar}). ESI-MS m/z (%): 343.5 (100) [M + H]$^+$.

2-(2-(3-(3-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3e). Reaction time: 4 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.51 g (76%). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.01 (s, 2H, CH_2), 4.05–4.11 (m, 2H, O-CH_2), 4.12–4.18 (m, 2H, O-CH_2), 6.06 (s, 1H, CH), 7.29–7.63 (m, 7H, H_{Ar}), 7.70 (s, 1H, H_{Ar}). ESI-MS m/z (%): 333.2 (100) [M + H]$^+$.

2-(2-(3-(2-Ethylphenyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3f). Reaction time: 4 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.46 g (79%). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.6 Hz, 3H, CH_3), 2.83 (q, J =

7.6 Hz, 2H, CH_2), 4.05 (s, 2H, CH_2), 4.06–4.10 (m, 2H, O-CH_2), 4.11–4.18 (m, 2H, O-CH_2), 6.07 (s, 1H, CH), 7.07–7.24 (m, 3H, H_{Ar}), 7.27–7.47 (m, 3H, H_{Ar}), 7.58 (dd, J = 1.8, 7.3 Hz, 1H, H_{Ar}), 7.63–7.72 (m, 1H, H_{Ar}). ESI-MS m/z (%): 293.2 (100) $[M + H]^+$, 263 (20) $[M - CH_2CH_3]^+$.

2-(2-(3-(3-Chloro-2-methylphenyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3g). Reaction time: 4 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.48 g (77%). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 4.06–4.11 (m, 2H, O-CH_2), 4.12–4.17 (m, 2H, O-CH_2), 6.06 (s, 1H, CH), 7.04 (t, J = 7.8 Hz, 1H, H_{Ar}), 7.28–7.44 (m, 4H, H_{Ar}), 7.58 (dd, J = 1.9, 7.3 Hz, 1H, H_{Ar}), 7.63 (dd, J = 1.0, 7.2 Hz, 1H, H_{Ar}). ESI-MS m/z (%): 313.1 (100) $[M + H]^+$.

2-(2-(3-(2-Isopropylphenyl)prop-2-yn-1-yl)phenyl)-1,3-dioxolane (3h). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.23 g (38%). Brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, J = 7.0 Hz, 6H, CH_3), 3.48 (sept, J = 7.0 Hz, 1H, CH), 4.05 (s, 2H, CH_2), 4.02–4.11 (m, 2H, O-CH_2), 4.12–4.17 (m, 2H, O-CH_2), 6.07 (s, 1H, CH), 7.07–7.16 (m, 1H, H_{Ar}), 7.24–7.29 (m, 2H, H_{Ar}), 7.32–7.41 (m, 2H, H_{Ar}), 7.42–7.51 (m, 1H, H_{Ar}), 7.58 (dd, J = 1.8, 7.4 Hz, 1H, H_{Ar}), 7.67 (d, J = 7.1 Hz, 1H, H_{Ar}). ESI-MS m/z (%): 307.2 (100) $[M + H]^+$.

2-(2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-5-fluorophenyl)-1,3-dioxolane (3i). Reaction time: 5.5 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 0.34 g (54%). Light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.92 (s, 2H, CH_2), 4.00–4.09 (m, 2H, O-CH_2), 4.10–4.21 (m, 2H, O-CH_2), 6.03 (s, 1H, CH), 6.99–7.18 (m, 2H, H_{Ar}), 7.21–7.42 (m, 4H, H_{Ar}), 7.54 (dd, J = 5.5, 8.5 Hz, 1H, H_{Ar}). ESI-MS m/z (%): 317.4 (100) $[M + H]^+$.

General procedure for the cleavage of 1,3-dioxolanes

p-Toluenesulfonic acid·H_2O (14 mg, 0.075 mmol) was added to a solution of the an appropriate amount of 1,3-dioxolanes **3a-i** (1.5 mmol) in a mixture of acetone–water = 1.2 : 1 (10 mL). The mixture was refluxed until completion of the reaction (2–3 h), detectable by TLC analysis (eluent: hexane–ethyl acetate 9 : 1). After cooling to rt, satd aqueous $NaHCO_3$ (40 mL) was added and the solution was extracted with diethyl ether (20 × 3). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and the solvent was removed at reduced pressure. The residue was purified by flash chromatography, affording the desired 2-propargylbenzaldehydes **4a–i**.

2-(3-Phenylprop-2-yn-1-yl)benzaldehyde (4a). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 280 mg (85%). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.30 (s, 2H, CH_2), 7.27–7.34 (m, 3H, H_{Ar}), 7.38–7.53 (m, 3H, H_{Ar}), 7.54–7.67 (m, 1H, H_{Ar}), 7.74–7.90 (m, 2H, H_{Ar}), 10.28 (s, 1H, CHO). These data are in good agreement with literature values.[9a]

2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)benzaldehyde (4b). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 359 mg (94%). Light yellow solid. Mp: 64–68 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.29 (s, 2H, CH_2), 7.27 (d, J = 8.7 Hz, 2H, H_{Ar}), 7.37 (d, J = 8.6 Hz, 2H, H_{Ar}), 7.48 (dt, J = 7.4, 1.3 Hz, 1H, H_{Ar}), 7.61 (dt, J = 1.5, 7.5 Hz, 1H, H_{Ar}), 7.76 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.84 (dd, J = 1.4, 7.5 Hz, 1H, H_{Ar}), 10.26 (s, 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.8 (CH_2), 83.0 (C_{sp}), 88.0 (C_{sp}), 122.2 (C_q), 127.7 (CH_{Ar}), 128.8 (CH_{Ar}), 130.2 (CH_{Ar}), 133.1 (CH_{Ar}), 133.5 (C_q), 134.0 (CH_{Ar}), 134.2 (C_q), 134.3 (CH_{Ar}), 138.6 (C_q), 192.9 (CHO). ESI-MS m/z (%): 255.0 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{16}H_{12}ClO_2$ 255.0571, found 255.0572.

2-(3-(*p*-Tolyl)prop-2-yn-1-yl)benzaldehyde (4c). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 337 mg (96%). Orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.11 (d, J = 7.9 Hz, 2H, H_{Ar}), 7.34 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.47 (m, 1H, H_{Ar}), 7.61 (dt, J = 1.5, 7.5 Hz, 1H, H_{Ar}), 7.82 (dt, J = 7.7, 1.4 Hz, 2H, H_{Ar}), 10.28 (s, 1H, CHO). These data are in good agreement with literature values.[9a]

2-(3-(4-(Methylsulfonyl)phenyl)prop-2-yn-1-yl)benzaldehyde (4d). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (8 : 2). Yield: 367 mg (82%). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.03 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.49 (dt, J = 1.0, 7.3 Hz, 1H, H_{Ar}), 7.59 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.57–7.67 (m, 1H, H_{Ar}), 7.72 (d, J = 7.4 Hz, 1H, H_{Ar}), 7.80–7.84 (m, 1H, H_{Ar}), 7.86 (d, J = 8.5 Hz, 2H, H_{Ar}), 10.22 (s, 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.8 (CH_2), 44.7 (CH_3), 82.4 (C_{sp}), 91.7 (C_{sp}), 127.5 (CH_{Ar}), 127.9 (CH_{Ar}), 129.6 (C_q), 130.2 (CH_{Ar}), 132.6 (CH_{Ar}), 133.5 (C_q), 134.3 (CH_{Ar}), 134.4 (CH_{Ar}), 137.9 (C_q), 139.7 (C_q). ESI-MS m/z (%): 619.0 (100) [dimer + Na]$^+$, 321.3 (40) $[M + Na]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{15}O_3S$ 299.0736, found 299.0732.

2-(3-(3-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)benzaldehyde (4e). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 337 mg (78%). Pale yellow solid. Mp: 42–46 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.32 (s, 2H, CH_2), 7.34–7.97 (m, 8H, H_{Ar}), 10.25 (s, 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.4 (CH_2), 82.6 (C_{sp}), 88.8 (C_{sp}), 123.9 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3), 124.1 (C_q), 124.6 (CH_{Ar}), 124.7 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 128.6 (q, $^3J_{C-F}$ = 3.8, CH_{Ar}), 129.0 (CH_{Ar}), 130.2 (CH_{Ar}), 131.1 (q, $^2J_{C-F}$ = 32.0 Hz, C_q), 133.5 (C_q), 134.3 (CH_{Ar}), 135.0 (CH_{Ar}), 138.3 (C_q), 193.1 (CHO). ESI-MS m/z (%): 289.4 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{12}F_3O$ 289.0835, found 289.0834.

2-(3-(2-Ethylphenyl)prop-2-yn-1-yl)benzaldehyde (4f). Reaction time: 2 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 331 mg (89%). Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.6 Hz, 3H, CH_3), 2.80 (q, J = 7.5 Hz, 2H, CH_2), 4.35 (s, 2H, CH_2), 7.04–7.30 (m, 3H, H_{Ar}), 7.38–7.53 (m, 2H, H_{Ar}), 7.61 (dt, J = 1.6, 7.5 Hz, 1H, H_{Ar}), 7.83 (dt, J = 7.2, 1.5 Hz, 2H, H_{Ar}), 10.28 (s, 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.1 (CH_3), 23.9 (CH_2), 28.0 (CH_2), 82.9 (C_{sp}), 90.3 (C_{sp}), 122.8 (C_q), 125.8 (CH_{Ar}), 127.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.4 (CH_{Ar}), 130.2 (CH_{Ar}), 132.5 (CH_{Ar}), 133.5 (C_q), 133.7 (CH_{Ar}), 134.2 (CH_{Ar}), 139.2 (C_q), 146.4 (C_q), 192.9 (CHO). ESI-MS m/z (%): 263.3 (100) $[M + CH_3]^+$, 249.2 (30) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{18}H_{17}O$ 249.1274, found 249.1277.

2-(3-(3-Chloro-2-methylphenyl)prop-2-yn-1-yl)benzaldehyde (4g). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 358 mg (89%). Pale yellow solid. Mp: 90–94 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3),

4.35 (s, 2H, CH_2), 7.05 (t, J = 7.8 Hz, 1H, H_{Ar}), 7.31 (m, 2H, H_{Ar}), 7.49 (dt, J = 1.2, 7.4 Hz, 1H, H_{Ar}), 7.62 (dt, J = 1.6, 7.5 Hz, 1H, H_{Ar}), 7.78 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.85 (dd, J = 1.6, 7.4 Hz, 1H, H_{Ar}), 10.26 (s, 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 18.5 (CH_3), 23.9 (CH_2), 82.9 (C_{sp}), 91.5 (C_{sp}), 125.4 (C_q), 126.6 (CH_{Ar}), 127.6 (CH_{Ar}), 129.2 (CH_{Ar}), 130.1 (CH_{Ar}), 130.1 (CH_{Ar}), 130.8 (CH_{Ar}), 133.5 (C_q), 134.1 (CH_{Ar}), 134.3 (CH_{Ar}), 134.9 (C_q), 138.2 (C_q), 138.8 (C_q), 193.0 (CHO). ESI-MS m/z (%): 269.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{14}ClO$ 269.0728, found 269.0725.

2-(3-(2-Isopropylphenyl)prop-2-yn-1-yl)benzaldehyde (4h). Reaction time: 2.5 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 322 mg (82%). Light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (d, J = 7.0 Hz, 6H, CH_3), 3.45 (sept, J = 7.0 Hz, 1H, CH), 4.35 (s, 2H, CH_2), 7.08–7.16 (m, 1H, H_{Ar}), 7.24–7.28 (m, 2H, H_{Ar}), 7.41–7.45 (m, 2H, H_{Ar}), 7.49 (dd, J = 1.1, 7.3 Hz, 1H, H_{Ar}), 7.61 (dt, J = 1.5, 7.3 Hz, 1H, H_{Ar}), 7.83 (dt, J = 1.5, 7.3 Hz, 1H, H_{Ar}), 10.29 (s, 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.3 (CH_3), 24.0 (CH_2), 31.7 (CH), 83.0 (C_{sp}), 90.5 (C_{sp}), 122.5 (C_q), 125.1 (CH_{Ar}), 125.7 (CH_{Ar}), 127.5 (CH_{Ar}), 128.6 (CH_{Ar}), 130.2 (CH_{Ar}), 132.7 (CH_{Ar}), 133.6 (C_q), 133.7 (CH_{Ar}), 134.2 (CH_{Ar}), 139.2 (C_q), 150.6 (C_q), 192.9 (CHO). ESI-MS m/z (%): 285.2 (100) $[M + Na]^+$, 263.3 (10) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{19}H_{19}O$ 263.1430, found 263.1428.

2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-5-fluorobenzaldehyde (4i). Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (99 : 1). Yield: 317 mg (78%). White solid. Mp: 65 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.21 (s, 2H, CH_2), 7.22–7.39 (m, 5H, H_{Ar}), 7.54 (dd, J = 2.8, 8.5 Hz, 1H, H_{Ar}), 7.70 (dd, J = 5.1, 8.5 Hz, 1H, H_{Ar}), 10.25 (d, J_{H-F} = 1.2 Hz 1H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.0 (CH_2), 83.1 (C_{sp}), 87.7 (C_{sp}), 119.1 (d, $^2J_{C-F}$ = 22.1 Hz, CH_{Ar}), 121.2 (d, $^2J_{C-F}$ = 21.0 Hz, CH_{Ar}), 121.9 (C_q), 128.8 (CH_{Ar}), 132.2 (d, $^3J_{C-F}$ = 7.2 Hz, CH_{Ar}), 133.1 (CH_{Ar}), 134.4 (C_q), 134.5 (d, $^4J_{C-F}$ = 3.4 Hz, C_q). 135.0 (d, $^3J_{C-F}$ = 5.7 Hz, C_q), 162.1 (d, $^1J_{C-F}$ = 248 Hz, C–F), 191.1 (d, $^4J_{C-F}$ = 1.5 Hz, CHO). ESI-MS m/z (%): 532.2 (100) [dimer + Na − Cl]$^+$. HRMS ESI $[M + H]^+$ calcd for $C_{16}H_{11}ClFO$ 273.0477, found 273.0479.

General procedure for the synthesis of 3-benzylisoquinolines (5a–i)

A stirred solution of the 2-propargylbenzaldehydes **4a–i** (0.318 mmol) in dry DMSO (2 mL) and ammonia acetate (489 mg, 6.36 mmol) was heated at 80 °C in a sealed vial for 30 min in a single-mode microwave synthesizer. The mixture was poured into water (40 mL), extracted with EtOAc (3 × 20 mL), and the organic layers were dried over Na_2SO_4. The solvent was removed at reduced pressure and the resulting crude was purified by flash column chromatography, affording the desired isoquinolines **5a–i**.

3-Benzylisoquinoline (5a). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 55 mg (78%). Red solid. Mp: 60–61 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.33 (s, 2H, CH_2), 7.21–7.29 (m, 1H, H_{Ar}), 7.32–7.34 (m, 4H, H_{Ar}), 7.43 (s, 1H, H_{Ar}), 7.53 (dt, J = 6.6, 1.5 Hz, 1H, H_{Ar}), 7.63 (dt, J = 6.6, 1.5 Hz, 1H, H_{Ar}), 7.72 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.93 (d, J = 7.3 Hz, 1H, H_{Ar}), 9.22 (s, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 44.6 (CH_2), 118.9 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 (CH_{Ar}), 127.4 (C_q), 127.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.5 (CH_{Ar}), 130.5 (CH_{Ar}), 136.8 (C_q), 140.1 (C_q), 152.6 (CH_{Ar}), 154.7 (C_q). ESI-MS m/z (%): 220.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1123.

3-(4-Chlorobenzyl)isoquinoline (5b). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 71 mg (93%). Light brown solid. Mp: 78–80 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.27 (s, 2H, CH_2), 7.16–7.34 (m, 4H, H_{Ar}), 7.42 (s, 1H, H_{Ar}), 7.48–7.63 (m, 1H, H_{Ar}), 7.67 (dd, J = 1.3, 6.6 Hz, 1H, H_{Ar}), 7.73 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.94 (d, J = 8.0 Hz, 1H, H_{Ar}), 9.21 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 43.6 (CH_2), 119.1 (CH_{Ar}), 126.49 (CH_{Ar}), 127.1 (CH_{Ar}), 127.4 (C_q), 127.8 (CH_{Ar}), 128.9 (CH_{Ar}), 130.8 (CH_{Ar}), 130.9 (CH_{Ar}), 132.5 (C_q), 136.8 (C_q), 138.4 (C_q), 152.4 (CH_{Ar}), 153.8 (C_q). ESI-MS m/z (%): 254.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{16}H_{13}ClN$ 254.0731, found 254.0730.

3-(4-Methylbenzyl)isoquinoline (5c). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 55 mg (74%). Brown solid. Mp: 55–59 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.13 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.22 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.42 (s, 1H, H_{Ar}), 7.47–7.57 (m, 1H, H_{Ar}), 7.58–7.68 (m, 1H, H_{Ar}), 7.71 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.93 (d, J = 7.5 Hz, 1H, H_{Ar}), 9.21 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.3 (CH_3), 44.0 (CH_2), 118.9 (CH_{Ar}), 126.5 (CH_{Ar}), 126.8 (CH_{Ar}), 127.3 (C_q), 127.8 (CH_{Ar}), 129.3 (CH_{Ar}), 129.5 (CH_{Ar}), 130.6 (CH_{Ar}), 136.1 (C_q), 136.9 (C_q), 152.3 (CH_{Ar}), 154.8 (C_q). ESI-MS m/z (%): 234.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{16}N$ 234.1277, found 224.1275.

3-(4-(Methylsulfonyl)benzyl)isoquinoline (5d). Eluent for chromatography: hexane–EtOAc (6 : 4). Yield: 64 mg (67%). Light brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.01 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.50 (m, 3H, H_{Ar}), 7.54–7.79 (m, 3H, H_{Ar}), 7.86 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.94 (m, 1H, H_{Ar}), 9.20 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.3 (CH_2), 44.8 (CH_3), 119.4 (CH_{Ar}), 126.5 (CH_{Ar}), 127.3 (CH_{Ar}), 127.6 (C_q), 127.8 (CH_{Ar}), 127.9 (CH_{Ar}), 130.3 (CH_{Ar}), 130.9 (CH_{Ar}), 136.71 (C_q), 138.8 (C_q), 146.7 (C_q), 152.8 (C_q), 152.9 (CH_{Ar}). ESI-MS m/z (%): 298.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{16}NO_2S$ 298.0896, found 298.0898.

3-(3-(Trifluoromethyl)benzyl)isoquinoline (5e). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 74 mg (81%). Brown solid. Mp: 60–65 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.36 (s, 2H, CH_2), 7.36–7.61 (m, 5H, H_{Ar}), 7.61–7.72 (m, 2H, H_{Ar}), 7.75 (m, 1H, H_{Ar}), 7.95 (m, 1H, H_{Ar}), 9.24 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.2 (CH_2), 119.2 (CH_{Ar}), 124.6 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3), 123.5 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 126.1 (q, $^3J_{C-F}$ = 3.8 Hz, CH_{Ar}), 126.5 (CH_{Ar}), 127.1 (CH_{Ar}), 127.5 (C_q), 127.8 (CH_{Ar}), 129.2 (CH_{Ar}), 130.8 (CH_{Ar}), 132.8 (CH_{Ar}), 136.8 (C_q), 140.9 (C_q), 152.7 (CH_{Ar}), 153.4 (C_q) (one C_q obscured). ESI-MS m/z (%): 288.4 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{13}F_3N$ 288.0995, found 288.0992.

3-(2-Ethylbenzyl)isoquinoline (5f). Eluent for chromatography: hexane–EtOAc (98 : 2). Yield: 56 mg (71%). Brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.5 Hz, 3H, CH_3), 2.68 (q, J = 7.5 Hz, 2H, CH_2), 4.39 (s, 2H, CH_2), 7.16–7.31 (m, 5H, H_{Ar}), 7.48–7.57 (m, 1H, H_{Ar}), 7.51–7.61 (m, 1H, H_{Ar}), 7.63–7.66 (m, 1H, H_{Ar}), 7.94 (dd, J = 7.9, 0.6 Hz, 1H, H_{Ar}), 9.23 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.2 (CH_3), 26.1 (CH_2), 41.6, (CH_2), 118.5 (CH_{Ar}), 126.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.8 (CH_{Ar}), 127.2 (CH_{Ar}), 127.7 (C_q), 128.8 (CH_{Ar}), 130.5 (CH_{Ar}), 130.9 (CH_{Ar}), 136.7 (C_q), 137.2 (C_q), 143.0 (C_q), 152.4 (CH_{Ar}), 154.9 (C_q). ESI-MS m/z (%): 248.3 (100) $[M + H]^+$, 270.1 (22) $[M + Na]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{18}H_{18}N$ 248.1434, found 248.1434.

3-(3-Chloro-2-methylbenzyl)isoquinoline (5g). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 71 mg (83%). Brown solid. Mp: 58–60 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.12–7.15 (m, 2H, H_{Ar}), 7.21 (s, 1H, H_{Ar}), 7.26–7.34 (m, 1H, H_{Ar}), 7.50–7.70 (m, 3H, H_{Ar}), 7.89–8.00 (dd, J = 1.1, 8.4 Hz, 1H, H_{Ar}), 9.23 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 16.6 (CH_3), 43.0 (CH_2), 118.5 (CH_{Ar}), 126.5 (CH_{Ar}), 126.9 (CH_{Ar}), 127.4 (C_q), 127.7 (CH_{Ar}), 128.1 (CH_{Ar}), 129.2 (CH_{Ar}), 130.6 (CH_{Ar}), 135.3 (C_q), 135.5 (C_q), 136.7 (C_q), 140.0 (C_q), 152.5 (CH_{Ar}), 153.7 (C_q). ESI-MS m/z (%): 268.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{17}H_{15}ClN$ 268.0888, found 268.0888.

3-(2-Isopropylbenzyl)isoquinoline (5h). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 63 mg (76%). Light brown solid. Mp: 62–64 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (d, J = 7.0 Hz, 6H, CH_3), 3.22 (sept, J = 7.0 Hz, 1H, CH), 4.43 (s, 2H, CH_2), 7.19–7.40 (m, 5H, H_{Ar}), 7.47–7.55 (m, 1H, H_{Ar}), 7.60–7.66 (m, 2H, H_{Ar}), 7.94 (m, 1H, H_{Ar}), 9.24 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 24.0 (CH_3), 29.4 (CH), 41.8 (CH_2), 118.5 (CH_{Ar}), 125.9 (CH_{Ar}), 126.1 (CH_{Ar}), 126.5 (CH_{Ar}), 126.7 (CH_{Ar}), 127.3 (C_q), 127.5 (CH_{Ar}), 127.7 (CH_{Ar}), 130.5 (CH_{Ar}), 131.1 (CH_{Ar}), 136.4 (C_q), 136.7 (C_q), 147.8 (C_q), 152.3 (CH_{Ar}), 155.2 (C_q). ESI-MS m/z (%): 262.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{19}H_{20}N$ 262.1590, found 262.1593.

3-(4-Chlorobenzyl)-7-fluoroisoquinoline (5i). Eluent for chromatography: hexane–EtOAc (95 : 5). Yield: 62 mg (71%). Brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.27 (s, 2H, CH_2), 7.18–7.33 (m, 4H, H_{Ar}), 7.37–7.49 (m, 2H, H_{Ar}), 7.54 (dd, J = 2.4, 8.7 Hz, 1H, H_{Ar}), 7.73 (dd, J = 5.2, 9.0 Hz, 1H, H_{Ar}), 9.17 (s, 1H, H_{Ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 43.3 (CH_2), 110.9 (d, $^2J_{C–F}$ = 20.6 Hz, CH_{Ar}), 119.1 (CH_{Ar}), 121.8 (d, $^2J_{C–F}$ = 25.5 Hz, CH_{Ar}), 127.9 (d, $^3J_{C–F}$ = 8.4 Hz, C_q), 129.0 (CH_{Ar}), 129.2 (d, $^3J_{C–F}$ = 8.4 Hz, CH_{Ar}), 130.8 (CH_{Ar}), 132.6 (C_q), 134.0 (C_q), 138.1 (C_q), 151.3 (d,$^4J_{C–F}$ = 5.7 Hz, CH_{Ar}), 153.2 (d,$^4J_{C–F}$ = 2.7 Hz, CH_{Ar}), 161.0 (d, $^1J_{C–F}$ = 249 Hz, C–F). ESI-MS m/z (%): 272.3 (100) $[M + H]^+$. HRMS ESI $[M + H]^+$ calcd for $C_{16}H_{12}ClFN$ 272.0637, found 227.0638.

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