Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2683

www.rsc.org/obc

PAPER

A new access to 3-substituted-1(2*H*)-isoquinolone by tandem palladium-catalyzed intramolecular aminocarbonylation annulation†

Antoine Dieudonné-Vatran,[a,b] Michel Azoulay[a] and Jean-Claude Florent*[a]

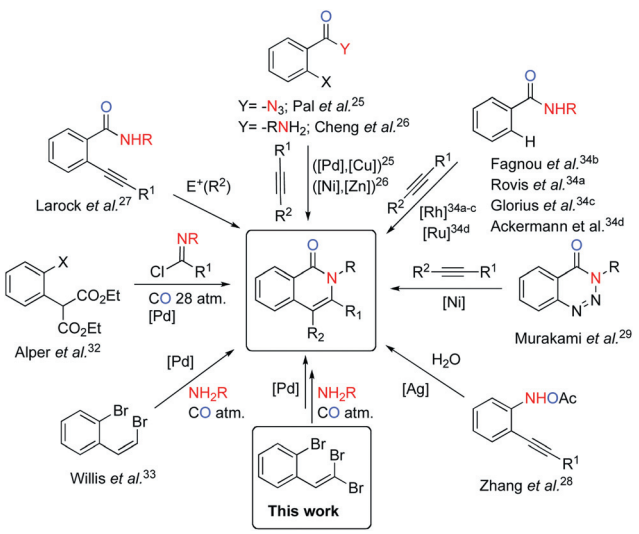
Received 3rd November 2011, Accepted 6th January 2012
DOI: 10.1039/c2ob06852d

An original tribromide derivative based, palladium-catalyzed synthesis of 3-substituted-1(2*H*)-isoquinolone is described based on a regioselective Suzuki–Miyaura C–C coupling on *o*-halo-(2,2-dihalovinyl)-benzene followed by a palladium catalyzed amination–carbonylation–cyclization reaction. This sequence efficiently proceeds to build up isoquinolone in fair to good yields over a one-pot 3-bond synthesis reaction.

Introduction

Isoquinolin-1(2*H*)-ones (isocarbostyrils) are the structurally related nitrogen containing analogues of isocoumarins (1*H*-2-benzopyran-1-ones). This scaffold is an important heterocycle in medicinal chemistry, with relevant biological activities such as antihypertensive activity[1] or as ligand for various receptors; for example it is an NK3 receptor antagonist,[2] melatonin MT1 and MT2 receptor agonist,[3] positive allosteric modulator of the metabotropic glutamate receptor 2 (mGluR2),[4] and 5-HT3 antagonist.[5] Furthermore, isoquinolin-1(2*H*)-ones also demonstrated anti-tumor activities, displaying cytotoxicity against different human tumor cell lines,[6] by inhibition of critical enzymes involved in cancer like topoisomerase I,[7] thymidylate synthase (TS),[8] some kinases, *e.g.* c-Jun N-terminal kinase (JNK),[9] ROCK-I,[10] RHO[11] and poly(ADP-ribose)polymerase-1 (PARP-1).[12] Regarding these biological activities, it is considered as a privileged scaffold for pharmaceutical drugs or as a versatile building block for the total synthesis of natural alkaloids.[13] Since the pioneering report on isoquinolone derivatives' synthesis by Gabriel and Coleman,[14] developing innovative strategies to build up this scaffold is an ongoing effort in heterocyclic chemistry, and many different synthetic pathways have been designed.[15–22]

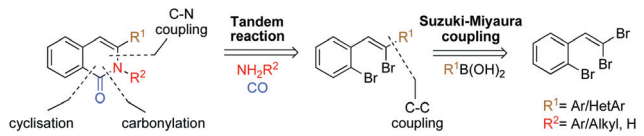
Recently, transition-metal-based catalysis has often been utilized for the synthesis of various heterocyclic compounds, including isoquinolone.[23] Among these, intramolecular annulation of 2-alkynyl benzamide,[24] intramolecular cyclization of 2-alkynyl acyl azide,[25] and the nickel-catalyzed annulation of 2-halobenzamides with alkynes,[26] have been reported. Other synthetic pathways, involving cyclization of *o*-acyl substituted alkynylaryl derivatives using halogen or silver salt activation of the alkyne moiety,[27] have been reported as well.[28] Furthermore, nickel-catalyzed strategies have been described, involving denitrogenative activation of triazinone,[29] or decarbonylative insertion of phthalimide.[30] Copper-catalyzed coupling–intramolecular condensation process between the substituted 2-halobenzamide and *β*-keto ester was also developed.[31] Eventually, the isoquinolone scaffold was prepared by carbonylative processes, under CO pressure[32] or at atmospheric CO pressure.[33] More recently, up-to-date reports highlighted rhodium-catalyzed C–H or NH activation pathways, involving external or substrate-containing oxidants,[34a–c] as well as the use of the cheaper ruthenium catalyst (Scheme 1).[34d]



Scheme 1

[a]*Institut Curie, Centre de Recherche, 26 rue d'Ulm, Paris 75248, France and CNRS, UMR 176, 26 rue d'Ulm, Paris 75248, France. E-mail: jean-claude.florent@curie.fr; Fax: +33 (0)1 56 24 66 31*
[b]*Université Paris Descartes, 4 avenue de l'Observatoire, Paris 75006, France*

†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c2ob06852d



Scheme 2

Such examples referring to very recent developments in transition-metal catalysis illustrate the remaining attractiveness of this heterocyclic scaffold. However, examples of syntheses of 3-substituted isoquinolone, featuring no substituent at the 4-position remain rare with these procedures. Recently, we became interested in the synthesis of such an isoquinolone scaffold to elaborate a library of substituted isoquinolones required for biological studies, following the discovery of hits originating from a phenotype cellular screen performed on the Institut Curie small compound library. Thus, in connection with our ongoing studies on the *gem*-dihaloolefin motif and the carbonylation reaction,[35] we imagined an original pathway to build up the isoquinolone scaffold through a tandem palladium-catalyzed C–N/CO/C–C reaction. Specifically enhancing the diversity at the 3-position of the isoquinolone drove our reflection to designing a synthetic route from *o*-bromo-(2,2-dibromovinyl)-benzene derivatives as key synthons. Indeed, *gem*-dihalovinyl compounds as versatile partners have attracted considerable interest in transition metal-catalyzed cross-coupling chemistry owing to their high reactivity and ready availability from inexpensive aldehydes. Recently, a variety of novel and elegant methods were developed to allow the Pd and/or Cu-catalyzed cross-couplings of *gem*-dihaloolefins with various reagents.[36]

We envisioned that an *o*-bromo-(2,2-dibromovinyl)-benzene derivative could act as a key platform to build the desired 3-aryl-isoquinolone scaffold *via* an original synthetic pathway involving sequential coupling of the three different C–Br bonds. Indeed, the vinyl-*trans* C–Br bond is known to react faster than the more hindered *cis* one.[36] Based on this cascade reactivity, diversity on the scaffold will be introduced first through a *trans* regioselective Suzuki–Miyaura C–C coupling.[37] In a second step, a one-pot, 2 step palladium-catalyzed amination of the remaining vinyl bromide followed by amino carbonylation would furnish the isoquinolone scaffold (Scheme 2).

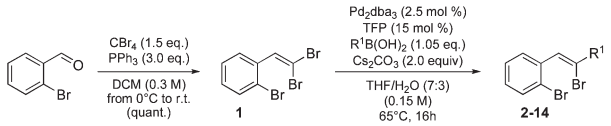
Such a process of palladium-catalyzed aminocarbonylation reaction involving an aryl halide together with an external amine in an intermolecular reaction has been extensively studied by Buchwald *et al.*[38] On the other hand, examples involving an internal amine, with the intramolecular formation of the amide bond inducing cyclization, remain more scarce[39] and thus more challenging. A recent report on such a tandem palladium-catalyzed amination–carbonylation–cyclization reaction to quinolone and isoquinolone synthesis has been reported by Willis *et al.*[33] However, major drawbacks have been noted, such as the limitations of the procedure to sterically hindered amines to avoid the competitive indol formation resulting from a non-efficient carbonylation process.

Results and discussion

Our synthesis started with the synthesis of the *o*-bromo-(2,2-dibromovinyl)-benzene intermediate **1** which was easily prepared on a multigram scale thanks to a Ramirez homologation, involving methane tetrabromide and triphenylphosphine, in a 10 min reaction in DCM (Table 1). The original styrene derivatives **2–14** were prepared according to a method described initially by Chelucci *et al.*[37] A regioselective Suzuki–Miyaura C–C coupling with Pd_2dba_3 and tris-2-furylphosphine (TFP), and caesium carbonate as a base in a THF–H_2O (7 : 3) mixture generated the desired derivatives. The TFP proved to be essential for the efficiency of the reaction.

A broad range of *trans* Aryl/HetAryl-substituted dibromides were prepared, with moderate to fair yields (from 39 to 72%),

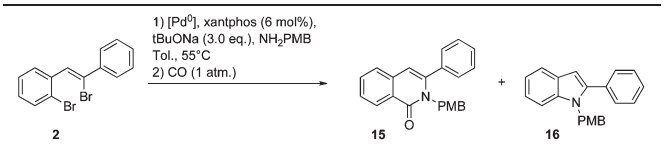
Table 1 Regioselective C–C Suzuki–Miyaura couplings[a]



Entry	R^1	Product	Yield (%)
1	Ph	2	70
2	4-Me–Ph	3	67
3	4-OMe–Ph	4	69
4	3-OMe–Ph	5	60
5	2-OMe–Ph	6	64
6	2,6-diOMe–C_6H_3	7	42
7	4-NO_2–Ph	8	62
8	4-CF_3–Ph	9	59
9	4-CO_2H–Ph	10	72
10	4-CO_2Me–Ph	11	51
11	3-Pyridine	12	46
12	5-Indole	13	39
13	3,4,5-TriOMe–C_6H_2	14	60

[a] Reaction conditions: substrate (1.0 mmol), $R^1B(OH)_2$ (1.05 mmol), Pd_2dba_3 (2.5 mol%), tris(2-furyl) phosphine (15 mol%), Cs_2CO_3 (2.0 mmol, 1 M aq. solution), 1,4-dioxane (0.15 M), 65 °C, 16 h.

Table 2 Optimization of amination and carbonylation reactions[a]



	1) Amination		2) Carbonylation		Yield over 2 steps	
Entry	Amine (eq.)	Time (h)	Temp. (°C)	Time (h)	**15** (%)	**16** (%)
1[b]	1.5	0.5	65 to 100	18	traces	traces
2	1.5	0.5	65 to 100	18	33	30
3	3.5	1	65 to 100	18	38	28
4	3.5	1.5	65 to 100	18	46	—
5	5.5	3.0	65 to 100	18	30	—
6[c]	3.5	1.5	90	16	53	—

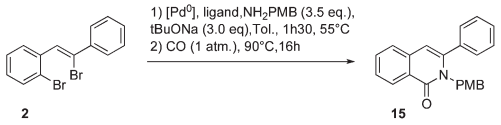
[a] Reaction conditions: 1) amination: **2** (0.25 mmol), NH_2PMB, Pd_2dba_3 (6.0 mol%, except for entry 1), xantphos (6.0 mol%), *t*BuONa (3.0 eq.), 55 °C, 1 h 30; 2) carbonylation: 65°C for 1 h, then 85 °C for 1 h and finally 100 °C for 16 h; [b] 6 mol% $Pddba_2$; [c] after argon to CO (1 atm) atmosphere exchange, reaction stirred at indicated temp. for 16 h.

affording a library of original styrene derivatives bearing a range of substituents with different electronic and steric properties (Table 1). Screening for the optimized amination and carbonylation reaction conditions was run on the phenyl substituted dibromide derivative **2** (Table 2). We initially used the aminocarbonylation conditions previously reported by Willis *et al.*[33] for 3-unsubstituted-1(2*H*)-isoquinolone synthesis. Thus, 1.5 eq. of the primary amine NH_2PMB and 3.0 eq. of NaO^tBu, at 55 °C, were stirred in toluene under argon for 30 min, with $Pddba_2$ (6 mol%) and xantphos (6 mol%) as catalyst. After 30 min reaction, the argon atmosphere was exchanged for CO (1 atm); the resulting mixture was stirred under CO (1 atm) at 65 °C for 1 h, then at 85 °C for 1 h, and finally at 100 °C for 16 h. However, only traces of both isoquinolone **15** and indole **16** were obtained and a rapid formation of palladium black early in the reaction led us to question the catalytic system (Table 2, entry 1). Thus, we decided to switch to Pd_2dba_3 to increase the catalyst loading. As previously observed from Willis' previous report regarding non-sterically hindered amines in this reaction,[33] 30% of the indole **16** were obtained together with the desired isoquinolone **15** (Table 2, entry 2). Still, we bypassed this drawback by increasing the amount of amine used and the duration of the amination reaction, which led to a higher yield of the desired product, without the formation of the indole (Table 2, entries 3 and 4). A larger excess of amine did not benefit the reaction (Table 2, entry 5). Focusing on the carbonylation, a HPLC analysis of the evolution of the carbonylation reaction allowed us to highlight the most suitable parameters, regarding both the time and temperature. We were able to adjust these two parameters to simplify the three temperature steps previously used, leading to an overall reaction that was easier to handle. These studies revealed that, when the carbonylation reaction was run exclusively at 90 °C for 16 h, the desired compound was obtained in good yield (53%) over 2 steps, without the formation of the indole **16**. Eventually, neither higher temperature (from 90 to 130 °C) nor rise in CO pressure (from 2 to 10 atm) improved the formation of the desired compound as degradation of the starting material was observed and no desired compound isolated.

These new amination and carbonylation conditions set the stage for the screening of the most appropriate catalyst system, base and solvent. Concerning the [Pd] : [L] ratio, changing the ratio from [1 : 1] to [2 : 1] did not have a tremendous impact on the reaction outcome, and the synthesis of compounds **15** was nicely achieved in fair yields ranging from 50 to 55% over 2 steps (Table 3, entries 1, 2 and 3). 5 mol% palladium seems to be the lowest loading, since a significant drop in yield to 11% was observed with 2.5 mol% (Table 3, entry 4). In addition, 5 mol% ligand seems to be the best loading of xantphos as well since less ligand strongly disfavors the reaction (Table 3, entry 5). One should note that no conversion was observed when 10 mol% xantphos was used with 2.5 mol% Pd_2dba_3, probably due to the formation of an inactive catalyst.[40] Another source of palladium, $Pd(OAc)_2$ together with 15 mol% of xantphos proved to be inefficient at catalyzing the tandem reaction (Table 3, entry 7).

Concerning the ligand, several monophosphines were first tested: triphenylphosphine along with tricyclohexylphosphine and the fluoroborate derivative of this latter. As expected from the literature regarding palladium-catalyzed aminocarbonylation,[38] none of them efficiently catalyzed the reaction. A range of diphosphines with different bite angles was then screened; *rac*-binap, dppp, dppb, and ferrocene derivative phosphine afforded the desired compound in similar yield, *i.e.* 19–37% over the 2 steps (Table 3, entries 8, 9, 10 and 11). It can be concluded from this screening that 5 mol% Pd_2dba_3 together with 5 mol% of xantphos is the most efficient catalytic system for the tandem reaction. Concerning the solvents, this tandem reaction was revealed to be highly solvent-specific. Switching from toluene to more polar solvents like 1,4-dioxane or DMF completely inhibited the conversion of the starting material into the desired compound (Table 4 entries 1 and 2). On the other hand the apolar cyclohexane or xylene afforded the desired

Table 3 Screening of [Pd] : [L] ratios and ligands[a]

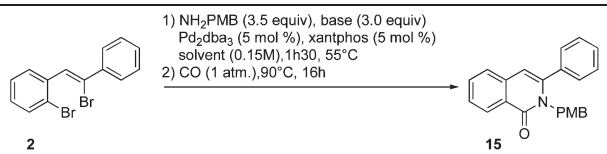


2 15

Entry	Palladium (mol%)	Ligand (mol%)	[Pd] : [L]	Yield over 2 steps (%)
1	Pd_2dba_3 (6.0)	Xantphos (12.0)	1 : 1	50
2	Pd_2dba_3 (6.0)	Xantphos (6.0)	2 : 1	53
3	Pd_2dba_3 (5.0)	Xantphos (5.0)	2 : 1	55
4	Pd_2dba_3 (2.5)	Xantphos (5.0)	1 : 1	11
5	Pd_2dba_3 (2.5)	Xantphos (2.5)	1 : 1	23
6	Pd_2dba_3 (2.5)	Xantphos (10.0)	1 : 2	nc
7	$Pd(OAc)_2$(10.0)	Xantphos (15.0)	1 : 1	—
8	Pd_2dba_3 (5.0)	*rac*-binap (5.0)	2 : 1	31
9	Pd_2dba_3 (5.0)	dppf (5.0)	2 : 1	37
10	Pd_2dba_3 (5.0)	dppb (5.0)	2 : 1	19
11	Pd_2dba_3 (5.0)	dppp (5.0)	2 : 1	30

[a] Reaction conditions: 1) amination: **2** (0.25 mmol), NH_2PMB (3.5 eq.), [Pd], ligand, *t*BuONa (3.0 eq.), 55 °C, 1 h 30; 2) carbonylation: after argon to CO (1 atm) atmosphere exchange, reaction stirred at 90 °C for 16 h.

Table 4 Bases and solvents screening[a]

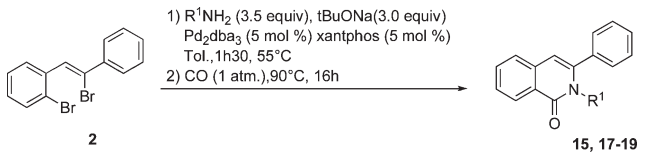


2 15

Entry	Solvent	Base	Yield (%)
1	1,4-Dioxane	NaO^tBu	—
2	DMF	NaO^tBu	—
3	Cyclohexane	NaO^tBu	23
4	Xylene	NaO^tBu	19
5	Toluene	NaO^tBu	55
6	Toluene	K_2CO_3	nc
7	Toluene	Cs_2CO_3	40
8	Toluene	NEt_3	nc

[a] Reaction conditions: 1) amination: substrates (0.25 mmol), NH_2PMB (3.5 eq.), [Pd], ligand, *t*BuONa (3.0 eq.), 55 °C, 1 h 30; 2) carbonylation: after argon to CO (1 atm) atmosphere exchange, reaction stirred at 90 °C for 16 h.

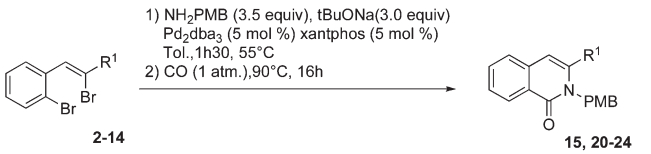
Table 5 Scope of the amine derivatives[a]



Entry	R^1	Product	Yield (%)
1	PMB	15	55
2	Ph	17	33
3	Cyclohexyl	18	46
4	Isopropyl	—	—
5	*n*Butyl	19	38
6	OMe	—	—
7	OBn	—	—

[a] Reaction conditions: 1) amination: substrates (0.25 mmol), NH_2PMB (3.5 eq.), [Pd], ligand, *t*BuONa (3.0 eq.), 55 °C, 1 h 30; 2) carbonylation: after argon to CO (1 atm) atmosphere exchange, reaction stirred at 90 °C for 16 h.

Table 6 Scope of the aryl derivatives[a]



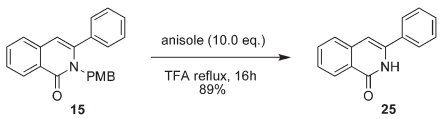
Entry	Substrates	R^1	Product	Yield (%)
1	**2**	Ph	15	55
2	**3**	4-Me–Ph	20	38
3	**4**	4-OMe–Ph	21	42
4	**5**	3-OMe–Ph	22	49
5	**6**	2-OMe–Ph	23	42
6	**7**	2,6-diOMe–C_6H_3	24	65
7	**14**	3,4,5-triOMe–C_6H_2	—	—
8	**8–11**	EWG	—	—
9	**12–13**	HetAr	—	—

[a] Reaction conditions: 1) amination: substrates (0.25 mmol), NH_2PMB (3.5 eq.), [Pd], ligand, *t*BuONa (3.0 eq.), 55 °C, 1 h 30; 2) carbonylation: after argon to CO (1 atm) atmosphere exchange, reaction stirred at 90 °C for 16 h.

compound in 23 and 19% yields respectively, still with less efficiency than toluene. Finally, several bases were tested: potassium and caesium carbonate, sodium *tert*-butoxide and triethyl amine. Sodium *tert*-butoxide proved to be the most efficient of all.

With these optimized parameters in our hands, we then turned our attention on the scope of the reaction. First, the aim was to determine the outcome of the reaction depending on both the steric and electronic properties of the amine moiety. It appears that an aryl amine such as aniline was tolerated, affording the desired compound **17** in 33% yield (Table 5, entry 2). The reaction also proceeded with electron rich bulky cyclohexyl amine, yielding the isoquinolone derivative **18** in 46% yield (Table 5, entry 3). *N*-Alkyl amine could also be introduced: thus **19** was obtained in 38% yield (Table 5, entry 5). Nevertheless, steric hindrance of the chain seemed to be a limitation, since the reaction failed with isopropyl amine (Table 5, entry 4), leading to only degradation of the starting material. Surprisingly, the tandem reaction did not succeed with electron rich *N*-alkoxy amine derivatives (Table 5, entries 6 and 7).

In a second study, we ran the tandem reaction with the library of aryl derivatives obtained by the Suzuki–Miyaura couplings. The reaction proceeded in a slightly less effective manner with compounds **20** and **21** bearing *p*-methyl or *p*-methoxy groups, respectively in 38 and 42% yield (Table 6, entries 2 and 3). However no conversion was observed using **14**, the tri-functionalized aryl, electronically enriched with 3 methoxy groups (Table 6, entry 7). The reaction led to complex unidentified degradation products. When focusing on examining the effects of the steric hindrance of the styryl dibromide starting material, it is worth noting that the tandem process does not suffer from sterically linked limitations. Indeed, the reaction performed on *m*-methoxy substituted dibromide derivative **5** furnished the desired compound **22** in 49% yield (Table 6, entry 4). Besides, the *o*-methoxy starting material **6** was successfully converted to the isoquinolone derivative **23** in 42% yield (Table 6, entry 5). Eventually, tandem reaction with the strongly sterically hindered *o*,*o*′-dimethoxy dibromide derivative **7** proceeded nicely in 65% yield over the 2 steps (compound **24**, Table 6, entry 6). The major limitation of the reaction stands with the electronically deficient aryls **8–11**. Indeed, the reaction failed with the 2-aryl-substituted styrene functionalized with electron-withdrawing groups, such as nitro **8**, acid **10**, ester **11** or trifluoromethane **9** (Table 6, entry 8). The same unreactivity was observed with heterocyclic derivatives **12** and **13**: no desired compounds were obtained, and degradation of the starting materials was observed (Table 6, entry 9).



Scheme 3

Interestingly, the PMB protecting group was removed using conditions described by Lamblin *et al.*,[41] with anisole as a cation scavenger, to afford the N-deprotected 3-aryl-1(2*H*)isoquinolone in good yield (Scheme 3).

Conclusion

As recently reported, the scope of carbon monoxide chemistry is currently expanding considerably with continuous flow processes[43] or *in situ* generation[44] of CO (g). In this work, we have designed an original and sequential 3-step methodology for the synthesis of 3-aryl-1(2*H*)isoquinolone, affording both *N*-protected or N-unprotected derivatives. The sequence proceeds through a regioselective Suzuki–Miyaura palladium-catalyzed C–C coupling on a *o*-bromo-(2,2-dibromo vinyl)benzene, affording a straightforward way to introduce diversity in the 3 position of the isoquinolone core. In a second step, a tandem palladium-catalyzed intramolecular lactamization under mild and convenient conditions allowed us to prepare a concise library of

3-substituted-1(2*H*)-isoquinolone compounds, whose biological activities will be reported in due time.

Experimental section

General considerations

All reactions were conducted in flame-dried or oven dried glassware under a dry argon atmosphere unless otherwise indicated. Toluene was distilled over CaH_2 under argon. All other commercial reagents and solvents were used as received without additional purification. Reactions were followed with TLC (0.25 mm silica gel 60-F plates). Visualization was accomplished with UV light. Flash chromatography was carried out on silica gel 320–400 mesh. ^{1}H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent peak ($CDCl_3$, DMSO-d_6) as the internal reference, coupling constants are given in Hertz. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet, dd = doublet doublet, dt = doublet triplet. IR spectra were taken with FT-IR. Melting points were determined on a Kofler bench and are uncorrected.

1-Bromo-2-(2,2-dibromovinyl)-benzene 1

To a solution of 2-bromobenzaldehyde (6.38 g, 34.5 mmol, 1.0 eq.) and CBr_4 (17.18 g, 51.78 mmol, 1.5 eq.) in dry DCM (60 ml) in an ice bath was added dropwisely a solution of PPh_3 (27.65 g, 103.11 mmol, 3.0 eq.) in dry DCM (50 ml). The reaction mixture became orange. The reaction was stirred at 0 °C for 10 min, then at r.t. for 10 min. The red heterogeneous mixture was diluted with ice-cold *n*-hexane; the suspension was filtered over celite/silica; the filtration cake washed two times with ice-cold *n*-hexane. Flash chromatography on silica gel (cyclohexane) afforded 11.7 g (quant.) of pure desired compound **1** as a yellow oil. **Rf** (cyclohexane) = 0.5. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 7.59 (dd, 2H, J = 9.0 Hz, 3.0 Hz), 7.52 (s, 1H), 7.34 (dt, 1H, J = 9.0 Hz, 3.0 Hz), 7.21 (dt, 1H, J = 9.0 Hz, 3.0 Hz). **^{13}C-NMR** (75 mHz, $CDCl_3$): δ 136.7, 136.1, 132.7, 130.4, 129.9, 127.2, 123.1, 92.9. **IR (CH_2Cl_2), ν (cm^{-1})**: 3073, 3023, 2926, 1463, 1430. **MS (EI)**: *m/z* = 339.9 [$M^{+\cdot}$]. **HRMS (EI)** *m/z* calculated for [$M^{+\cdot}$]: 337.7938. Found: 337.7938.

Procedure A for Suzuki–Miyaura coupling (Table 1, compounds 2–14)

In a sealed tube, to an argon degassed 1,4-dioxane solution of 1-bromo-2-(2,2-dibromovinyl)-benzene **1** (340.8 mg, 1.0 mmol, 1.0 eq.), Ar/HetB$(OH)_2$ (X mg, 1.05 mmol, 1.05 eq.), Cs_2CO_3 (2.0 ml, 1 M aqueous solution, 2.0 eq.) was added Pd_2dba_3 (22.8 mg, 0.025 mmol, 2.5 mol%) and TFP (34. 8 mg, 0.15 mmol, 15 mol%). The reaction mixture was stirred at 65 °C for 15 h. After cooling down to r.t., the mixture was diluted with water, the organic layer extracted with ethyl acetate, washed with sat. brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography on silica gel afforded the desired compound.

(*Z*)-1-Bromo-2-(2-bromo-2-phenylvinyl)benzene, 2

According to procedure A described above, **2** was isolated in 70% yield after flash chromatography on silica gel (cyclohexane) as a pale yellow solid. **Mp**: 50–51 °C. **Rf** (cyclohexane) = 0.48; **^{1}H NMR** (300 mHz, $CDCl_3$): δ 7.78 (dd, 1H, J = 9.0 Hz, 3.0 Hz), 7.72 (m, 2H), 7.63 (dd, 1H, J = 9.0 Hz, 3.0 Hz), 7.39 (m, 4 H), 7.28 (s, 1H), 7.21 (dt, 1H, J = 9.0, 3.0 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 140.0, 137.0, 132.4, 131.2, 129.7, 129.6, 129.3, 128.6 (2C), 128.1 (2C), 127.2 (2C), 126.8, 124.1. **IR (CH_2Cl_2), ν (cm^{-1})**: 3082, 3022, 2925, 1491, 1463, 1442. **MS (EI)** *m/z* = 338.0 [$M^{+\cdot}$]; **HRMS (EI)** *m/z* calculated for [$M^{+\cdot}$]: 335.9144. Found: 335.9147.

(*Z*)-1-Bromo-2-(2-bromo-2-*p*-tolylvinyl)benzene, 3

According to procedure A described above, **3** was isolated in 67% yield after flash chromatography on silica gel (cyclohexane) as an off white solid. **Mp**: 53–54 °C. **Rf** (cyclohexane) = 0.50. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 7.76 (dd, 1H, J = 1.2, 7.8 Hz), 7.63–7.58 (m, 3H), 7.36 (dt, 1H, J = 1.2, 7.8 Hz), 7.22–7.16 (m, 4H) 2.40 (bs, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 139.7, 137.8, 137.7, 132.9, 131.6, 129.7, 129.6 (2C), 129.1, 128.3 (2C), 127.6, 127.3, 124.7, 27.8. **IR (CH_2Cl_2), ν (cm^{-1})**: 3080, 3028, 2923, 1508, 1462, 1434. **MS (EI)** *m/z* = 351.8 [$M^{+\cdot}$]; **HRMS (EI)** *m/z* calculated for [$M^{+\cdot}$]: 349.9300. Found: 349.9302.

(*Z*)-1-Bromo-2-(2-bromo-2-(4-methoxyphenyl)vinyl)benzene, 4

According to procedure A described above, **4** was isolated in 69% yield after flash chromatography on silica gel (toluene–cyclohexane 1 : 1) as an orange–brown solid. **Mp**: 69–70 °C. **Rf** (toluene–cyclohexane 1 : 1) = 0.48. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 7.78 (dd, 1H, J = 1.2, 7.8 Hz), 7.67 (d, 2H, J = 6.9 Hz), 7.63 (dd, 1H, J = 1.2, 8.0 Hz), 7.37 (dt, 1H, J = 1.2, 7.5 Hz), 7.22–7.17 (m, 2H), 6.94 (d, 2H, J = 9 Hz), 3.86 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 160.4, 137.5, 132.7, 132.6, 132.2, 129.5 (2C), 129.4, 128.0, 127.0, 126.9, 124.3, 113.8 (2C), 55.6. **IR (CH_2Cl_2), ν (cm^{-1})**: 3072, 3010, 2963, 2936, 1605, 1574, 1508, 1463. **MS (EI)** *m/z* = 367.7 [$M^{+\cdot}$]; **HRMS (EI)** *m/z* calculated for [$M^{+\cdot}$]: 365.9249. Found: 365.9250.

(*Z*)-1-Bromo-2-(2-bromo-2-(3-methoxyphenyl)vinyl)benzene, 5

According to the procedure A described above, **5** was isolated in 60% yield after flash chromatography on silica gel (cyclohexane–toluene 8 : 2) as brown oil. **Rf** (cyclohexane–toluene 8 : 2) = 0.49. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 7.73 (dd, 1H, J = 1.5, 7.8 Hz), 7.68 (dd, 1H, J = 0.9, 8.1 Hz), 7.45 (dt, 1H, J = 0.9, 7.8 Hz), 7.40–7.27 (m, 5H), 7.00 (dt, 1H, J = 2.1, 6 Hz), 3.85 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 160.6, 141.9, 138.1, 133.2, 131.9, 130.8, 130.7, 130.5, 128.1, 127.5, 127.6, 124.4, 120.9, 115.7, 114.4, 55.8. **IR (CH_2Cl_2), ν (cm^{-1})**: 3080, 2970 2939, 1601, 1508, 1485, 1463. **MS (IE)** *m/z* = 367.9 [$M^{+\cdot}$]. **HRMS (EI)** *m/z* calculated for [$M^{+\cdot}$]: 365.9249. Found: 365.9250.

(*Z*)-1-Bromo-2-(2-bromo-2-(2-methoxyphenyl)vinyl)benzene, 6

According to procedure A described above, **6** was isolated in 64% yield after flash chromatography on silica gel (cyclohexane–toluene 8 : 2) as a brown solid. **Mp**: 78–79 °C. **Rf** (cyclohexane–toluene 8 : 2) = 0.48. **^{1}H NMR** (300 mHz, $CDCl_3$): 7.91 (dd, 1H, J = 1.2, 7.5 Hz), 7.65 (dd, 1H, J = 0.9, 8.1 Hz), 7.54 (dd, 1H, J = 1.5, 7.5 Hz), 7.43–7.35 (m, 2H), 7.25–7.19 (m, 2H), 7.04 (t, 1H, J = 0.9, 7.5 Hz), 6.97 (d, 1H, J = 8.1 Hz), 3.91 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 156.6, 137.1, 132.5, 132.4, 131.2, 131.0, 130.4, 130.1, 129.4, 126.9, 124.1, 122.1, 122.0; 120.5, 111.6, 55.9. **IR (CH_2Cl_2), ν (cm^{-1})**: 3077, 3011, 2942, 1595, 1578, 1490, 1464. **MS (IE)** m/z = 367.7 [$M^{+\cdot}$]. **HRMS (EI)** m/z calculated for [$M^{+\cdot}$]: 365.9249. Found: 365.9250.

(*Z*)-2-(1-Bromo-2-(2-bromophenyl)vinyl)-1,3-dimethoxybenzene, 7

According to procedure A described above, **7** was isolated in 42% yield after flash chromatography on silica gel (cyclohexane–toluene 1 : 1) as a brown solid. **Mp**: 77–78 °C. **Rf** (cyclohexane–toluene 1 : 1) = 0.25. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 7.85 (d, 1H, J = 7.8 Hz), 7.65 (d, 1H, J = 8.1 Hz), 7.44 (t, 1H, J = 7.5 Hz), 7.35–7.27 (m, 2H), 6.84 (s, 1H), 6.69 (d, 2H, J = 8.4 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 158.6, 137.7, 133.5, 133.3, 132.0, 131.5, 130.4, 127.9, 124.2, 119.8, 118.4, 104.9 (2C), 56.4 (2C). **IR (CH_2Cl_2), ν (cm^{-1})**: 3010, 2940, 2840, 1589, 1473, 1434. **MS (ES^+)** m/z = 398.9 [M + H]. **HRMS (ESI^+)** m/z calculated for [$M^{+\cdot}$]: 396.9439. Found: 396.9438.

(*Z*)-1-Bromo-2-(2-bromo-2-(4-nitrophenyl)vinyl)benzene, 8

According to procedure A described above, **8** was isolated in 62% yield after flash chromatography on silica gel (cyclohexane–ethyl acetate 1 : 1) as a brown solid. **Mp**: 106–107 °C. **Rf** (cyclohexane–ethyl acetate 1 : 1) = 0.50. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 8.36–8.33 (m, 2H); 8.09–8.05 (m, 2H), 7.74 (dd, 2H, J = 0.9, 8.1 Hz), 7.63 (s, 1H), 7.51 (dt, 1H, J = 0.9, 7.5 Hz), 7.37 (dt, 1H, J = 1.8, 7.8 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 148.9, 146.4, 137.6, 134.0, 133.4, 131.8, 131.2, 129.8 (2C), 128.3, 125.0, 124.6 (2C), 124.3. **IR (CH_2Cl_2), ν (cm^{-1})**: 2923, 1594, 1522, 1490, 1463, 1435. **MS (EI)** m/z = 382.9 [$M^{+\cdot}$]. **HRMS (EI)**: m/z calculated for [$M^{+\cdot}$]: 380.8985. Found: 380.8993.

(*Z*)-1-Bromo-2-(2-bromo-2-(4-(trifluoromethyl)phenyl)vinyl) benzene, 9

According to the procedure A described above, **9** was isolated in 59% yield after flash chromatography on silica gel (cyclohexane) as an off white solid. **Mp**: 58–59 °C. **Rf** (cyclohexane–ethyl acetate) = 0.54. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 8.01–7.97 (m, 2H), 7.88–7.82 (m, 2H), 7.76 (dd, 2H, J = 1.2, 8.1 Hz), 7.54 (s, 1H), 7.50 (dt, 1H, J = 1.2, 7.5 Hz), 7.35 (dt, 1H, J = 1.5, 7.8 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 144.5, 137.9, 133.6, 132.9, 132.0, 131.1, 129.5 (2C), 129.0; 128.4, 127.0, 126.6, 126.5, 126.0, 124.0. **IR (CH_2Cl_2), ν (cm^{-1})**: 2916, 1617, 1577, 1462, 1435, 1407, 1068, 1018. **MS (IE)** m/z = 405.9 [$M^{+\cdot}$]. **HRMS (ESI^+)** m/z calculated for [$M^{+\cdot}$]: 403.9018. Found: 403.9017.

(*Z*)-4-(1-Bromo-2-(2-bromophenyl)vinyl)benzoic acid, 10

According to procedure A described above, **10** was isolated in 72% yield after flash chromatography on silica gel (cyclohexane–ethyl acetate–acetic acid 50 : 49 : 1) as brown solid. **Mp**: 202–203 °C. **Rf** (cyclohexane–ethyl acetate–acetic acid 50 : 49 : 1) = 0.26. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 8.14–8.09 (m, 2H), 7.93–7.88 (m, 2H), 7.75 (dd, 1H, J = 1.5, 7.8 Hz), 7.70 (dd, 1H, J = 1.5, 8.1 Hz), 7.50 (dt, 1H, J = 1.2, 7.5 Hz), 7.34 (dt, 1H, J = 1.5, 7.5 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 166.9, 144.6, 137.9, 133.3, 132.4, 132.0, 131.9, 130.9, 130.7 (2C), 128.7 (2C), 128.3, 126.4, 124.3. **IR (CH_2Cl_2), ν (cm^{-1})**: 3083, 2916, 1732, 1694, 1570, 1461. **MS (ESI^+)** m/z = 378.7 [M]; **HRMS (ESI^+)** m/z calculated for [$M^{+\cdot}$]: 378.8969. Found: 378.8955.

(*Z*)-Methyl 4-(1-bromo-2-(2-bromophenyl)vinyl)benzoate, 11

According to procedure A described above, **11** was isolated in 51% yield after flash chromatography on silica gel (cyclohexane–ethyl acetate 90 : 10) and trituration in pentane as an off white solid. **Mp**: 98–99 °C. **Rf** (cyclohexane–ethyl acetate 90 : 10) = 0.50. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 8.10–8.06 (m, 2H), 7.92–7.88 (m, 2H), 7.74 (dd, 1H, J = 1.5, 7.5 Hz), 7.70 (dd, 1H, J = 1.2, 6 Hz), 7.53 (s, 1H), 7.49 (dt, 1H, J = 0.9, 7.5 Hz), 7.33 (dt, 1H, J = 1.8, 7.8 Hz), 3.91 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 166.7, 144.7, 138.0, 135.5, 132.6, 132.0, 131.0, 130.6 (2C), 128.9 (2C), 126.5, 126.5, 124.4, 52.7. **IR (CH_2Cl_2), ν (cm^{-1})**: 2954, 1721, 1568, 1436. **MS (ESI^+)** m/z = 418.8 [M + Na]. **HRMS (ESI^+)**: calculated for [$M^{+\cdot}$]: 394.9282. Found: 394.9283.

(*Z*)-3-(1-Bromo-2-(2-bromophenyl)vinyl)pyridine, 12

According to procedure A described above, **12** was isolated in 46% yield after flash chromatography on silica gel (cyclohexane–ethyl acetate 9 : 1) as a brown solid. **Mp**: 42–43 °C. **Rf** (cyclohexane–ethyl acetate 1 : 1) = 0.25. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 9.96 (d, 1H, J = 1.8 Hz), 8.61 (d, 1H, J = 4.8 Hz), 8.11 (dt, 1H, J = 2.1, 8.1 Hz), 7.76–7.70 (m, 2H), 7.52–7.37 (m, 3H), 7.33 (dt, 1H, J = 1.5, 7.5 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 150.6, 148.6, 137.3, 135.9, 135.6, 132.9, 131.7, 131.3, 130.4, 127.8, 123.8. **IR (CH_2Cl_2), ν (cm^{-1})**: 3045, 1624, 1476, 1414. **MS (ESI^+)** m/z = 339.1 [M + H^+]. **HRMS (ESI^+)**: calculated for [$M^{+\cdot}$]: 337.9280. Found: 337.9170.

(*Z*)-5-(1-Bromo-2-(2-bromophenyl)vinyl)-1*H*-indole, 13

According to procedure A described above, **13** was isolated in 39% yield after flash chromatography on silica gel (cyclohexane–ethyl acetate 9 : 1) as a yellow solid. **Rf** (cyclohexane–ethyl acetate 9 : 1) = 0.45. **Mp**: 132–133 °C. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 10.48 (bs, 1H, NH), 8.00 (s, 1H), 7.78

(dd, 1H, J = 1.5, 7.8 Hz), 7.69 (dd, 1H, J = 0.8, 7.8 Hz), 7.56–7.42 (m, 4H), 7.28–7.23 (m, 2H), 6.59 (t, 1H, J = 2.4 Hz). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 138.6, 137.6, 133.1, 132.1 (2C), 130.2, 129.9, 128.9, 128.4, 128.0, 127.2, 124.6, 122.3, 121.3, 112.1, 103.2. **IR (CH_2Cl_2), ν (cm^{-1})**: 3044, 1619, 1471, 1433, 1416. **MS (ESI$^+$)** m/z = [M + Cl] 307.0; **HRMS (ESI$^+$)** m/z calculated for [$M^{+\cdot}$]: 306.9525. Found: 306.9530.

(*Z*)-5-(1-Bromo-2-(2-bromophenyl)vinyl)-1,2,3-trimethoxy benzene, 14

According to procedure A described above, **14** was isolated in 60% yield after flash chromatography on silica gel (cyclohexane–ethyl acetate 95 : 05) and trituration in pentane as an off white solid. **Rf** (cyclohexane–ethyl acetate 95 : 05) = 0.25. **Mp**: 99–100 °C. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 7.72–7.67 (m, 2H), 7.47 (t, 1H, J = 7.5 Hz), 7.35 (t, 1H, J = 6.6 Hz), 7.05 (s, 2H), 3.90 (s, 6H), 3.78 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 154.1, 140.4, 138.4, 136.0, 133.4, 132.0, 130.0, 130.3, 128.3, 127.7, 124.4, 106.5 (2C), 60.7, 56.6 (2C). **IR (CH_2Cl_2), ν (cm^{-1})**: 2941, 1581, 1505, 1463, 1265, 1241. **MS (ES$^+$)** m/z = 450.1 [M + Na]. **HRMS (ESI$^+$)** m/z calculated for [M + H$^+$]: 426.9544. Found: 426.9542.

Procedure B for tandem reaction (Tables 3–6, compounds 15–23)

In a flamed dried round bottom flask was added NaO*t*Bu (68.23 mg, 0.71 mmol, 3.0 eq.), xantphos (6.8 mg, 0.012 mmol, 5 mol%), Pd_2dba_3 (10.8 mg, 0.012 mmol, 5 mol%). Reagents were dissolved in dry toluene (0.8 ml). The red mixture was degassed with argon while sonicating for 1 min. A toluene solution of **X** (80 mg, 0.24 mmol, 1.0 eq.) and NH_2PMB (114 mg, 0.83 mmol, 3.5 eq.) previously argon degassed was added. The reaction mixture was argon degassed again for 1 min, then stirred vigorously at 55 °C for 1 h 30 under argon. Then, the reaction mixture was degassed with CO (1 atm, balloon) for 30 min at 55 °C; then stirred at 90 °C for 18 h. The reaction mixture was allowed to cooled down to r.t. and diluted with 10 ml of HCl (1 N); the organic layers were extracted with DCM (2×), washed with sat.brine (2×), dried over $MgSO_4$, and then concentrated *in vacuo*. Flash chromatography on silica gel afforded the desired compound.

2-(4-Methoxybenzyl)-3-phenylisoquinolin-1(2*H*)-one, 15

According to procedure B described above, **3a** was isolated in 55% yield after flash chromatography on silica gel (pentane–ethyl oxide 7 : 3) as a yellow solid. **Mp**: 111–112 °C. **Rf** (pentane–ethyl oxide 7 : 3) = 0.35; **^{1}H NMR** (300 mHz, $CDCl_3$): δ 8.49 (d, 1H, J = 7.0 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.52–7.44 (m, 2H), 7.39–7.33 (m, 3H), 7.22 (d, 2H, J = 7.5 Hz), 5.20 (s, 2H), 3.73 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 163.2, 158.6, 143.9, 136.5, 136.0, 132.5, 129.8, 129.3 (2C), 128.9, 128.5 (2C), 128.3 (3C), 126.7, 125.6, 125.3, 113.7 (2C), 108.2, 55.2, 48.0. **IR (CH_2Cl_2), ν (cm^{-1})**: 3050, 2930, 1650, 1621, 1512. **MS (ESI$^+$)** m/z = 342.1 [M + H]; **HRMS (ESI$^+$)** m/z calculated for [M + H]: 342.1494, found: 342.1504.

1-(4-Methoxybenzyl)-2-phenyl-1*H*-indole, 16

According to procedure B described above, **16** was isolated in 30% yield after flash chromatography on silica gel (pentane–ethyl oxide 7 : 3) as an off white solid in accordance with previously reported data.[42]

2,3-Diphenylisoquinolin-1(2*H*)-one, 17

According to procedure B described above, **17** was isolated in 33% yield after flash chromatography on silica gel (pentane–ethyl oxide 8 : 2 to 6 : 4) as a pale yellow solid. **Mp**: 174–175 °C. **Rf** (pentane–ethyl oxide 7 : 3) = 0.36; **^{1}H NMR** (300 mHz, $CDCl_3$): δ 8.46 (d, 1H, J = 8.1 Hz, H-8), 7.67 (t, 1H, J = 6.9 Hz, H-6), 7.56 (d, 1H, J = 7.8 Hz, H-5), 7.54 (t, 1H, J = 6.9 Hz, H-7), 7.26–7.11 (m, 10H, H-Ar), 6.61 (s, 1H, H-4). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 163.2, 143.8, 139.3, 136.9, 136.4, 132.5, 132.9, 129.6 (2*C), 129.4 (2*C), 128.7 (2*C), 128.6, 128.2, 127.9 (2*C), 127.7, 127.0, 126.1, 125.7, 107.9. **IR (CH_2Cl_2), ν (cm^{-1})**: 3054, 1657, 1491. **MS (ESI$^+$)** m/z = 298.13 [M + H]; **HRMS (ESI$^+$)** m/z calculated for $C_{21}H_{15}NO$: 298.1226. Found: 298.1236.

2-Cyclohexyl-3-phenylisoquinolin-1(2*H*)-one, 18

According to procedure B described above, **18** was isolated in 46% yield after flash chromatography on silica gel (pentane–ethyl oxide 7 : 3) as a pale yellow solid. **Mp**: 123–124 °C. **Rf** (pentane–ethyl oxide 7 : 3) = 0.41; **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 7.71–7.68 (m, 1H), 7.60–7.56 (m, 3H), 7.47–7.43 (m, 6H), 3.96–3.90 (m, 1H), 2.00–1.97 (m, 2H), 1.75–1.71 (m, 2H), 1.62–1.57 (m, 1H), 1.43–1.37 (m, 4H, 2H-15), 1.22–1.13 (m, 1H). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 166.1, 139.2, 133.3, 131.8 (2*C), 129.9, 129.2, 128.9 (3*C), 128.8, 123.2, 120.4, 93.9, 87.9, 49.0, 33.1 (2*C), 25.9 (C), 25.16 (2*C). **IR (CH_2Cl_2), ν (cm^{-1})**: 3055, 2934, 1648, 1451. **MS (ESI$^+$)** m/z = 277.10 [$M^{+\cdot}$]. **HRMS (ESI$^+$)** m/z calculated for [$M^{+\cdot}$]: 277.1461. Found: 277.1460.

2-Butyl-3-phenylisoquinolin-1(2*H*)-one, 19

According to procedure B described above, **19** was isolated in 38% yield after flash chromatography on silica gel (pentane–ethyl oxide 7 : 3) as a pale yellow solid. **Mp**: 195–196 °C. **Rf** (pentane–ethyl oxide 7 : 3) = 0.34; **^{1}H NMR** (300 mHz, DMSO-d_6): δ. 8.39–8.35 (m, 1H), 7.62–7.58 (m, 1H), 7.51–7.34 (m, 8H), 3.26 (q, 2H, J = 6.6 Hz, H-13), 1.46 (q, 2H, J = 7.5 Hz, H-14), 1.33 (q, 2H, J = 7.6 Hz, H-15), 0.92–0.85 (m, 3H, H-16). **^{13}C-{^{1}H} NMR** (75 mHz, DMSO-d_6): δ 167.3, 140.1, 132.3 (C8), 131.2 (2*C10), 129.4 (C5), 128.9 (C6), 128.7 (2*C11), 128.6 (C7), 127.6 (C4), 92.4, 87.8, 31.3 (C13), 29.0 (C14), 19.7 (C15), 13.7 (C16). **IR (CH_2Cl_2), ν (cm^{-1})**: 3055, 2928, 1655. **MS (EI)** m/z = 303.10 [$M^{+\cdot}$]; **HRMS (EI)**: calculated for [$M^{+\cdot}$]: 303.1618. Found: 303.1618.

2-(4-Methoxybenzyl)-3-*p*-tolylisoquinolin-1(2*H*)-one, 20

According to procedure B described above, **20** was isolated in 38% yield after flash chromatography on silica gel

(pentane–ethyl oxide 1 : 1) as a pale yellow solid. **Mp**: 118–119 °C. **Rf** (pentane–ethyl oxide 1 : 1) = 0.30. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 8.49 (d, 1H, J = 8.1 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.49–7.47 (m, 7.49), 7.18–7.10 (m, 4H), 6.86 (d, 2H, J = 8.4 Hz), 6.71 (d, 2H, J = 8.7 Hz), 6.42 (s, 1H), 5.18 (s, 2H), 3.73 (s, 3H), 2.40 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 163.4, 158.6, 144.1, 139.0, 136.7, 133.3, 132.6, 130.1, 129.3 (2C), 129.1 (2C), 128.6 (2C), 128.4, 126.8, 126.0, 125.4, 113.7, 108.2 (2C), 55.3, 48.1, 21.5. **IR (CH_2Cl_2), ν (cm^{-1})**: 2935, 1653, 1613, 1512, 1465. **MS (ES$^+$)**: m/z = 356.19 [M + H]; **HRMS (ESI$^+$)**: calculated for $C_{24}H_{21}NO_2$ [M + H]: 356.1651, found: 356.1647.

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)isoquinolin-1(2*H*)-one, 21

According to procedure B described above, **21** was isolated in 42% yield after flash chromatography on silica gel (pentane–ethyl oxide 1 : 1) as yellow solid. **Mp**: 94–95 °C. **Rf** (pentane–ethyl oxide 1 : 1) = 0.27. **^{1}H NMR** (300 mHz, $CDCl_3$): 8.47 (d, 2H, J = 7.8 Hz), 7.61 (t, 1H, J = 7.0 Hz), 7.49–7.46 (m, 2H), 7.13 (d, 2H, J = 8.4 Hz), 6.89–6.85 (m, 4H), 6.70 (d, 2H, J = 8.7 Hz), 6.41 (s, 1H), 5.19 (s, 2H), 3.84 (s, 3H), 3.73 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 163.4, 160.0, 158.6, 143.8, 136.6, 132.5, 130.6 (2C), 130.0, 128.5 (2C), 128.4, 126.7, 125.9, 125.3, 114.4 (2C), 114.2 (2C), 108.3, 55.5, 55.4, 48.1. **IR (CH_2Cl_2), ν (cm^{-1})**: 3053, 2936, 1652, 1606, 1512, 1465. **MS (ES$^+$)**: m/z = 372.19 [M + H]. **HRMS (ESI$^+$):** calculated for $C_{24}H_{22}NO_3$ [M + H]: 372.1600, found: 372.1590.

2-(4-Methoxybenzyl)-3-(3-methoxyphenyl)isoquinolin-1(2*H*)-one, 22

According to procedure B described above, **22** was isolated in 49% yield after flash chromatography on silica gel (pentane–ethyl oxide 1 : 1) as a white solid. **Mp**: 71–72 °C. **Rf** (pentane–ethyl oxide 1 : 1) = 0.43. **^{1}H NMR** (300 mHz, $(CD_3)_2CO$): δ 8.06 (bs, 1H), 7.78–7.75 (m, 1H), 7.63–7.60 (m, 1H), 7.52–7.46 (m, 2H), 7.37 (d, 2H, J = 8.4 Hz), 7.30–7.24 (t, 1H, J = 8.7Hz), 6.99–6.97 (m, 2H), 6.79 (d, 2H, J = 8.7 Hz), 4.59 (s, 1H), 4.57 (s, 1H); 3.76 (s, 3H), 3.74 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $(CD_3)_2CO$): δ 167.5, 160.5, 159.8, 139.3, 133.9, 132.1, 130.8, 130.5, 129.9 (2C), 129.6, 129.5, 124.9, 124.6, 120.9, 117.3, 116.0, 114.6 (2C), 94.7, 88.1, 55.7, 55.5, 43.8. **IR (CH_2Cl_2), ν (cm^{-1})**: 3054, 2938, 1655, 1512. **MS (ES$^+$)**: m/z = 394.18 [M + Na]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{22}NO_3$ [M + H]: 372.1600, found: 372.1602.

2-(4-Methoxybenzyl)-3-(2-methoxyphenyl)isoquinolin-1(2*H*)-one, 23

According to procedure B described above, **23** was isolated in 42% yield after flash chromatography on silica gel (pentane–ethyl oxide 1 : 1) as yellow solid. **Mp**: 104–105 °C. **Rf** (pentane–ethyl oxide 1 : 1) = 0.23. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 8.36 (bs, 1H), 8.23–8.20 (m, 1H), 7.63–7.59 (m, 2H), 7.32 (t, 1H, J = 8.7 Hz), 7.26 (d, 2H, J = 8.1 Hz), 7.22 (d, 1H, J = 7.8 Hz), 6.92–6.83 (m, 2H), 6.72 (d, 2H, J = 8.4 Hz), 4.65 (s, 1H), 4.64 (s, 1H), 3.72 (s, 6H, H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 166.0, 160.1, 158.9, 134.6, 133.7, 133.3, 130.8 (2C), 130.7, 130.5, 128.9 (3C), 120.7, 120.0, 114.0 (2C), 111.3, 110.7, 55.9, 55.3, 43.8. **IR (CH_2Cl_2), ν (cm^{-1})**: 3054, 2936, 1652, 1512, 1466. **MS (ES$^+$)**: m/z = 394.18 [M + Na]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{22}NO_3$ [M + H]: 372.1600, found: 372.1617.

3-(2,6-Dimethoxyphenyl)-2-(4-methoxybenzyl)isoquinolin-1(2*H*)-one, 24

According to procedure B described above, **24** was isolated in 65% yield after flash chromatography on silica gel (pentane–ethyl oxide 1 : 1) as yellow oil. **Rf** (pentane–ethyl oxide 1 : 1) = 0.38. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 8.74 (s, 1H), 8.28–8.25 (m, 1H), 7.67–7.64 (m, 1H), 7.45–7.42 (m, 2H), 7.29–7.16 (m, 3H), 6.72 (d, 2H, J = 8.7 Hz), 6.53 (d, 2H, 8.4 Hz), 4.67 (s, 1H), 4.65 (s, 1H), 3.76 (s, 6H), 3.71 (s, 3H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 165.8, 161.3, 158.4, 133.4, 130.6, 130.5, 128.5, 128.2, 128.1, 120.2, 113.6 (2C), 103.4 (2C), 100.3, 96.0, 89.3, 56.0 (2C), 55.1, 43.3. **IR (CH_2Cl_2), ν (cm^{-1})**: 3053, 2942, 1651, 1584, 1512, 1474. **MS (ES$^+$)**: m/z = 402.13 [M + H]; **HRMS (ESI$^+$)**: calculated for $C_{25}H_{24}NO_4$ [M + H]: 402.1705, found: 402.1708.

3-Phenylisoquinolin-1(2*H*)-one, 25

A solution of **15** (50.0 mg, 0.14 mmol, 1.0 eq.) and anisole (159.0 mg, 1.4 mmol, 10.0 eq.) in TFA (2.5 ml, 0.05 M) was stirred at 90 °C for 12 h in a sealed tube. The reaction mixture was allowed to reach r.t. then concentrated *in vacuo*. Resulting brown solid was dissolved in DCM, the solution was neutralized to pH 7 with a triethylamine. Then organic layers were extracted with DCM, washed with sat. brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (cyclohexane–ethyl acetate–triethyl amine 50 : 49 : 1) afforded 27 mg of the desired compound **25** as an off white solid. **Rf** (cyclohexane–ethyl acetate–triethyl amine 50 : 49 : 1) = 0.5. **Mp**: 175–176 °C. **^{1}H NMR** (300 mHz, $CDCl_3$): δ 10.55 (bs, 1H), 8.42 (d, 1H, J = 8.1 Hz), 7.78 (d, 2H, J = 6.9 Hz), 7.70–7.66 (m, 1H), 7.61–7.59 (m, 1H), 7.55–7.47 (m, 4H), 6.79 (s, 1H). **^{13}C-{^{1}H} NMR** (75 mHz, $CDCl_3$): δ 164.1, 139.6, 138.3, 134.3, 132.8, 129.5, 129.1 (2C), 127.5, 126.6, 126.5, 126.3 (2C), 125.0, 104.3. **IR (CH_2Cl_2), ν (cm^{-1})**: 3390, 3053, 2927, 1659, 1486. **MS (ES$^+$)**: m/z = 244.2 [M + Na] **HRMS (ESI$^+$)**: calculated for $C_{15}H_{11}NONa$ [M + Na]: 244.0738, found: 244.0739.

Acknowledgements

A. Dieudonné-Vatran thanks Université Paris Descartes (V) financial support (A. D. V.). The authors are grateful to Dr Martin Arthuis for helpful discussions relating to this work.

Notes and references

1 J. F. Guastavino, S. M. Barolo and R. A. Rossi, *Eur. J. Org. Chem.*, 2006 (17), 3898–3902; A. Saeed and Z. Ashraf, *Pharm. Chem. J.*, 2008, **42**, 277 and references therein.

2 K. B. Simonsen, J. Kehler, K. Juhl, N. Khanzhin and S. M. Nielsen, Patent WO2008131779A1; K. B. Simonsen, K. Juhl, B. Steiger-Brach and S. M. Nielsen, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 379 and references therein.
3 Y. H. Wong, M. K. C. Ho, Y. Q. Hu, D. C. New, X. X. He and H. H. Pang, Patent WO2008092292A1.
4 A. A. Trabanco, G. Duvey, J. M. Cid, G. J. Macdonald, P. Cluzeau, V. Nhem, R. Furnari, N. Behaj, G. Poulain, T. Finn, H. Lavreysen, S. Poli, A. Raux, Y. Thollon, N. Poirier, D. D'Addona, J. I. Andres, R. Lutjens, E. Le Poul, H. Imogai and J. P. Rocher, *Bioorg. Med. Chem.*, 2011, **21** (3), 971–976.
5 T. Matsui, T. Sugiura, H. Nakai, S. Iguchi, S. Shigeoka, H. Takada, Y. Odagaki, Y. Nagao, Y. Ushio, K. Ohmoto, H. Iwamura, S. Yamazaki, Y. Arai and M. Kawamura, *J. Med. Chem.*, 1992, **35** (18), 3307–3319.
6 S. H. Yang, H. T. M. Van, T. N. Le, D. B. Khadka, S. H. Cho, K. T. Lee, E. S. Lee, Y. B. Lee, C. H. Ahn and W. J. Cho, *Eur. J. Med. Chem.*, 2010, **45** (11), 5493–5497.
7 M. Cushman, M. Jayaraman, J. A. Vroman, A. K. Fukunaga, B. M. Fox, G. Kohlhagen, D. Strumberg and Y. Pommier, *J. Med. Chem.*, 2000, **43** (20), 3688–3698.
8 S. W. Li, M. G. Nair, D. M. Edwards, R. L. Kisliuk, Y. Gaumont, I. K. Dev, D. S. Duch, J. Humphreys, G. K. Smith and R. Ferone, *J. Med. Chem.*, 1991, **34** (9), 2746–2754.
9 Y. Asano, S. Kitamura, T. Ohra, F. Itoh, M. Kajino, T. Tamura, M. Kaneko, S. Ikeda, H. Igata, T. Kawamoto, S. Sogabe, S. I. Matsumoto, T. Tanaka, M. Yamaguchi, H. Kimura and S. Fukumoto, *Bioorg. Med. Chem.*, 2008, **16** (8), 4699–4714.
10 P. Ray, J. Wright, J. Adam, S. Boucharens, D. Black, A. R. Brown, O. Epemolu, D. Fletcher, M. Huggett, P. Jones, S. Laats, A. Lyons, J. de Man, R. Morphy, B. Sherborne, L. Sherry, N. van Straten, P. Westwood and M. York, *Bioorg. Med. Chem. Lett.*, 2011, **21** (4), 1084–1088.
11 O. Plettenburg, K. Lorenz, J. Goerlitzer and M. Löhn, WO/2008/07 7555, 2008.
12 C. Y. Watson, W. J. D. Whish and M. D. Threadgill, *Bioorg. Med. Chem.*, 1998, **6** (6), 721–734.
13 D. Gonzalez, T. Martinot and T. Hudlicky, *Tetrahedron Lett.*, 1999, **40** (16), 3077–3080.
14 S. Gabriel and J. Coleman, *Ber.*, 1900, **33**, 980–996.
15 V. A. Glushkov and Y. V. Shklyaev, *Chem. Heterocycl. Compd.*, 2001, **37** (6), 663–687 and references therein.
16 J. E. Semple, R. M. Rydzewski and G. Gardner, *J. Org. Chem.*, 1996, **61** (22), 7967–7972.
17 C.-Y. Cheng, H.-B. Tsai and M.-S. Lin, *J. Heterocycl. Chem.*, 1995, **32**, 73.
18 A. Sugimoto, H. Shinba-Tanaka and M. Ishikawa, *Synthesis*, 1995, **04**, 431, 434..
19 S. Roy, S. Roy, B. Neuenswander, D. Hill and R. C. Larock, *J. Comb. Chem.*, 2009, **11** (6), 1128–1135.
20 T. Minami, A. Nishimoto and M. Hanaoka, *Tetrahedron Lett.*, 1995, **36** (52), 9505–9508.
21 M. S. Chern and W. R. Li, *Tetrahedron Lett.*, 2004, **45** (45), 8323–8326.
22 N. Briet, M. H. Brookes, R. J. Davenport, F. C. A. Galvin, P. J. Gilbert, S. R. Mack and V. Sabin, *Tetrahedron*, 2002, **58** (29), 5761–5766.
23 For reviews, see: I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104** (5), 2127–2198; J. E. R. Sadig and M. C. Willis, *Synthesis*, 2011, **1**, 1–22.
24 H. Sashida and A. Kawamukai, *Synthesis*, 1999 (07), 1145–1148.
25 V. R. Batchu, D. K. Barange, D. Kumar, B. R. Sreekanth, K. Vyas, E. A. Reddy and M. Pal, *Chem. Commun.*, 2007, **19**, 1966–1968.
26 C.-C. Liu, K. Parthasarathy and C.-H. Cheng, *Org. Lett.*, 2010, **12** (15), 3518–3521.
27 T. Yao and R. C. Larock, *J. Org. Chem.*, 2005, **70** (4), 1432–1437.
28 H. Gao and J. Zhang, *Adv. Synth. Catal.*, 2009, **351** (1–2), 85–88.
29 T. Miura, M. Yamauchi and M. Murakami, *Org. Lett.*, 2008, **10** (14), 3085–3088.
30 Y. Kajita, S. Matsubara and T. Kurahashi, *J. Am. Chem. Soc.*, 2008, **130** (19), 6058–6059.
31 F. Wang, H. Liu, H. Fu, Y. Jiang and Y. Zhao, *Org. Lett.*, 2009, **11** (11), 2469–2472.
32 Z. Zheng and H. Alper, *Org. Lett.*, 2008, **10** (21), 4903–4906.
33 A. C. Tadd, A. Matsuno, M. R. Fielding and M. C. Willis, *Org. Lett.*, 2009, **11** (3), 583–586.
34 (*a*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132** (30), 10565–10569; (*b*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133** (16), 6449–6457; (*c*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133** (8), 2350–2353; (*d*) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50** (28), 6379–6382.
35 M. Arthuis, R. Pontikis and J.-C. Florent, *Org. Lett.*, 2009, **11** (20), 4608–4611.
36 For a review, see: *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley-Interscience, New York, 2002, p. 650; G. Chelucci, F. Capitta and S. Baldino, *Tetrahedron*, 2008, **64** (44), 10250–10257; Y.-Q. Fang and M. Lautens, *J. Org. Chem.*, 2007, **73** (2), 538–549.
37 G. Chelucci and S. Baldino, *Tetrahedron Lett.*, 2008, **49** (17), 2738–2742.
38 J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2008, **73** (18), 7102–7107.
39 B. M. Trost and M. K. Ameriks, *Org. Lett.*, 2004, **6** (11), 1745–1748.
40 L. M. Klingensmith, E. R. Strieter, T. E. Barder and S. L. Buchwald, *Organometallics*, 2005, **25** (1), 82–91.
41 M. Lamblin, A. Couture, E. Deniau and P. Grandclaudon, *Org. Biomol. Chem.*, 2007, **5** (9), 1466–1471.
42 L. Ackermann, *Org. Lett.*, 2005, **7** (3), 439–442.
43 P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133** (15), 6061–6071.
44 P. Koos, U. Gross, A. Polyzos, M. O'Brien, I. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2011, **9** (20), 6903–6908.