Approaches to the Synthesis of 2,3-Dihaloanilines. Useful Precursors of 4-Functionalized-1*H*-indoles

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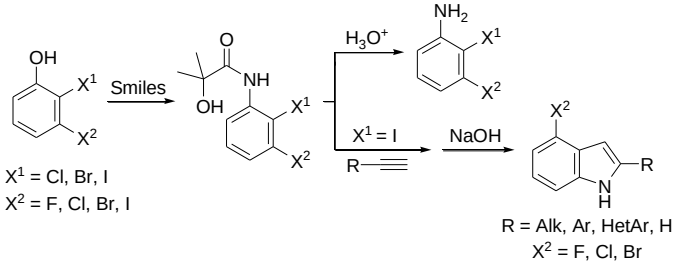
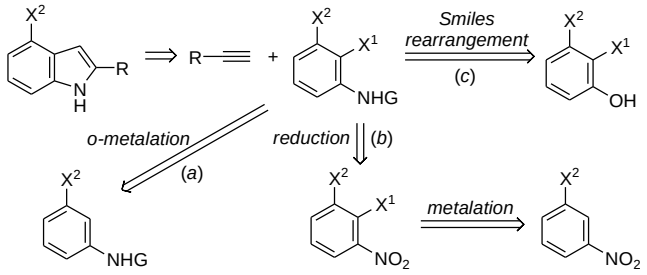


Abstract. 2,3-Dihaloanilines have been proved as useful starting materials for synthesizing 4-halo-1*H*-indoles. Subsequent or in situ functionalization of the prepared haloindoles allows the access to a wide variety of 2,4- or 2,3,4-regioselectively functionalized indoles in good overall yields. As no efficient synthetic routes to 2,3-dihaloanilines have been described in the literature, different approaches to the preparation of these 1,2,3-functionalized aromatic precursors are now presented. The most general one involves a Smiles rearrangement from the corresponding 2,3-dihalophenols and allows the preparation of 2,3-dihaloanilides in a straightforward and synthetically useful manner.

Introduction

Indole derivatives are usually referred to as privileged structures due to their excellent binding ability to many receptors and so, the indole core represents one of the ubiquitous heterocyclic scaffolds in biologically active compounds.[1] This prevalence in bioactive molecules has prompted the development of efficient and practical syntheses of indoles bearing a variety of substitution patterns, which provides a continual challenge to organic chemists.[2] In this field, considerable efforts are needed to obtain valuable 4-substituted indoles and few methods have been described. Some reported examples involve the metalation of adequately 3-functionalized indoles,[3] regioselective hydrodebromination of 4,6-dibromoindoles,[4] C–H activation of 4-acetoxy-6,7-dihydroindoles,[5] and selective lithiation of 4,7-dibromoindoles.[6] In recent years, a few particular examples of 4-haloindoles have also been prepared by different metal-catalyzed processes.[7] Nevertheless, the most general strategy to prepare these 4-functionalized-1*H*-indoles involves the construction of the heterocyclic ring using an annelative method from properly substituted aromatic precursors.[8] Its main disadvantage is the requirement of a specifically functionalized benzene derivative that are in general difficult to get. Within the current approach, we reasoned that one of the most direct entries to 4-haloindoles, which are valuable precursors for further functionalization, could involve a selective Sonogashira cross coupling with the appropriate 2,3-dihaloaniline derivative and a subsequent heteroannulation reaction (Scheme 1). However, this easy approach to 4-haloindoles has not been previously reported probably due to the fact that no direct routes are known for accessing to 2,3-dihaloanilines.[9] Among 3-halo-2-iodoanilines, only 3-bromo-2-iodoaniline has been described although its preparation requires a sequence involving diazotation/iodide displacement/reduction from 2-bromo-6-nitroaniline, which is obtained as the minor isomer in the nitration of 2-bromoaniline.[10] In the same way, the syntheses of 2-bromo-3-chloroaniline[11] and 2,3-dibromoaniline[12] have been performed by using analogous multi-step and inefficient strategies.

SCHEME 1. Retrosynthetic Analysis of 4-Haloindoles and 2,3-Dihaloanilines



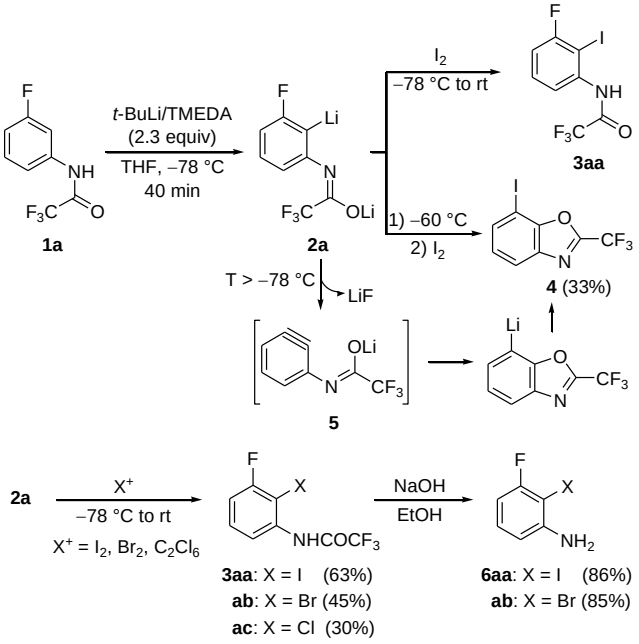
Taking into account the foreseeable potential of 2,3-dihaloanilines as precursors of 4-haloindoles, we decided to develop an efficient synthesis of these 1,2,3-functionalized benzene derivatives. We envisaged three different pathways to access these substrates. As shown in Scheme 1, route (a) would involve an *ortho*-metalation reaction of a 3-haloaniline derivative. To the best of our knowledge, the only reported example of this approach is due to Soll and co-workers, who reported the *o*-lithiation of *N*-trifluoroacetyl-3-fluoroaniline **1a** and were able to prepare 2-bromo-3-fluoroaniline.[13] Alternatively, the desired anilines could be prepared by reduction of the corresponding 2,3-dihalonitrobenzenes (Scheme 1, route (*b*)).[14] However, the only efficient and direct route to these latter compounds is limited to the synthesis of 2-bromo-3-fluoronitrobenzene by a base-mediated halogenation reaction.[15] Finally, taking advantage of the efficient synthesis of 2,3-dihalophenols that we have previously developed,[16] we also reasoned that the corresponding 2,3-dihaloanilines could be obtained from their phenol counterparts through a "Smiles rearrangement" strategy (Scheme 1, route (*c*)).[17] Herein, we report our results on the synthesis of 2,3-dihaloanilines and their application to the preparation of 4-halo-1*H*-indoles and different regioselectively functionalized indoles.[18]

Results and Discussion

As above established, the *o*-lithiation of *N*-trifluoroacetyl-3-fluoroaniline (**1a**) has been previously described.[13] Its treatment with *t*-BuLi in the presence of TMEDA gives rise to the generation of the organolithium intermediate **2a**, which was trapped with methyl disulfide or bromine. This *o*-metalation

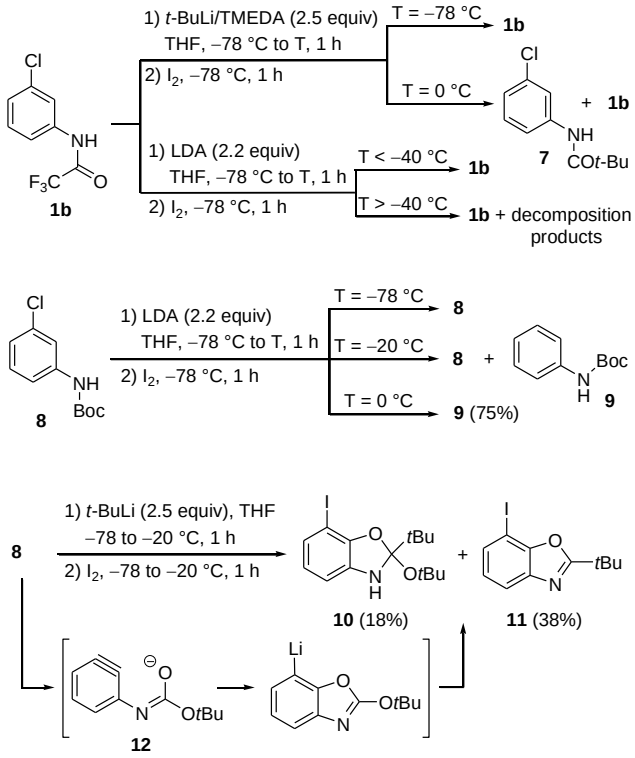
reaction has not been further used in synthesis in spite of the potential interest in the resulting 2,3-difunctionalized aniline derivatives for the preparation of fluorine-containing indoles. So, first we tried to apply the reported reaction conditions to get 3-fluoro-2-iodotrifluoroacetanilide (**3aa**) from **1a** employing iodine as an electrophile. Thus, using a slight excess of *t*-BuLi/TMEDA in THF at −78 ºC, we were able to generate the dilithiated species **2a** and trap it with iodine, allowing the isolation of **3aa** in 63% yield (Scheme 2). We also observed that working at temperatures over ca. −60 ºC a competitive lithium fluoride elimination takes place affording benzyne[19] intermediate **5** that intramolecularly evolve to afford, after electrophilic quenching, the iodinated benzoxazole **4** in moderate yield (Scheme 2). This observation has been previously described by Clark and Caroon in the directed metalation of 3-fluoroaniline bearing pivaloyl, *N*-Boc, or benzoyl as directing groups.[20] In an analogous way, the addition of bromine or hexachloroethane as electrophilic reagents to **2a** afforded the corresponding 3-fluoro-2-halo-trifluoroacetanilides **3ab** and **3ac** in 45 and 30% yield. Moreover, the basic hydrolysis of some of these trifluoroacetanilides **3** furnished 3-fluoro-2-haloanilines **6aa** and **6ab** in high yields (Scheme 2).

SCHEME 2. Synthesis of 3-Fluoro-2-halotrifluoroacetanilides 3 and 3-Fluoro-2-haloanilines 6



However, when we tried to apply the *o*-lithiation strategy, under the same reaction conditions used for the metalation of **1a** (*t*-BuLi/TMEDA, THF, −78 ºC), to 3-chlorotrifluoroacetanilide **1b** we could not obtain the corresponding 3-chloro-2-iodoaniline derivative and the starting material was recovered. When the reaction mixture was allowed to reach higher temperatures (over –40 ºC), the addition of *t*-BuLi to the trifluoroacetamido moiety was observed and N-(3-chlorophenyl)pivalamide (**7**) could be isolated (Scheme 3).[21] The use of *n*-BuLi instead of *t*-BuLi precludes the addition reaction but no metalation was observed below –30 ºC.[22] On the other hand, the use of LDA as metalating agent did not give satisfactory results either. Thus, below ca. –40 ºC, no reaction occurred, whereas allowing the reaction mixture to reach higher temperatures led to decomposition products (Scheme 3).[23] Then, we attempted to exploit the well known *ortho*-directing ability of the Boc group[24] for the synthesis of 3-chloro-2-iodoaniline starting from *N*-(Boc)-3-chloroaniline (**8**). In this case, treatment with LDA in THF gave rise to a different result. At low temperature, the starting material remained intact, but upon warming the reaction mixture *N*-(Boc)-aniline (**9**) started to form and at 0 ºC it could be isolated in high yield (Scheme 3).[25] It is known that *t*-BuLi is able to abstract the proton from the double activated position in the *meta* isomers of *N*-(Boc)fluoro- and chloroanilines already at low temperature, and also it has been shown that the subsequent elimination of lithium halide and generation of a benzyne intermediate is not possible to prevent, thus leading to 7-lithiobenzoxazole derivatives.[26] However, as this reaction has not been carried out with **8**, we decided to check its metalation with *t*-BuLi and further trapping with iodine. As expected from previous results, 7-iodobenzoxazole derivatives **10** and **11**,[27] whose formation could be understood through generation of an aryne intermediate, such as **12**, were obtained in a moderate combined yield (Scheme 3).

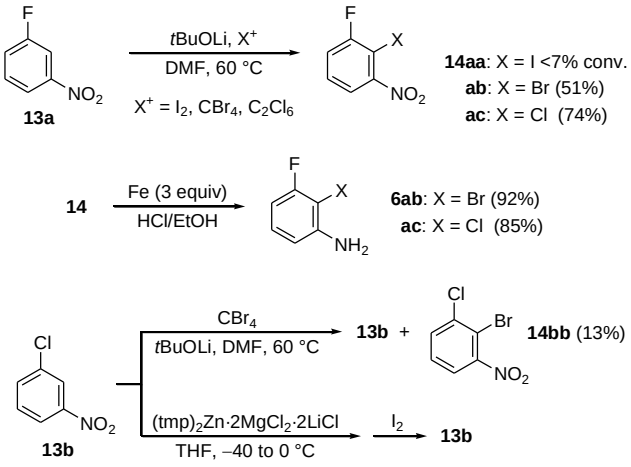
SCHEME 3. Unsuccessful Synthesis of 3-Chloro-2-iodoaniline from 3-Chloroaniline Derivatives 1b and 8



Having seen that the directed *ortho*-metalation strategy for the synthesis of 2,3-dihaloanilines is only useful for preparing 3-fluoro-2-haloanilines, we turned our attention to the preparation of 2,3-dihalonitrobenzenes. Daugulis and co-workers reported the base-mediated halogenation of acidic sp^2 C–H bonds and described the synthesis of 2-bromo-3-nitrofluorobenzene (**14ab**) by treatment of 3-nitrofluorobenzene (**13a**) with lithium *t*-butoxide and carbon tetrabromide in DMF.[15] We were able to reproduce this result and moreover, we explored the extension of this protocol to the preparation of other 2,3-dihalonitrobenzenes **14**. Therefore 2-chloro-3-nitrofluorobenzene (**14ac**) was formed in high yield using hexachloroethane as the electrophile. However, the employment of iodine as the halogen electrophile in order to prepare 2-iodo-3-nitrofluorobenzene (**14aa**) gave rise to low conversion to the desired adduct (<10%) (Scheme 4). With a suitable method for the preparation of 2,3-dihalonitrobenzenes **14ab** and **14ac** from commercially available 3-nitrofluorobenzene (**13a**), the corresponding anilines **6ab** and **6ac** were readily synthesized in high yields by reduction with iron

(Scheme 4). Nevertheless, when we applied this strategy to 3-nitrochlorobenzene (**13b**), only a 13% yield of the corresponding 2-bromo-3-nitrochlorobenzene (**14bb**)[28] was obtained, showing that the deprotonation of **13b** was not efficient (Scheme 4). In addition, we tried to metalate this arene derivative by using $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ as the base, which has been described by Knochel and co-workers for the chemoselective zincation of sensitive arenes and heteroarenes, such as 2-nitrobenzo[*b*]furan.[29] However, **13b** was not zincated with this base even at 0 ºC (Scheme 4).

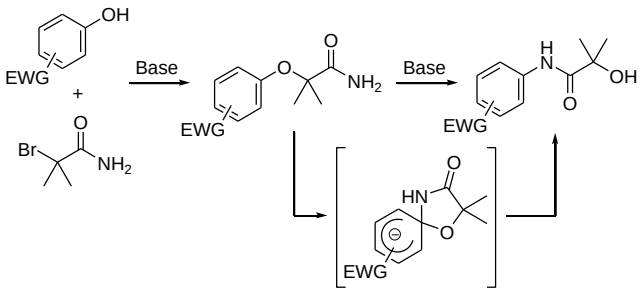
SCHEME 4. Synthesis of 2-Halo-3-nitrofluorobenzenes 14 and Alternative Preparation of 3-Fluoro-2-haloanilines 6ab and 6ac



Taking into account that only 2-halo-3-fluoroanilines **6aa-ac** could be accessed by the first two of our envisaged approaches (Scheme 1, routes (a) and (b)), we then examined the use of 2,3-dihalophenol derivatives as starting materials (Scheme 1, route (c)). The direct conversion of phenols into anilines represents an intriguing organic transformation and few general methods have been reported for this reaction. Some of them include the conversion of phenols to aryl diethyl phosphates and subsequent treatment with KNH_2,[30] their activation with 4-chloro-2-phenylquinazoline and further thermal rearrangement,[31] as well as the Bucherer reaction of phenols with ammonium sulfite that is generally limited to naphthols and hydroxy- and aminophenols.[32] More recently, the Pd-catalyzed coupling of amines with aryl triflates or tosylates has meant an important advance in this field.[33] However, aryl

halides are also useful partners for these metal-catalyzed C–N bond forming reactions,[34] so the use of this strategy is precluded for our halophenol derivatives. Besides the Pd- and Cu-catalyzed processes, Smiles rearrangement, which works especially well with an activated phenoxy component bearing at least one halogen subsituent, could be considered a complementary and valuable alternative for the preparation of *N*-arylamines from phenols (Scheme 5).[35] This methodology requires the initial conversion of the corresponding phenol into a substituted aryloxyacetamide derivative in which oxygen and nitrogen atoms are connected by a $COC(R)_2$ group. The phenol is usually alkylated with 2-bromo-2-methylpropionamide affording a 2-aryloxy-2-methylpropanamide that undergoes rearrangement to give an *N*-aryl-2-hydroxypropionamide under basic conditions.[36] The formation of the final product must involve a nucleophilic attack of the amide anion leading to a spiro intermediate followed by its breakdown and protonoation (Scheme 5). For this two-step sequence, some one-pot procedures have been reported in literature avoiding the isolation of the intermediate 2-aryloxy-2-methylpropanamide.[37] In addition, subsequent hydrolysis of the generated anilide could afford the corresponding aniline.

SCHEME 5. Smiles Rearrangement



As we had reported, a new and efficient synthesis of 2,3-dihalophenols from 3-halophenols using the *O*-carbamate-directed metalation methodology,[16a] we thought that the Smiles rearrangement could be suitable for our initial purpose of developing an efficient approach to 2,3-dihaloanilines. The required 2,3-dihalophenols **16** were obtained by basic hydrolysis of the corresponding *O*-2,3-dihalophenylcarbamates **15**, which in turn were efficiently accessed from 3-halophenylcarbamates by *o*-

lithiation and trapping with halogen electrophiles (Scheme 6).[16a] For the introduction of bromine, better yields have been obtained by using carbon tetrabromide as the electrophilic reagent compared to the use of 1,2-dibromoethane, which was used in our previous report.[38] The crude phenols **16** were treated with an excess of 2-bromo-2-methylpropionamide[39] and NaOH in DMF at room temperature forming 2-aryloxy-2-methylpropionamides **17** that were isolated in high yields by simple addition of water to the reaction mixture and filtration of the crystallized compound (Scheme 6 and Table 1). Interestingly, addition of an excess of NaOH to a DMF solution of crude derivatives **17** and subsequent warming to 60 ºC for 2 h afforded *N*-aryl-2-hydroxypropionamides **18** in high overall yields relative to the starting carbamates **15** (Scheme 6 and Table 1). In this way, 2,3-dihaloanilides **18** can be efficiently synthesized from 2,3-dihalophenylcarbamates **15** in a three-step (carbamate hydrolysis–phenol alkylation–rearrangement), two-pot process. Furthermore, simple addition of water at the end of the rearrangement leads to crystallization of anilides **18** from the reaction solution, which proved to be pure enough without further chromatographic purification.

SCHEME 6. Synthesis of *N*-(2,3-Dihalophenyl)-2-hydroxy-2-methylpropanamides 18

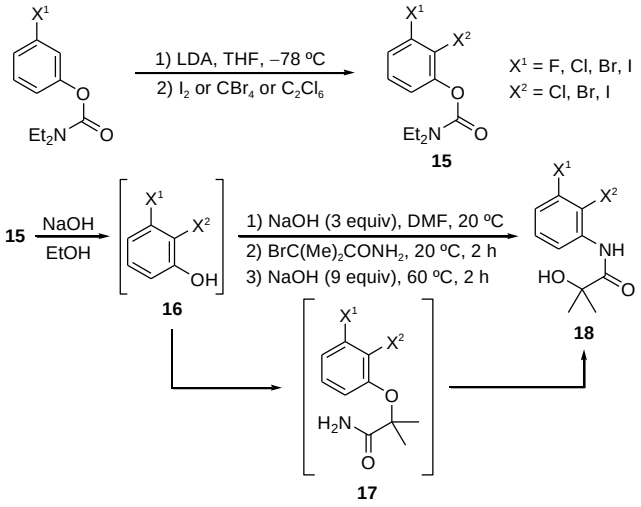


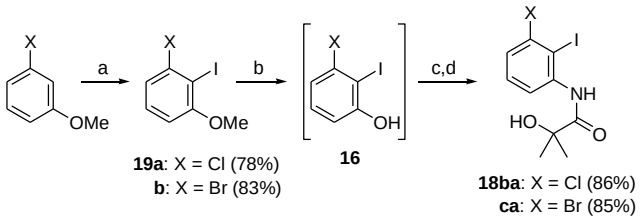
TABLE 1. Preparation of Propanamides 17 and Dihaloanilides 18 from *O*-2,3-Dihalophenyl carbamates 15

entry	starting material	X^1	X^2	**17**	yield[a] (%)	**18**	yield[a] (%)
1	**15aa**	F	I	**17aa**	86	**18aa**	83
2	**15ab**	F	Br	**17ab**	83	**18ab**	77
3	**15ac**	F	Cl	**17ac**	82	**18ac**	76
4	**15ba**	Cl	I	**17ba**	86	**18ba**	82
5	**15bb**	Cl	Br	**17bb**	80	**18bb**	78
6	–[b]	Cl	Cl	**17bc**	87	**18bc**	84
7	**15ca**	Br	I	**17ca**	85	**18ca**	81
8	**15cb**	Br	Br	**17cb**	86	**18cb**	83
9	**15cc**	Br	Cl	**17cc**	82	**18cc**	77
10	**15da**	I	I	**17da**	83	**18da**	79
11	**15db**	I	Br	**17db**	80	**18db**	77
12	**15dc**	I	Cl	**17dc**	79	**18dc**	75

[a] Isolated yield referred to starting material **15**. [b] Commercially available 2,3-dichlorophenol was used as starting material.

On the other hand, we have also established an alternative synthesis of 3-chloro-2-iodoanisole (**19a**) and 3-bromo-2-iodoanisole (**19b**) by *o*-zincation of the corresponding 3-haloanisoles with lithium di-*t*-butyltetramethylpiperidinozincate,[40] and further treatment with iodine of the intermediate arylzincate.[16b] These 2,3-dihaloanisoles **19** also proved to be useful starting materials to afford 2,3-dihaloanilides **18ba** and **18ca** in high yields by an analogous three-step (BBr_3-mediated deprotection–phenol alkylation–rearrangement), two-pot process (Scheme 7).

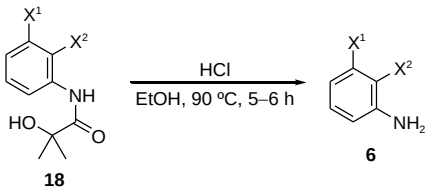
SCHEME 7. Alternative Synthesis of *N*-(3-Halo-2-iodophenyl)-2-hydroxy-2-methylpropanamides 18ba and 18ca



[a] Reagents and conditions: (a) (1) *t*-$Bu_2Zn(tmp)Li$, THF, –45 ºC (for X = Cl) or –30 ºC (for X = Br); (2) I_2, THF; (b) (1) BBr_3, CH_2Cl_2; (2) $NaHCO_3$, MeOH; (c) (1) NaOH (3 equiv), DMF, rt; (2) $BrC(Me)_2CONH_2$ (3 equiv), rt; (d) NaOH (9 equiv), 60 ºC.

Once we have developed a reliable procedure for accessing 2,3-dihaloanilides **18** and due to the lack of methods for the preparation of 2,3-dihaloanilines, we tried to synthesize 2,3-dihaloanilines **6** by hydrolysis of the corresponding anilides **18**. We found that, in general, their reaction with ethanolic 6 M HCl at 90 ºC for 6 h afforded **6** in high yields (Table 2). However, iodine-containing rearranged amides **18** did not cleanly furnish the expected haloiodoanilines as partial loss of the iodine atom occurred under the reaction conditions. For instance, 2,3-diiodoanilide **18da** led to 2,3-diiodoaniline (**6da**) and 3-iodoaniline in a ca. 1:2 ratio (78% combined yield), whereas 3-chloro-2-iodoanilide **18ba** afforded a 2:3 mixture of 3-chloro-2-iodoaniline (**6ba**) and 3-chloroaniline in 80% overall yield.[41]

TABLE 2. Synthesis of 2,3-Dihaloanilines 6



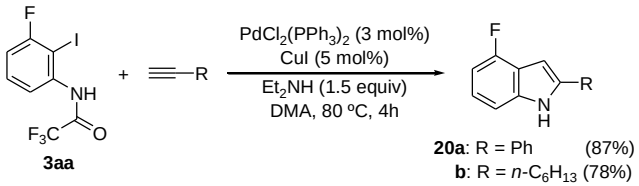
entry	starting material	X^1	X^2	product	yield[a] (%)
1	**18ab**	F	Br	**6aa**	89

2	**18ac**	F	Cl	**6ab**	66[b]
3	**18bb**	Cl	Br	**6bb**	94
4	**18bc**	Cl	Cl	**6bc**	90
5	**18cb**	Br	Br	**6cb**	89
6	**18cc**	Br	Cl	**6cc**	95

[a] Isolated yield based on the starting material **18**. [b] Lower yield probably due to volatility of this aniline.

Considering our retrosynthetic analysis for the synthesis of 4-haloindoles (Scheme 1), and having developed convenient routes for accessing 2,3-dihaloanilides **3** and **18**, then we tackle the preparation of a wide range of different 4-haloindoles. First, an efficient preparation of 4-fluoro-2-substituted-1*H*-indoles **20** was achieved by reaction of 3-fluoro-2-iodotrifluoroacetanilide (**3aa**) with terminal aromatic and aliphatic alkynes through a domino Pd/Cu-catalyzed coupling-cyclization process (Scheme 8).[42]

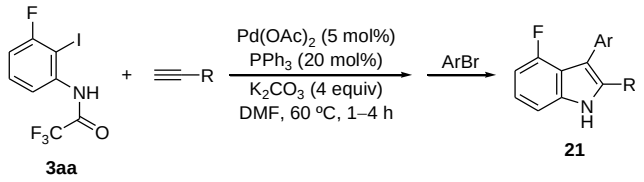
SCHEME 8. Synthesis of 4-Fluoro-2-substituted-1*H*-indoles 20



On the other hand, the aminopalladation–reductive elimination domino reaction, mainly developed by Cacchi and co-workers,[43] has been employed as a useful strategy for the regioselective construction of 2,3-disubstituted indole rings from *o*-alkynyltrifluoroacetanilides. Interestingly, some methodologies have been reported for the one pot–three component (*o*-haloanilide, terminal alkyne, aryl halide) synthesis of 2,3-disubstituted-1*H*-indoles.[44] Based on the report of Lu and co-workers,[44b] we have been able to prepare a wide variety of 3-aryl-4-fluoro-2-substituted-1*H*-indoles **21** from 3-fluoro-2-iodotrifluoroacetanilide (**3aa**), terminal alkynes and aryl bromides in a one-pot process through tandem Sonogashira–Cacchi reactions (Table 3). Moderate to high yields were obtained for a selection of

terminal alkynes and aryl bromides, which could be added after the starting iodoanilide **3aa** was consumed (Table 3, entries 1, 2, 5–8) or from the beginning of the reaction (Table 3, entries 3 and 4).

TABLE 3. Synthesis of 3-Aryl-4-fluoro-2-substituted-1*H*-indoles 21a-h

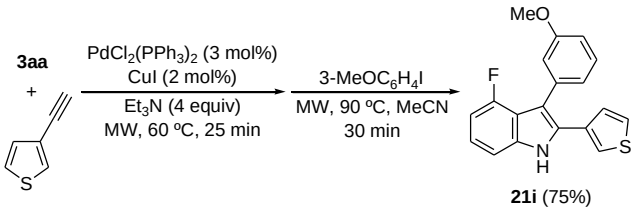


entry	R	Ar	product	Yield[a] (%)
1	Ph	2-$NO_2C_6H_4$	**21a**	72
2	*n*-Bu	2-$NO_2C_6H_4$	**21b**	80
3[b]	Ph	3-$MeOC_6H_4$	**21c**	84
4[b]	*n*-C_6H_{13}	4-MeO-3-MeC_6H_3	**21d**	56
5	3-Th	3-CNC_6H_4	**21e**	86
6	*c*-C_6H_9	4-$NO_2C_6H_4$	**21f**	85
7	4-$MeOC_6H_4$	3-CNC_6H_4	**21g**	90
8	*n*-C_6H_{13}	2-CNC_6H_4	**21h**	46

[a] Isolated yield based on starting material **3aa**. [b] The aryl bromide was added from the beginning of the reaction.

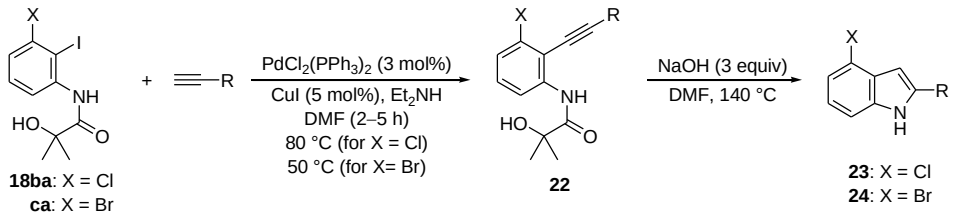
In addition, we have also prepared trisubstituted indole **21i** by a microwave-assisted one-pot, three-component coupling reactions described by Larock and co-workers.[44c] In this case, an aryl iodide was used instead of the corresponding bromide for the introduction of the aryl group at the C-3 position of the indole ring. Interestingly, although the addition of an inorganic base, such as K_2CO_3 or Cs_2CO_3, is usually required for the Cacchi reaction, in our hands this microwave-irradiated process works efficiently under the exclusive influence of Et_3N as base (Scheme 9).

SCHEME 9. Synthesis of 3-Aryl-4-fluoro-2-substituted-1*H*-indole 21i



In order to prepare 4-chloro- and 4-bromo-1*H*-indoles we decided to check the suitability of the 3-halo-2-iodoanilides **18ba** and **18ca** for a selective Sonogashira coupling with terminal alkynes. Gratifyingly, we found that under standard conditions (Pd-Cu catalysis), and without the use of special phosphine ligands, these 2,3-dihaloanilides underwent selective coupling at the iodine atom despite this *ortho*-position is the most sterically crowded one. However, to avoid dialkynylation processes in the case of **18ca**, bearing a bromo substituent, a careful control of the reaction temperature should be exerted. A broad array of terminal alkynes, including aryl-, alkyl-, heteroaryl-, alkenyl-, and trialkylsilyl-substituted ones, were efficiently coupled with anilides **18**, providing 2-alkynyl-3-haloanilides **22** in high yields (Table 4). With these *o*-alkynylanilides **22** in our hands and taking advantage of our previously reported methodology for the synthesis of indoles through NaOH-mediated cyclization of *o*-alkynylaniline derivatives,[45] we obtained 4-chloro-1*H*-indoles **23** and 4-bromo-1*H*-indoles **24** in usually high yields by treatment of **22** with excess of NaOH at high temperature (Table 4).[46] It is interesting to note that *N*-deprotection also occurred under the reaction conditions. In addition, starting from *o*-trimethylsilylethynylanilides **22be** or **22ce**, 2-unsubstituted 4-halo-1*H*-indoles **23e** and **24e** were respectively obtained, showing that the cleavage of the silyl group also takes place under the reaction conditions (Table 4, entries 5 and 10).

TABLE 4. Selective Sonogashira Couplings from 3-Halo-2-iodoanilides 18 and Synthesis of 4-Halo-1*H*-indoles 23 and 24 from 2-Alkynyl-3-haloanilides 22



18ba: X = Cl
ca: X = Br

22

23: X = Cl
24: X = Br

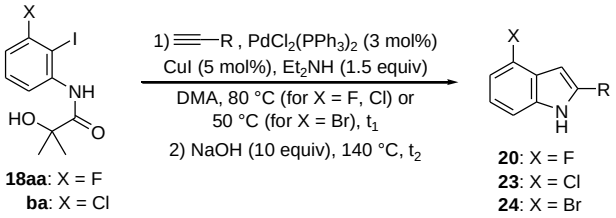
entry	starting material	X	alkyne (R)	time (h)	product	yield[a] (%)	time (h)	product	yield[b] (%)
1	**18ba**	Cl	Ph	2	**22ba**	86	4	**23a**	79
2	**18ba**	Cl	*n*-Bu	2.5	**22bb**	90	2.5	**23b**	86
3	**18ba**	Cl	*n*-C_5H_{11}	2.5	**22bc**	81	2.5	**23c**	84
4	**18ba**	Cl	*c*-C_6H_9[c]	3	**22bd**	80	2.5	**23d**	81
5	**18ba**	Cl	$SiMe_3$	5.6[d]	**22be**	81	4	**23e**[e]	73
6	**18ca**	Br	Ph	3.5	**22ca**	80	5	**24a**	83
7	**18ca**	Br	*n*-Bu	3.5	**22cb**	85	3	**24b**	80
8	**18ca**	Br	*n*-C_5H_{11}	3.5	**22cc**	79	2.5	**24c**	82
9	**18ca**	Br	*c*-C_6H_9[c]	5	**22cd**	86	4	**24d**	76
10	**18ca**	Br	$SiMe_3$	3[d]	**22ce**	71	5	**24e**[f]	75
11	**18ca**	Br	3-Thienyl	3.5	**22cf**	74	3	**24f**	71

[a] Isolated yield based on the corresponding starting material **18**. [b] Isolated yield based on the corresponding starting material **22**. [c] 1-Cyclohexenyl. [d] Conducted at 40 ºC for 6 h. [e] 4-Chloro-1*H*-indole (R = H). [f] 4-Bromo-1*H*-indole (R = H).

We had also shown that 2-substituted-1*H*-indoles could be prepared in a one-pot manner starting from *o*-iodoaniline derivatives and terminal alkynes, involving an initial Sonogashira coupling, followed by NaOH-mediated cyclization, without the need for isolation of the intermediate *o*-alkynylaniline.[45] In this way 4-fluoro-, 4-chloro-, and 4-bromo-1*H*-indoles **20**, **23**, and **24**, respectively, were synthesized from 3-halo-2-iodoanilides **18aa-ca** and a selection of terminal alkynes by a one-pot, two-step procedure (Table 5). Using this procedure, 4-fluoroindoles **20** (Table 5, entries 1 and 2) as well as 4-chloroindoles **23** (Table 5, entries 3–8) were obtained in overall good yields based on the starting materials **18**,

whereas 3-bromo-2-iodoanilide **18ca** formed the corresponding 4-bromoindoles **24** in lower yields (Table 5, entries 9–11). As in this one-pot protocol, Pd salts are not removed after the Sonogashira coupling and prior to the subsequent cyclization step; the isolation of these indole derivatives **24** in lower yields could be due to competitive Pd-catalyzed processes involving the C–Br bond, which could lead to different side-products. So, for accessing 4-bromoindoles the two-step sequence involving isolation of intermediates **22** proved more appropriate.

TABLE 5. One-pot Synthesis of 4-Halo-1*H*-indoles 20, 23, and 24 from 2,3-Dihalonanilides 18



18aa: X = F
ba: X = Cl
ca: X = Br

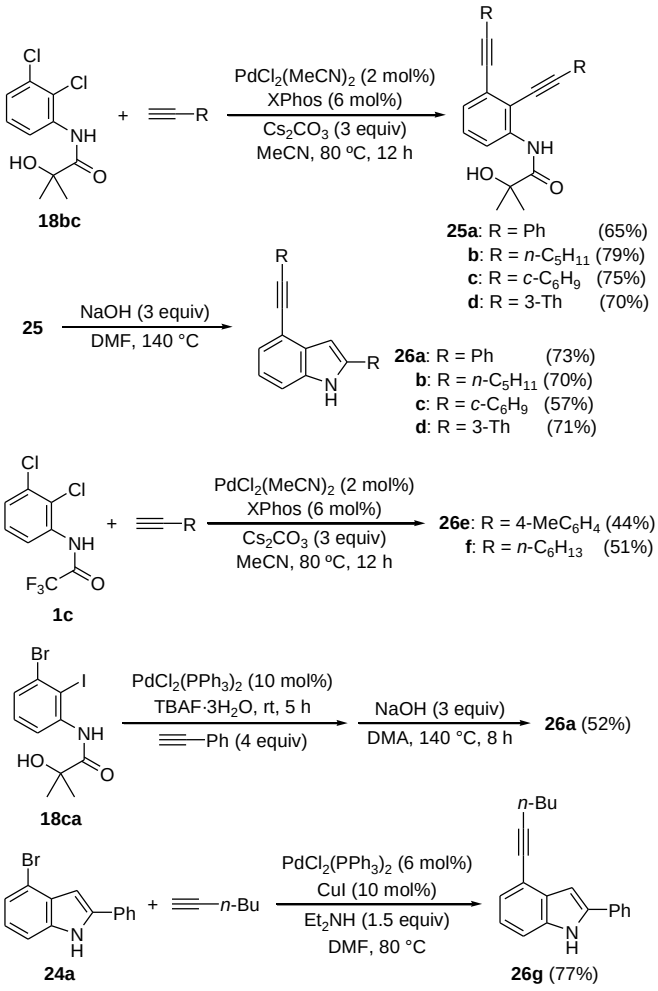
20: X = F
23: X = Cl
24: X = Br

entry	starting material	X	R	time$_1$ (h)	time$_2$ (h)	product	yield[b] (%)
1	**18aa**	F	Ph	3	4	**20a**	85
2	**18aa**	F	*n*-Bu	3	3	**20c**	77
3	**18ba**	Cl	Ph	3	4	**23a**	81
4	**18ba**	Cl	*n*-Bu	2.5	3	**23b**	71
5	**18ba**	Cl	*c*-C_6H_9[c]	2	3	**23d**	82
6	**18ba**	Cl	$SiMe_3$	5.5	3	**23e**[e]	61
7	**18ba**	Cl	3-ClC_6H_4	2	3	**23f**	75
8	**18ba**	Cl	4-F-3-MeC_6H_3	2	4	**23g**	72
9	**18ca**	Br	Ph	3	4	**24a**	49
10	**18ca**	Br	*n*-Bu	2	3	**24b**	55
11	**18ca**	Br	3-ClC_6H_4	2	4	**24g**	48

[a] Isolated yield based on the corresponding starting material **18**. [b] Isolated yield based on the corresponding starting material **22**. [c] 1-Cyclohexenyl. [d] Carried out at 40 ºC for 6 h. [e] 4-Chloro-1*H*-indole (R = H). [f] 4-Bromo-1*H*-indole (R = H).

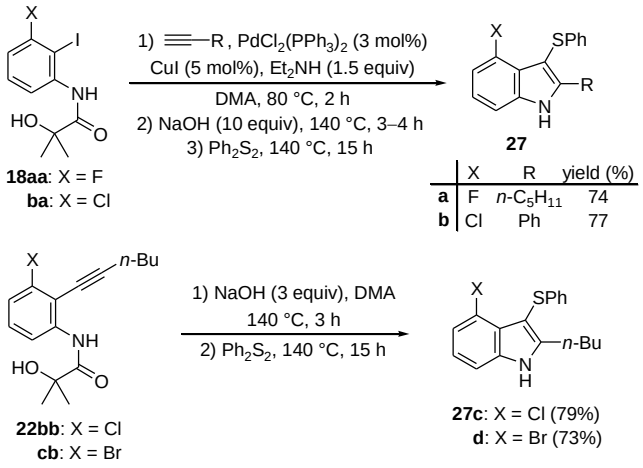
Although selective Sonogashira couplings of 3-halo-2-iodoanilides **18aa-ca** have been efficiently achieved (Tables 4 and 5), the presence of two halogen atoms in the starting anilides **18** prompted us to attempt the synthesis of 4-alkynyl-2-substituted-1*H*-indoles **26** (Scheme 10). First we chose 2,3-dichloroanilide **18bc** as starting material and performed the dialkynylation reaction[47] with different terminal alkynes using the catalytic system described by Buchwald and Gelman for the Sonogashira coupling of aryl chlorides.[48] In this way, 2,3-dialkynylanilides **25** were obtained in good yields. Further cyclization reaction of the former substrates under basic conditions afforded 4-alkynyl-1*H*-indoles **26** bearing the same substituent at the terminal position of the triple bond and at C-2 (Scheme 10). As 2,3-dichloroaniline is commercially available, we also decided to check the usefulness of easily available trifluoroacetamide **1c** for the synthesis of the same type of indoles **26**. Due to the presence of the trifluoroacetamido group on the nitrogen atom, the corresponding intermediates **25** could not be isolated and the final indole derivatives **26e,f** were obtained in a one-pot process though with similar overall yield compared with the two-step protocol. Moreover, other 2,3-dihaloanilides, such as **18ca**, are suitable substrates for the preparation of 4-alkynylindoles **26**. In this case, **26a** was synthesized in moderate yield by using a copper- and solvent-free methodology[49] for the Sonogashira couplings (Scheme 10). Finally, to prepare a 4-alkynylindole with different substituents at C-2 and at the terminal position of the triple bond, 4-bromoindole **24a** was used as starting material and treated under standard Sonogashira conditions. Using this approach, 4-hex-1-ynyl-2-phenyl-1*H*-indole **26g** was obtained in good yield (Scheme 10).

SCHEME 10. Synthesis of 4-Alkynyl-2-substituted-1*H*-indoles 26 from 2,3-Dichloroanilides 1c,18bc and 4-Bromoindole 24a



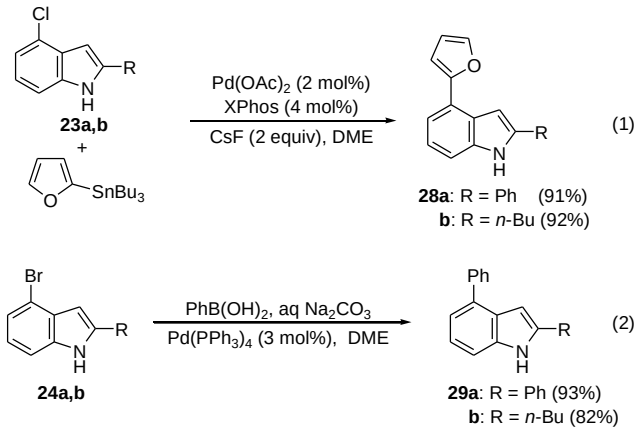
With the aim of getting highly functionalized indole derivatives from our 2,3-dihaloanilides **18**, we tried to introduce an arylthio group at C-3 under the reaction conditions employed for the synthesis of haloindoles **24**. Starting from 3-halo-2-iodoanilides **18aa** and **18ba** and two different terminal alkynes we were able to prepare 4-halo-3-phenylthio-2-substituted-1*H*-indoles **27** in a one-pot, three-step protocol involving the addition of diphenyl disulfide after the NaOH-mediated cyclization step. It should be noted that these 2,3,4-functionalized indole derivatives **27** have been prepared in high yield from easily available 2,3-dihaloanilides **18** without the isolation of any intermediate (Scheme 11). Also, this type of trifunctionalized indoles **27** could be accessed from 2-alkynyl-3-haloanilides **22** by their treatment with NaOH and subsequent addition of the disulfide (Scheme 11).

SCHEME 11. Synthesis of 4-Halo-3-phenylthio-2-substituted-1*H*-indoles 27



Finally, we decided to explore the synthetic utility of the obtained 4-haloindoles **23** and **24** as precursors of other 4-functionalized-1*H*-indoles using Pd-catalyzed coupling reactions. For instance, 4-heteroarylindoles **28** were formed in high yields by Stille coupling of 4-chloroindoles **23** with 2-(tributylstannyl)furan (Scheme 12, eq 1).[50] In addition, 4-phenyl-2-substituted-1*H*-indoles **29** have been also prepared in high yields by Suzuki coupling of 4-bromoindoles **24** with phenylboronic acid (Scheme 12, eq 2).[51]

SCHEME 12. 4-Aryl-2-substituted-1*H*-indoles 28 and 29 from 4-Haloindoles 23 and 24



Conclusions

In summary, we have studied different approaches to the synthesis of 2,3-dihaloanilines and we have found that the most efficient route involves a Smiles rearrangement from 2,3-dihalophenols. By using this strategy, 2,3-dihaloanilides were obtained in high yields from *O*-2,3-dihalophenyl *N*,*N*-diethylcarbamates or 3-halo-2-iodoanisoles without any chromatographic purification. 3-Halo-2-iodoanilides have been shown as useful precursors for the synthesis of 4-halo-1*H*-indoles through their coupling with terminal alkynes, followed by cyclization under treatment with NaOH. In this way, a wide variety of challenging and interesting 4-haloindoles have been prepared, usually in high yields. In addition, the usefulness of these 4-haloindoles as intermediates for further transformations has been briefly outlined, including reactions that afford 2,4- and 2,3,4-functionalized indoles.

Experimental Section

All reactions involving air-sensitive compounds were carried out under a N_2 atmosphere in oven-dried glassware with magnetic stirring. Temperatures are reported as bath temperatures. Solvents used in extraction and purification were distilled prior to use. TLC was performed on alumina-backed plates coated with silica gel 60 with F_{254} indicator; the chromatograms were visualized by UV light (254 nm) and/or by staining with a Ce/Mo reagent, anisaldehyde or phosphomolybdic acid solution and subsequent heating. R_f values refer to silica gel. Flash column chromatography was carried out on silica gel 60, 230-400 mesh. Melting points were obtained with open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded at 400 or 300 MHz. Chemical shifts are reported in ppm with the residual solvent resonance as the internal standard ($CHCl_3$: δ 7.26, Acetone-d_6: δ 2.05, DMSO-d_6: δ 2.50). Data are reported as follows: chemical shift, multiplicity (s: singlet, br s: broad singlet, d: doublet, dd: doublet of doublets, dt: doublet of triplets, ddd doublet of doublet of doublets, t: triplet, appt: apparent triplet, td: triplet of doublets, tdd triplet of doublet of doublets, q: quartet, m: multiplet), coupling constants (*J* in Hz) and integration. ^{13}C NMR spectra were recorded at 100.6 or 75.4 MHz using broadband proton

decoupling. Chemical shifts are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: δ 77.16, Acetone-d_6: δ 29.84, DMSO-d_6: δ 39.51). Low-resolution electron impact mass spectra (EI-LRMS) were obtained at 70 eV on a mass spectrometer and only the molecular ions and/or base peaks as well as significant peaks in MS are given. High-resolution mass spectrometry (HRMS) was carried out on a mass spectrometer. Infrared spectra were recorded with a FT-IR spectrophotometer. The microwave heating was performed in a Microwave, CEM Discover S-Class single-mode microwave cavity producing continuous irradiation (Temperature measurements were conducted using an IR sensor located below the microwave cavity floor, and reaction times refer to the total hold time at the indicated temperature. The maximum wattage supplied was 300 W). All commercially available reagents were used without purification unless otherwise indicated and were purchased from standard chemical suppliers.

Synthesis of trifluoroacetamides 1: These compounds were prepared following a reported procedure.[13]

2,2,2-Trifluoro-*N*-(3-fluorophenyl)acetamide (1a): purification by recrystallization in hexane afforded **1a** (6.37 g, 77%) as a white solid: 67–69 ºC (lit.[13] mp 68–70 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (br s, 1H), 7.48 (dt, *J* = 10.2, 2.1 Hz, 1H), 7.34 (td, *J* = 8.2, 2.1 Hz, 1H), 7.26 (ddd, *J* = 8.2, 2.1, 1.1 Hz, 1H), 6.95 (tdd, *J* = 8.2, 2.5, 1.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 162.9 (d, *J* = 246.6 Hz, C), 155.3 (q, *J* = 37.8 Hz, C), 136.5 (d, *J* = 10.6 Hz, C), 130.7 (d, *J* = 9.2 Hz, CH), 116.2 (d, *J* = 3.2 Hz, CH), 115.7 (q, *J* = 288.4 Hz, C), 113.5 (d, *J* = 21.2 Hz, CH), 108.5 (d, *J* = 26.6 Hz, CH); EI-LRMS *m/z* 207 (M^+, 100), 138 (45), 110 (36), 95 (32), 83 (18).

***N*-(3-Chlorophenyl)-2,2,2-trifluoroacetamide (1b):** purification by recrystallization in hexane afforded **1b** (7.15 g, 80%) as a white solid: mp 68–70 ºC (lit.[52] mp 66–68 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.66 (t, *J* = 2.0 Hz, 1H), 7.42 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 155.3 (q, *J* = 37.8 Hz, C),

136.2 (C), 135.2 (C), 130.5 (CH), 126.7 (CH), 121.0 (CH), 118.8 (CH), 115.7 (q, J = 288.5 Hz, C); EI-LRMS *m/z* 225 (M^++2, 33), 223 (M^+, 100), 154 (51), 126 (19).

General Procedure for the Synthesis of *N*-(3-fluoro-2-halophenyl)-2,2,2-trifluoroacetamides 3: *t*-BuLi (2.5 equiv of a 1.5 M solution in hexane) was added slowly To a solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (2.5 equiv) in anhydrous THF (3.5 mL/mmol) at −80 ºC. After 5 min a solution of **1a** (1 equiv) in THF (1 mL/mmol) was added dropwise avoiding temperature exceed −70 ºC. After 40 min at −80 ºC, a solution of iodine, bromine or hexachloroethane (1.4 equiv) in THF (1 mL/mmol) was added dropwise. The resulting solution was stirred for 40 min at −80 ºC. Then, the reaction mixture was allowed to reach rt and was quenched with H_2O (a solution of aqueous $Na_2S_2O_3$ in the case of using iodine as electrophile). The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with 1 M HCl, dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. The crude was purified by column chromatography (hexane/EtOAc, 8/1) on silica gel to afford the title compounds **3**:

2,2,2-Trifluoro-*N*-(3-fluoro-2-iodophenyl)acetamide (3aa): The reaction of **1a** (2.48 g, 12 mmol) with iodine (4.26 g, 16.8 mmol) afforded **3aa** (2.51 g, 63%) as a white-pale reddish solid: mp 104−106 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.40 (td, J = 8.3, 2.1 Hz, 1H), 7.01−6.94 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.9 (d, J = 245.6 Hz, C), 155.0 (q, J = 37.7 Hz, C), 137.4 (d, J = 3.6 Hz, C), 130.9 (d, J = 8.9 Hz, CH), 117.5 (d, J = 3.1 Hz, CH), 115.7 (q, J = 288.5 Hz, C), 113.3 (d, J = 23.8 Hz, CH), 79.0 (d, J = 28.8 Hz, C); EI-LRMS *m/z* 333 (M^+, 53), 206 (100), 186 (26), 137 (13), 109 (22); IR (KBr) 3218, 3061, 1717, 1580, 1548, 1463, 1207, 1165, 788, 733 cm^{-1}; HRMS calcd for $C_8H_4F_4INO$, 332.9274; found, 332.9283.

***N*-(2-Bromo-3-fluorophenyl)-2,2,2-trifluoroacetamide (3ab):** The reaction of **1a** (414 mg, 2 mmol) with bromine (447 mg, 2.8 mmol) afforded **3ab** (256 mg, 45%) as a white solid: mp 55−57 ºC (lit.[13] mp 55−56 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 8.14 (dt, J = 8.4, 1.3 Hz, 1H), 7.38 (td, J =

8.4, 6.0 Hz, 1H), 7.04 (td, *J* = 8.4, 1.3 Hz, 1H); ^{13}C NMR (75.4, $CDCl_3$) δ 159.3 (d, *J* = 247.9 Hz, C), 154.9 (q, *J* = 37.9 Hz, C), 134.8 (C), 129.6 (d, *J* = 8.7 Hz, CH), 117.3 (d, *J* = 3.3 Hz, CH), 115.6 (q, *J* = 288.9 Hz, C), 113.8 (d, *J* = 22.0 Hz, CH), 102.0 (d, *J* = 24.1 Hz, C); EI-LRMS *m/z* 287 (M^++2, 21), 285 (M^+, 21), 206 (100), 186 (20), 109 (22); HRMS calcd for $C_8H_4BrF_4NO$, 284.9412; found, 284.9414.

***N*-(2-Chloro-3-fluorophenyl)-2,2,2-trifluoroacetamide (3ac):** The reaction of **1a** (1.03 g, 5 mmol) with hexachloroethane (1.66 g, 7 mmol) afforded **3ac** (362 mg, 30%) as a pale brown solid: mp 38–40 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.97 (br s, 1H), 7.07 (td, *J* = 8.4, 5.9 Hz, 1H), 7.04 (td, *J* = 8.4, 1.3 Hz, 1H); ^{13}C NMR (75.4, $CDCl_3$) δ 158.3 (d, *J* = 249.4 Hz, C), 154.9 (q, *J* = 37.9 Hz, C), 133.7 (C), 128.5 (d, *J* = 8.6 Hz, CH), 117.5 (C), 117.4 (d, *J* = 3.5 Hz, CH), 113.8 (d, *J* = 20.7 Hz, CH), 112.0 (d, *J* = 20.6 Hz, C); EI-LRMS *m/z* 243 (M^++2, 11), 241 (M^+, 35), 206 (100), 144 (27), 117 (18), 69 (13); HRMS calcd for $C_8H_4ClF_4NO$, 240.9918; found, 240.9924.

Synthesis of 2-(trifluoromethyl)-7-iodobenzo[*d*]oxazole 4: *t*-BuLi (16.2 mL of a 1.5 M solution in hexane, 27.5 mmol) was added slowly to a solution of TMEDA (4.2 mL, 27.8 mmol) in anhydrous THF (40 mL) at –78 ºC. After 5 min a solution of **1a** (2.27 g, 11 mmol) in THF (10 mL) was added at –78 ºC. After 40 min at –60 ºC, a solution of iodine (3.91 g, 15.4 mmol) in THF (10 mL) was added dropwise. The resulting solution was stirred for 40 min at –60 ºC. Then, the reaction mixture was allowed to reach rt and was quenched with a solution of aqueous $Na_2S_2O_3$. The aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with 1 M HCl, dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. The crude was purified by column chromatography (hexane/EtOAc, 12/1) on silica gel affording **4** (1.13 g, 33%) as a red solid: mp 64–66 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.3 (C), 151.1 (q, *J* = 44.4 Hz, C), 138.7 (C), 136.9 (CH), 127.5 (CH), 121.7 (CH), 116.6 (q, *J* = 272.1 Hz, C), 72.9 (C); EI-LRMS *m/z* 313 (M^+, 44), 294 (6), 186 (6), 127 (50), 69 (100); HRMS calcd for $C_8H_3F_3INO$, 312.9211; found, 312.9211.

General Procedure for the Synthesis of 3-Fluoro-2-haloanilines 6aa and 6ab: To a solution of the corresponding *N*-(3-fluoro-2-halophenyl)-2,2,2-trifluoroacetamide **3aa** or **3ab** (1 equiv) in EtOH (10 mL/mmol) was added a large excess of NaOH (10 equiv) and the mixture was refluxed for 2 h (completion of the hydrolysis was monitored by GC-MS). After the mixture was cooled to rt, most of the EtOH was removed under reduced pressure and the residue was diluted with EtOAc and water. The aqueous solution was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. The crude was purified by column chromatography on silica gel to afford the title compounds:

3-Fluoro-2-iodoaniline (6aa): Treatment of **3aa** (666 mg, 2 mmol) with NaOH (800 mg, 20 mmol), and purification by column chromatography (hexane/EtOAc, 6/1) gave **6aa** (407 mg, 86%) as a white solid: mp 52–54 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (td, J = 8.1, 1.6 Hz, 1H), 6.53–6.48 (m, 1H), 6.45 (td, J = 8.1, 1.3 Hz, 1H), 4.29 (br s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 162.2 (d, J = 242.2 Hz, C), 148.8 (d, J = 4.6 Hz, C), 130.0 (d, J = 10.0 Hz, CH), 109.9 (d, J = 2.4 Hz, CH), 104.6 (d, J = 24.4 Hz, CH), 71.8 (d, J = 28.2 Hz, C); EI-LRMS *m/z* 237 (M^+, 100), 110 (12), 83 (12); IR (KBr) 3399, 3299, 3184, 1616, 1553, 1456, 1242, 1020, 771 cm^{-1}; HRMS calcd for C_6H_5FIN, 236.9451; found, 236.9455.

2-Bromo-3-fluoroaniline (6ab): Treatment of **3ab** (285 mg, 1 mmol) with NaOH (400 mg, 10 mmol), and purification by column chromatography (hexane/EtOAc, 6/1) gave **6ab** (160 mg, 85%) as a white solid: mp 32–34 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (tdd, J = 8.1, 6.1, 0.7 Hz, 1H), 6.55–6.47 (m, 2H), 4.23 (br s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.9 (d, J = 244.2 Hz, C), 146.1 (d, J = 3.1 Hz, C), 128.6 (d, J = 9.8 Hz, CH), 110.8 (d, J = 2.7 Hz, CH), 105.3 (d, J = 22.6 Hz, CH), 96.4 (d, J = 23.6 Hz, C); EI-LRMS *m/z* 191 (M^++2, 88), 189 (M^+, 100), 110 (22), 90 (14), 83 (28); IR (KBr) 3443, 3317, 1625, 1464, 763, 582 cm^{-1}; HRMS calcd for C_6H_5BrFN, 188.9589; found, 188.9592.

Synthesis of *N*-(3-Chlorophenyl)pivalamide (7): *t*-BuLi (1.6 mL of a 1.6 M solution in pentane, 2.5 mmol) was slowly added to a solution of TMEDA (0.38 mL, 2.52 mmol) in anhydrous THF (3 mL) at –80 ºC. After 5 min a solution of **1b** (223 mg, 1 mmol) in THF (2 mL) was added dropwise at this

temperature. The reaction mixture was allowed to reach −45 ºC and, after 1 h at this temperature, iodine (355 mg, 1.4 mmol) was added. The resulting solution was stirred for 40 min at −45 ºC. Then, the reaction mixture was allowed to reach rt and was quenched with a solution of aqueous $Na_2S_2O_3$. The aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with 1 M HCl, dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. As analyzed by ^{1}H NMR and GC-MS, the crude resulted to be a ca. 1:1 mixture of **7** and **1b**. After purification by column chromatography (hexane/EtOAc, 10/1) on silica gel, **7** was isolated as a white solid: mp 124−126 ºC (lit.[53] 124−126 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (t, J = 2.0 Hz, 1H), 7.43 (br s, 1H), 7.37−7.32 (m, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.08−7.03 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.9 (C), 139.2 (C), 134.6 (C), 130.0 (CH), 124.3 (CH), 120.3 (CH), 118.1 (CH), 39.8 (C), 27.6 (3 × CH_3); EI-LRMS *m/z* 213 (M^++2, 11), 211 (M^+, 34), 168 (5), 127 (49), 57 (100); HRMS calcd for $C_{11}H_{14}ClNO$, 211.0764; found 211.0764.

Synthesis of *N*-(*t*-Butoxycarbonyl)-3-chloroaniline (8): Prepared according to a published procedure.[24a] The residue was recrystallized from hexane to give **8** as a white solid: mp 67−69 ºC (lit.[54] mp 69−70 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.19−7.12 (m, 2H), 6.98 (dt, J = 7.2, 1.7 Hz, 1H), 6.58 (br s, 1H), 1.50 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.6 (C), 139.7 (C), 134.8 (C), 130.0 (CH), 123.1 (CH), 118.6 (CH), 116.5 (CH), 81.1 (C), 28.4 (3 × CH_3); EI-LRMS *m/z* 227 (M^+, 3), 171 (16), 153 (26), 129 (33), 127 (100).

Synthesis of *N*-(*t*-Butoxycarbonyl)aniline (9): *n*-BuLi (0.7 mL of a 1.6 M solution in hexane, 1.1 mmol) was added to a solution of *i*-Pr_2NH (154 μL, 1.1 mmol) in THF (4 mL) at 0 ºC. After 30 min at 0 ºC, the LDA solution was cooled to −78 ºC, and **8** (114 mg, 0.5 mmol) was added. The resulting solution was stirred for 30 min at 0 ºC and then iodine (178 mg, 0.7 mmol) was added at −78 ºC. After 1 h at 0 ºC, the reaction mixture was allowed to warm to rt and was quenched with aqueous $Na_2S_2O_3$. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic layers were dried over

anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. The crude was purified by column chromatography (hexane/EtOAc, 12/1) on silica gel affording **9** (72 mg, 75%) as a white solid: mp 135–137 ºC (lit.[24a] mp 136–137 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2H), 7.31–7.25 (m, 2H), 7.06–6.99 (m, 1H), 6.56 (br s, 1H), 1.52 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.9 (C), 138.4 (C), 129.1 (2 × CH), 123.1 (2 × CH), 118.6 (CH), 80.6 (C), 28.5 (3 × CH_3); EI-LRMS *m/z* 193 (M^+, 5), 137 (26), 119 (20), 93 (100).

Synthesis of 2-*t*-Butyl-7-iodobenzo[*d*]oxazole (10) and 2-*t*-Butoxy-2-*t*-butyl-7-iodobenzo[*d*]oxazole (11): *t*-BuLi (1.6 mL of a 1.6 M solution in pentane, 2.5 mmol) was added to a solution of **8** (227 mg, 1 mmol) in THF (5mL) at –78 ºC. The reaction mixture was allowed to reach –20 ºC for 1 h. Iodine (355 mg, 1.4 mmol) was added at –78 ºC and the reaction was stirred at –20 ºC for 1 h. After this time, the reaction mixture was allowed to warm to rt and was quenched with aqueous $Na_2S_2O_3$. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. The crude was purified by column chromatography (hexane/EtOAc, 12/1) on silica gel affording a ca. 1:2 mixture of **10** (67 mg, 18%) and **11** (114 mg, 38%):

2-*t*-Butoxy-*t*-butyl-7-iodobenzo[*d*]oxazole (10): white solid: mp 134–136 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 6.71 (t, J = 7.8 Hz, 1H), 6.28 (br s, 1H), 1.64 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.1 (C), 145.2 (C), 143.4 (CH), 136.2 (C), 131.0 (CH), 127.6 (CH), 95.9 (C) , 80.4 (C), 38.2 (C), 32.4 (3 × CH_3), 28.5 (3 × CH_3); EI-LRMS *m/z* 375 (M^+, 6), 319 (99), 275 (77), 260 (99), 232 (25), 127 (67), 57 (100); HRMS calcd for $C_{15}H_{22}INO_2$, 375.0695; found, 375.0693.

2-*t*-Butyl-7-iodobenzo[*d*]oxazole (11): colorless oil: R_f 0.48 (hexane/EtOAc, 7/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.9, 0.9 Hz, 1H), 7.59 (dd, J = 7.9, 0.9 Hz, 1H), 7.03 (t, J = 7.9 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.2 (C), 152.5 (C), 140.5 (C), 133.4 (CH), 125.8 (CH),

119.7 (CH), 72.3 (C), 34.4 (C), 28.5 (3 × CH_3); EI-LRMS *m/z* 301 (M^+, 90), 286 (100), 259 (35), 245 (39), 127 (17); HRMS calcd for $C_{11}H_{12}INO$, 300.9964; found, 300.9969.

Synthesis of 2-Halo-3-nitrofluorobenzenes 14 from 3-Nitrofluorobenzene 13a: *t*-BuOLi (2.5 equiv) was added to a flask charged under N_2 with 3-nitrofluorobenzene (1 equiv), the halogenating reagent (1.5–2.0 equiv) and dry DMF (1 mL/mmol). The resulting mixture was heated at 60 ºC for the indicated time and then was allowed to cool to rt. The crude was subjected to flash chromatography on silica gel (hexane/EtOAc, 10/1) to afford the title compounds:

2-Bromo-1-fluoro-3-nitrobenzene (14ab): Reaction of **13a** (350 mg, 2.5 mmol) with CBr_4 (1.25 g, 3.75 mmol) and *t*-BuOLi (500 mg, 6.25 mmol) for 4 h afforded **14ab** (279 mg, 51 %) as a yellow solid: mp 43–45 ºC (lit.[15] mp 42–44 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 8.1 1.4 Hz, 1H), 7.47 (td, *J* = 8.1, 5.2 Hz, 1H), 7.36 (td, *J* = 8.1, 1.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.8 (d, *J* = 251.1 Hz, C), 151.0 (C), 129.2 (d, *J* = 8.4 Hz, CH), 121.0 (d, *J* = 3.5 Hz, CH), 120.1 (d, *J* =23.4 Hz, CH), 103.6 (d, *J* = 25.5 Hz, C); EI-LRMS *m/z* 219 (M^+, 81), 189 (26), 175 (68), 163 (31), 94 (100).

2-Chloro-1-fluoro-3-nitrobenzene (14ac):[55] Reaction of **13a** (350 mg, 2.5 mmol) with C_2Cl_6 (1.18 g, 5 mmol) and *t*-BuOLi (500 mg, 6.25 mmol) for 6 h afforded **14ac** (323 mg, 74%) as a colorless oil: R_f 0.43 (hexane/EtOAc, 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.65 (m, 1H), 7.50–7.39 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 158.8 (d, *J* = 252.9 Hz, C), 148.9 (C), 128.1 (d, *J* = 8.3 Hz, CH), 121.0 (d, *J* = 3.7 Hz, CH), 120.5 (d, *J* = 21.9 Hz, CH), 116.0 (d, *J* = 21.8 Hz, C); EI-LRMS *m/z* 177 (M^++2, 23), 175 (M^+, 72), 145 (21), 131 (35), 129 (77), 117 (36), 84 (80), 49 (100); HRMS calcd for $C_6H_3ClFNO_2$, 174.9836; found, 174.9837.

2-Bromo-1-chloro-3-nitrobenzene (14bb): Reaction of **13b** (788 mg, 5 mmol) with CBr_4 (2.49 g, 5 mmol) and *t*-BuOLi (1000 mg, 12.5 mmol) for 17 h afforded **14bb** (154 mg, 13%) as a white solid: mp 83–85 ºC (lit.[11a] mp 83–84 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.61 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.6 (C), 133.3 (CH),

128.7 (CH), 123.1 (CH), 115.4 (C); EI-LRMS *m/z* 239 (M^++4, 26), 237 (M^++2, 100), 235 (M^+, 76), 191 (89), 179 (63), 110 (71), 75 (74); HRMS calcd for $C_6H_3ClBrNO_2$, 234.9036; found, 234.9025.

Synthesis of 3-Fluoro-2-haloanilines 6ab and 6ac from Nitroaromatics 14*:* Powder Fe (3 equiv) was added to a solution of the corresponding 2-halo-3-nitrofluorobenzene **14** (1 equiv) in HCl:EtOH (1:7) and the mixture was refluxed for 2 h (completion of the reduction was monitored by GC-MS). After the mixture was cooled to rt, most of the EtOH was removed under reduced pressure and the residue was diluted with EtOAc and water. The aqueous solution was carefully neutralized with a 1 M NaOH solution. The aqueous solution was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, and solvents evaporated under reduced pressure. The crude was purified by column chromatography on silica gel to afford the title compounds (data for **6ab** have been reported above):

2-Chloro-3-fluoroaniline (6ac):[55] Treatment of **14ac** (175 mg, 1 mmol) with Fe (168 mg, 3 mmol), and purification by column chromatography (hexane/EtOAc, 6/1) gave **6ac** (123 mg, 85%) as a colorless oil: R_f 0.35 (hexane/EtOAc, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (td, J = 8.2, 6.0 Hz, 1H), 6.57–6.49 (m, 2H), 4.18 (br s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.0 (d, J = 245.6 Hz, C), 144.9 (d, J = 2.4 Hz, C), 127.6 (d, J = 9.7 Hz, CH), 110.8 (d, J = 2.8 Hz, CH), 106.5 (d, J = 20.3 Hz, C), 105.4 (d, J = 21.3 Hz, CH); EI-LRMS *m/z* 147 (M^++2, 31), 145 (M^+, 100), 118 (7), 110 (9), 83 (18); IR (KBr) 3390, 1622, 1470, 987, 767 cm^{-1}; HRMS calcd for C_6H_5ClFN, 145.0095; found, 145.0103.

General Procedure for the Synthesis of 2-(2,3-Dihalophenoxy)-2-methylpropanamides 17 from *O*-2,3-Dihalophenyl *N,N´*-Diethylcarbamates 15: To a solution of the corresponding carbamate **15**[16a] (1 equiv) in EtOH (10 mL/mmol) was added a large excess of NaOH (10 equiv) and the mixture was refluxed for 5–8 h (completion of the hydrolysis was monitored by GC-MS). After the mixture was cooled to rt, most of the EtOH was removed under reduced pressure and the residue was diluted with Et_2O and water. The organic phase was rejected and then, the aqueous solution was carefully neutralized

with a 1 M HCl solution. The aqueous solution was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and solvents evaporated under reduced pressure. Without further purification, the crude product was dissolved in dry DMF (1.5 mL/mmol) under N_2 and NaOH (3 equiv) was added. After 1 h at rt, 2-bromo-2-methylpropanamide (3 equiv) was added and the reaction was stirred for additional 2 h (completion of the reaction was monitored by GC-MS). The reaction was quenched with H_2O and propanamides **17** were filtrated and recovered as solids that were not further purified:

2-(3-Fluoro-2-iodophenoxy)-2-methylpropanamide (17aa): Reaction of *O*-3-fluoro-2-iodophenyl-*N,N*-diethylcarbamate (**15aa**, 168 mg, 0.5 mmol) afforded **17aa** (138 mg, 86%) as a white solid: mp 100–102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (td, J = 8.2, 6.6 Hz, 1H), 6.85 (br s, 1H), 6.84–6.76 (m, 2H), 5.84 (br s, 1H), 1.65 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.0 (C), 163.0 (d, J = 245.8 Hz, C), 156.1 (d, J = 4.9 Hz, C), 129.9 (d, J = 9.6 Hz, CH), 114.8 (d, J = 3.0 Hz, CH), 110.4 (d, J = 24.1 Hz, CH), 83.8 (C), 80.3 (d, J = 25.7 Hz, C), 25.0 (2 × CH_3); EI-LRMS *m/z* 323 (M^+, 1), 279 (41), 238 (81), 196 (60), 152 (19), 112 (19), 86 (100); IR (KBr) 3451, 3416, 1673, 1458, 1237, 1152, 600 cm^{-1}; Anal. Calcd for $C_{10}H_{11}FINO_2$: C, 37.17; H, 3.43; N, 4.34. Found: C, 37.44; H, 3.55; N, 4.43.

2-(2-Bromo-3-fluorophenoxy)-2-methylpropanamide (17ab): Reaction of *O*-2-bromo-3-fluorophenyl-*N,N*-diethylcarbamate (**15ab**, 870 mg, 3 mmol) afforded **17ab** (684 mg, 83%) as a white solid: mp 91–93 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (td, J = 8.3, 6.5 Hz, 1H), 6.98 (br s, 1H), 6.91–6.82 (m, 2H), 6.48 (br s, 1H), 1.60 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.4 (C), 160.2 (d, J = 247.7 Hz, C), 153.4 (d, J = 3.0 Hz, C), 128.2 (d, J = 9.5 Hz, CH), 116.4 (d, J = 3.2 Hz, CH), 111.2 (d, J = 22.4 Hz, CH), 104.9 (d, J = 21.2 Hz, C), 83.9 (C), 24.8 (2 × CH_3); EI-LRMS *m/z* 277 (M^++2, 1), 275 (M^+, 1), 233 (27), 231 (28), 196 (52), 192 (39), 190 (39), 86 (100); IR (KBr) 3428, 3212, 1683, 1463, 1018, 794, 596 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrFNO_2$, 274.9957; found, 274.9953.

2-(2-Cloro-3-fluorophenoxy)-2-methylpropanamide (17ac): Reaction of *O*-2-chloro-3-fluorophenyl-*N,N*-diethylcarbamate (**15ac**, 122 mg, 0.5 mmol) afforded **17ac** (95 mg, 82%) as a white

solid: mp 92–94 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (td, J = 8.3, 6.3 Hz, 1H), 6.98 (br s, 1H), 6.92–6.84 (m, 2H), 6.73 (br s, 1H), 1.56 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.5 (C), 159.2 (d, J = 249.2 Hz, C), 152.2 (d, J = 2.2 Hz, C), 127.1 (d, J = 9.4 Hz, CH), 117.0 (d, J = 3.2 Hz, CH), 115.3 (d, J = 18.1 Hz, C), 111.4 (d, J = 21.2 Hz, CH), 83.9 (C), 24.7 (2 × CH_3); EI-LRMS *m/z* 231 (M^+, 1), 196 (20), 187 (49), 146 (53), 86 (100), 58 (29); IR (KBr) 3425, 3214, 1684, 1465, 1452, 1140, 1020, 795, 605 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClFNO_2$, 231.0462; found, 231.0469.

2-(3-Chloro-2-iodophenoxy)-2-methylpropanamide (17ba): Reaction of *O*-3-chloro-2-iodophenyl-*N,N*-diethylcarbamate (**15ba**, 176 mg, 0.5 mmol) afforded **17ba** (145 mg, 86%) as a white solid: mp 101–103 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.16 (m, 2H), 6.89–6.82 (m, 2H), 5.71 (br s, 1H), 1.65 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.1 (C), 156.2 (C), 140.1 (C), 129.5 (CH), 124.1 (CH), 116.8 (CH), 97.3 (C), 83.9 (C), 25.1 (2 × CH_3); EI-LRMS *m/z* 339 (M^+, 1), 295 (12), 254 (42), 212 (44), 128 (17), 86 (100), 58 (24); IR (KBr) 3453, 3418, 1673, 1563, 1439, 1151, 1134, 980, 958, 771, 576 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClINO_2$, 338.9523; found, 338.9524.

2-(2-Bromo-3-chlorophenoxy)-2-methylpropanamide (17bb): Reaction of *O*-2-bromo-3-chlorophenyl-*N,N*-diethylcarbamate (**15bb**, 153 mg, 0.5 mmol) afforded **17bb** (116 mg, 80%) as a white solid: mp 84–86 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.13 (m, 2H), 7.01–6.94 (m, 2H), 6.11 (br s, 1H), 1.61 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.2 (C), 153.4 (C), 136.1 (C), 128.1 (CH), 125.1 (CH), 118.9 (CH), 118.1 (C), 84.0 (C), 24.9 (2 × CH_3); EI-LRMS *m/z* 291 (M^+, 1), 249 (12), 214 (10), 212 (33), 168 (11), 86 (100), 58 (26); IR (KBr) 3467, 3156, 1698, 1570, 1445, 1260, 1149, 963, 544 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrClNO_2$, 290.9662; found, 290.9650.

2-(2,3-Dichlorophenoxy)-2-methylpropanamide (17bc): 2,3-Dichlorophenol (81 mg, 0.5 mmol) (commercially available) was dissolved in dry DMF (0.75 mL) under N_2 and NaOH (60 mg, 1.5 mmol) was added. After 1 h at rt, 2-bromo-2-methylpropanamide (250 mg, 1.5 mmol) was added and the reaction was stirred for 2 h at rt (completion of the reaction was monitored by GC-MS). The reaction was quenched with H_2O and **17bc** (107 mg, 87%) was recovered as a white solid after filtration: mp

100–102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.09 (m, 2H), 7.05–6.89 (m, 2H), 6.21 (br s, 1H), 1.58 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.3 (C), 152.1 (C), 134.1 (C), 127.2 (CH), 126.7 (C), 125.3 (CH), 119.8 (CH), 84.1 (C), 24.8 (2 × CH_3); EI-LRMS *m/z* 249 (M^++2, 1), 247 (M^+, 1), 212 (23), 203 (30), 162 (50), 126 (14), 86 (100), 58 (25); IR (KBr) 3474, 3155, 1699, 1450, 1264, 1145, 783, 550 cm^{-1}.

2-(3-Bromo-2-iodophenoxy)-2-methylpropanamide (17ca): Reaction of *O*-3-bromo-2-iodophenyl-*N,N*-diethylcarbamate (**15ca**, 199 mg, 0.5 mmol) afforded **17ca** (162 mg, 85%) as a white solid: mp 114–116 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.1, 1.1 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H), 6.89 (dd, J = 8.1, 1.1 Hz, 1H), 6.83 (br s, 1H), 5.82 (br s, 1H), 1.64 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.3 (C), 156.2 (C), 131.2 (C), 129.8 (CH), 127.4 (CH), 117.2 (CH), 100.3 (C), 83.9 (C), 25.0 (2 × CH_3); EI-LRMS *m/z* 341 (M^+–$CONH_2$+2, 6), 339 (M^+–$CONH_2$, 6), 300 (25), 298 (25), 258 (25), 256 (26), 207 (14), 86 (100), 58 (27); IR (KBr) 3461, 3146, 1674, 1434, 1146, 966, 911, 575 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrINO_2$, 382.9018; found, 382.9005.

2-(2,3-Dibromophenoxy)-2-methylpropanamide (17cb): Reaction of *O*-2,3-dibromophenyl-*N,N*-diethylcarbamate (**15cb**, 174 mg, 0.5 mmol) afforded **17cb** (144 mg, 86%) as a white solid: mp 111–113 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 7.8 Hz, 1H), 7.14–6.94 (m, 3H), 6.42 (br s, 1H), 1.60 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.3 (C), 153.2 (C), 128.6 (CH), 128.4 (CH), 126.3 (C), 120.3 (C), 119.5 (CH), 84.0 (C), 24.9 (2 × CH_3); EI-LRMS *m/z* 295 (M^+–$CONH_2$+4, 5), 293 (M^+–$CONH_2$+2, 11), 291 (M^+–$CONH_2$, 5), 252 (26), 86 (100), 58 (22); IR (KBr) 3467, 3147, 1698, 1440, 1260, 1147, 953, 779, 548 cm^{-1}; HRMS calcd for $C_{10}H_{11}Br_2NO_2$, 334.9157; found, 334.9150.

2-(3-Bromo-2-chlorophenoxy)-2-methylpropanamide (17cc): Reaction of *O*-3-bromo-2-chlorophenyl *N,N*-diethylcarbamate (**15cc**, 153 mg, 0.5 mmol) afforded **17cc** (120 mg, 82%) as a white solid: mp 117–119 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, J = 6.7, 2.7 Hz, 1H), 7.23–7.04 (m, 2H), 6.94 (br s, 1H), 5.67 (br s, 1H), 1.59 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.2 (C), 151.9 (C), 128.5

(CH), 127.7 (CH), 124.0 (CH), 120.4 (CH), 84.1 (C), 24.8 (2 × CH_3); EI-LRMS *m/z* 293 (M^++2, 1), 291 (M^+, 1), 258 (11), 249 (19), 247 (14), 208 (33), 206 (24), 86 (100), 58 (23); IR (KBr) 3471, 3153, 1699, 1446, 1263, 1149, 953, 912, 548 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClBrNO_2$, 290.9662; found, 290.9667.

2-(2,3-Diiodophenoxy)-2-methylpropanamide (17da): Reaction of *O*-2,3-diiodophenyl *N,N*-diethylcarbamate (**15da**, 222 mg, 0.5 mmol) afforded **17da** (179 mg, 83%) as a white solid: mp 131–133 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.7, 1.4 Hz, 1H), 7.01 (appt, J = 8.0 Hz, 1H), 6.91 (dd, J = 8.2, 1.4 Hz, 1H), 6.84 (br s, 1H), 6.29 (br s, 1H), 1.63 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.2 (C), 155.5 (C), 134.1 (CH), 130.3 (CH), 117.7 (CH), 109.5 (C), 106.4 (C), 83.9 (C), 25.1 (2 × CH_3); EI-LRMS *m/z* 431 (M^+, 1), 387 (16), 346 (88), 304 (100), 260 (10), 218 (11), 86 (59), 58 (18); IR (KBr) 3465, 3263, 1682, 1429, 1141, 953, 564 cm^{-1}; HRMS calcd for $C_{10}H_{11}I_2NO_2$, 430.8879; found, 430.8891.

2-(2-Bromo-3-iodophenoxy)-2-methylpropanamide (17db): Reaction of *O*-2-bromo-3-iodophenyl *N,N*-diethylcarbamate (**15db**, 199 mg, 0.5 mmol) afforded **17db** (153 mg, 80%) as a white solid: mp 134–136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.98–6.92 (m, 2H), 6.27 (br s, 1H), 1.59 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.4 (C), 152.4 (C), 134.9 (CH), 129.2 (CH), 124.8 (C), 120.3 (CH), 102.8 (C), 84.2 (C), 24.9 (2 × CH_3); EI-LRMS *m/z* 385 (M^++2, 1), 383 (M^+, 1), 341 (17), 339 (18), 304 (100), 300 (50), 298 (53), 86 (96); IR (KBr) 3444, 3184, 1680, 1566, 1437, 1154, 966, 764, 584 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrINO_2$, 382.9018; found, 382.9001.

2-(2-Chloro-3-iodophenoxy)-2-methylpropanamide (17dc): Reaction of *O*-2-chloro-3-iodophenyl *N,N*-diethylcarbamate (**15dca**, 176 mg, 0.5 mmol) afforded **17dc** (133 mg, 79%) as a white solid: mp 130–132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.1, 1.1 Hz, 1H), 7.06 (dd, J = 8.1, 1.1 Hz, 1H), 6.95 (br s, 1H), 6.90 (t, J = 8.1 Hz, 1H), 6.24 (br s, 1H), 1.57 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.3 (C), 151.0 (C), 134.9 (CH), 132.2 (C), 128.4 (CH), 121.4 (CH), 99.6 (C), 84.1 (C), 24.9 (2 × CH_3); EI-LRMS *m/z* 339 (M^+, 1), 304 (38), 295 (25), 256 (19), 254 (59), 86 (100); IR (KBr) 3454,

3175, 1680, 1568, 1442, 1155, 968, 765, 586 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClINO_2$, 338.9523; found, 338.9524.

General Procedure for the Synthesis of *N*-(2,3-Dihalophenyl)-2-hidroxy-2-methylpropanamides 18 from *O*-2,3-Dihalophenyl *N,N´*-Diethylcarbamates 15: To a solution of the corresponding carbamate **15**[16a] (1 equiv) in EtOH (10 mL/mmol) was added a large excess of NaOH (10 equiv) and the mixture was refluxed for 5–8 h (completion of the hydrolysis was monitored by GC-MS). After the mixture was cooled to rt, most of the EtOH was removed under reduced pressure and the residue was diluted with Et_2O and water. The organic phase was rejected and then, the aqueous solution was carefully neutralized with a 1 M HCl solution. The aqueous solution was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. Without further purification, the corresponding crude phenol **16** was dissolved in dry DMF (1.5 mL/mmol) under N_2 and NaOH (3 equiv) was added to the mixture. After 1 h at rt, 2-bromo-2-methylpropanamide (3 equiv) was added and the reaction was stirred for 2 h at rt. After complete formation of the corresponding propanamide **17** (monitored by GC-MS), an excess of NaOH (9 equiv) was added and the mixture was heated at 60 ºC for 2 h. The reaction was quenched with H_2O and the corresponding propanamide **18** was recovered as a solid after filtration, which was not further purified.

***N*-(3-Fluoro-2-iodophenyl)-2-hydroxy-2-methylpropanamide (18aa):** Reaction of *O*-3-fluoro-2-iodophenyl-*N,N*-diethylcarbamate (**15aa**, 674 mg, 2 mmol) afforded **18aa** (536 mg, 83%) as a white solid: mp 95–97 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.35–7.26 (m, 1H), 6.83 (t, J = 8.3 Hz, 1H), 2.71 (s, 1H), 1.58 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0 (C), 161.8 (d, J = 243.7 Hz, C), 139.8 (d, J = 3.5 Hz, C), 130.5 (d, J = 9.0 Hz, CH), 116.5 (d, J = 2.9 Hz, CH), 111.2 (d, J = 23.8 Hz, CH), 78.1 (d, J = 27.9 Hz, C), 74.7 (C), 28.1 (2 × CH_3); EI-LRMS *m/z* 323 (M^+, 27), 265 (33), 237 (100), 138 (19), 59 (81); IR (KBr) 3420, 3368, 3289, 1661, 1462, 1416, 776 cm^{-1}; HRMS calcd for $C_{10}H_{11}FINO_2$, 322.9819; found, 322.9812.

***N*-(2-Bromo-3-fluorophenyl)-2-hydroxy-2-methylpropanamide (18ab):** Reaction of *O*-2-bromo-3-fluorophenyl-*N,N*-diethylcarbamate (**15ab**, 580 mg, 2 mmol) afforded **18ab** (425 mg, 77%) as a white solid: mp 102–104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 8.20 (dt, J = 8.3, 1.4 Hz, 1H), 7.25 (td, J = 8.3, 6.2 Hz, 1H), 6.87 (td, J = 8.3, 1.4 Hz, 1H), 3.01 (s, 1H), 1.56 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (C), 159.2 (d, J = 245.9 Hz, C), 137.2 (d, J = 2.2 Hz, C), 129.0 (d, J = 8.8 Hz, CH), 116.3 (d, J = 3.2 Hz, CH), 111.6 (d, J = 22.0 Hz, CH), 101.3 (d, J = 23.2 Hz, C), 74.7 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 277 (M^++2, 12), 275 (M^+, 13), 219 (15), 217 (15), 191 (61), 189 (73), 59 (100); IR (KBr) 3326, 3310, 1665, 1601, 1469, 1422, 1252, 777 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrFNO_2$, 274.9957; found, 274.9958.

***N*-(2-Chloro-3-fluorophenyl)-2-hydroxy-2-methylpropanamide (18ac):** Reaction of *O*-2-chloro-3-fluorophenyl-*N,N*-diethylcarbamate (**15ac**, 490 mg, 2 mmol) afforded **18ac** (351 mg, 76%) as a white solid: mp 106–108 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (br s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.27–7.16 (m, 1H), 6.90 (t, J = 8.4 Hz, 1H), 2.84 (s, 1H), 1.56 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.9 (C), 158.2 (d, J = 247.4 Hz, C), 136.0 (d, J = 1.2 Hz, C), 128.0 (d, J = 8.7 Hz, CH), 116.0 (d, J = 3.4 Hz, CH), 111.5 (d, J = 20.7 Hz, CH), 111.0 (d, J = 20.0 Hz, C), 74.7 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 233 (M^++2, 7), 231 (M^+, 21), 173 (25), 147 (28), 145 (97), 59 (100); IR (KBr) 3418, 3340, 1677, 1522, 1472, 1253, 1132, 782 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClFNO_2$, 231.0462; found, 231.0462.

***N*-(3-Chloro-2-iodophenyl)-2-hydroxy-2-methylpropanamide (18ba):** Reaction of *O*-3-chloro-2-iodophenyl-*N,N*-diethylcarbamate (**15ba**, 3.53 g, 10 mmol) afforded **18ba** (2.78 g, 82%) as a white solid: mp 113–115 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (br s, 1H), 8.21 (dd, J = 7.8, 1.5 Hz, 1H), 7.31–7.21 (m, 2H), 2.47 (s, 1H), 1.58 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0 (C), 140.4 (C), 139.1 (C), 129.8 (CH), 125.1 (CH), 118.9 (CH), 95.1 (C), 74.7 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 341 (M^++2, 3), 339 (M^+, 8), 281 (10), 253 (62), 194 (15), 154 (24), 59 (100); IR (KBr) 3398, 3291, 1662, 1575, 1539, 1444, 1396, 1126, 776 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClINO_2$, 338.9523; found, 338.9514.

***N*-(2-Bromo-3-chlorophenyl)-2-hydroxy-2-methylpropanamide (18bb):** Reaction of *O*-2-bromo-3-chlorophenyl-*N,N*-diethylcarbamate (**15bb**, 612 mg, 2 mmol) afforded **18bb** (454 mg, 78%) as a white solid: mp 107–109 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 8.34 (dd, J = 7.5, 2.3 Hz, 1H), 7.28–7.19 (m, 2H), 2.56 (s, 1H), 1.57 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.7 (C), 137.5 (C), 134.9 (C), 128.7 (CH), 125.5 (CH), 119.1 (CH), 114.4 (C), 74.8 (C), 28.1 (2xCH_3); EI-LRMS *m/z* 293 (M^++2, 5) 291 (M^+, 4), 235 (5), 233 (5), 207 (35), 205 (27), 154 (14), 59 (100); IR (KBr) 3390, 3315, 1663, 1582, 1543, 1450, 1404, 777 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrClNO_2$, 290.9662; found, 290.9661.

***N*-(2,3-Dichlorophenyl)-2-hydroxy-2-methylpropanamide (18bc):** 2,3-Dichlorophenol (1.63 g, 10 mmol) (commercially available) was dissolved in dry DMF (15mL) under N_2 and NaOH (1.20 g, 30 mmol) was added. After 1 h at rt, 2-bromo-2-methylpropanamide (4.98 g, 30 mmol) was added and the reaction was stirred for 2 h at rt. After completion of the alkylation reaction (monitored by GC-MS), an excess of NaOH (3.60 g, 90 mmol) was added and the mixture was heated at 60 ºC for 2 h. The reaction was quenched with H_2O and **18bc** (2.08 g, 84%) was isolated after filtration as a white solid: mp 109–111 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 8.37–8.29 (m, 1H), 7.22–7.15 (m, 2H), 3.11 (s, 1H), 1.55 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (C), 136.0 (C), 132.8 (C), 127.8 (CH), 125.4 (CH), 122.0 (C), 118.9 (CH), 74.6 (C), 27.9 (2 × CH_3); EI-LRMS *m/z* 251 (M^++4, 2), 249 (M^++2, 12), 247 (M^+, 21), 189 (20), 163 (56), 161 (89), 59 (100); IR (KBr) 3422, 3337, 1671, 1509, 1407, 1124, 778, 701 cm^{-1}; Anal. Calcd for $C_{10}H_{11}Cl_2NO_2$: C, 48.41; H, 4.47; N, 5.65. Found: C, 48.49; H, 4.47; N, 5.76.

***N*-(3-Bromo-2-iodophenyl)-2-hydroxy-2-methylpropanamide (18ca):** Reaction of *O*-3-bromo-2-iodophenyl-*N,N*-diethylcarbamate (**15ca**, 796 mg, 2 mmol) afforded **18ca** (620 mg, 81%) as a white solid: mp 118–120 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (br s, 1H), 8.23 (dd, J = 8.1, 1.4 Hz, 1H), 7.40 (dd, J = 8.1, 1.4 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 2.55 (s, 1H), 1.57 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.9 (C), 140.5 (C), 130.4 (C), 130.1 (CH), 128.5 (CH), 119.4 (CH), 98.2 (C), 74.7 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 385 (M^++2, 3), 383 (M^+, 3), 325 (4), 299 (24), 297 (25), 240 (10), 238 (10),

200 (15), 198 (15), 59 (100); IR (KBr) 3387, 3285, 1652, 1651, 1525, 1392, 776, 693 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrINO_2$, 382.9018; found, 382.9012.

***N*-(2,3-Dibromophenyl)-2-hydroxy-2-methylpropanamide (18cb):** Reaction of *O*-2,3-dibromophenyl *N,N*-diethylcarbamate (**15cb**, 698 mg, 2 mmol) afforded **18cb** (556 mg, 83%) as a white solid: mp 119–121 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 8.34 (dd, J = 8.1, 1.4 Hz, 1H), 7.36 (dd, J= 8.1, 1.4 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 3.01 (br s, 1H), 1.55 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (C), 137.4 (C), 129.0 (CH), 128.9 (CH), 125.2 (C), 119.7 (CH), 116.6 (C), 74.6 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 339 (M^++4, 2), 337 (M^++2, 5), 335 (M^+, 2), 279 (6), 253 (19), 251 (38), 249 (19), 58 (100); IR (KBr) 3444, 3224, 1668, 1575, 1567, 1515, 780 cm^{-1}; HRMS calcd for $C_{10}H_{11}Br_2NO_2$, 334.9157; found, 334.9165.

***N*-(3-Bromo-2-chlorophenyl)-2-hydroxy-2-methylpropanamide (18cc):** Reaction of *O*-3-bromo-2-chlorophenyl-*N,N*-diethylcarbamate (**15cc**, 612 mg, 2 mmol) afforded **18cc** (448 mg, 77%) as a white solid: mp 114–116 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 8.36 (dd, J = 8.2, 1.1 Hz, 1H), 7.34 (dd, J = 8.2, 1.1 Hz, 1H), 7.10 (t, J = 8.2, 1H), 3.22 (s, 1H), 1.55 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.2 (C), 135.9 (C), 128.7 (CH), 128.2 (CH), 123.8 (C), 122.7 (C), 119.6 (CH), 74.5 (C), 27.9 (2 × CH_3); EI-LRMS *m/z* 295 (M^++4, 2), 293 (M^++2, 10) 291 (M^+, 9), 258 (5), 256 (5), 235 (11), 233 (11), 209 (14), 207 (60), 205 (46), 200 (12), 198 (12), 125(9), 90 (12), 59 (100); IR (KBr) 3343, 3323, 1664, 1526, 1406, 1132, 777, 569 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClBrNO_2$, 290.9662; found, 290.9672.

***N*-(2,3-Diiodophenyl)-2-hydroxy-2-methylpropanamide (18da):** Reaction of *O*-2,3-diiodophenyl-*N,N*-diethylcarbamate (**15da**, 890 mg, 2 mmol) afforded **18da** (680 mg, 79 %) as a white solid: mp 144–146 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (br s, 1H), 8.24 (dd, J = 8.2, 1.4 Hz, 1H), 7.67 (dd, J = 7.8, 1.4 Hz, 1H), 7.09 (appt, J = 8.0 Hz, 1H), 2.53 (br s, 1H), 1.57 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (C), 140.0 (C), 135.4 (CH), 130.4 (CH), 120.2 (CH), 108.8 (C), 104.5 (C), 74.5 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 431 (M^+, 21), 372 (8), 345 (85), 286 (62), 246 (44), 218 (14), 91 (15), 59

(100); IR (KBr) 3318, 1651, 1568, 1523, 1386, 773 cm^{-1}; HRMS calcd for $C_{10}H_{11}I_2NO_2$, 430.8879; found, 430.8873.

***N*-(2-Bromo-3-iodophenyl)-2-hydroxy-2-methylpropanamide (18db):** Reaction of *O*-2-bromo-3-iodophenyl-*N,N*-diethylcarbamate (**15db**, 796 mg, 2 mmol) afforded **18db** (591 mg, 77%) as a white solid: mp 110–112 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 8.36 (dd, J = 8.1, 1.1 Hz, 1H), 7.60 (dd, J = 8.1, 1.1 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 3.01 (br s, 1H), 1.54 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (C), 136.7 (C), 135.5 (CH), 129.5 (CH), 121.1 (C), 120.6 (CH), 101.5 (C), 74.5 (C), 27.9 (2 × CH_3); EI-LRMS *m/z* 385 (M^++2, 11), 383 (M^+, 11), 327 (12), 325 (12), 304 (40), 299 (55), 297 (46), 286 (18), 246 (34), 207 (77), 59 (100); IR (KBr) 3334, 1661, 1578, 1529, 1392, 774 cm^{-1}; HRMS calcd for $C_{10}H_{11}BrINO_2$, 382.9018; found, 382.9001.

***N*-(2-Chloro-3-iodophenyl)-2-hydroxy-2-methylpropanamide (18dc):** Reaction of *O*-2-chloro-3-iodophenyl-*N,N*-diethylcarbamate (**15dc**, 706 mg, 2 mmol) afforded **18dc** (508 mg, 75%) as a white solid: mp 101–103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 8.33 (dd, J = 8.1, 1.2 Hz, 1H), 7.52 (dd, J = 8.1, 1.2 Hz, 1H), 6.89 (t, J = 8.1 Hz, 1H), 2.94 (s, 1H), 1.48 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (C), 135.2 (CH), 135.1 (C), 128.8 (CH), 127.5 (C), 120.6 (CH), 98.2 (C), 74.6 (C), 27.9 (2 × CH_3); EI-LRMS *m/z* 341 (M^++2, 10), 339 (M^+, 30), 304 (41), 281 (31), 255 (31), 253 (99), 246 (36), 59 (100); IR (KBr) 3343, 3325, 1662, 1568, 1528, 1397, 776 cm^{-1}; HRMS calcd for $C_{10}H_{11}ClINO_2$, 338.9523; found, 338.9522.

General Procedure for the Synthesis of *N*-(2,3-dihalophenyl)-2-hydroxy-2-methylpropanamides 18 from 3-Halo-2-iodoanisoles 19: BBr_3 (20 mL of a 1 M solution in CH_2Cl_2, 20 mmol) was added dropwise to a solution of the corresponding 3-halo-2-iodoanisole **19a** or **19b** (4 mmol), prepared as previously described,[16b] in CH_2Cl_2 (120 mL) at −78 ºC. The mixture was warmed to rt overnight, and then $NaHCO_3$ (1.68 g, 20 mmol) was added. The resulting mixture was cooled to 0 ºC, and MeOH (70 mL) was added dropwise. After 30 min at 0 ºC, the mixture was warmed to rt and stirred for 1 h. Most

of the solvent was removed under reduced pressure and the residue was diluted with water and CH_2Cl_2. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Without further purification, the corresponding crude dihalophenol **16** was dissolved in anhydrous DMF (6 mL) under N_2 and NaOH (480mg, 12 mmol) was added to the mixture. After 1 h at rt, 2-bromo-2-methylpropanamide (1.99 g, 12 mmol) was added and the reaction was stirred for 2 h at rt. After complete alkylation of **16** (monitored by GC-MS), NaOH (9 equiv) was added and the mixture was heated at 60 ºC for 2 h. The reaction was quenched with H_2O and the corresponding propanamide **18ba** or **18ca** was recovered as a solid after filtration. Their spectroscopic data have been reported above.

General Procedure for the Synthesis of 2,3-Dihaloanilines 6 from Anilides 18: A solution of the corresponding *N*-(2,3-dihalophenyl)-2-hydroxy-2-methylpropanamide **18** (1 mmol) in 6 M HCl:EtOH (1:1) (20 mL) was refluxed for 5–6 h (completion of the hydrolysis was monitored by GC-MS). After the mixture was cooled to rt, most of the EtOH was removed under reduced pressure and the residue was diluted with EtOAc and water. The aqueous solution was carefully neutralized with a 1 M NaOH solution. The aqueous solution was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, and the solvents evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (hexane/EtOAc, 6/1) to afford the title compounds **6**:

2-Bromo-3-fluoroaniline (6ab): Reaction of **18ab** (275 mg, 1 mmol) gave **6ab** (169 mg, 89%). Spectroscopic and characterization data are reported above.

2-Chloro-3-fluoroaniline (6ac): Reaction of **18ac** (231 mg, 1 mmol) gave **6ac** (96 mg, 66%). Spectroscopic and characterization data are reported above.

2-Bromo-3-chloroaniline (6bb):[56] Reaction of **18bb** (291 mg, 1 mmol) gave **6bb** (193 mg, 94%) as a white solid: mp 41–43 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, J = 8.0 Hz, 1H), 6.84 (dd, J = 8.0, 1.5 Hz, 1H), 6.63 (dd, J = 8.0, 1.5 Hz, 1H), 4.26 (br s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.1 (C), 135.1 (C), 128.4 (CH), 119.5 (CH), 113.5 (CH), 109.3 (C); EI-LRMS *m/z* 209 (M^++4, 23), 207 (M^++2,

100), 205 (M^+, 77), 126 (16), 90 (30), 63 (12); IR (KBr) 3473, 3381, 1610, 1462, 1018, 769 cm^{-1}; HRMS calcd for C_6H_5ClBrN, 204.9294; found, 204.9293.

2,3-Dichloroaniline (6bc): Reaction of **18bc** (248 mg, 1 mmol) gave **6bc** (144 mg, 90%) as a white solid: mp 26–28 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, J = 8.0 Hz, 1H), 6.84 (dd, J = 8.0, 1.5 Hz, 1H), 6.63 (dd, J = 8.0, 1.5 Hz, 1H), 4.20 (br s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.6 (C), 132.9 (C), 127.6 (CH), 119.4 (CH), 117.3 (C), 113.7 (CH); EI-LRMS *m/z* 165 (M^++4, 9), 163 (M^++2, 61), 161 (M^+,100), 126 (9), 90 (17), 63 (9); IR (KBr) 3479, 3390, 1615, 1464, 905, 768 cm^{-1}; HRMS calcd for $C_6H_5Cl_2N$, 160.9799; found, 160.9792.

2,3-Dibromoaniline (6cb): Reaction of **18cb** (335 mg, 1 mmol) gave **6cb** (223 mg, 89%) as a white solid: mp 41–43 ºC (lit.[57] mp 45–46 ºC) ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (dd, J = 7.8, 1.8 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 6.68 (dd, J = 7.8, 1.8 Hz, 1H), 4.28 (br s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.1 (C), 128.9 (CH), 125.7 (C), 122.9 (CH), 114.1 (CH), 111.5 (C); EI-LRMS *m/z* 253 (M^++4, 48), 251 (M^++2, 100), 249 (M^+, 53), 172 (12), 170 (12), 90 (43); IR (KBr) 3382, 1611, 1455, 1287, 1014, 768, 695 cm^{-1}; HRMS calcd for $C_6H_5Br_2N$, 248.8789; found, 248.8777.

3-Bromo-2-chloroaniline (6cc): Reaction of **18cc** (291 mg, 1 mmol) gave **6cc** (195 mg, 95%) as a white solid: mp 31–33 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 8.0, 1.5 Hz, 1H), 6.90 (t, J = 8.0 Hz, 1H), 6.67 (dd, J = 8.0, 1.5 Hz, 1H), 4.16 (br s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6 (C), 128.1 (CH), 123.2 (C), 122.8 (CH), 119.2 (C), 114.4 (CH); EI-LRMS *m/z* 209 (M^++4, 22), 207 (M^++2, 100), 205 (M^+, 71), 126 (13), 90 (29), 63 (12); IR (KBr) 3480, 3388, 1615, 1462, 1435, 767 cm^{-1}; HRMS calcd for C_6H_5ClBrN, 204.9294; found, 204.9286.

General Procedure for the Synthesis of 4-Fluoro-2-substituted-1*H*-indoles 20 from 3aa: A mixture of **3aa** (1 equiv), the corresponding alkyne (1.5 equiv), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (5 mol%) and Et_2NH (1.5 equiv) in anhydrous DMA (5 mL/mmol) was heated for 4 h at 80 ºC under N_2 (cyclization was completed as monitored by GC-MS). CH_2Cl_2 (20 mL) and water (20 mL) were added to

the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (2 × 60 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography (hexane/EtOAc, 10/1) on silica gel affording the corresponding 4-fluoro-1*H*-indoles **20**:

4-Fluoro-2-phenyl-1*H*-indole (20a): Treatment of **3aa** (167 mg, 0.5 mmol) with phenylacetylene (77 mg, 0.75 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 3 mol%), CuI (5 mg, 5 mol%) and Et_2NH (54 mg, 0.75 mmol) afforded **20a** (92 mg, 87%) as a brown solid: mp 62−64 ºC (lit.[58] mp 65−67 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.70−7.63 (m, 2H), 7.51−7.43 (m, 2H), 7.41−7.33 (m, 1H), 7.21−7.09 (m, 2H), 6.93 (dd, *J* = 2.2, 0.7 Hz, 1H), 6.84 (ddd, *J* = 10.3, 7.4 1.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156.5 (d, *J* = 246.8 Hz, C), 139.3 (d, *J* = 11.2 Hz, C), 138.0 (C), 131.9 (C), 129.2 (2 × CH), 128.1 (CH), 125.3 (2 × CH), 122.8 (d, *J* = 7.6 Hz, CH), 118.6 (d, *J* = 22.4 Hz, C), 107.1 (d, *J* = 3.6 Hz, CH), 105.1 (d, *J* = 18.9 Hz, CH), 95.8 (CH); HRMS calcd for $C_{14}H_{10}FN$, 211.0797; found, 211.0787.

4-Fluoro-2-hexyl-1*H*-indole (20b): Treatment of **3aa** (200 mg, 0.6 mmol) with 1-octyne (99 mg, 0.9 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 3 mol%), CuI (6 mg, 5 mol%) and Et_2NH (66 mg, 0.9 mmol) afforded **20b** (102 mg, 78%) as a brown oil: R_f 0.45 (hexane/EtOAc, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.15−6.93 (m, 2H), 6.79 (ddd, *J* = 10.4, 6.9, 1.7 Hz, 1H), 6.35 (dd, *J* = 2.2, 0.8 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.80−1.62 (m, 2H), 1.47−1.21 (m, 6H), 0.94 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.4, $CDCl_3$) δ 155.8 (d, *J* = 245.1 Hz, C), 140.2 (C), 138.5 (d, *J* = 11.9 Hz, C), 121.3 (d, *J* = 7.7 Hz, CH), 117.8 (d, *J* = 22.4 Hz, C), 106.5 (d, *J* = 3.4 Hz, CH), 104.5 (d, *J* = 19.1 Hz, CH), 95.4 (CH), 31.7 (CH_2), 29.14 (CH_2), 29.08 (CH_2), 28.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3); EI-LRMS *m/z* 219 (M^+, 27), 162 (32), 148 (100), 101 (9); HRMS calcd for $C_{14}H_{18}FN$, 219.1423; found, 219.1418.

General Procedure for the Synthesis of 3-Aryl-4-fluoro-2-sustituted-1*H*-indoles 21a-h: A mixture of **3aa** (166 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 5 mol%), PPh_3 (26 mg, 20 mol%), K_2CO_3 (4 276 mg, 2 mmol) and the corresponding alkyne (0.6 mmol) in DMF (3 mL) was stirred under N_2 at 70 ºC until the complete formation of the 2-alkynylacetamide was observed (monitored by GC-MS). Then, the

corresponding aryl bromide (0.6 mmol) was added and the reaction was stirred overnight at 70 ºC. For the synthesis of **21c** and **21d**, the corresponding aryl bromide was added from the beginning of the reaction and the mixture was stirred under N_2 at 70 ºC until the complete formation of the corresponding 2,3-disubstituted-4-fluoroindole was observed (monitored by GC-MS). In both cases, the resulting mixture was quenched with water, and the aqueous solution was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (2 × 30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc) on silica gel to afford the title compounds **21**:

4-Fluoro-3-(2-nitrophenyl)-2-phenyl-1*H*-indole (21a): Treatment of **3aa** with phenylacetylene (61 mg, 0.6 mmol) for 1.5 h, further reaction with 1-bromo-2-nitrobenzene (121 mg, 0.6 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) gave **21a** (119 mg, 72%) as a yellow-orange solid: mp 177–179 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 8.10–8.05 (m, 1H), 7.52–7.42 (m, 2H), 7.38–7.34 (m, 1H), 7.29 (s, 4H), 7.16 (t, J = 8.2 Hz, 2H), 7.13–7.06 (m, 1H), 6.74 (dd, J = 11.7, 7.70 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156.7 (d, J = 247.1 Hz, C), 150.0 (C), 138.2 (d, J = 10.4 Hz, C), 135.2 (d, J = 0.9 Hz, C), 134.6 (CH), 132.6 (CH), 131.4 (C), 130.7 (d, J = 0.6 Hz, C), 129.0 (2 × CH), 128.4 (CH), 128.1 (2 × CH), 128.1 (CH), 124.8 (CH), 123.3 (d, J = 8.0 Hz, CH), 116.9 (d, J = 18.6 Hz, C), 108.4 (d, J = 1.7 Hz, C), 107.5 (d, J = 3.7 Hz, CH), 105.9 (d, J = 19.2 Hz, CH); EI-LRMS *m/z* 332 (M^+, 44), 285 (15), 105 (100), 77 (16); HRMS calcd for $C_{20}H_{13}FN_2O_2$, 332.0961; found, 332.0949.

2-Butyl-4-fluoro-3-(2-nitrophenyl)-1*H*-indole (21b): Treatment of **3aa** with 1-hexyne (49 mg, 0.6 mmol) for 2.5 h, further reaction with 1-bromo-2-nitrobenzene (121 mg, 0.6 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) gave **21b** (124 mg, 80%) as an orange solid: mp 85–87 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 8.08–8.03 (m, 1H), 7.65–7.58 (m, 1H), 7.52–7.45 (m, 2H), 7.12–7.08 (m, 1H), 7.08–7.00 (m, 1H), 6.70 (ddd, J = 11.1, 7.5, 1.2 Hz, 1H), 2.71–2.54 (m, 2H), 1.64–1.53 (m, 2H), 1.36–1.21 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ

156.2 (d, J = 245.7 Hz, C), 150.0 (C), 137.8 (d, J = 11.0 Hz, C), 137.2 (C), 134.2 (CH), 132.3 (CH), 130.5 (C), 127.8 (CH), 124.5 (CH), 122.1 (d, J = 7.8 Hz, CH), 116.2 (d, J = 18.8 Hz, C), 107.6 (d, J = 1.6 Hz, C), 107.0 (d, J = 3.5 Hz, CH), 105.3 (d, J = 19.3 Hz, CH), 31.5 (CH_2), 25.8 (CH_2), 22.3 (CH_2), 13.8 (CH_3); EI-LRMS *m/z* 312 (M^+, 100), 253 (86), 228 (71), 199 (25); IR (KBr) 3411, 2953, 2927, 1519, 1351, 1046, 779, 753, 740 cm^{-1}; HRMS calcd for $C_{18}H_{17}FN_2O_2$, 312.1274; found, 312.1276.

4-Fluoro-3-(3-methoxyphenyl)-2-phenyl-1*H*-indole (21c): Treatment of **3aa** with phenylacetylene (61 mg, 0.6 mmol) and 3-bromoanisole (112 mg, 0.6 mmol) for 5 h, and purification by column chromatography (hexane/EtOAc, 10/1) gave **21c** (133 mg, 84%) as a brown solid: 120–122 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.41–7.24 (m, 5H), 7.24–7.10 (m, 3H), 7.03 (s, 2H), 6.92–6.77 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.2 (C), 157.1 (d, J = 249.0 Hz, C), 138.3 (d, J = 10.8 Hz, C), 136.3 (C), 134.7 (C), 132.2 (C), 128.9 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 123.6 (d, J = 1.9 Hz, CH), 122.9 (d, J = 8.0 Hz, CH), 117.2 (d, J = 18.0 Hz, C), 116.3 (d, J = 2.6 Hz, CH), 113.1 (d, J = 3.0 Hz, C), 112.6 (CH), 107.1 (d, J = 3.7 Hz, CH), 105.9 (d, J = 20.1 Hz, CH), 55.2 (CH_3); EI-LRMS *m/z* 317 (M^+, 100), 285 (10), 272 (20), 259 (4); HRMS calcd for $C_{21}H_{16}FNO$, 317.1216; found, 317.1216.

4-Fluoro-2-hexyl-3-(4-methoxy-3-methylphenyl)-1*H*-indole (21d): Treatment of **3aa** with 1-octyne (66 mg, 0.6 mmol) and 4-bromo-2-methylanisole (120 mg, 0.6 mmol)) for 6 h, and purification by column chromatography (hexane/EtOAc, 10/1) gave **21d** (95 mg, 56%) as a brown solid: mp 211–213 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.27 (s, 2H), 7.15–7.02 (m, 2H), 6.92 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 10.0, 7.3 Hz, 1H), 3.91 (s, 3H), 2.76 (t, J = 7.7 Hz 2H), 2.32 (s, 3H), 1.71–1.61 (m, 2H), 1.40–1.20 (m, 6H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156.6 (d, J = 247.4 Hz, C), 156.4 (C), 137.9 (d, J = 11.4 Hz, C), 136.3 (C), 132.9 (d, J = 1.9 Hz, CH), 130.5 (d, J = 2.1 Hz, C), 128.8 (d, J = 1.9 Hz, CH), 127.9 (C), 127.1 (C), 125.8 (CH), 121.6 (d, J = 8.0 Hz, CH), 116.6 (d, J = 18.1 Hz, C), 112.4 (d, J =2.6 Hz, C), 109.5 (CH), 106.5 (d, J = 3.5 Hz, CH), 105.2 (d, J = 20.2 Hz, CH), 55.4 (CH_3), 31.6 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 16.5 (CH_3),

14.2 (CH_3); EI-LRMS *m/z* 339 (M^+, 100), 295 (21), 268 (43), 253 (12), 237 (23), 224 (36); HRMS calcd for $C_{22}H_{26}FNO$, 339.1998; found, 339.1996.

3-(4-Fluoro-2-(thiophen-3-yl)-1*H*-indol-3-yl)benzonitrile (21e): Treatment of **3aa** with 3-ethynylthiophene (64 mg, 0.6 mmol) for 2.5 h, further reaction with 3-bromobenzonitrile (108 mg, 0.6 mmol), and purification by column chromatography (hexane/EtOAc, 10/1) gave **21e** (136 mg, 86%) as a brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (br s, 1H), 7.82–7.73 (m, 2H), 7.69 (ddd, J = 7.8, 3.1, 1.6 Hz, 1H), 7.62–7.49 (m, 3H), 7.27 (d, J = 8.0 Hz, 1H), 7.11 (td, J = 8.0, 5.1 Hz, 1H), 6.92 (dd, J = 3.9, 2.6 Hz, 1H), 6.77 (dd, J = 11.8, 7.3 Hz, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 155.9 (d, J = 245.2 Hz, C), 138.3 (d, J = 10.8 Hz, C), 136.7 (C), 135.7 (C), 134.0 (d, J = 1.9 Hz, C), 132.0 (CH), 131.3 (C), 130.4 (CH), 129.3 (CH), 127.0 (CH), 126.8 (CH), 123.8 (CH), 122.5 (d, J = 7.9 Hz, C), 118.9 (CH), 116.0 (d, J = 17.7 Hz, C), 111.2 (CH), 108.9 (d, J = 2.7 Hz, C), 108.0 (d, J = 3.4 Hz, CH), 104.9 (d, J = 19.4 Hz, CH); EI-LRMS *m/z* 318 (M^+, 100), 285 (11), 273 (9); HRMS calcd for $C_{19}H_{11}FN_2S$, 318.0627; found, 318.0621.

2-Cyclohexenyl-4-fluoro-3-(4-nitrophenyl)-1*H*-indole (21f): Treatment of **3aa** with 1-ethynylcyclohexene (63 mg, 0.6 mmol) for 2.5 h, further reaction with 4-bromonitrobenzene (120 mg, 0.6 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) gave **21f** (142 mg, 85%) as an orange solid: mp 239–241 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.7 (s, 1H), 8.19 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.1 Hz, 1H), 7.07 (dd, J = 12.7, 7.7 Hz, 1H), 6.76 (dd, J = 11.9, 7.7 Hz, 1H), 5.88 (s, 1H), 2.19–1.96 (m, 4H), 1.65–1.46 (m, 4H); ^{13}C NMR (75.4, DMSO-d_6) δ 155.7 (d, J = 245.0 Hz, C), 145.3 (C), 143.4 (C), 139.2 (C), 138.0 (d, J = 11.0 Hz, C), 131.1 (d, J = 3.0 Hz, 2 × CH), 130.7 (CH), 129.0 (CH), 122.9 (2 × CH), 122.2 (d, J = 8.0 Hz, C), 115.1 (d, J = 17.7 Hz, C), 108.3 (d, J = 2.8 Hz, C), 108.0 (d, J = 3.2 Hz, CH), 105.0 (d, J = 20.0 Hz, CH), 27.5 (CH_2), 25.2 (CH_2), 22.2 (CH_3), 21.4 (CH_3); EI-LRMS *m/z* 336 (M^+, 100), 290 (35), 261 (24), 248 (29), 235 (21), 222 (10); HRMS calcd for $C_{20}H_{17}FN_2O_2$, 336.1274; found, 336.1274.

3-(4-Fluoro-2-(4-methoxyphenyl)-1*H*-indol-3-yl)benzonitrile (21g): Treatment of **3aa** with *p*-tolylacetylene (79 mg, 0.6 mmol) for 4 h, further reaction with 3-bromobenzonitrile (108 mg, 0.6 mmol), and purification by column chromatography (hexane/EtOAc, 10/1) gave **21g** (153 mg, 90%) as a pale brown solid: mp 186–188 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.67–7.62 (m, 1H), 7.56–7.52 (m, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.25–7.19 (m, 3H), 7.18–7.10 (m, 1H), 6.87 (d, J = 8.9 Hz, 2H), 6.83–6.78 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (75.4, $CDCl_3$) δ 159.9 (C), 156.7 (d, J = 248.0 Hz, C), 138.2 (d, J = 10.7 Hz, C), 136.7 (C), 135.6 (d, J = 2.4 Hz, CH), 134.4 (d, J = 2.6 Hz, CH), 130.0 (CH), 129.8 (2 × CH), 128.8 (CH), 123.7 (C), 123.1 (d, J = 8.0 Hz, CH), 119.3 (C), 116.8 (d, J = 18.1 Hz, C), 114.6 (2 × CH), 112.1 (C), 110.1 (C), 107.2 (d, J = 3.7 Hz, CH), 106.2 (d, J = 20.0 Hz, CH), 55.4 (CH_3); EI-LRMS *m/z* 342 (M^+, 100), 297 (17), 272 (4); HRMS calcd for $C_{22}H_{15}FN_2O$, 342.1168; found, 342.1172.

2-(4-Fluoro-2-hexyl-1*H*-indol-3-yl)benzonitrile (21h): Treatment of **3aa** with 1-octyne (66 mg, 0.6 mmol) for 2.5 h, further reaction with 2-bromobenzonitrile (108 mg, 0.6 mmol), and purification by column chromatography (hexane/EtOAc, 10/1) gave **21h** (73 mg, 46%) as a pale brown solid: mp 100–102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 7.76 (d, J = 7.5, 1.4 Hz, 1H), 7.62 (td, J = 7.5, 1.4 Hz, 1H), 7.56–7.49 (m, 1H), 7.43 (td, J = 7.5, 1.4 Hz, 1H), 7.14–7.00 (m, 2H), 6.76 (ddd, J = 11.2, 7.5, 1.1 Hz, 1H), 2.80–2.57 (m, 2H), 1.73–1.46 (m, 2H), 1.34–1.08 (m, 6H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4, $CDCl_3$) δ 156.2 (d, J = 246.6 Hz, C), 139.7 (C), 138.1 (C), 137.8 (d, J = 10.9 Hz, C), 132.7 (CH), 132.4 (d, J = 1.7 Hz, CH), 132.1 (CH), 127.1 (CH), 122.3 (d, J = 7.9 Hz, CH), 119.1 (C), 116.4 (d, J = 18.5 Hz, C), 114.2 (C), 108.8 (d, J = 2.0 Hz, C), 107.0 (d, J = 3.6 Hz, CH), 105.6 (d, J = 19.5 Hz, CH), 31.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); EI-LRMS *m/z* 320 (M^+, 74), 263 (22), 249 (100), 229 (22), 84 (18); HRMS calcd for $C_{21}H_{21}FN_2$, 320.1689; found, 320.1691.

Synthesis of 4-Fluoro-3-(3-methoxyphenyl)-2-thiophen-3-yl-1*H*-indole (21i): A mixture of **3aa** (100 mg, 0.3 mmol), $PdCl_2(PPh_3)_2$ (6.3 mg, 0.009 mmol), CuI (1.4 mg, 0.006 mmol) and 3-

ethynylthiophene (39 mg, 0.36 mmol) in Et_3N (1.5 mL) was charged in a 10 mL sealed tube under N_2 and irradiated in the microwave cavity at 60 ºC for 25 min. Then, 3-iodoanisole (84 mg, 0.36 mmol) and MeCN (1.5 mL) were added and the mixture was irradiated for 30 min at 90 ºC. The reaction was cooled to rt and then, EtOAc (10 mL) and water (10 mL) were added. The separated aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 10/1) to afford **21i** (72 mg, 75%) as a brown oil: R_f 0.50 (hexane/EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.26–7.22 (m, 2H), 7.18–7.05 (m, 4H), 6.98 (ddd, J = 4.2, 2.2, 0.5 Hz, 1H), 6.95–6.90 (m, 1H), 6.84–6.77 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (100.8 MHz, $CDCl_3$) δ 159.3 (C), 157.0 (d, J = 248.9 Hz, C), 138.1 (d, J = 10.7 Hz, C), 136.4 (C), 132.9 (C), 130.5 (C), 129.0 (CH), 127.0 (CH), 126.1 (C), 126.0 (CH), 123.6 (d, J = 1.7 Hz, CH), 123.0 (d, J = 7.9 Hz, CH), 122.4 (CH), 117.4 (d, J = 18.0 Hz, C), 116.3 (d, J = 2.1 Hz, CH), 112.9 (CH), 107.0 (d, J = 3.7 Hz, CH), 105.8 (d, J = 19.9 Hz, CH), 55.3 (CH_3); EI-LRMS *m/z* 323 (M^+, 100), 291 (14), 280 (17), 246 (9), 235 (8); HRMS calcd for $C_{19}H_{14}FNOS$, 323.0780; found, 323.0789.

General Procedure for the Synthesis of 2-Alkynyl-3-haloanilides 22: A mixture of the corresponding *N*-(3-halo-2-iodophenyl)propanamide **18ba** or **18ca** (1 equiv), alkyne (1.5 equiv when X = Cl, or 1.2 equiv when X = Br), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (5 mol%) and Et_2NH (1.5 equiv) in anhydrous DMF (4 mL/mmol) was stirred under N_2 at 40, 50 or 80 ºC until complete consumption of starting material, as monitored by GC-MS (2−6 h). CH_2Cl_2 (20 mL/mmol) and 0.5 M HCl (20 mL/mmol) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (2 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 5/1) to afford the title products **22**.

***N*-(3-Chloro-2-(2-phenylethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22ba):** Reaction of **18ba** (339 mg, 1 mmol) with 1-phenylacetylene (153 mg, 1.5 mmol) for 2 h at 80 ºC afforded **22ba** (269 mg, 86%) as a white solid: mp 139–141 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (br s, 1H), 8.42 (dd, J = 8.2, 1.1 Hz, 1H), 7.65–7.57 (m, 2H), 7.40–7.34 (m, 3H), 7.24 (t, J = 8.2 Hz, 1H), 7.15 (dd, J = 8.2, 1.1 Hz, 1H), 2.35 (br s, 1H), 1.58 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.7 (C), 140.2 (C), 135.7 (C), 131.8 (2 × CH), 129.9 (CH), 129.2 (CH), 128.7 (2 × CH), 124.2 (CH), 122.4 (C), 116.8 (CH), 112.9 (C), 101.7 (C), 81.6 (C), 74.8 (C), 28.1 (2 × CH_3); EI-LRMS *m/z* 315 (M^++2, 17), 313 (M^+, 51), 254 (54), 229 (33), 227 (100), 190 (27), 59 (41); IR (KBr) 3365, 3321, 1665, 1571, 1534, 1452, 759, 692 cm^{-1}; HRMS calcd for $C_{18}H_{16}ClNO_2$, 313.0870; found, 313.0857.

***N*-(3-Chloro-2-(hex-1-ynyl)phenyl)-2-hydroxy-2-methylpropanamide (22bb):** Reaction of **18ba** (339 mg, 1 mmol) with 1-hexyne (123 mg, 1.5 mmol) for 2.5 h at 80 ºC afforded **22bb** (263 mg, 90%) as a pale brown solid: mp 66–68 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (br s, 1H), 8.37 (d, J = 8.1 Hz, 1H), 7.24–7.07 (m, 2H), 2.55 (t, J = 6.9 Hz, 2H), 2.45 (br s, 1H), 1.70–1.46 (m, 4H), 1.56 (s, 6H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.8 (C), 140.2 (C), 135.6 (C), 129.0 (CH), 124.1 (CH), 116.7 (CH), 113.5 (C), 103.7 (C), 74.5 (C), 73.1 (C), 30.7 (CH_2), 28.1 (2 × CH_3), 22.1 (CH_2), 19.6 (CH_2), 13.7 (CH_3); EI-LRMS *m/z* 295 (M^++2, 17), 293 (M^+, 51), 207 (48), 193 (41), 178 (64), 164 (88), 59 (100); IR (KBr) 3419, 3322, 1670, 1572, 1516, 1450, 981 cm^{-1}; HRMS calcd for $C_{16}H_{20}ClNO_2$, 293.1183; found, 293.1184.

***N*-(3-Chloro-2-(hept-1-ynyl)phenyl)-2-hydroxy-2-methylpropanamide (22bc)**: Reaction of **18ba** (339 mg, 1 mmol) with 1-hetptyne (144 mg, 1.5 mmol) for 2.5 h at 80 ºC afforded **22bc** (248 mg, 81%) as a pale brown solid: mp 76–78 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (br s, 1H), 8.32 (dd, J = 7.6, 1.8 Hz, 1H), 7.15–7.05 (m, 2H), 3.49 (s, 1H), 2.49 (t, J = 7.1 Hz, 2H), 1.68–1.56 (m, 2H), 1.53 (s, 6H), 1.47–1.21 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.3 (C), 140.0 (C), 135.6 (C), 128.8 (CH), 124.0 (CH), 116.6 (CH), 113.6 (C), 103.8 (C), 74.2 (C), 73.0 (C), 31.1 (CH_2), 28.2 (CH_2), 27.9 (2 × CH_3), 22.2 (CH_2), 19.7 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 309 (M^++2, 7), 307 (M^+, 21),

206 (20), 180 (35), 164 (44), 59 (100); IR (KBr) 3311, 2953, 1662, 1569, 1520, 1453, 1139, 790, 731 cm^{-1}; HRMS calcd for $C_{17}H_{22}ClNO_2$, 307.1339; found, 307.1342.

***N*-(3-Chloro-2-(2-cyclohexenylethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22bd):** Reaction of **18ba** (339 mg, 1 mmol) with 1-ethynylcyclohexene (159 mg, 1.5 mmol) for 3 h at 80 ºC afforded **22bd** (253 mg, 80%) as a white solid: mp 145–147 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (br s, 1H), 8.36 (dd, J = 8.1, 1.3 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.10 (dd, J = 8.1, 1.3 Hz, 1H), 6.36–6.30 (m, 1H), 2.80 (s, 1H), 2.30–2.22 (m, 2H), 2.18–2.10 (m, 2H), 1.72–1.57 (m, 4H), 1.55 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.9 (C), 139.7 (C), 137.0 (CH), 135.4 (C), 129.2 (CH), 124.1 (CH), 120.3 (C), 116.6 (CH), 113.4 (C), 103.8 (C), 79.0 (C), 74.5 (C), 29.0 (CH_2), 28.0 (2 × CH_3), 26.0 (CH_2), 22.3 (CH_2), 21.5 (CH_2); EI-LRMS *m/z* 319 (M^++2, 23), 317 (M^+, 72), 281 (25), 231 (57), 207 (100), 180 (26), 59 (55); IR (KBr) 3372, 3320, 1652, 1572, 1532, 1450, 1435, 1197, 1184, 778, 725 cm^{-1}; HRMS calcd for $C_{18}H_{20}ClNO_2$, 317.1183; found, 317.1190.

***N*-(3-Chloro-2-(2-(trimethylsilyl)ethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22be)**: Reaction of **18ba** (339 mg, 1 mmol) with trimethylsilylacetylene (147 mg, 1.5 mmol) for 5.5 h at 40 ºC afforded **22be** (251 mg, 81%) as a pale brown solid: mp 144–146 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (br s, 1H), 8.37 (dd, J = 8.3, 0.9 Hz, 1H), 7.21 (t, J = 8.3 Hz, 1H), 7.09 (dd, J = 8.3, 0.9 Hz, 1H), 2.60 (br s, 1H), 1.55 (s, 6H), 0.29 (d, J = 0.9 Hz, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0 (C), 140.8 (C), 135.8 (C), 130.0 (CH), 124.1 (CH), 116.8 (CH), 112.8 (C), 108.1 (C), 96.6 (C), 74.6 (C), 28.1 (2 × CH_3), 0.0 (3 × CH_3); EI-LRMS *m/z* 311 (M^++2, 10), 309 (M^+, 29), 236 (100), 208 (39); HRMS calcd for $C_{15}H_{20}ClNO_2Si$, 309.0952; found, 309.951.

***N*-(3-Bromo-2-(2-phenylethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22ca)**: Reaction of **18ca** (383 mg, 1 mmol) with phenylacetylene (122 mg, 1.2 mmol) for 3.5 h at 50 ºC afforded **22ca** (285 mg, 80%) as a white solid: mp 131–133 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 8.44 (dd, J = 8.2, 1.0 Hz, 1H), 7.63–7.58 (m, 2H), 7.38–7.29 (m, 4H), 7.13 (t, J = 8.2 Hz, 1H), 2.87 (s, 1H), 1.55 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0 (C), 140.1 (C), 131.7 (2 × CH), 130.1 (CH), 129.2 (CH),

128.6 (2 × CH), 127.3 (CH), 125.0 (C), 122.3 (C), 117.3 (CH), 115.0 (C), 101.1 (C), 83.4 (C), 74.7 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 359 (M^++2, 62), 357 (M^+, 62), 300 (60), 298 (58), 273 (100), 271 (100), 191 (60), 165 (53), 59 (83); IR (KBr) 3372, 3312, 1661, 1566, 1532, 1446, 1200, 1131, 752, 726, 689 cm^{-1}; HRMS calcd for $C_{18}H_{16}BrNO_2$, 357.0364; found, 357.0368.

***N*-(3-Bromo-2-(hex-1-ynyl)phenyl)-2-hydroxy-2-methylpropanamide (22cb):** Reaction of **18ca** (576 mg, 1.5 mmol) with 1-hexyne (148 mg, 1.8 mmol) for 3.5 h at 50 ºC afforded **22cb** (429 mg, 85%) as a pale brown solid: mp 70–72 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 8.36 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.25 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.05 (t, *J* = 8.2 Hz, 1H), 3.42 (s, 1H), 2.50 (t, *J* = 7.0 Hz, 2H), 1.64–1.43 (m, 4H), 1.52 (s, 6H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.3 (C), 140.1 (C), 129.2 (CH), 127.2 (CH), 125.0 (C), 117.1 (CH), 115.6 (C), 103.1 (C), 74.8 (C), 74.2 (C), 30.5 (CH_2), 27.9 (2 × CH_3), 22.1 (CH_2), 19.5 (CH_2), 13.7 (CH_3); EI-LRMS *m/z* 339 (M^++2, 37), 337 (M^+, 36), 253 (29), 251 (30), 226 (50), 210 (51), 157 (25), 129 (26), 59 (100); IR (KBr) 3419, 3319, 1673, 1567, 1520, 1427, 980, 729 cm^{-1}; HRMS calcd for $C_{16}H_{20}BrNO_2$, 337.0677; found, 337.0676.

***N*-(3-Bromo-2-(hept-1-ynyl)phenyl)-2-hydroxy-2-methylpropanamide (22cc)**: Reaction of **18ca** (383 mg, 1 mmol) with 1-heptyne (115 mg, 1.2 mmol) for 3.5 h at 50 ºC afforded **22cc** (277 mg, 79%) as a white solid: mp 79–81 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.35 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.24 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.03 (t, *J* = 8.2 Hz, 1H), 3.58 (s, 1H), 2.47 (t, *J* = 7.2 Hz, 2H), 1.68–1.57 (m, 2H), 1.52 (s, 6H), 1.49–1.24 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.4 (C), 140.1 (C), 129.1 (CH), 127.1 (CH), 125.0 (C), 117.1 (CH), 115.6 (C), 103.2 (C), 74.8 (C), 74.2 (C), 31.1 (CH_2), 28.2 (CH_2), 27.8 (2 × CH_3), 22.2 (CH_2), 19.7 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 353 (M^++2, 15), 351 (M^+, 15), 226 (28), 210 (30), 157 (21), 59 (100); IR (KBr) 3295, 2930, 1661, 1564, 1520, 1449, 1130, 981, 788, 730 cm^{-1}; HRMS calcd for $C_{17}H_{22}BrNO_2$, 351.0834; found, 351.0822.

***N*-(3-Bromo-2-(2-cyclohexenylethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22cd)**: Reaction of **18ca** (383 mg, 1 mmol) with 1-ethynylcyclohexene (127 mg, 1.2 mmol) for 5 h at 50 ºC

afforded **22cd** (310 mg, 86%) as a white solid: mp 154–156 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (br s, 1H), 8.42 (dd, J = 8.2, 1.1 Hz, 1H), 7.29 (dd, J = 8.2, 1.1 Hz, 1H), 7.12 (t, J = 8.2 Hz, 1H), 6.37–6.32 (m, 1H), 2.48 (br s, 1H), 2.32–2.22 (m, 2H), 2.21–2.12 (m, 2H), 1.77–1.58 (m, 4H), 1.56 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.7 (C), 139.9 (C), 137.0 (CH), 129.6 (CH), 127.2 (CH), 124.9 (C), 120.4 (C), 117.2 (CH), 115.4 (C), 103.2 (C), 80.9 (C), 74.7 (C), 29.0 (CH_2), 28.1 (2 × CH_3), 26.0 (CH_2), 22.3 (CH_2), 21.5 (CH_2); EI-LRMS *m/z* 363 (M^++2, 100), 361 (M^+, 100), 277 (53), 275 (53), 167 (34), 59 (63); IR (KBr) 3376, 3318, 2929, 1653, 1566, 1530, 1446, 1433, 976, 775, 724 cm^{-1}; HRMS calcd for $C_{18}H_{20}BrNO_2$, 361.0677; found, 361.0677.

***N*-(3-Bromo-2-(2-(trimethylsilyl)ethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22ce)**: Reaction of **18ca** (383 mg, 1 mmol) with trimethylsilylacetylene (147 mg, 1.5 mmol) for 3 h at 40 ºC afforded **22ce** (251 mg, 71%) as a pale brown solid: mp 150–152 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 8.40 (dt, J = 8.2, 0.9 Hz, 1H), 7.27 (td, J = 8.2, 0.9 Hz, 1H), 7.12 (t, J = 8.2 Hz, 1H), 2.83 (s, 1H), 1.54 (d, J = 0.6 Hz, 6H), 0.28 (d, J = 0.8 Hz, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1 (C), 140.8 (C), 130.3 (CH), 127.2 (CH), 125.0 (C), 117.3 (CH), 114.8 (C), 107.5 (C), 98.3 (C), 74.4 (C), 28.0 (2 × CH_3), –0.1 (3 × CH_3); EI-LRMS *m/z* 355 (M^++2, 28), 353 (M^+, 27), 282 (100), 280 (100), 254 (37), 252 (37), 238 (19), 236 (18); HRMS calcd for $C_{15}H_{20}BrNO_2Si$, 353.0447; found, 353.0450.

***N*-(3-Bromo-2-(2-(thiophen-3-yl)ethynyl)phenyl)-2-hydroxy-2-methylpropanamide (22cf):** Reaction of **18ca** (383 mg, 1 mmol) with 3-ethynylthiophene (129 mg, 1.2 mmol) for 3.5 h at 50 ºC afforded **22cf** (268 mg, 74%) as a white solid: mp 132–134 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (br s, 1H), 8.41 (d, J = 8.3 Hz, 1H), 7.63 (dd, J = 2.9, 1.1 Hz, 1H), 7.31–7.27 (m, 2H), 7.24 (dd, J = 4.9, 1.1 Hz, 1H), 7.11 (t, J = 8.3 Hz, 1H), 2.90 (s, 1H), 1.53 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.0 (C), 140.1 (C), 130.0 (CH), 129.9 (CH), 129.8 (CH), 127.3 (CH), 125.9 (CH), 124.7 (C), 121.4 (C), 117.3 (CH), 115.1 (C), 96.3 (C), 83.1 (C), 74.7 (C), 28.0 (2 × CH_3); EI-LRMS *m/z* 365 (M^++2, 40), 363 (M^+, 44), 305 (19), 279 (61), 277 (59), 226 (14), 198 (29), 196 (32), 171 (23), 59 (100); HRMS calcd for $C_{16}H_{14}BrNO_2S$, 362.9929 ; found, 362.9928.

General Procedure for the Synthesis of 4-Halo-2-sustituted-1*H*-indoles 23 and 24: To a solution of the corresponding 3-halo-2-alkynylpropanamide **22** (1 equiv) in DMF (3 mL/mmol) an excess of freshly powdered NaOH (3 equiv) was added. The resulting mixture was refluxed under N_2 at 140 ºC until the cyclization was completed (2–5 h), as monitored by GC-MS. CH_2Cl_2 (10 mL) and 0.5 M HCl (10 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the corresponding 4-haloindoles **23** and **24**:

4-Chloro-2-phenyl-1*H*-indole (23a): Reaction of **22ba** (94 mg, 0.3 mmol) with NaOH (36 mg, 0.9 mmol) for 4 h, and purification by column chromatography (hexane/EtOAc, 7/1) afforded **23a** (54 mg, 79%) as a white solid: mp 73–75 ºC (lit.[59] mp 76–77 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.70–7.63 (m, 2H), 7.50–7.43 (m, 2H), 7.39–7.33 (m, 1H), 7.31–7.27 (m, 1H), 7.17–7.08 (m, 2H), 6.94 (dd, J = 2.2, 0.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.6 (C), 137.4 (C), 131.8 (C), 129.2 (2 × CH), 128.3 (CH), 128.2 (C), 125.9 (C), 125.4 (2 × CH), 122.9 (CH), 120.1 (CH), 109.6 (CH), 98.5 (CH); EI-LRMS *m/z* 229 (M^++2, 33), 227 (M^+, 100), 191 (10), 165 (16), 113 (10); IR (KBr) 3449, 2961, 2924, 1452, 1261, 1098, 803, 756, 688 cm^{-1}; HRMS calcd for $C_{14}H_{10}ClN$, 227.0502; found, 227.0501.

2-Butyl-4-chloro-1*H*-indole (23b): Reaction of **22bb** (88 mg, 0.3 mmol) with NaOH (36 mg, 0.9 mmol) for 2.5 h, and purification by column chromatography (hexane/EtOAc, 7/1) afforded **23b** (54 mg, 86%) as a colorless oil: R_f 0.46 (hexane/EtOAc, 6/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.18 (dt, J = 7.7, 1.0 Hz, 1H), 7.12 (dd, J = 7.7, 1.0 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.38 (dd, J = 2.2, 0.9 Hz, 1H), 2.74 (t, J = 7.6 Hz, 2H), 1.77–1.66 (m, 2H), 1.51–1.38 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.0 (C), 136.5 (C), 127.6 (C), 125.0 (C), 121.6 (CH), 119.4 (CH), 109.1 (CH), 98.1 (CH), 31.2 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 209 (M^++2, 10), 207 (M^+, 33), 164 (100), 128 (8), 101 (6); IR (KBr) 3417, 2957, 2929, 1575, 1548, 1433, 1330, 1182, 941, 765 cm^{-1}; HRMS calcd for $C_{12}H_{14}ClN$, 207.0815; found, 207.0822.

4-Chloro-2-pentyl-1*H*-indole (23c):[59] Reaction of **22bc** (154 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol) for 2.5 h, and purification by column chromatography (hexane/EtOAc, 7/1) afforded **23c** (93 mg, 84%) as a pale brown solid: mp 24–26 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.19 (dd, J = 7.6, 0.9 Hz, 1H), 7.11–7.00 (m, 2H), 6.36 (d, J = 0.9 Hz, 1H), 2.75 (t, J = 7.6 Hz, 2H), 1.79–1.68 (m, 2H), 1.43–1.25 (m, 4H), 0.93 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.0 (C), 136.5 (C), 127.7 (C), 125.0 (C), 121.6 (CH), 119.4 (CH), 109.0 (CH), 98.1 (CH), 31.6 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3); EI-LRMS *m/z* 223 (M^++2, 11), 221, (M^+, 34), 178 (24), 164 (100), 128 (9), 101 (6); IR (KBr) 3417, 2956, 2928, 1547, 1433, 1329, 1182, 939, 765 cm^{-1}; HRMS calcd for $C_{13}H_{16}ClN$, 221.0971; found, 221.0980.

4-Chloro-2-cyclohexenyl-1*H*-indole (23d)*:* Reaction of **22bd** (94 mg, 0.3 mmol) with NaOH (36 mg, 0.9 mmol) for 2.5 h, and purification by column chromatography (hexane/EtOAc, 8/1) afforded **23d** (56 mg, 81%) as a pale brown oil: R_f 0.70 (hexane/EtOAc, 6/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.21–7.17 (m, 1H), 7.09–7.02 (m, 2H), 6.54 (d, J = 2.0 Hz, 1H), 6.17–6.12 (m, 1H), 2.51–2.44 (m, 2H), 2.29–2.21 (m, 2H), 1.85–1.76 (m, 2H), 1.75–1.65 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.1 (C), 136.8 (C), 128.8 (C), 127.8 (C), 125.6 (C), 123.8 (CH), 122.5 (CH), 119.5 (CH), 109.1 (CH), 97.1 (CH), 26.0 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 22.2 (CH_2); EI-LRMS *m/z* 233 (M^++2, 32), 231 (M^+, 100), 203 (35), 164 (34), 151 (29); IR (neat) 3433, 2928, 1569, 1432, 1334, 1184, 947, 764, 731 cm^{-1}; HRMS calcd for $C_{14}H_{14}ClN$, 231.0815; found, 231.0814.

4-Chloro-1*H*-indole (23e): Reaction of **22be** (154 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol) for 4 h, and purification by column chromatography (hexane/EtOAc, 8/1) afforded **23e** (56 mg, 73%) as a brown oil: R_f 0.33 (hexane/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.31−7.21 (m, 2H), 7.16−7.08 (m, 2H), 6.70−6.62 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 136.6 (C), 126.9 (C), 126.2 (C), 124.9 (CH), 122.7 (CH), 119.7 (CH), 109.8 (CH), 101.4 (CH); EI-LRMS *m/z* 153 (M^++2, 31), 151 (M^+, 100), 116 (18), 89 (27).

4-Bromo-2-phenyl-1*H*-indole (24a): Reaction of **22ca** (178 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol) for 5 h, and purification by column chromatography (hexane/EtOAc, 8/1) afforded **24a** (113 mg, 83%) as a white solid: mp 100–102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.42 (br s, 1H), 7.65 (dd, J = 8.4, 1.0 Hz, 2H), 7.49–7.42 (m, 2H), 7.40–7.29 (m, 3H), 7.06 (t, J = 7.9 Hz, 1H), 6.91–6.89 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.5 (C), 137.0 (C), 131.7 (C), 130.1 (C), 129.2 (2 × CH), 128.3 (CH), 125.3 (2 × CH), 123.2 (CH), 114.6 (C), 110.2 (CH), 100.2 (CH); EI-LRMS *m/z* 273 (M^++2, 98), 271 (M^+, 100), 191 (27), 165 (34), 136 (11); IR (KBr) 3445, 1475, 1452, 1352, 1289, 1181, 916, 758, 691 cm^{-1}; HRMS calcd for $C_{14}H_{10}BrN$, 270.9997; found, 270.9995.

4-Bromo-2-butyl-1*H*-indole (24b): Reaction of **22cb** (101 mg, 0.3 mmol) with NaOH (36 mg, 0.9 mmol) for 3 h, and purification by column chromatography (hexane/EtOAc, 7/1) afforded **24b** (60 mg, 80%) as a white solid: mp 29–31 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.26 (dd, J = 7.8, 0.8 Hz, 1H), 7.22 (dt, J = 7.8, 0.8 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 6.32 (dd, J = 2.2, 0.9 Hz, 1H), 2.74 (t, J = 7.6 Hz, 2H), 1.77–1.66 (m, 2H), 1.50–1.37 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.0 (C), 136.0 (C), 129.6 (C), 122.5 (CH), 121.9 (CH), 113.7 (C), 109.6 (CH), 99.8 (CH), 31.2 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 253 (M^++2, 37), 251 (M^+, 37), 210 (100), 208 (98), 129 (32); IR (KBr) 3407, 2958, 2929, 1539, 1430, 1329, 1178, 917, 763, 729 cm^{-1}; HRMS calcd for $C_{12}H_{14}BrN$, 251.0310; found, 251.0309.

4-Bromo-2-pentyl-1*H*-indole (24c)*:* Reaction of **22cc** (123 mg, 0.35 mmol) with NaOH (42 mg, 1.05 mmol) for 2.5 h, and purification by column chromatography (hexane/EtOAc, 7/1) afforded **24c** (76 mg, 82%) as a pale brown oil: R_f 0.42 (hexane/EtOAc, 6/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.28–7.20 (m, 2H), 6.98 (t, J = 8.0 Hz, 1H), 6.31 (dd, J = 2.2, 0.8 Hz, 1H), 2.74 (t, J = 7.7 Hz, 2H), 1.79–1.68 (m, 2H), 1.43–1.34 (m, 4H), 0.93 (t, J= 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.0 (C), 136.1 (C), 129.6 (C), 122.5 (CH), 121.9 (CH), 113.7 (C), 109.6 (CH), 99.9 (CH), 31.6 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3); EI-LRMS *m/z* 267 (M^++2, 41), 265 (M^+, 42), 224 (19), 210

(100), 208 (98), 129 (32); IR (neat) 3411, 2956, 2928, 1548, 1430, 1327, 1178, 917, 763 cm^{-1}; HRMS calcd for $C_{13}H_{16}BrN$, 265.0466; found, 265.0467.

4-Bromo-2-cyclohexenyl-1*H*-indole (24d): Reaction of **22cd** (180 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol) for 4 h, and purification by column chromatography (hexane/EtOAc, 10/1) afforded **24d** (105 mg, 76%) as a colorless oil: R_f 0.5 (hexane/EtOAc, 6/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.27–7.20 (m, 2H), 6.99 (t, J = 7.8 Hz, 1H), 6.48 (d, J = 1.9 Hz, 1H), 6.17–6.12 (m, 1H), 2.51–2.43 (m, 2H), 2.28–2.20 (m, 2H), 1.84–1.75 (m, 2H), 1.75–1.65 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.2 (C), 136.4 (C), 129.7 (C), 128.9 (C), 123.8 (CH), 122.8 (CH), 122.7 (CH), 114.3 (C), 109.7 (CH), 98.9 (CH), 26.1 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 22.2 (CH_2); EI-LRMS *m/z* 277 (M^++2, 98), 275 (M^+, 100), 247 (24), 195 (23), 167 (38); IR (KBr) 3427, 2927, 1568, 1524, 1429, 1332, 1179, 917, 762, 730 cm^{-1}; HRMS calcd for $C_{14}H_{14}BrN$, 275.0310; found, 275.0314.

4-Bromo-1*H*-indole (24e): Reaction of **22ce** (176 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol) for 5 h, and purification by column chromatography (hexane/EtOAc, 10/1) afforded **24e** (74 mg, 75%) as a colorless oil: R_f 0.29 (hexane/EtOAc, 6/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.37−7.23 (m, 3H), 7.06 (t, J = 7.9 Hz, 1H), 6.64−6.60 (m, 1H); ^{13}CNMR (75.4 MHz, $CDCl_3$) δ 136.1 (C), 128.8 (C), 124.8 (CH), 123.0 (CH), 122.9 (CH), 114.9 (C), 110.4 (CH), 103.2 (CH); EI-LRMS *m/z* 197 (M^++2, 100), 195 (M^+, 100), 184 (7), 116 (77), 89 (44); HRMS calcd for C_8H_6BrN, 194.9684; found, 194.9679.

4-Bromo-2-(thiophen-3-yl)-1*H*-indole (24f): Reaction of **22cf** (181 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol) for 3 h, and purification by column chromatography (hexane/EtOAc, 10/1) afforded **24f** (99 mg, 71%) as a pale brown solid: mp 44–46 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 7.47–7.38 (m, 3H), 7.29 (d, J = 7.7 Hz, 2H), 7.07–7.00 (m, 1H), 6.75 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 136.6 (C), 134.6 (C), 133.5 (C), 129.9 (C), 127.0 (CH), 125.7 (CH), 123.25 (CH), 123.19 (CH), 119.9 (CH), 114.5 (C), 110.0 (CH), 100.2 (CH); EI-LRMS *m/z* 281 (M^++2, 100), 279 (M^+, 96), 198 (38), 171 (61), 154 (27), 126 (32); HRMS calcd for $C_{12}H_8BrNS$, 276.9561; found, 276.9576.

General Procedure for the One-pot Synthesis of 4-Halo-2-sustituted-1*H*-indoles 20, 23 and 24 from 2,3-Dihaloanilides 18: A mixture of the corresponding 2,3-dihaloanilide **18** (1 equiv), alkyne (1.5 equiv when X = F, Cl, or 1.2 equiv if X = Br), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (5 mol%) and Et_2NH (1.5 equiv) in DMA (4 mL/mmol) was stirred under N_2 at 80 ºC (for **18aa** and **18ba**), at 50 ºC (for **18ca**), or at 40 ºC (when trimetylsilylacetylene was used as alkyne) until complete consumption of starting material, as monitored by GC-MS (2–6 h). Then, a large excess of freshly powdered NaOH (10 equiv) was added to the reaction mixture and it was refluxed under N_2 at 140 ºC until the cyclization was completed (2–12 h), as monitored by GC-MS. CH_2Cl_2 (20 mL) and 0.5 M HCl (20 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (2 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the corresponding 4-haloindoles **20, 23** and **24**. The characterization data of **20a**, **23a-e** and **24a-f** have been reported above:

2-Butyl-4-fluoro-1*H*-indole (20c): Treatment of **18aa** (161 mg, 0.5 mmol) with 1-hexyne (62 mg, 0.75 mmol) for 3 h and then, with NaOH (200 mg, 5 mmol) for 3 h, and purification by column chromatography (hexane/EtOAc, 8/1) afforded **20b** (73 mg, 77%) as a pale brown oil: R_f 0.50 (hexane/EtOAc, 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.11–7.00 (m, 2H), 6.78 (ddd, J = 10.4, 6.9, 1.7 Hz, 1H), 6.35 (dd, J = 2.2, 0.8 Hz, 1H), 2.75 (t, J = 7.6 Hz, 2H), 1.77–1.66 (m, 2H), 1.51–1.38 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 155.9 (d, J = 245.2 Hz, C), 140.1 (C), 138.6 (d, J = 11.8 Hz, C), 121.4 (d, J = 7.6 Hz, CH), 117.8 (d, J = 22.4 Hz, C), 106.5 (d, J = 3.4 Hz, CH), 104.5 (d, J = 19.1 Hz, CH), 95.4 (CH), 31.3 (CH_2), 27.9 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS calcd for $C_{12}H_{14}FN$, 191.1110; found, 191.1106.

4-Chloro-2-(3-chlorophenyl)-1*H*-indole (23f): Treatment of **18ba** (170 mg, 0.5 mmol) with 1-chloro-3-ethynylbenzene (102 mg, 0.75 mmol) for 2 h and then, with NaOH (200 mg, 5 mmol) for 3 h, and purification by column chromatography (hexane/EtOAc, 7/1) afforded **23f** (98 mg, 75%) as a brown

solid: mp 80–82 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.62 (t, *J* = 1.6 Hz, 1H), 7.50 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.32–7.24 (m, 2H), 7.17–7.08 (m, 2H), 6.92 (dd, *J* = 2.2, 0.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.5 (C), 136.9 (C), 135.1 (C), 133.5 (C), 130.4 (CH), 128.1 (CH), 128.0 (C), 126.1 (C), 125.3 (CH), 123.39 (CH), 123.38 (CH), 120.3 (CH), 109.7 (CH), 99.4 (CH); EI-LRMS *m/z* 265 (M^++4, 13), 263 (M^++2, 62), 261 (M^+, 100), 226 (13), 199 (30), 190 (35), 164 (30), 89 (49); HRMS calcd for $C_{14}H_9Cl_2N$, 261.0112; found, 261.0112.

4-Chloro-2-(4-fluoro-3-methylphenyl)-1*H*-indole (23g): Treatment of **18ba** (136 mg, 0.4 mmol) with 4-ethynyl-1-fluoro-2-methylbenzene (80 mg, 0.6 mmol) for 2 h and then, with NaOH (160 mg, 4 mmol) for 4 h, and purification by column chromatography (hexane/EtOAc, 8/1) afforded **23g** (74 mg, 72%) as a brown solid: mp 114–116 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.46–7.39 (m, 1H), 7.29–7.24 (m, 1H), 7.15–7.03 (m, 3H), 6.84 (d, *J* = 0.9 Hz, 1H), 2.34 (br s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.4 (d, *J* = 247.0 Hz, C), 138.0 (C), 137.4 (C), 128.6 (d, *J* = 5.3 Hz, CH), 128.2 (C), 127.8 (d, *J* = 3.7 Hz, C), 125.9 (d, *J* = 7.2 Hz, C), 125.7 (C), 124.4 (d, *J* = 8.2 Hz, CH), 122.9 (CH), 120.1 (CH), 115.8 (d, *J* = 22.9 Hz, CH), 109.6 (CH), 98.2 (CH), 14.8 (d, *J* = 3.4 Hz, CH_3); EI-LRMS *m/z* 261 (M^++2, 49), 259 (M^+, 100), 223 (14), 208 (13), 197 (14), 129 (16), 111 (23); HRMS calcd for $C_{15}H_{11}ClFN$, 259.0564; found, .259.0561.

4-Bromo-2-(3-chlorophenyl)-1*H*-indole (24g): Treatment of **18ca** (191 mg, 0.5 mmol) with 1-chloro-3-ethynylbenzene (102 mg, 0.75 mmol) for 2 h and then, with NaOH (200 mg, 5 mmol) for 4 h, and purification by column chromatography (hexane/EtOAc, 8/1) afforded **24g** (73 mg, 48%) as a brown solid: mp 89–91 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.67–7.64 (m, 1H), 7.55 (ddd, *J* = 7.6, 2.8, 1.3 Hz, 1H), 7.43–7.27 (m, 4H), 7.06 (td, *J* = 8.1, 1.2 Hz, 1H), 6.90–6.87 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.1 (C), 137.0 (C), 135.2 (C), 133.6 (C), 130.5 (CH), 129.9 (C), 128.2 (CH), 125.4 (CH), 123.8 (CH), 123.5 (CH), 123.4 (CH), 114.9 (C), 110.3 (CH), 101.2 (CH); EI-LRMS *m/z* 309 (M^++4, 23), 307 (M^++2, 100), 305 (M^+, 80), 226 (16), 199 (34), 190 (74), 163 (60); HRMS calcd for $C_{14}H_9BrClN$, 304.9607; found, 304.9620.

General Procedure for the Synthesis of *N*-(2,3-Dialkynylphenyl)-2-methylpropanamides 25: A mixture of **18bc** (148 mg, 0.6 mmol), $PdCl_2(MeCN)_2$ (3 mg, 2 mol%), XPhos (17 mg, 3 mol%) and Cs_2CO_3 (586 mg, 1.8 mmol) in anhydrous MeCN (2 mL) was stirred under N_2 at rt for 25 min. Then, the corresponding alkyne (1.8 mmol) was added and the reaction was stirred at reflux overnight. AcOEt and water were added to the cooled reaction mixture. The separated aqueous phase was extracted with AcOEt (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the corresponding title compounds **25**:

***N*-(2,3-Bis(2-phenylethynyl)phenyl)-2-hydroxy-2-methylpropanamide (25a)**: Reaction of **18bc** with phenylacetylene (198 μL, 1.8 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) afforded **25a** (147 mg, 65%) as a brown solid: mp 162−164 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 8.53−8.45 (m, 1H), 7.65−7.54 (m, 4H), 7.41−7.33 (m, 6H), 7.34−7.27 (m, 2H), 2.45 (s, 1H), 1.60 (s, 6H); ^{13}C NMR (75.4, $CDCl_3$) δ 174.7 (C), 139.0 (C), 131.8 (2 × CH), 131.6 (2 × CH), 129.1 (CH), 129.0 (CH), 128.7 (3 × CH), 128.6 (2 × CH), 127.0 (CH), 125.8 (C), 123.2 (C), 122.8 (C), 118.5 (CH), 115.1 (C), 100.8 (C), 93.7 (C), 88.2 (C), 83.6 (C), 74.8 (C), 28.1 (2 × CH_3); EI-LRMS *m/z* 379 (M^+, 61), 361 (73), 321 (61), 292 (58), 265 (56), 189 (20), 59 (100); HRMS calcd for $C_{26}H_{21}NO_2$, 379.1572; found, 379.1569.

***N*-(2,3-Di(hept-1-ynyl)phenyl)-2-hydroxy-2-methylpropanamide (25b):** Reaction of **18bc** with 1-heptyne (236 μL, 1.8 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) afforded **25b** (173 mg, 79%) as a brown oil: R_f 0.48 (hexane/EtOAc, 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.34 (dd, J = 7.9, 1.3 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.08 (dd, J = 7.9, 1.3 Hz, 1H), 2.72 (s, 1H), 2.51 (t, J = 7.1 Hz, 2H), 2.43 (t, J = 7.1 Hz, 2H), 1.68−1.57 (m, 4H), 1.53 (s, 6H), 1.49−1.41 (m, 4H), 1.39−1.30 (m, 4H), 0.90 (td, J = 7.2, 3.8 Hz, 6H); ^{13}C NMR (100.6, $CDCl_3$) δ 174.8 (C), 138.9 (C), 128.1 (CH), 127.0 (CH), 126.6 (C), 117.7 (CH), 115.8 (C), 101.8 (C), 94.4 (C), 79.5 (C), 75.0 (C), 74.4 (C), 31.23 (CH_2), 31.17 (CH_2), 28.58 (CH_2), 28.56 (CH_2), 28.0 (2 × CH_3), 22.4 (2 × CH_2), 19.9 (CH_2),

19.7 (CH_2), 14.11 (CH_3), 14.09 (CH_3); EI-LRMS *m/z* 367 (M^+, 20), 320 (37), 296 (87), 278 (100), 167 (29), 59 (40); HRMS calcd for $C_{24}H_{33}NO_2$, 367.2511; found, 367.2518.

***N*-(2,3-Bis(2-cyclohexenylethynyl)phenyl)-2-hydroxy-2-methylpropanamide (25c):** Reaction of **18bc** with 1-ethynylcyclohexene (212 μL, 1.8 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) afforded **25c** (174 mg, 75%) as a pale yellow solid: mp 156–158 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 8.38 (dd, J = 8.0, 1.3 Hz, 1H), 7.27–7.19 (m, 1H), 7.17–7.12 (m, 1H), 6.33–6.27 (m, 1H), 6.27–6.22 (m, 1H), 2.50 (br s, 1H), 2.30–2.21 (m, 4H), 2.20–2.11 (m, 4H), 1.72–1.59 (m, 8H), 1.56 (d, J = 1.1 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.7 (C), 138.5 (C), 136.3 (CH), 135.9 (CH), 128.4 (CH), 126.8 (CH), 126.0 (C), 120.9 (C), 120.7 (CH), 117.9 (C), 115.3 (C), 102.6 (C), 95.4 (C), 85.7 (C), 81.0 (C), 74.6 (C), 29.3 (CH_2), 29.2 (CH_2), 28.1 (2 × CH_3), 26.03 (CH_2), 25.98 (CH_2), 22.45 (CH_2), 22.40 (CH_2), 21.61 (CH_2), 21.55 (CH_2); EI-LRMS *m/z* 387 (M^+, 92), 369 (32), 328 (38), 300 (36), 207 (100), 59 (83); HRMS calcd for $C_{26}H_{29}NO_2$, 387.2198; found, 387.2198.

***N*-(2,3-Bis(2-(thiophen-3-yl)ethynyl)phenyl)-2-hydroxy-2-methylpropanamide (25d):** Reaction of **18bc** with 3-ethynylthiophene (211 μL, 1.8 mmol), and purification by column chromatography (hexane/EtOAc, 5/1) afforded **25d** (164 mg, 70%) as a pale brown solid: mp 206–208 ºC; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.1 (s, 1H), 8.56 (dd, J = 8.3, 1.2 Hz, 1H), 7.83 (dd, J = 3.0, 1.2 Hz, 1H), 7.81 (dd, J = 3.0, 1.2 Hz, 1H), 7.57 (dd, J = 5.0, 3.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.32 (dd, J = 5.0, 1.2 Hz, 1H), 7.30 (dd, J = 2.2, 1.2 Hz, 1H), 7.28 (dd, J = 1.2, 0.4 Hz, 1H), 5.41 (s, 1H), 1.51 (s, 6H); ^{13}C NMR (75.4, acetone-d_6) δ = 176.0 (C), 140.6 (C), 130.7 (CH), 130.6 (CH), 130.5 (CH), 130.4 (CH), 129.9 (CH), 127.3 (CH), 127.2 (CH), 127.0 (CH), 126.2 (C), 122.8 (C), 122.4 (C), 118.8 (CH), 115.3 (C), 96.8 (C), 89.6 (C), 88.1 (C), 83.6 (C), 74.6 (C), 28.1 (2 × CH_3); EI-LRMS *m/z* 391 (M^+, 82), 372 (20), 345 (100), 305 (76), 277 (57), 245 (23), 207 (78), 59 (47); HRMS calcd for $C_{22}H_{17}NO_2S_2$, 391.0701; found, 391.0701.

General Procedure for the Synthesis of 4-Alkynyl-2-substituted-1*H*-indoles 26a-d: To a solution of the corresponding 2,3-dialkynylpropanamide **25** (1 equiv) in DMF (3mL/mmol) was added an excess of freshly powdered NaOH (3 equiv). The resulting mixture was refluxed under N_2 at 140 ºC until the cyclization was completed (6 h), as monitored by GC-MS. CH_2Cl_2 (10 mL) and 0.5 M HCl (10 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (2 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the corresponding title compounds **26a-d**:

2-Phenyl-4-(2-phenylethynyl)-1*H*-indole (26a): Reaction of **25a** (189 mg, 0.5 mmol) with NaOH (60 mg, 1.5 mmol), and purification by column chromatography (hexane/EtOAc, 15/1) afforded **26a** (106 mg, 73%) as a pale brown solid: mp 132–134 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.73–7.57 (m, 4H), 7.50–7.34 (m, 8H), 7.19 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.6 (C), 136.5 (C), 132.1 (C), 131.8 (2 × CH), 130.9 (C), 129.1 (2 × CH), 128.5 (2 × CH), 128.2 (CH), 128.1 (CH), 125.4 (2 × CH), 124.2 (CH), 123.9 (C), 122.2 (CH), 114.7 (C), 111.6 (CH), 99.8 (CH), 92.1 (C), 88.5 (C); EI-LRMS *m/z* 293 (M^+, 100), 207 (12), 189 (10), 146 (12); IR (KBr) 3427, 3056, 1597, 1487, 1451, 1422, 1283, 753, 687 cm^{-1}; HRMS calcd for $C_{22}H_{15}N$, 293.1204; found, 293.1205.

4-(Hept-1-ynyl)-2-pentyl-1*H*-indole (26b): Reaction of **25b** (147 mg, 0.4 mmol) with NaOH (48 mg, 1.2 mmol), and purification by column chromatography (hexane/EtOAc, 15/1) afforded **26b** (78 mg, 70%) as a pale brown oil: R_f 0.50 (hexane/EtOAc, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.24–7.13 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.40 (dd, J = 1.5, 0.6 Hz, 1H), 2.74 (t, J = 7.6 Hz, 2H), 2.52 (t, J = 7.0 Hz, 2H), 1.81–1.61 (m, 4H), 1.61–1.45 (m, 2H), 1.45–1.26 (m, 6H), 0.94 (dt, J = 9.2, 7.2 Hz, 6H); ^{13}C NMR (75.4, $CDCl_3$) δ 140.6 (C), 135.4 (C), 130.6 (C), 123.2 (CH), 120.8 (CH), 114.7 (C), 110.2 (CH), 99.3 (CH), 92.5 (C), 79.6 (C), 31.6 (CH_2), 31.3 (CH_2), 28.95 (CH_2), 28.86 (CH_2), 28.4

(CH_2), 22.6 (CH_2), 22.4 (CH_2), 19.8 (CH_2), 14.22 (CH_3), 14.16 (CH_3); EI-LRMS *m/z* 281 (M^+, 89), 238 (24), 224 (100), 167 (53); HRMS calcd for $C_{20}H_{27}N$, 281.2143; found, 281.2141.

2-Cyclohexenyl-4-(2-cyclohexenylethynyl)-1*H*-indole (26c): Reaction of **25c** (116 mg, 0.3 mmol) with NaOH (36 mg, 0.9 mmol), and purification by column chromatography (hexane/EtOAc, 15/1) afforded **26c** (51 mg, 57%) as a colorless oil: R_f 0.40 (hexane/EtOAc, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.23 (dt, J = 7.9, 1.0 Hz, 1H), 7.16 (dd, J = 7.4, 1.0 Hz, 1H), 7.09–7.03 (m, 1H), 6.58 (d, J = 1.8 Hz, 1H), 6.29–6.25 (m, 1H), 6.17–6.12 (m, 1H), 2.52–2.45 (m, 2H), 2.37–2.22 (m, 4H), 2.21–2.14 (m, 2H), 1.84–1.76 (m, 2H), 1.75–1.60 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.0 (C), 135.8 (C), 134.7 (CH), 130.5 (C), 130.0 (C), 129.2 (C), 123.5 (CH), 123.3 (CH), 121.9 (CH), 121.3 (C), 115.0 (C), 110.5 (CH), 98.7 (CH), 93.8 (C), 85.9 (C), 29.7 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.3 (CH_2), 21.7 (CH_2); EI-LRMS *m/z* 301 (M^+, 100), 273 (9), 230 (6), 204 (8), 191 (6); HRMS calcd for $C_{22}H_{23}N$, 301.1830; found, 301.1835.

2-(Thiophen-3-yl)-4-(2-(thiophen-3-yl)ethynyl)-1*H*-indole (26d): Reaction of **25d** (117 mg, 0.3 mmol) with NaOH (36 mg, 0.9 mmol), and purification by column chromatography (hexane/EtOAc, 15/1) afforded **26d** (64 mg, 71%) as a white solid: mp 200–202 ºC; ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.92 (s, 1H), 7.88 (dd, J = 2.9, 1.3 Hz, 1H), 7.80 (dd, J = 2.9, 1.3 Hz, 1H), 7.69 (dd, J = 5.0, 1.3 Hz, 1H), 7.59 (ddd, J = 6.7, 5.0, 2.9 Hz, 2H), 7.42 (dt, J = 8.0, 1.0 Hz, 1H), 7.33 (dd, J = 5.0, 1.3 Hz, 1H), 7.22 (dd, J = 7.4, 1.0 Hz, 1H), 7.12 (dd, J = 8.0, 7.4 Hz, 1H), 7.03 (dd, J = 2.3, 1.0 Hz, 1H); ^{13}C NMR (100.6, Acetone-d_6) δ 137.5 (C), 136.1 (C), 134.9 (C), 131.4 (C), 130.7 (CH), 129.4 (CH), 127.6 (CH), 126.9 (CH), 126.8 (CH), 124.1 (CH), 123.6 (C), 122.4 (CH), 120.8 (CH), 114.8 (C), 112.5 (CH), 99.4 (CH), 88.8 (C), 87.4 (C); EI-LRMS *m/z* 305 (M^+, 100), 281 (27), 253 (12), 207 (98), 191 (10); HRMS calcd for $C_{18}H_{11}NS_2$, 305.0333; found, 305.0333.

General Procedure for the Synthesis of 4-Alkynyl-2-substituted-1*H*-indoles 26e-f: A mixture of **1c** (231 mg, 0.9 mmol)**,** $PdCl_2(MeCN)_2$ (5 mg, 2 mol%), XPhos (26 mg, 3 mol%) and Cs_2CO_3 (880 mg, 2.7 mmol) in anhydrous MeCN (3 mL) was stirred under N_2 at rt for 25 min. Then, the corresponding

alkyne (2.7 mmol) was added and the reaction was stirred at reflux for 40 h. AcOEt and water were added to the cooled reaction mixture. The separated aqueous phase was extracted with AcOEt (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the corresponding title compounds **26e-f**:

2-*p*-Tolyl-4-(2-*p*-tolylethynyl)-1*H*-indole (26e): Reaction of **1c** (231 mg, 0.9 mmol) with *p*-tolylacetylene (313 mg, 2.7 mmol), and purification by column chromatography (hexane/EtOAc, 15/1) afforded **26e** (127 mg, 44%) as a brown oil R_f 0.40 (hexane/EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.36–7.30 (m, 2H), 7.25 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 7.14 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 1.3 Hz, 1H), 2.39 (d, J = 1.8 Hz, 6H); ^{13}C NMR (100.4, $CDCl_3$) δ 138.8 (C), 138.3 (C), 138.1 (C), 136.4 (C), 131.7 (2 × CH), 131.0 (C), 129.9 (2 × CH), 129.4 (C), 129.2 (2 × CH), 125.3 (2 × CH), 124.1 (CH), 122.0 (CH), 120.9 (C), 114.8 (C), 111.3 (CH), 99.3 (CH), 92.2 (C), 87.9 (C), 21.7 (CH_3), 21.4 (CH_3); EI-LRMS *m/z* 321 (M^+, 100), 281 (10), 207 (31), 160 (7); HRMS calcd for $C_{24}H_{19}N$, 321.1517; found, 321.1518.

2-Hexyl-4-(oct-1-ynyl)-1*H*-indole (26f): Reaction of **1c** (231 mg, 0.9 mmol) with 1-octyne (398 μL, 2.7 mmol), and purification by column chromatography (hexane/EtOAc, 20/1) afforded **26f** (141 mg, 51%) as a brown oil R_f 0.50 (hexane/EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.19 (dt, J = 8.1, 0.9 Hz, 1H), 7.15 (dd, J = 7.4, 0.9 Hz, 1H), 7.02 (dd, J = 8.1, 7.4 Hz, 1H), 6.39 (dd, J = 2.2, 0.9 Hz, 1H), 2.73 (t, J = 7.7 Hz, 2H), 2.51 (t, J = 7.0 Hz, 2H), 1.77–1.63 (m, 4H), 1.57–1.48 (m, 2H), 1.44–1.18 (m, 10H), 0.96–0.87 (m, 6H); ^{13}C NMR (100.6, $CDCl_3$) δ 140.6 (C), 135.5 (C), 130.7 (C), 123.2 (CH), 120.8 (CH), 114.8 (C), 110.2 (CH), 99.4 (CH), 92.5 (C), 79.7 (C), 31.8 (CH_2), 31.6 (CH_2), 29.25 (CH_2), 29.18 (CH_2), 29.15 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 19.9 (CH_2), 14.23 (CH_3), 14.23 (CH_3); EI-LRMS *m/z* 309 (M^+, 100), 281 (19), 252 (27), 238 (84), 207 (46), 167 (56); HRMS calcd for $C_{22}H_{31}N$, 309.2457; found, 309.2456.

Synthesis of 2-Phenyl-4-(2-phenylethynyl)-1*H*-indole 26a from 3-Bromo-2-iodoanilide 18ca: A mixture of anilide **18ca** (383 mg, 1 mmol), phenylacetylene (408 mg, 4 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 10 mol%), and $TBAF{\cdot}3H_2O$ (947 mg, 3 mmol) was stirred under N_2 at 60 ºC until complete consumption of starting material, as monitored by GC-MS (5 h). The mixture was washed with water, extracted with Et_2O (3 × 20 mL), and evaporated under reduced pressure. To remove Pd salts, the crude was filtered through a short pad of silica gel. The residue was treated with an excess of freshly powdered NaOH (120 mg, 3 mmol) in DMA (3 mL) under N_2 at 140 ºC for 8 h. The formation of the indole was monitored by GC-MS. CH_2Cl_2 (20 mL) and 0.5 M HCl (20 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (2 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 10/1) to afford **26a** (152 mg, 52%), whose spectroscopic data have been reported above.

Synthesis of 4-(Hex-1-ynyl)-2-phenyl-1*H*-indole 26g: A mixture of 4-bromo-2-phenyl-1*H*-indole **24a** (81 mg, 0.3 mmol), phenylacetylene (46 mg, 0.45 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 6 mol%), CuI (6 mg, 10 mol%) and Et_2NH (33 mg, 0.45 mmol) in DMF (2 mL) was stirred under N_2 at 80 ºC for 17 h. CH_2Cl_2 (20 mL) and 0.5 M HCl (20 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (2 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 8/1) to afford **26g** (63 mg, 77%) as a brown solid: mp 33–35 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.7 Hz, 2H), 7.33 (d, J = 7.3 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 6.99–6.97 (m, 1H), 2.55 (t, J = 6.9 Hz, 2H), 1.75–1.63 (m, 2H), 1.62–1.50 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.2 (C), 136.5 (C), 132.3 (C), 131.1 (C), 129.2 (2 × CH), 128.0 (CH), 125.3 (2 × CH), 123.9 (CH), 122.3 (CH), 115.8 (C), 110.7 (CH), 99.9

(CH), 93.2 (C), 79.3 (C), 31.2 (CH_2), 22.2 (CH_2), 19.6 (CH_2), 13.9 (CH_3); EI-LRMS *m/z* 273 (M^+, 89), 258 (16), 244 (38), 230 (100), 202 (29), 127 (23); HRMS calcd for $C_{20}H_{19}N$, 273.1517; found, 273.1511.

General Procedure for the Synthesis of 4-Halo-3-(phenylthio)-2-substituted-1*H*-indoles 27a-b from Anilides 18: A mixture of the corresponding anilide **18aa** or **18ba** (0.4 mmol), alkyne (0.6 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 3 mol%), CuI (4 mg, 5 mol%) and Et_2NH (44 mg, 0.6 mmol) in DMA (2 mL) was stirred for 2 h at 80 ºC and then, freshly powdered NaOH (160 mg, 4 mmol) was added. The resulting mixture was heated under N_2 at 140 ºC for 3 h (until the cyclization was completed as monitored by GC-MS). Then, Ph_2S_2 (105 mg, 0.48 mmol) was added and the reaction mixture was stirred overnight at 140 ºC. Then, CH_2Cl_2 (10 mL) and 0.5 M HCl (10 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 6/1) to afford the title compounds **27**:

4-Fluoro-2-pentyl-3-(phenylthio)-1*H*-indole (27a): Reaction of **18aa** (129 mg, 0.4 mmol) with 1-heptyne (58 mg, 0.6 mmol), and then with Ph_2S_2 afforded **27a** (92 mg, 74%) as a brown solid: mp 78–80 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.26–7.02 (m, 7H), 6.76 (ddd, *J* = 10.9, 7.5, 1.1 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.70–1.60 (m, 2H), 1.34–1.24 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156.4 (d, *J* = 248.9 Hz, C), 146.1 (C), 140.3 (C), 138.2 (C), 128.7 (2 × CH), 125.8 (2 × CH), 124.7 (CH), 122.5 (d, *J* = 7.8 Hz, CH), 118.7 (d, *J* = 17.3 Hz, C), 107.1 (d, *J* = 3.9 Hz, CH), 106.4 (d, *J* = 19.2 Hz, CH), 97.0 (d, *J* = 2.3 Hz, C), 31.5 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 22.5 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 313 (M^+, 100), 256 (48), 222 (16), 148 (24), 69 (16); HRMS calcd for $C_{19}H_{20}FNS$, 313.1300; found, 313.1291.

4-Chloro-2-phenyl-3-(phenylthio)-1*H*-indole (27b): Reaction of **18ba** (136 mg, 0.4 mmol) with phenylacetylene (61 mg, 0.6 mmol), and then with Ph_2S_2 afforded **27b** (103 mg, 77 %) as a white solid:

mp 131–133 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.66 (dd, J = 6.6, 2.9 Hz, 2H), 7.43–7.38 (m, 3H), 7.36–7.29 (m, 1H), 7.26–7.05 (m, 7H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.3 (C), 141.4 (C), 137.3 (C), 131.0 (C), 129.2 (CH), 128.9 (2 × CH), 128.7 (4 × CH), 127.0 (C), 126.8 (C), 125.3 (2 × CH), 124.6 (CH), 123.7 (CH), 122.8 (CH), 110.2 (CH), 98.8 (C); EI-LRMS *m/z* 337 (M^++2, 22), 335 (M^+, 51), 299 (16), 267 (15), 223 (100), 190 (12), 121 (22), 119 (23), 77 (86), 51 (67); HRMS calcd for $C_{20}H_{14}ClNS$, 335.0535; found, 335.0534.

General Procedure for the Synthesis of 4-Halo-3-phenylsulfanyl-1*H*-indoles 27c-d from 3-Halo-2-alkynylpropanamides 22: An excess of freshly powdered NaOH (120 mg, 3 mmol) was added to a solution of the corresponding 3-halo-2-alkynylpropanamide **22bb** or **22cb** (0.3 mmol) in DMA (1 mL). The resulting mixture was refluxed under N_2 at 140 ºC until the cyclization was completed (2–3 h) (monitored by GC-MS). Then, Ph_2S_2 (78 mg, 0.36 mmol) was added to the mixture and the reaction was stirred overnight at 140 ºC. CH_2Cl_2 (10 mL) and 0.5 M HCl (10 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (2 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 6/1) to afford the title compounds **27**:

2-Butyl-4-chloro-3-(phenylthio)-1*H*-indole (27c): Reaction of **22bb** (88 mg, 0.3 mmol) with NaOH for 3 h at 140 ºC, and then with Ph_2S_2 afforded **27c** (74 mg, 79%) as a white solid: mp 76–78 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.25 (ddd, J = 6.5, 2.4, 0.4 Hz, 1H), 7.22–7.15 (m, 2H), 7.12–7.03 (m, 5H), 2.91 (t, J = 7.6 Hz, 2H), 1.68–1.56 (m, 2H), 1.41–1.27 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.5 (C), 141.3 (C), 136.9 (C), 128.7 (2 × CH), 126.3 (C), 126.1 (C), 125.4 (2 × CH), 124.4 (CH), 122.6 (CH), 122.2 (CH), 109.8 (CH), 98.6 (C), 31.6 (CH_2), 26.2 (CH_2), 22.5 (CH_2), 13.9 (CH_3); EI-LRMS *m/z* 317 (M^++2, 39), 315 (M^+, 83), 272 (22), 236 (100), 204 (50), 164 (96), 119 (23), 77 (59); HRMS calcd for $C_{18}H_{18}ClNS$, 315.0848; found, 315.0849.

4-Bromo-2-butyl-3-(phenylthio)-1*H*-indole (27d): Reaction of **22cb** (101 mg, 0.3 mmol) with NaOH for 2.5 h, and then with Ph_2S_2 afforded **27d** (78 mg, 73%) as a pale brown solid: mp 86–88 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.30 (tdd, J = 8.0, 4.4, 0.9 Hz, 2H), 7.22–7.15 (m, 2H), 7.09–6.99 (m, 4H), 2.92 (t, J = 7.7 Hz, 2H), 1.67–1.56 (m, 2H), 1.41–1.26 (m, 2H), 0.89 (td, J = 7.1, 0.7 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.9 (C), 141.5 (C), 136.7 (C), 128.7 (2 × CH), 127.3 (C), 125.7 (CH), 125.3 (2 × CH), 124.4 (CH), 123.0 (CH), 113.9 (C), 110.4 (CH), 99.4 (C), 31.6 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 13.9 (CH_3); EI-LRMS *m/z* 361 (M^++2, 25), 359 (M^+, 25), 236 (100), 223 (27), 208 (30), 77 (60), 51 (59); HRMS calcd for $C_{18}H_{18}BrNS$, 359.0343; found, 359.0346.

General Procedure for the Synthesis of 4-(Furan-2-yl)-2-sustituted-1*H*-indoles 28: A mixture of pre-milled $Pd(OAc)_2$ (1.3 mg, 2 mol%) and XPhos (5.7 mg, 4 mol%), CsF (100 mg, 0.66 mmol), the corresponding 4-chloroindole **23a** or **23b** (0.3 mmol) and tributyl(furan-2-yl)stannane (118 mg, 0.33 mmol) in DME (0.8 mL) were stirred under N_2 at 80 ºC for 3 h (the completion of the coupling reaction was monitored by GC-MS). The reaction mixture was allowed to cool to rt and the crude was filtered through celite and washed with EtOAc (20 mL). The solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc) to afford the title compounds **28**:

4-(Furan-2-yl)-2-phenyl-1*H*-indole (28a): Reaction of **23a** (68 mg, 0.3 mmol), and purification by column chromatography (hexane/EtOAc, 8/1) afforded **28a** (71 mg, 91%) as a colorless oil: R_f 0.31 (hexane/AcOEt, 8/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.73–7.64 (m, 3H), 7.58 (dd, J = 6.7, 1.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.40–7.35 (m, 2H), 7.31–7.24 (m, 2H), 6.92 (d, J = 3.3 Hz, 1H), 6.63 (dd, J = 3.3, 1.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.6 (C), 141.8 (CH), 138.5 (C), 137.6 (C), 132.1 (C), 129.0 (2 × CH), 127.9 (CH), 125.3 (2 × CH), 124.9 (C), 123.0 (C), 122.4 (CH), 116.9 (CH), 111.7 (CH), 110.5 (CH), 106.5 (CH), 100.2 (CH); EI-LRMS *m/z* 259 (M^+, 100), 230 (40), 202 (8), 127 (8); HRMS calcd for $C_{18}H_{13}NO$, 259.0997; found, 259.0994.

2-Butyl-4-(furan-2-yl)-1*H*-indole (28b): Reaction of **23b** (62 mg, 0.3 mmol), and purification by column chromatography (hexane/EtOAc, 7/1) afforded **28b** (66 mg, 92%) as a white solid: mp 50–52 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.56–7.52 (m, 1H), 7.23–7.20 (m, 2H), 6.85 (d, J = 3.3 Hz, 1H), 6.75 (s, 1H), 6.60 (ddd, J = 3.3, 1.8, 0.6 Hz, 1H), 2.76 (t, J = 7.6 Hz, 2H), 1.79–1.68 (m, 2H), 1.52–1.39 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.8 (C), 141.5 (CH), 141.0 (C), 136.6 (C), 124.4 (C), 122.1 (C), 121.0 (CH), 116.4 (CH), 111.6 (CH), 110.0 (CH), 106.2 (CH), 99.6 (CH), 31.4 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 239 (M^+, 56), 196 (100), 167 (14), 154 (4); HRMS calcd for $C_{16}H_{17}NO$, 239.1310; found, 239.1319.

General Procedure for the Synthesis of 4-Aryl-*1H*-indoles 29: In a Schlenk tube 4-bromo-1*H*-indole **24a** or **24b** (1 equiv), phenylboronic acid (1.5 equiv) and [$Pd(PPh_3)_4$] (3 mol%) were introduced under N_2. Then, DME (15 mL/mmol) was added followed by the addition of Na_2CO_3 (1.5 equiv) in H_2O (7 mL/mmol). The reaction mixture was vigorously stirred and heated at 80 ºC overnight (the progress of the reaction was monitored by GC-MS). Then, CH_2Cl_2 (10 mL) and H_2O were added to the cooled reaction mixture. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 8/1) on silica gel to afford the title compounds **29**:

2,4-Diphenyl-1*H*-indole (29a): Reaction of **24a** (81 mg, 0.3 mmol) with phenylboronic acid (55 mg, 0.45 mmol) and [$Pd(PPh_3)_4$] (10 mg, 3 mol%), followed by the addition of Na_2CO_3 (48 mg, 0.45 mmol) in H_2O (2 mL) afforded **29a** (74 mg, 93%) as a white solid: mp 205–207 ºC (lit.[60] mp 209 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.89–7.82 (m, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.61 (t, J = 7.7 Hz, 2H), 7.53–7.44 (m, 3H), 7.43–7.25 (m, 4H), 7.12 (d, J = 2.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.3 (C), 138.3 (C), 137.3 (C), 134.5 (C), 132.2 (C), 129.1 (2 × CH), 128.9 (2 × CH), 128.7 (2 × CH), 127.8 (CH), 127.6 (C), 127.1 (CH), 125.2 (2 × CH), 122.7 (CH), 120.2 (CH), 110.2 (CH), 99.6 (CH);

EI-LRMS *m/z* 269 (M^+, 100), 190 (10), 165 (53), 133 (11), 77 (28); HRMS calcd for $C_{20}H_{15}N$, 269.1204; found, 269.1204.

2-Butyl-4-phenyl-1*H*-indole (29b): Reaction of **24b** (200 mg, 0.8 mmol) with phenylboronic acid (146 mg, 1.2 mmol) and [$Pd(PPh_3)_4$] (24 mg, 3 mol%), followed by the addition of Na_2CO_3 (127 mg, 1.2 mmol) in H_2O (6 mL) afforded **29b** (163 mg, 82%) as a pale brown oil: R_f 0.64 (hexane/EtOAc, 6/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 3H), 7.60 (t, J = 7.6 Hz, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.33–7.30 (m, 3H), 6.56 (d, J = 1.7 Hz, 1H), 2.77 (t, J = 7.6 Hz, 2H), 1.81–1.71 (m, 2H), 1.54–1.44 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.6 (C), 140.6 (C), 136.3 (C), 133.4 (C), 128.8 (2 × CH), 128.5 (2 × CH), 127.0 (C), 126.8 (CH), 121.3 (CH), 119.6 (CH), 109.7 (CH), 98.9 (CH), 31.4 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3); EI-LRMS *m/z* 249 (M^+, 23), 206 (100), 178 (15), 165 (16); HRMS calcd for $C_{18}H_{19}N$, 249.1517; found, 249.1528.

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Supporting Information Available. Copies of ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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