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ortho-Lithiation Reactions of *O*-3,n-Dihalophenyl *N*,*N*-Diethylcarbamates: Synthesis of Dihalosalicylamides and 2,3,n-Trihalophenol Derivatives

Claudia Feberero,[a] Rocío Velasco,[a] and Roberto Sanz*[a]

In memory of my admired teacher and mentor Professor José Barluenga

Abstract: New dihalosalicylamides and trihalophenol derivatives have been synthesized from easily available *O*-3,n-dihalophenyl *N*,*N*-diethylcarbamates through the DoM strategy. Their *o*-lithiation with *s*BuLi takes regioselectively place at the doubly activated C-2 position, showing the power of *O*-carbamates as directed metalating groups. In addition, highly functionalized arylnitriles are accessed from intermediate organolithiums by a tandem transnitrilation–S_NAr sequence.

Introduction

Directed *ortho*-metalation (DoM) is a powerful methodology for the functionalization of (hetero)arenes that leads to substitution patterns hardly accessible by classical aromatic substitution reactions.[1] Considering that substituted phenols are important scaffolds in pharmaceutical and fine chemicals, as well as in material science,[2] and that different phenolic derivatives display interesting biological activity,[3] a variety of Directed Metalating Groups (DMGs) have been reported for the regioselective *ortho*-lithiation of phenols.[4] Among them, *O*-carbamates remain one of the most powerful ones due to the soft conditions required for their metalation,[5] and to the fact that the functionalized phenol derivatives obtained with this strategy could be subsequently released.[6] Apart from *O*-aryl *N*,*N*-diethyl carbamates, pioneered by Snieckus,[5a] other carbamate DMGs such as *N*-cumyl-*N*-methyl[7] and *N*-isopropyl-*N*-trimethylsilyl[8] ones have been introduced with the advantage of an easier removal, but also with the drawback of a less straight and easy preparation compared with the parent *N*,*N*-diethyl carbamates. In addition, by combining DoM chemistry of phenols with other processes such as "halogen dance"[9] or transition-metal catalyzed coupling reactions,[10] the synthetic potential of this strategy has been considerably expanded. However, a careful control of the reaction temperature should be exerted in order to avoid spontaneous anionic Fries rearrangement,[5a] although the use of heterometalic bases such as lithium zincates has been described to suppress this carbamoyl shift even at room temperature.[11]

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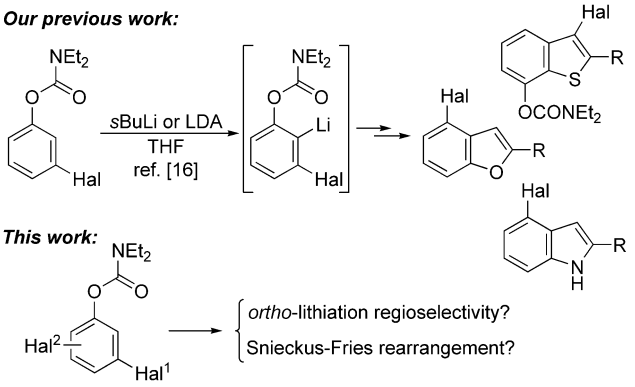
With regard to regioselectivity issues, although the presence of a powerful DMG usually ensures *o*-lithiation, when an aromatic derivative possesses more than one DMG in a non-cooperative relative position (i.e. two DMGs are 1,4- or 1,2-disposed on the arene), regioisomeric aryllithiums could be generated hampering further synthetic applications.[12] However, with *meta*-oriented DMGs electronic effects almost always direct lithiation to the *ortho* position between them, although steric effects can also operate disfavoring this selectivity.[13] So, this strategy is a useful approach for accessing 1,2,3-trisubstituted aromatic compounds in a regioselective way.[14]

Following our interest in organolithium chemistry,[15] we have previously described the regioselective lithiation of *O*-3-halophenyl *N*,*N*-diethyl carbamates at C-2 position, and its application to the synthesis of 2,3-dihalophenols, 2,3-dihaloanilines and regioselectively functionalized heterocyclic compounds such as benzo[*b*]furans, benzo[*b*]thiophenes and indoles (Scheme 1).[16] At this point we planned to study the *o*-lithiation of *O*-3-halophenyl *N*,*N*-diethyl carbamates bearing an additional halogen atom in their structure. However, it should be taken into account that fluorine and chlorine are also efficient DMG for aromatic lithiation[17] and moreover, substrates with two fluorine atoms in a *meta* relationship efficiently promote *o*-lithiation.[18] In this way, although the *O*-carbamoyl group is one of the most powerful DMG making the site between it and the halide more prone to deprotonation, the hydrogen atom flanked by one or, specially two fluorine atoms is highly acidic and less sterically demanding.[19] Herein, we report our results in the *o*-lithiation of *O*-3,n-dihalophenyl *N*,*N*-diethyl carbamates and its application to the synthesis of functionalized phenol derivatives (Scheme 1).

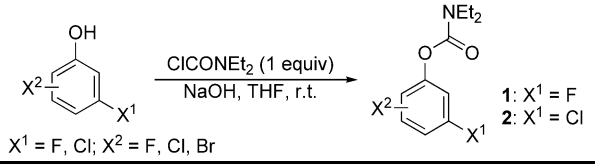


Scheme 1. Regioselectivity in the *ortho*-lithiation of *O*-halo-functionalized *N*,*N*-diethylcarbamates.

Results and Discussion

In order to tackle the proposed target, preparation of starting *O*-dihalophenyl *N*,*N*-diethylcarbamates **1** and **2** was carried out using a variety of commercially available dihalophenols, which were treated with one equivalent of diethylcarbamoyl chloride and NaOH (pearl) in THF. Using this simple procedure the desired carbamates were isolated in pure form with an almost quantitative yield (Table 1).

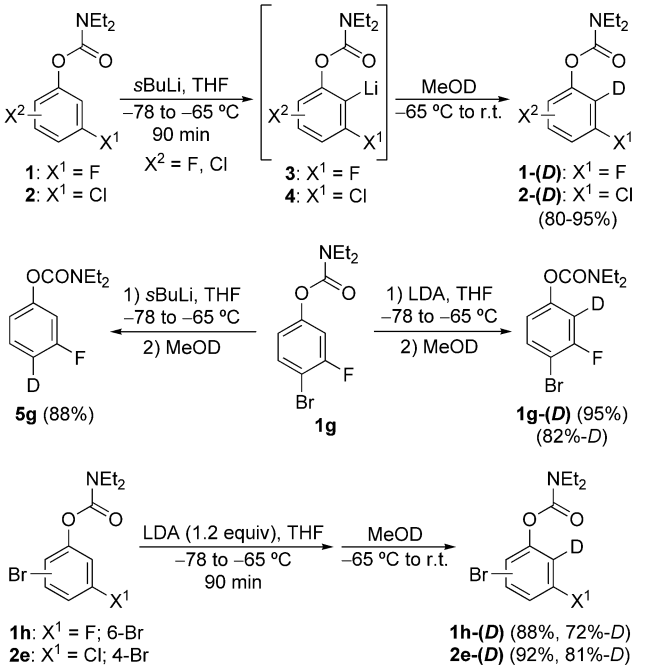
Table 1. Synthesis of starting *O*-dihalophenyl *N*,*N*-diethylcarbamates **1** and **2**.



Entry	Carbamate	X^1	$X^{2[a]}$	Yield (%)[b]
1	**1a**	F	4-F	97
2	**1b**	F	5-F	96
3	**1c**	F	6-F	92
4	**1d**	F	4-Cl	91
5	**1e**	F	5-Cl	97
6	**1f**	F	6-Cl	88
7	**1g**	F	4-Br	89
8	**1h**	F	6-Br	87
9	**2a**	Cl	4-F	94
10	**2b**	Cl	4-Cl	90
11	**2c**	Cl	5-Cl	93
12	**2d**	Cl	6-Cl	87
13	**2e**	Cl	4-Br	87

[a] Position of the second halogen atom (X^2) considering that X^1 is always at the C-3 position. [b] Isolated yields based on starting commercially available phenol.

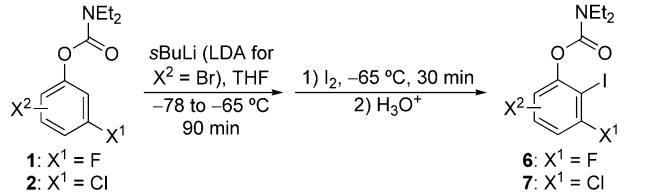
We have previously reported the efficient and regioselective *o*-lithiation of *O*-3-chloro(fluoro)phenyl *N,N*-diethyl carbamates at the sterically disfavored 2-position, likely due to the cooperative effect of the halide and carbamate DMGs, with *s*BuLi/TMEDA or LDA in THF at low temperature.[16a] However, when starting from *O*-3,4-difluorophenyl carbamate **1a** and using a slight excess (1.3 equiv) of LDA, there was not complete lithiation at C-2, either at –78 ºC or at –65 ºC, even running the deprotonation for a longer time (4 h). The use of higher amounts of base (1.6 equiv) in order to achieve complete metalation resulted in non-selective lithiation processes as demonstrated by the formation of a mixture of monoiodinated and diiodinated carbamates after quenching with iodine.[20] Gratifyingly, we found out that these undesirable further metalations can be easily prevented by using *s*BuLi. The use of *s*BuLi (1.1 equiv) in THF from –78 to –65 ºC resulted in the regioselective and almost quantitative *ortho*-lithiation of starting carbamates **1a-f** and **2a-d** bearing two halide atoms in their structure (Scheme 2). After deuteriolysis of the reactions with MeOD, the corresponding 2-deuteriophenyl carbamates **1-(*D*)** and **2-(*D*)** could be isolated and characterized.[21] It is interesting to note that although the use of *s*BuLi/TMEDA (1:1 complex) constitutes the typical and more reliable conditions for *o*-lithiation of *O*-aryl carbamates and other aromatic compounds,[1,5] in our case the addition of TMEDA did not improve at all the outcome of the reaction. Not unexpectedly, when *O*-4-bromo-3-fluorophenyl carbamate **1g** was tried under the standard conditions (*s*BuLi/THF), bromine–lithium exchange took place in preference to the *o*-lithiation reaction giving rise, after quenching with MeOD, to the *O*-3-fluoro-4-deuteriophenyl carbamate **5g** (Scheme 2). Fortunately, the use of LDA as metalating agent avoids the Br–Li exchange, although no complete *o*-lithiation could be achieved and **1g-(*D*)** was obtained with 82% of deuterium incorporation (Scheme 2). In the same way starting carbamates **1h** and **2e**, also bearing bromine atoms, were *o*-lithiated with LDA (72%-*D* for **1h**, 81%-*D* for **2e**) (Scheme 2). Remarkably, all the studied starting carbamates undergo regioselective deprotonation at the position flanked by the carbamate and the halide, showing the powerful ability of *N*,*N*-diethyl *O*-carbamoyl group as DMG.[22]



Scheme 2. *ortho*-Lithiation of *O*-dihalophenyl *N,N*-diethylcarbamates **1** and **2** and trapping with MeOD.

Once we had established the conditions for the regioselective *o*-lithiation of *O*-3,n-dihalophenyl carbamates **1** and **2**, we decided to trap the intermediate organolithiums **3** and **4** (see Scheme 2) with iodine in order to access to 2,3,n-trihalophenol derivatives **6** and **7** possessing three different halogen atoms in their structure located at specific positions. As shown in Table 2, high yields were generally obtained for a wide variety of *O*-2-iodophenyl carbamates **6** and **7**.

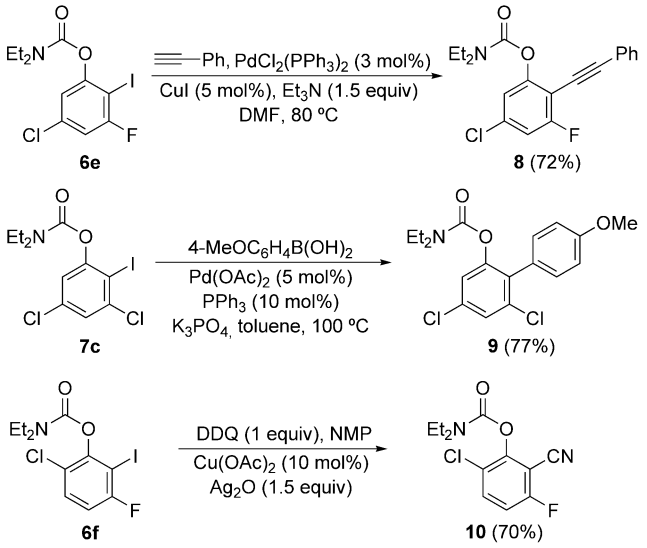
Table 2. Synthesis of *O*-2-iodo-3.n-dihalophenyl *N*,*N*-diethylcarbamates **6** and **7**.



Entry	Product	X^1	$X^{2[a]}$	Yield (%)[b]
1	**6a**	F	4-F	83
2	**6b**	F	5-F	75
3	**6c**	F	6-F	70
4	**6d**	F	4-Cl	78
5	**6e**	F	5-Cl	84
6	**6f**	F	6-Cl	86
7	**6g**	F	4-Br	88
8	**6i**	F	6-Br	84
9	**7a**	Cl	4-F	83
10	**7b**	Cl	4-Cl	78
11	**7c**	Cl	5-Cl	87
12	**7d**	Cl	6-Cl	83
13	**7e**	Cl	4-Br	88

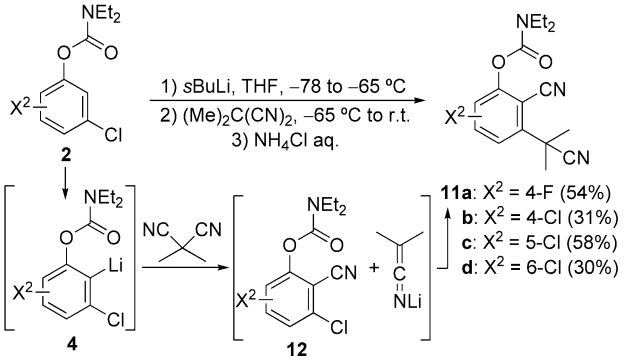
[a] Position of the second halogen atom (X^2) considering that X^1 is always at the C-3 position. [b] Isolated yields based on starting carbamate **1** or **2**.

To further demonstrate the synthetic usefulness of the iodinated carbamates **6** and **7**,[23] we selected iodo derivatives **6e** and **7c** that were smoothly transformed into the alkynyl or aryl functionalized products **8** and **9**, respectively, under standard Suzuki or Sonogashira cross-coupling conditions (Scheme 3). In addition, the cyanation reaction of **6f** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave rise to *O*-2-cyanophenyl carbamate **10** in good yield.[24] As expected, the iodine atom from the polyfunctionalized starting substrates **6** or **7** was selectively reacted while the other halogen atoms remained intact (Scheme 3).



Scheme 3. Further functionalization of *O*-2-iodophenyl *N*,*N*-diethylcarbamates **6** and **7**. Synthesis of carbamates **8**-**10**.

Considering the importance of aryl nitriles in organic synthesis, and taking into account a recent report from Reeves and coworkers reporting the transnitrilation of aryl Grignard and lithium reagents with dimethylmalononitrile (DMMN),[25] we decided to evaluate the reaction of our *ortho*-lithiated carbamates with DMMN to find a more straight access to *O*-2-cyanophenyl carbamates such as **10**. And so, when organolithium intermediates **4**, derived from dihalophenyl carbamates **2**, were treated with DMMN we isolated in moderate yields the new carbamates **11** that possess two different nitrile groups in their structure (Scheme 4). Their formation can be understood by considering that the initially generated cyano derivative **12** undergoes an S_NAr reaction with the isobutyronitrile anion, which has been released from the initial reaction of **4** with DMMN.[26] Remarkably, a complete regioselective attack of the isobutyronitrile anion to the *ortho*- vs. the *para*-position in intermediate **12c**, bearing chlorine substituents at both positions, was found in the case of starting from 3,5-dichlorophenyl carbamate **2c**. However, we have not got a clear explanation for the observed regioselectivity. Interestingly, the overall process represents a 2,3-difunctionalization of the starting *O*-3,n-dihalophenyl carbamate (Scheme 4).



Scheme 4. Reactions *O*-2-lithiophenyl *N,N*-diethylcarbamates **4** with dimethylmalononitrile Synthesis of dinitriles **11**.

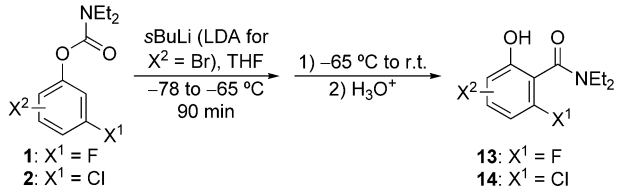
Snieckus–Fries Rearrangement

The anionic Snieckus–Fries rearrangement[5a,27] of *O*-aryl carbamates consists of an O→C 1,3-carbamoyl migration that, although sometimes can complicate the efficient functionalization of the corresponding intermediate organolithiums generated by the *o*-lithiation reaction, many times can be a useful synthetic transformation. For instance, the tandem *o*-lithiation / anionic Snieckus–Fries rearrangement sequence has been employed for accessing salicylamides[28] and arenol-based Mannich bases,[29] among other aromatic derivatives.

To study the behavior of intermediate organolithiums **3** and **4** towards the rearrangement, their solutions were allowed to warm to room temperature. After acidic workup salicylamides **13** and **14** were obtained in high yields (Table 3). Remarkably, these regioselectively dihalo-functionalized *N*,*N*-diethyl salicylamides are new compounds with potential applications for further synthetic transformations.

We have also determined the approximate temperature the rearrangement starts at. As expected, we found that organolithium intermediates **3**, derived from *O*-3-fluorophenyl carbamates **1**, are stable at higher temperatures than organolithiums **4**, generated from *O*-3-chlorophenyl carbamates **2**. Whereas **3** underwent rearrangement from ca. –30 ºC, **4** started to rearrange from ca. –60 ºC.[30]

Moreover, we have also found that the synthesis of several of these *N*,*N*-diethyl dihalosalicylamides **13** and **14** can also be carried out using LDA as base instead of *s*BuLi. In this case, an excess of the amide base (1.6 equiv for **1** and 1.3 equiv for **2**) was required for complete conversion.[31] To account for this observation it should be considered the high complexity of the LDA-mediated *ortho*-lithiation and anionic Fries rearrangement of aryl carbamates due to the role of ArLi–LDA aggregates, as elegantly established by Collum and co-workers.[32]



Entry	Product	X^1	$X^{2[a]}$	Yield (%)[b]
1	**13a**	F	4-F	81
2	**13b**	F	5-F	88
3	**13c**	F	6-F	81
4	**13d**	F	4-Cl	85
5	**13e**	F	5-Cl	87
6	**13f**	F	6-Cl	86
7	**13g**	F	4-Br	91
8	**13h**	F	6-Br	77
9	**14a**	Cl	4-F	84
10	**14b**	Cl	4-Cl	80
11	**14c**	Cl	5-Cl	79
12	**14d**	Cl	6-Cl	76
13	**14e**	Cl	4-Br	86

[a] Position of the second halogen atom (X^2) considering that X^1 is always at the C-3 position. [b] Isolated yields based on starting carbamate **1** or **2**.

Table 3. Synthesis of *N,N*-diethyl dihalosalicylamides **13** and **14**.

Conclusions

We have found that the regioselective *ortho*-lithiation of *O*-3-halophenyl *N,N*-diethyl carbamates at the C-2 position can be extended to a wide selection of related carbamates functionalized with an additional halogen atom. The cooperative effect of the *meta* halide and the carbamate group seems to overcome the disfavored steric effect or competitive *ortho* directed lithiation of the remaining halide.[33] The intermediate organolithium can be trapped at low temperature with iodine to give high yields of a variety of trihalophenol derivatives that can be further selectively functionalized by Pd-catalyzed cross-coupling reactions. Allowing the reaction mixture to reach room temperature the Snieckus–Fries rearrangement provides a convenient access to a wide family of new dihalosalicylamides, which are also obtained in high yields. In addition, a selection of highly functionalized arylnitriles has been also synthesized through a tandem transnitrilation–S_NAr reaction.

Experimental Section

General Remarks: All reactions involving air sensitive compounds were carried out under a N_2 atmosphere (99.99 %). All glassware was oven-dried (120 °C), evacuated and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers and used without any further purification. Solvents were dried by standard methods. Hexane and ethyl acetate were purchased as extra pure grade reagents and used as received. TLC was performed on aluminum-backed plates coated with silica gel 60 with F_{254} indicator; the chromatograms were visualized under ultraviolet light and/or by staining with a Ce/Mo reagent and subsequent heating. R_f values are reported on silica gel. Flash column chromatography was carried out on silica gel 60, 230–240 mesh. NMR spectra were measured on Varian Mercury-Plus 300 MHz and Varian Inova-400 MHz spectrometers. ^{1}H-NMR: splitting pattern abbreviations are: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; sext, sextet; sept, septet; dd, doublet of doublets; td, triplet of doublets; qd, quartet of doublets; m, multiplet; the chemical shifts are reported in ppm using residual solvent peak as reference ($CHCl_3$: δ 7.26; DMSO: δ 2.50). ^{13}C NMR spectra were recorded at 75.4 MHz or 100.6 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference ($CDCl_3$: δ 77.16; DMSO-d_6: δ 39.51). High resolution mass spectra (HRMS) were recorded on a Micromass Autospec spectrometer using EI at 70 eV. GC-MS and low resolution mass spectra (LRMS) measurements were recorded on an Agilent 6890N/5973 Network GC System, equipped with a HP-5MS column. Elemental analyses were performed on a microanalyzer LECO CHNS-932. Melting points were measured on a Gallenkamp apparatus using open capillary tubes and are uncorrected.

General Procedure for the Synthesis of *O*-2-Iodo-3,n-dihalophenyl *N,N*-Diethylcarbamates 6 and 7: A solution of starting carbamate **1** or **2** (0.5 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with a solution of *s*-BuLi (0.39 mL of a 1.4 M solution in cyclohexane, 0.55 mmol, for **1a-f** and **2a-d**) or LDA (1.2 equiv, for **1g-i** and **2e**). The reaction mixture was allowed to reach –65 ºC for 5 min, and stirred at this temperature for 90 min. Then, iodine (140 mg, 0.55 mmol) was added and the resulting solution was allowed to stir for 30 min at –65 ºC. The reaction mixture was quenched with HCl (1 N) and the solution was allowed to warm to room temperature. The mixture was diluted with EtOAc and aqueous $Na_2S_2O_3$ solution and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc = 20:1), affording the *O*-2-iodo-3,n-dihalophenyl *N,N*-diethylcarbamates **6** and **7** as white solids.

***O*-3,4-Difluoro-2-iodophenyl *N,N*-diethylcarbamate (6a):** The reaction of *O*-3,4-difluorophenyl *N,N*-diethylcarbamate (**1a**) (115 mg, 0.5 mmol) following the general procedure yielded **6a** as a white solid (83% yield); m.p. 188–190 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.16 (m, 1H), 7.03–6.97 (m, 1H), 3.55 (q, *J* = 7.1 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 152.5 (C), 150.6 (dd, *J* = 244.2 Hz, 14.3 Hz, C), 150.5 (dd, *J* = 244.9 Hz, 14.6 Hz, C), 145.5 (d, *J* = 14.9, C), 118.4 (dd, *J* = 6.4 Hz, 3.7 Hz, CH), 116.8 (d, *J* = 18.9, CH), 81.42 (d, *J* = 23.2, C), 42.4 (CH_2), 42.1 (CH_2), 14.2 (CH_3), 13.2 (CH_3) ppm. LRMS (EI): *m/z* (%) = 355 (M^+, 2), 100 (100), 72 (41). HRMS (EI): calcd. for $C_{11}H_{12}F_2INO_2$ $[M]^+$ 354.9881; found 354.9880.

***O*-3,5-Difluoro-2-iodophenyl *N,N*-diethylcarbamate (6b):** The reaction of *O*-3,5-difluorophenyl *N,N*-diethylcarbamate (**1b**) (115 mg, 0.5 mmol), following the general procedure yielded **6b** as a white solid (75% yield); m.p. 42–44 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93–6.78 (m, 1H), 6.78–6.70 (m, 1H), 3.51 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 163.8 (dd, *J* = 249.0 Hz, 14.3 Hz, C), 162.8 (dd, *J* = 245.9 Hz, 14.6 Hz, C), 154.1 (dd, *J* = 13.5, 7.0 Hz, C), 152.7 (C), 107.6 (dd, *J* = 25.1, 3.8 Hz, CH), 101.2 (dd, *J* = 32.2, 5.8 Hz, CH), 73.9 (dd, *J* = 27.7, 4.9 Hz, C), 42.4 (CH_2), 42.1 (CH_2), 14.1 (CH_3), 13.0 (CH_3) ppm. LRMS (EI): *m/z* (%) = 355 (M^+, 6), 256 (16), 100 (100), 72 (49). HRMS (EI): calcd. for $C_{11}H_{12}F_2INO_2$ $[M]^+$ 354.9881; found 354.9879.

***O*-3,6-Difluoro-2-iodophenyl *N,N*-diethylcarbamate (6c):** The reaction of *O*-2,5-difluorophenyl *N,N*-diethylcarbamate (**1c**) (115 mg, 0.5 mmol) following the general procedure yielded **6c** as a white solid (70% yield); m.p. 67–69 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.09 (m, 1H), 6.96–6.89 (m, 1H), 3.55–3.37 (m, 4H), 1.36–1.20 (m, 6H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 158.7 (d, *J* = 243.1 Hz, C), 153.4 (d, *J* = 15.1 Hz, C), 152.0 (C), 151.5 (d, *J* = 244.9 Hz, C), 116.8 (dd, *J* = 21.6, 8.9 Hz, CH), 112.6 (dd, *J* = 26.4, 7.5 Hz, CH), 81.9 (d, *J* = 28.9 Hz, C), 42.6 (CH_2), 42.2 (CH_2), 13.9 (CH_3), 12.9 (CH_3) ppm. LRMS (EI): *m/z* (%) = 355 (M^+, 6), 256 (13), 100 (100), 72 (45). HRMS (EI): calcd. for $C_{11}H_{12}F_2INO_2$ $[M]^+$ 354.9881; found 354.9866.

***O*-4-Chloro-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (6d):** The reaction of *O*-4-chloro-3-fluorophenyl *N,N*-diethylcarbamate (**1d**) (123 mg, 0.5 mmol) following the general procedure yielded **6d** as a white solid (78% yield); m.p. 70–72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 8.8, 1.7 Hz, 1H), 3.51 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 157.9 (d, *J* = 246.4 Hz, C), 152.5 (C), 151.9 (d, *J* = 3.6 Hz, C), 130.3 (CH), 119.4 (d, *J* = 3.8 Hz, CH), 117.6 (d, *J* = 20.6 Hz, C), 81.1 (d, *J* = 26.9 Hz, C), 42.6 (CH_2), 42.3 (CH_2), 14.5 (CH_3), 13.4 (CH_3) ppm. LRMS (EI): *m/z* (%) = 373 (M^++2, 1), 371 (M^+, 2), 244 (17), 100 (100), 72 (58). HRMS (EI): calcd. for $C_{11}H_{12}ClFINO_2$ $[M]^+$ 370.9585; found 370.9595.

***O*-5-Chloro-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (6e):** The reaction of *O*-3-chloro-5-fluorophenyl *N,N*-diethylcarbamate (**1e**) (123 mg, 0.5 mmol) following the general procedure yielded **6e** as a white solid (84% yield); m.p. 66–68 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08–7.06 (m, 1H), 6.96 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.51 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 6.7 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 162.1 (d, *J* = 247.7 Hz, C), 153.4 (d, *J* = 5.9 Hz, C), 152.0 (C), 135.1 (d, *J* = 12.3 Hz, C), 119.6 (d, *J* = 3.5 Hz, CH), 113.1 (d, *J* = 27.7 Hz, CH), 78.0 (d, *J* = 27.4 Hz, C), 42.4 (CH_2), 42.1 (CH_2), 14.3 (CH_3), 13.2 (CH_3) ppm. LRMS (EI): *m/z* (%) = 373 (M^++2, 1), 371 (M^+, 2), 244 (12), 100 (100), 72 (42). HRMS (EI): calcd. for $C_{11}H_{12}ClFINO_2$ $[M]^+$ 371.9664; found 371.9668.

***O*-6-Chloro-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (6f):** The reaction of *O*-2-chloro-5-fluorophenyl *N,N*-diethylcarbamate (**1f**) (123 mg, 0.5 mmol) following the general procedure yielded **6f** as a white solid (86% yield); m.p. 69–71 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 1H), 6.94–6.88 (m, 1H), 3.58–3.37 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm.^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 161.2 (d, *J* = 246.4 Hz, C), 151.3 (C), 149.5 (d, *J* = 4.9 Hz, C), 130.3 (d, *J* = 8.8 Hz, CH), 123.7 (d, *J* = 4.0 Hz, C), 113.3 (d, *J* = 25.4 Hz, CH), 82.4 (d, *J* = 28.1 Hz, C), 42.8 (CH_2), 42.4 (CH_2), 14.4 (CH_3), 13.4 (CH_3) ppm. LRMS (EI): *m/z* (%) = 373 (M^++2, 1), 371 (M^+, 2), 100 (100), 72 (36). HRMS (EI): calcd. for $C_{11}H_{12}ClFINO_2$ $[M]^+$ 370.9585; found 370.9599.

***O*-4-Bromo-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (6g):** The reaction of *O*-4-bromo-3-fluorophenyl *N,N*-diethylcarbamate (**1g**) (145 mg, 0.5 mmol) following the general procedure yielded **6g** as a white solid (88% yield); m.p. 74–76 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 8.8, 7.6 Hz, 1H), 6.93 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 158.5 (d, *J* = 244.6 Hz, C), 152.6 (d, *J* = 3.5 Hz, C), 152.3 (C), 133.0 (CH), 119.8 (d, *J* = 3.6 Hz, CH), 104.6 (d, *J* = 24.1 Hz, C), 80.9 (d, *J* = 28.4 Hz, C), 42.5 (CH_2), 42.2 (CH_2), 14.4 (CH_3), 13.3 (CH_3) ppm. LRMS (EI): *m/z* (%) = 417 (M^++2, 3), 415 (M^+, 3), 100 (100), 72 (32). HRMS (EI): calcd. for $C_{11}H_{12}BrFINO_2$ $[M]^+$ 414.9080; found 414.9082.

***O*-6-Bromo-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (6h):** The reaction of *O*-2-bromo-5-fluorophenyl *N,N*-diethylcarbamate (**1h**) (145 mg, 0.5 mmol) following the general procedure yielded **6h** as a white solid (84% yield); m.p. 75–77 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 8.9, 5.7 Hz, 1H), 6.84 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.57–3.37 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 161.9 (d, *J* = 246.9 Hz, C), 151.2 (C), 150.7 (d, *J* = 4.9 Hz, C), 133.2 (d, *J* = 8.7 Hz, CH), 113.8 (d, *J* = 25.1 Hz, CH), 112.2 (d, *J* = 4.0 Hz, C), 82.4 (d, *J* = 27.6 Hz, C), 42.8 (CH_2), 42.40 (CH_2), 14.5 (CH_3), 13.4 (CH_3) ppm. LRMS (EI): *m/z* (%) = 417 (M^++2, 1), 415 (M^+, 1), 336 (11), 100 (100), 72 (35). HRMS (EI): calcd. for $C_{11}H_{12}BrFINO_2$ $[M]^+$ 414.9080; found 414.9070.

***O*-3-Chloro-4-fluoro-2-iodophenyl *N,N*-diethylcarbamate (7a):** The reaction of *O*-3-chloro-4-fluorophenyl *N,N*-diethylcarbamate (**2a**) (123 mg, 0.5 mmol) following the general procedure yielded **7a** as a white solid (83% yield); m.p. 78–80 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.14 (m, 1H), 7.11–7.06 (m, 1H), 3.52 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 154.9 (d, *J* = 249.7 Hz, C), 152.6 (C), 149.1 (d, *J* = 3.4 Hz, C), 126.5 (d, *J* = 19.7 Hz, C), 121.9 (d, *J* = 7.6 Hz, CH), 116.0 (d, *J* = 23.3 Hz, CH), 98.0 (C), 42.4 (CH_2), 42.0 (CH_2), 14.3 (CH_3), 13.2 (CH_3) ppm. LRMS (EI): *m/z* (%) = 373 (M^++2, 1), 371 (M^+, 3), 100 (100), 72 (36). HRMS (EI): calcd. for $C_{11}H_{12}ClFINO_2$ $[M]^+$ 370.9585; found 370.9584.

***O*-3,4-Dichloro-2-iodophenyl *N,N*-diethylcarbamate (7b):** The reaction of *O*-3,4-dichlorophenyl *N,N*-diethylcarbamate (**2b**) (131 mg, 0.5 mmol) following the general procedure yielded **7b** as a white solid (78% yield); m.p. 66–68 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 152.6 (C), 152.1 (C), 137.6 (C), 130.2 (CH), 129.1 (C), 122.1 (CH), 98.2 (C), 42.6 (CH_2), 42.3 (CH_2), 14.5 (CH_3), 13.4 (CH_3) ppm. LRMS (EI): *m/z* (%) = 391 (M^++4, 1), 389 (M^++2, 2), 387 (M^+, 3), 100 (100), 72 (37), 44 (8). HRMS (EI): calcd. for $C_{11}H_{12}Cl_2INO_2$ $[M]^+$ 386.9290; found 386.9290.

***O*-3,5-Dichloro-2-iodophenyl *N,N*-diethylcarbamate (7c):** The reaction of *O*-3,5-dichlorophenyl *N,N*-diethylcarbamate (**2c**) (131 mg, 0.5 mmol) following the general procedure yielded **7c** as a white solid (87% yield); m.p. 59–61 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 2.3 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 3.51 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 153.9 (C), 152.4 (C), 140.2 (C), 135.2 (C), 126.3 (CH), 122.2 (CH), 94.9 (C), 42.7 (CH_2), 42.4 (CH_2), 14.6 (CH_3), 13.5 (CH_3) ppm. LRMS (EI): *m/z* (%) = 391 (M^++4, 1), 389 (M^++2, 5), 387 (M^+, 7), 100 (100), 72 (35). HRMS (EI): calcd. for $C_{11}H_{12}Cl_2INO_2$ $[M]^+$ 386.9290; found 386.9280.

***O*-3,6-Dichloro-2-iodophenyl *N,N*-diethylcarbamate (7d):** The reaction of *O*-2,5-dichlorophenyl *N,N*-diethylcarbamate (**2d**) (131 mg, 0.5 mmol) following the general procedure yielded **7d** as a white solid (83% yield); m.p. 76–78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 3.59–3.37 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 151.3 (C), 149.9 (C), 138.1 (C), 130.2 (CH), 126.7 (CH), 126.4 (C), 99.1 (C), 42.8 (CH_2), 42.4 (CH_2), 14.5 (CH_3), 13.4 (CH_3) ppm. LRMS (EI): *m/z* (%) = 391 (M^++4, 1), 389 (M^++2, 1), 387 (M^+, 1), 352 (11), 100 (100), 72 (36). HRMS (EI): calcd. for $C_{11}H_{12}Cl_2INO_2$ $[M]^+$ 386.9290; found 386.9283.

***O*-4-Bromo-3-chloro-2-iodophenyl *N,N*-diethylcarbamate (7e):** The reaction of *O*-4-bromo-3-chlorophenyl *N,N*-diethylcarbamate (**2e**) (145 mg, 0.5 mmol) following the general procedure yielded **7e** as a white solid (83% yield); m.p. 68–70 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.7, 1H), 6.97 (d, *J* = 8.7, 1H), 3.56–3.36 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 152.6 (C), 152.4 (C), 139.4 (C), 133.4 (CH), 122.6 (CH), 118.0 (C), 97.9 (C), 42.5 (CH_2), 42.2 (CH_2), 14.5 (CH_3), 13.3 (CH_3) ppm. LRMS (EI): *m/z* (%) = 435 (M^++4, 1), 433 (M^++2, 3), 431 (M^+, 3), 100 (100), 72 (28). HRMS (EI): calcd. for $C_{11}H_{12}BrClINO_2$ $[M]^+$ 430.8785; found 430.8776.

Sonogashira Reaction: Synthesis of *O*-5-chloro-3-fluoro-2-(phenylethynyl)phenyl *N,N*-Diethylcarbamate (8): A solution of *O*-5-chloro-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (**6e**) (186 mg, 0.5 mmol) in DMF (3 mL) under nitrogen, was mixed with Et_2NH_2 (55 mg, 0.75 mmol), phenylacetylene (62 mg, 0.6 mmol), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol) and CuI (2.9 mg, 0.015 mmol). The mixture was stirred at 80 ºC for 48 h. After completion of the reaction the solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) and **8** was isolated as brown oil (72% yield); R_f = 0.16 (hexane/EtOAc = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 2H), 7.37–7.32 (m, 3H), 7.14–7.13 (m, 1H), 7.03–7.00 (m, 1H), 3.49 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 162.6 (d, *J* = 254.6 Hz, C), 153.4 (d, *J* = 5.6 Hz, C), 152.7 (C), 134.5 (d, *J* = 12.6 Hz, C), 131.6 (2 × CH), 129.0 (CH), 128.4 (2 × CH), 122.7 (C), 119.5 (d, *J* = 3.7 Hz, CH), 113.4 (d, *J* = 24.7 Hz, CH), 106.4 (d, *J* = 18.1 Hz, C), 99.3 (d, *J* = 3.5 Hz, C), 42.63 (CH_2), 42.3 (CH_2), 14.2 (CH_3), 13.4 (CH_3) ppm. LRMS (EI): *m/z* (%) = 347 (M^++2, 7), 345 (M^+, 22), 181 (19), 100 (100), 72 (38). HRMS (EI): calcd. for $C_{19}H_{17}ClFNO_2$ $[M]^+$ 345.0932; found 345.0936.

Suzuki Reaction: Synthesis of *O*-4,6-Dichloro-4'-methoxy-[1,1'-biphenyl]-2-yl *N,N*-Diethylcarbamate (9): A solution of *O*-3,5-dichloro-2-iodophenyl *N,N*-diethylcarbamate (**7c**) (194 mg, 0.5 mmol) in toluene (1 mL) under nitrogen, was mixed with (4-methoxyphenyl)boronic acid (152 mg, 1.0 mmol), $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), PPh_3 (5.25 mg, 0.02 mmol) and K_3PO_4 (212 mg, 1.0 mmol). The mixture was stirred at 100 ºC overnight. After completion of the reaction the solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) and **9** was isolated as a yellow oil (77% yield); R_f = 0.20 (hexane/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.34 (m, 1H), 7.17 (t, *J* = 2.2 Hz, 2H), 7.15 (s, 1H), 6.93 (s, 1H), 6.91 (s, 1H), 3.82 (s, 3H), 3.17 (q, *J* = 7.0 Hz, 2H), 3.01 (q, *J* = 7.0 Hz, 2H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 159.4 (C), 153.2 (C), 150.7 (C), 135.1 (C), 133.3 (C), 133.2 (C), 131.1 (2 × CH), 126.6 (CH), 126.3 (C), 122.5 (CH), 113.6 (2 × CH), 55.4 (CH_3), 42.2 (CH_2), 41.8 (CH_2), 13.7 (CH_3), 13.2 (CH_3) ppm. LRMS (EI): *m/z* (%) = 371 (M^++4, 4), 369 (M^++2, 16), 367 (M^+, 24), 100 (100), 72 (128). HRMS (EI): calcd. for $C_{18}H_{19}Cl_2NO_3$ $[M]^+$ 367.0742; found 367.0734.

Cyanation Reaction: Synthesis of *O*-6-Chloro-2-cyano-3-fluorophenyl *N,N*-Diethylcarbamate (10): A solution of *O*-6-chloro-3-fluoro-2-iodophenyl *N,N*-diethylcarbamate (**6f**) (186 mg, 0.5 mmol) in NMP (3 mL) under air, was mixed with DDQ (113 mg, 0.5 mmol), $Cu(OAc)_2$ (91 mg, 0.05 mmol) and Ag_2O (174 mg, 0.75 mmol). The mixture was stirred at 120 ºC for 48 h. After completion of the reaction the solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) and **10** was isolated as a white solid (70% yield); m.p. 76–78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 9.1, 5.6 Hz, 1H), 7.06 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.50 (q, *J* = 7.1 Hz, 2H), 3.40 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 261.0 Hz, C), 151.5 (C), 150.9 (d, *J* = 3.7 Hz, C), 135.4 (d, *J* = 9.3 Hz, CH), 125.2 (d, *J* = 4.2 Hz, C), 114.5 (d, *J* = 20.9 Hz, CH), 110.3 (C), 100.6 (d, *J* = 18.0 Hz, C), 42.9 (CH_2), 42.4 (CH_2), 13.8 (CH_3), 12.9 (CH_3) ppm. LRMS (EI): *m/z* (%) = 272 (M^++2, 1), 270 (M^+, 1), 171 (13), 100 (100), 72 (44). HRMS (EI): calcd. for $C_{12}H_{12}ClFN_2O_2$ $[M]^+$ 270.0571; found 270.0573.

General Procedure for the Synthesis of *O*-n-Halo-2-cyano-3-(2-cyanopropan-2-yl)phenyl *N,N*-Diethylcarbamates 11: A solution of the corresponding carbamate **2** (0.5 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with a solution of *s*-BuLi (0.39 mL of a 1.4 M solution in cyclohexane, 0.55 mmol). The reaction mixture was allowed to reach –65 ºC for 5 min, and stirred at this temperature for 90 min. Then, dimethylmalononitrile (52 mg, 0.55 mmol) was added and allowed to stir at –65 ºC for 15 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting solution was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 4:1), affording the *O*-n-halo-2-cyano-3-(2-cyanopropan-2-yl)phenyl *N,N*-diethylcarbamates **11**.

***O*-2-Cyano-3-(2-cyanopropan-2-yl)-4-fluorophenyl *N,N*-diethylcarbamate (11a):** The reaction of *O*-3-chloro-4-fluorophenyl *N,N*-diethylcarbamate (**2a**) (123 mg, 0.5 mmol) following the general procedure yielded **11a** as a pink oil (54% yield); R_f = 0.38 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 1H), 7.33 (d, *J* = 1.6 Hz, 1H), 3.49 (q, *J* = 7.1 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 2.00 (d, *J* = 1.1 Hz, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 156.9 (d, *J* = 250.0 Hz, C), 152.3 (C), 152.0 (d, *J* = 2.9 Hz, C), 130.1 (d, *J* = 13.5 Hz, C), 124.9 (d, *J* = 10.1 Hz, CH), 122.4 (C), 122.4 (d, *J* = 27.0 Hz, CH), 113.5 (d, *J* = 4.2 Hz, C), 106.5 (C), 42.77 (CH_2), 42.3 (CH_2), 34.9 (C), 28.3 (CH_3), 28.3 (CH_3), 14.1 (CH_3), 13.2 (CH_3) ppm. LRMS (EI): *m/z* (%) = 303 (M^+, 7), 100 (100), 72 (100), 29 (21). HRMS (EI): calcd. for $C_{16}H_{18}ClN_3O_2$ $[M]^+$ 303.1383; found 303.1379.

***O*-4-Chloro-2-cyano-3-(2-cyanopropan-2-yl)phenyl *N,N*-diethylcarbamate (11b):** The reaction of *O*-3,4-dichlorophenyl *N,N*-diethylcarbamate (**2b**) (131 mg, 0.5 mmol) following the general procedure yielded **11b** as a white solid (31% yield); m.p. 102–104 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 3.50 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.1 Hz, 2H), 2.10 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 154.9 (C), 152.1 (C), 139.5 (C), 136.8 (CH), 131.5 (C), 124.2 (CH), 122.4 (C), 114.0 (C), 106.8 (C), 42.8 (CH_2), 42.3 (CH_2), 37.7 (C), 28.5 (2 × CH_3), 14.1 (CH_3), 13.2 (CH_3) ppm. LRMS (EI): *m/z* (%) = 321 (M^++2, 1), 319 (M^+, 3), 100 (100), 72 (30). HRMS (EI): calcd. for $C_{16}H_{18}ClN_3O_2$ [M]$^+$ 319.1088; found 319.1101.

***O*-5-Chloro-2-cyano-3-(2-cyanopropan-2-yl)phenyl *N,N*-diethylcarbamate (11c):** The reaction of *O*-3,5-dichlorophenyl *N,N*-diethylcarbamate (**2c**) (131 mg, 0.5 mmol) following the general procedure yielded **11c** as a yellow oil (58% yield); R_f = 0.43 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (q, *J* = 1.7 Hz, 2H), 3.47 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.2 Hz, 2H), 1.71 (s, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 154.8 (C), 151.6 (C), 148.2 (C), 137.5 (C), 123.1 (CH), 122.5 (C), 118.8 (CH), 112.3 (C), 107.7 (C), 42.7 (CH_2), 42.3 (CH_2), 37.4 (C), 28.5 (2 × CH_3), 14.0 (CH_3), 13.0 (CH_3) ppm. LRMS (EI): *m/z* (%) = 321 (M^++2, 1), 319 (M^+, 3), 100 (100), 72 (33). HRMS (EI): calcd. for $C_{16}H_{18}ClN_3O_2$ [M]$^+$ 319.1088; found 319.1095.

***O*-6-Chloro-2-cyano-3-(2-cyanopropan-2-yl)phenyl *N,N*-diethylcarbamate (11d):** The reaction of *O*-2,5-dichlorophenyl *N,N*-diethylcarbamate (**2d**) (131 mg, 0.5 mmol) following the general procedure yielded **11d** as a white solid (30% yield); m.p. 99–101 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.6 Hz, 1H), 7.58–7.65 (d, *J* = 8.7 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 1.95 (s, 6H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 152.2 (C), 151.2 (C), 143.1 (C), 134.4 (CH), 129.3 (C), 124.7 (CH), 122.4 (C), 113.5 (C), 108.1 (C), 43.0 (CH_2), 42.5 (CH_2), 37.8 (C), 27.3 (2 × CH_3), 14.1 (CH_3), 13.3 (CH_3) ppm. LRMS (EI): *m/z* (%) = 321 (M^++2, 1), 319 (M^+, 3), 100 (100), 72 (26). HRMS (EI): calcd. for $C_{16}H_{18}ClN_3O_2$ [M]$^+$ 319.1088; found 319.1095.

General Procedure for the Synthesis of Dihalosalicylamides 13 and 14: A solution of the corresponding carbamate **1** or **2** (0.5 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with *s*-BuLi (0.39 mL of a 1.4 M solution in cyclohexane, 0.55 mmol, for **1a-f** and **2a-d**) or LDA (1.2 equiv, for **1g-i** and **2e**). The resulting solution was allowed to reach –65 ºC for 5 min, and stirred at this temperature for 90 min. The mixture was allowed to warm slowly to room temperature and then stirred for 60 min. The reaction mixture was quenched with HCl (1 N) solution, the acidic aqueous solution was then extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrate under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1) affording the salicylamides **13** and **14** as white solids.

***N,N*-Diethyl-2,3-difluoro-6-hydroxybenzamide (13a):** The reaction of *O*-3,4-difluorophenyl *N,N*-diethylcarbamate (**1a**) (115 mg, 0.5 mmol) following the general procedure yielded **13a** as a white solid (81% yield); m.p. 172–174 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.72 (br s, 1H), 6.64 (td, *J* = 9.6, 2.2 Hz, 1H), 6.49 (d, *J* = 10.7 Hz, 1H), 3.42–3.36(m, 2H), 3.11–3.06 (m, 2H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 162.4 (dd, *J* = 244.6, 16.4 Hz, C), 162.2 (dd, *J* = 3.2, 1.1 Hz, C), 159.1 (dd, *J* = 242.8, 16.4 Hz, C), 156.0 (dd, *J* = 13.8, 11.3 Hz, C), 110.5 (dd, *J* = 22.3, 3.9 Hz, C), 99.1 (dd, *J* = 24.7, 7.8 Hz, CH), 94.7 (dd, *J* = 8.1, 3.7 Hz, CH), 42.5 (CH_2), 38.7 (CH_2), 14.0 (CH_3), 12.9 (CH_3) ppm. LRMS (EI): *m/z* (%) = 229 (M^+, 24), 157 (100), 101 (24), 58 (55). HRMS (EI): calcd. for $C_{11}H_{13}F_2NO_2$ [M]$^+$ 229.0914; found 229.0909. $C_{11}H_{13}F_2NO_2$ (229.2232): calcd. C 57.64, H 5.72, N 6.11; found C 57.53, H 5.75, N 6.06.

***N,N*-Diethyl-2,4-difluoro-6-hydroxybenzamide (13b):** The reaction of *O*-3,5-difluorophenyl *N,N*-diethylcarbamate (**1b**) (115 mg, 0.5 mmol) following the general procedure yielded **13b** as a white solid (88% yield); m.p. 168–170 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (br s, 1H), 7.21 (dt, *J* = 18.8, 9.4 Hz, 1H), 6.64 (ddd, *J* = 9.1, 3.5, 1.8 Hz, 1H), 3.41 (q, *J* = 7.0 Hz, 2H), 3.10 (q, *J* = 6.9 Hz, 2H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 161.6 (dd, *J* = 7.8, 3.2 Hz, C), 150.3 (dd, *J* = 6.7, 2.0 Hz, C), 145.9 (dd, *J* = 243.5, 14.7 Hz, C), 142.9 (dd, *J* = 236.7, 12.9 Hz, C), 117.0 (d, *J* = 18.1, Hz, CH), 115.2 (dd, *J* = 18.0, 3.1 Hz, C), 111.2 (dd, *J* = 10.3, 7.1 Hz, C), 42.5 (CH_2), 38.7 (CH_2), 14.0 (CH_3), 12.8 (CH_3) ppm. LRMS (EI): *m/z* (%) = 229 (M^+, 60), 210 (37), 157 (100), 58 (73). HRMS (EI): calcd. for $C_{11}H_{13}F_2NO_2$ [M]$^+$ 229.0914; found 229.0921.

***N,N*-Diethyl-3,6-difluoro-2-hydroxybenzamide (13c):** The reaction of *O*-2,6-difluorophenyl *N,N*-diethylcarbamate (**1c**) (115 mg, 0.5 mmol) following the general procedure yielded **13c** as a white solid (81% yield); m.p. 153–155 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.44 (br s, 1H), 7.25–7.17 (m, 1H), 6.74–6.67 (m, 1H), 3.42 (q, *J* = 7.1 Hz, 2H), 3.10 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 161.7 (s, C), 154.2 (d, *J* = 239.0, C), 148.0 (d, *J* = 236.2, C), 141.9 (dd, *J* = 17.6, 9.1 Hz, C), 116.6 (d, *J* = 2.5, 2.4 Hz, C), 116.0 (dd, *J* = 21.2, 10.5 Hz, CH), 105.8 (dd, *J* = 24.4, 7.0 Hz, CH), 42.5 (CH_2), 38.7 (CH_2), 14.0 (CH_3), 12.9 (CH_3) ppm. LRMS (EI): *m/z* (%) = 229 (M^+, 31), 210 (21), 157 (100), 58 (58). HRMS (EI): calcd. for $C_{11}H_{13}F_2NO_2$ [M]$^+$ 229.0914; found 229.0917.

3-Chloro-*N,N*-diethyl-2-fluoro-6-hydroxybenzamide (13d): The reaction of *O*-4-chloro-3-fluorophenyl *N,N*-diethylcarbamate (**1d**) (123 mg, 0.5 mmol) following the general procedure yielded **13d** as a white solid (85% yield); m.p. 122–124 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.49 (s, 1H), 7.38–7.32 (m, 1H), 6.74–6.71 (m, 1H), 3.41 (q, *J* = 7.3 Hz, 2H), 3.10 (q, *J* = 7.0 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 161.7 (C), 153.8 (d, *J* = 7.7 Hz, C), 153.6 (d, *J* = 244.0 Hz, C), 130.2 (CH), 115.1 (d, *J* = 21.4 Hz, C), 112.8 (d, *J* = 3.0 Hz, CH), 109.0 (d, *J* = 18.2 Hz, C), 42.4 (CH_2), 38.7 (CH_2), 14.0 (CH_3), 12.8 (CH_3) ppm. LRMS (EI): *m/z* (%) = 247 (M^++2, 5), 245 (M^+, 18), 210 (40), 173 (100), 58 (65). HRMS (EI): calcd. for $C_{11}H_{13}ClFNO_2$ [M]$^+$ 245.0619; found 245.0610.

4-Chloro-*N,N*-diethyl-2-fluoro-6-hydroxybenzamide (13e): The reaction of *O*-3-chloro-5-fluorophenyl *N,N*-diethylcarbamate (**1e**) (123 mg, 0.5 mmol) following the general procedure yielded **13e** as a white solid (87% yield); m.p. 120–122 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.72 (br s, 1H), 6.89 (dd, *J* = 9.0, 1.8 Hz, 1H), 6.74–6.73 (m, 1H), 3.43–3.37 (m, 2H), 3.09 (q, *J* = 6.9 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.0 (C), 158.8 (d, *J* = 244.7 Hz, C), 155.7 (d, *J* = 10.2 Hz, C), 133.7 (d, *J* = 14.2 Hz, C), 113.0 (d, *J* = 22.0 Hz, C), 111.9 (d, *J* = 2.9 Hz, CH), 106.8 (d, *J* = 26.0 Hz, CH), 42.5 (CH_2), 38.8 (CH_2), 14.0 (CH_3), 12.9 (CH_3) ppm. LRMS (EI): *m/z* (%) = 247 (M^++2, 6), 245 (M^+, 21), 210 (41), 173 (100), 58 (76). HRMS (EI): calcd. for $C_{11}H_{13}ClFNO_2$ [M]$^+$ 245.0619; found: 245.0624.

3-Chloro-*N,N*-diethyl-6-fluoro-2-hydroxybenzamide (13f): The reaction of *O*-2-chloro-5-fluorophenyl *N,N*-diethylcarbamate (**1f**) (123 mg, 0.5 mmol) following the general procedure yielded **13f** as a white solid (86% yield); m.p. 123–125 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.21 (br s, 1H), 7.40 (dd, *J* = 8.9, 6.1 Hz, 1H), 6.82–6.77 (m, 1H), 3.44–3.39 (m, 2H), 3.09 (q, *J* = 7.0 Hz, 2H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.5 (C), 157.8 (d, *J* = 243.0 Hz, C), 150.6 (d, *J* = 8.7 Hz, C), 130.6 (d, *J* = 10.3 Hz, CH), 117.3 (C), 117.1 (d, *J* = 23.3 Hz, C), 108.3 (d, *J* = 23.3 Hz, CH), 42.6 (CH_2), 38.7 (CH_2), 13.8 (CH_3), 12.7 (CH_3) ppm. LRMS (EI): *m/z* (%) = 247 (M^++2, 10), 245 (M^+, 31), 175 (33), 173 (100), 58 (74). HRMS (EI): calcd. for $C_{11}H_{13}ClFNO_2$ [M]$^+$ 245.0619; found 245.0619. $C_{11}H_{13}ClFNO_2$ (245.6778): calcd. C 53.78, H 5.33, N 5.70; found C 53.67, H 5.38, N 5.76.

3-Bromo-*N,N*-diethyl-2-fluoro-6-hydroxybenzamide (13g): The reaction of *O*-4-bromo-3-fluorophenyl *N,N*-diethylcarbamate (**1g**) (145 mg, 0.5 mmol) following the general procedure yielded **13g** as a white solid (91% yield); m.p. 161–163 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.38 (t, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 5.60 (br s, 1H), 3.41 (q, *J* = 7.0 Hz, 2H), 3.15–3.06 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 162.7 (C), 155.4 (d, *J* = 3.6 Hz, C), 155.3 (d, *J* = 242.5 Hz, C), 133.4 (CH), 115.5 (d, *J* = 21.6 Hz, C), 113.9 (CH), 96.6 (d, *J* = 21.6 Hz, C), 42.6 (CH_2), 38.8 (CH_2), 13.9 (CH_3), 12.7 (CH_3) ppm. LRMS (EI): *m/z* (%) = 291 (M^++2, 12), 289 (M^+, 12), 219 (50), 217 (52), 210 (100), 58 (37). HRMS (EI): calcd. for $C_{11}H_{13}BrFNO_2$ [M]$^+$ 289.0114; found 289.0108.

3-Bromo-*N,N*-diethyl-6-fluoro-2-hydroxybenzamide (13h): The reaction of *O*-2-bromo-5-fluorophenyl *N,N*-diethylcarbamate (**1h**) (145 mg, 0.5 mmol) following the general procedure yielded **13h** as a white solid (77% yield); m.p. 189–191 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.04 (br s, 1H), 7.54 (dd, *J* = 8.8, 6.3, 0.8 Hz, 1H), 7.05–6.38 (m, 1H), 3.42 (s, 2H), 3.15–3.01 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 161.8 (C), 157.7 (d, *J* = 243.5 Hz, C), 151.0 (d, *J* = 8.4 Hz, C), 133.1 (d, *J* = 10.1 Hz, CH), 116.4 (d, *J* = 22.8 Hz, C), 108.5 (d, *J* = 23.1 Hz, CH), 106.5 (d, *J* = 3.3 Hz, C), 42.5 (CH_2), 38.7 (CH_2), 13.9 (CH_3), 12.8 (CH_3) ppm. LRMS (EI): *m/z* (%) = 291 (M^++2, 40), 289 (M^+, 40), 272 (55), 270 (40), 219 (96), 217 (100), 58 (39). HRMS (EI): calcd. for $C_{11}H_{13}BrFNO_2$ $[M]^+$ 289.0114; found 289.0114.

2-Chloro-*N,N*-diethyl-3-fluoro-6-hydroxybenzamide (14a): The reaction of *O*-3-chloro-4-fluorophenyl *N,N*-diethylcarbamate (**2a**) (123 mg, 0.5 mmol) following the general procedure yielded **14a** as a white solid (84% yield); m.p. 152–154 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.14 (s, 1H), 7.24–7.18 (m, 1H), 6.82 (dd, *J* = 9.0, 4.0 Hz, 1H), 3.56–3.46 (m, 2H), 3.11–3.02 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 163.5 (d, *J* = 2.2 Hz, C), 150.8 (d, *J* = 237.9 Hz, C), 150.4 (d, *J* = 2.2 Hz, C), 125.5 (C), 116.8 (C), 116.4 (d, *J* = 22.3 Hz, CH), 115.2 (d, *J* = 6.8 Hz, CH), 42.4 (CH_2), 38.6 (CH_2), 13.9 (CH_3), 12.8 (CH_3) ppm. LRMS (EI): *m/z* (%) = 247 (M^++2, 13), 245 (M^+, 40), 210 (82), 173 (84), 58 (100). HRMS (EI): calcd. for $C_{11}H_{13}ClFNO_2$ $[M]^+$ 245.0619; found 245.0623.

2,3-Dichloro-*N,N*-diethyl-6-hydroxybenzamide (14b): The reaction of *O*-3,4-dichlorophenyl *N,N*-diethylcarbamate (**2b**) (131 mg, 0.5 mmol) following the general procedure yielded **14b** as a white solid (80% yield); m.p. 199–201 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.41 (br s, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 3.55–3.27 (m, 2H), 3.10–3.01 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 163.7 (C), 153.4 (C), 130.2 (C), 128.0 (C), 126.3 (C), 121.1 (CH), 115.9 (CH), 42.2 (CH_2), 38.4 (CH_2), 13.8 (CH_3), 12.6 (CH_3) ppm. LRMS (EI): *m/z* (%) = 265 (M^++4, 1), 263 (M^++2, 17), 261 (M^+, 29), 226 (80), 189 (100), 58 (42). HRMS (EI): calcd. for $C_{11}H_{13}Cl_2NO_2$ $[M]^+$ 261.0323; found 261.0324.

2,4-Dichloro-*N,N*-diethyl-6-hydroxybenzamide (14c): The reaction of *O*-3,5-dichlorophenyl *N,N*-diethylcarbamate (**2c**) (131 mg, 0.5 mmol) following the general procedure yielded **14c** as a white solid (79% yield); m.p. 155–157 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.71 (s, 1H), 7.03 (dd, *J* = 1.8, 0.5 Hz, 1H), 6.86 (dd, *J* = 1.8, 0.5 Hz, 1H), 3.54–3.48 (m, 1H), 3.32–3.25 (m, 1H), 3.09–3.00 (m, 2H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 164.0 (C), 155.8 (C), 133.9 (C), 131.5 (C), 124.2 (C), 119.6 (CH), 114.8 (CH), 42.7 (CH_2), 38.9 (CH_2), 14.3 (CH_3), 13.0 (CH_3) ppm. LRMS (EI): *m/z* (%) = (M^++4, 1), 263 (M^++2, 19), 261 (M^+, 29), 226 (99), 191 (100), 58 (81). HRMS (EI): calcd. for $C_{11}H_{13}Cl_2NO_2$ $[M]^+$ 261.0323; found 261.0319. $C_{11}H_{13}Cl_2NO_2$ (262.1324): calc. C 50.40, H 5.00, N 5.34; found C 50.27, H 5.06, N 5.29.

2,5-Dichloro-*N,N*-diethyl-6-hydroxybenzamide (14d): The reaction of *O*-2,5-dichlorophenyl *N,N*-diethylcarbamate (**2d**) (131 mg, 0.5 mmol) following the general procedure yielded **14d** as a white solid (76% yield); m.p. 154–156 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.16 (s, 1H), 7.39–7.36 (m, 1H), 7.00–6.97 (m, 1H), 3.58–3.29 (m, 2H), 3.07–3.01 (m, 2H), 1.12 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 163.5 (C), 149.9 (C), 130.1 (C), 128.7 (C), 127.2 (C), 121.3 (CH), 120.2 (CH), 42.3 (CH_2), 38.5 (CH_2), 13.8 (CH_3), 12.6 (CH_3) ppm. LRMS (EI): *m/z* (%) = 265 (M^++4, 1), 263 (M^++2, 23), 261 (M^+, 35), 226 (80), 189 (100), 58 (26). HRMS (EI): calcd. for $C_{11}H_{13}Cl_2NO_2$ $[M]^+$ 261.0323; found 261.0323.

3-Bromo-2-chloro-*N,N*-diethyl-6-hydroxybenzamide (14e): The reaction of *O*-4-bromo-3-chlorophenyl *N,N*-diethylcarbamate (**2e**) (145 mg, 0.5 mmol) following the general procedure yielded **14e** as a white solid (86% yield); m.p. 152–154 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.45 (br s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 3.56–3.46 (m, 1H), 3.36–3.27 (m, 1H), 3.12–2.98 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6): δ = 163.8 (C), 154.0 (C), 133.3 (C), 129.8 (C), 126.4 (C), 116.3 (CH), 110.5 (CH), 42.2 (CH_2), 38.4 (CH_2), 13.8 (CH_3), 12.6 (CH_3) ppm. LRMS (EI): *m/z* (%) = 309 (M^++4, 9), 307 (M^++2, 53), 305 (M^+, 41), 272 (100), 270 (100), 235 (81), 233 (64), 58 (95). HRMS (EI): calcd. for $C_{11}H_{13}BrClNO_2$ $[M]^+$ 304.9818; found 304.9821. $C_{11}H_{13}BrClNO_2$ (306.5834): calcd. C 43.09, H 4.27, N 4.57; found C 43.20, H 4.29, N 4.53.

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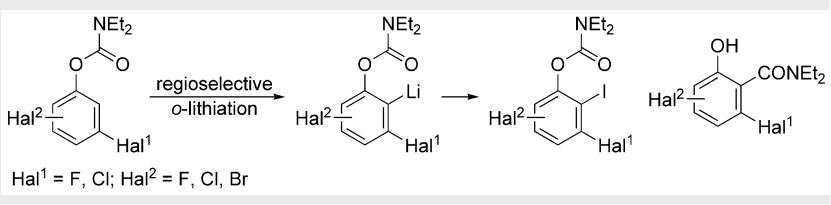

The *o*-lithiation of a variety of *O*-3,n-dihalophenyl *N*,*N*-diethylcarbamates is reported. The metalation always takes place at the position flanked by the carbamate and the halide groups. New families of dihalosalicylamides and trihalophenol derivatives have been synthesized in high yields.

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ortho*-Lithiations

*Claudia Feberero, Rocío Velasco, Roberto Sanz**

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ortho-Lithiation Reactions of _O_-3,n-Dihalophenyl _N_,_N_-Diethylcarbamates: Synthesis of Dihalosalicylamides and 2,3,n-Trihalophenol Derivatives