Article

Experimental and Computational Study of the 1,5-O#N Carbamoyl Snieckus-Fries-Type Rearrangement

Claudia Feberero, Carlos Sedano, Samuel Suarez-Pantiga, Carlos Silva López, and Roberto Sanz

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01732 • Publication Date (Web): 08 Sep 2020

Experimental and Computational Study of the 1,5-O→N Carbamoyl Snieckus–Fries-Type Rearrangement

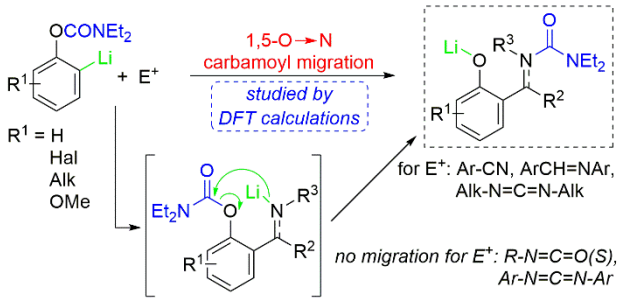
Claudia Feberero,[†] Carlos Sedano,[†] Samuel Suárez-Pantiga,[†] Carlos Silva López,[‡] and Roberto Sanz[†]**

[†]Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos (Spain)

[‡]Departamento de Química Orgánica and CITACA (Agri-Food Research and Transfer Cluster), Universidade de Vigo, 36310-Vigo (Spain)

rsd@ubu.es

carlos.silva@uvigo.es



ABSTRACT:

The reactions of *o*-lithiated *O*-aryl *N,N*-diethylcarbamates with different C–N multiple bond electrophiles have been thoroughly studied. A 1,5-O→N carbamoyl shift, a new variation of the anionic Fries-type rearrangement, takes place when nitriles, imines or alkylcarbodiimides are

employed. In these cases, the carbamoyl group plays a dual role as directing group and building up a variety of functional groups through the 1,5-O→N carbamoyl migration. On the other hand, the use of iso(thio)cyanates and arylcarbodiimides led to non-rearranged *o*-functionalized *O*-arylcarbamates. This reactivity was further computationally explored, and the governing factor could be traced back to the relative basicity of the alternative products (migrated vs non-migrated substrates). This exploration also provided interesting insight about the degree of complexation of the lithium cation onto these substrates. A new access to useful 2-hydroxybenzophenone derivatives has also been developed.

INTRODUCTION

The directed *ortho*-metalation (D*o*M) reaction is currently considered a useful tool for the synthesis of regioselectively functionalized (hetero)aromatic compounds.[1] The metalation of arenes bearing an appropriate directing metalation group (DMG) with organolithiums or lithium amides, known as *ortho*-lithiation,[2] nicely complements the classical electrophilic aromatic substitution, as well as other transition metal–based methodologies mainly related with C–H activation reactions,[3] for making regiospecifically functionalized aromatic rings. Among oxygen-based DMGs employed for the functionalization of phenols,[4] *O*-aryl carbamates have been recognized arguably as one of the most powerful DMGs,[5] and usefully leading to phenol derivatives,[6] with many applications in the synthesis of complex molecules.[7] In addition, the carbamate group could undergo subsequent useful cross-coupling reactions under transition metal-catalysis.[8]

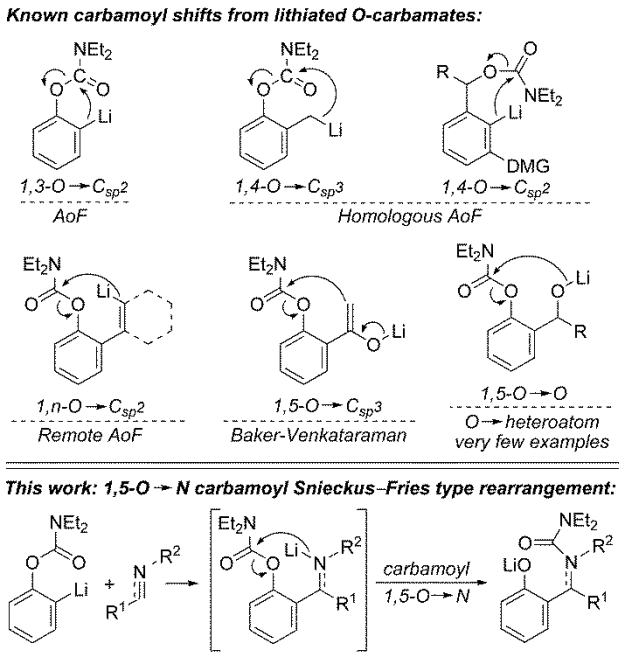
On the other hand, the original Fries rearrangement, initially reported for the 1,3-O→C migration of carbonyl groups in aromatic esters in the presence of Lewis acids, was cationic in nature.[9] The anionic version of this process,[10] also known as the Snieckus–Fries rearrangement, was pioneered by Snieckus in 1983.[5a] *o*-Lithiated *O*-aryl *N*,*N*-dialkylcarbamates are not stable in the face of an increase of temperature evolving through an O→C 1,3-carbamoyl rearrangement that provides salicylamide derivatives and a variety of useful synthetic transformations.[11] The rate of this anionic *ortho*-Fries

(A*o*F) rearrangement mainly depends on the presence of additional functional groups on the aromatic ring and on the nature of the *N*-substituents.[12] Typically for *N*,*N*-diethylcarbamates, upon slow warming to room temperature from −78 °C, the intermediate lithiated species efficiently undergo the carbamoyl shift.[13] Several different O→C carbamoyl transfer reactions have been reported (Scheme 1). Apart from the original 1,3-O→C shift, homologous versions,[14] including the rearrangement of benzylic *O*-carbamates,[15] and remote[16] Snieckus–Fries rearrangements involving 1,4-O→C and 1,5- or 1,6-O→C migrations, respectively, have been described and also employed as useful strategies for the construction of complex molecules.[17]

In particular, the 1,5-O→C shift of the carbamoyl group to an *ortho*-enolate is a variant of the well-known Baker-Venkataraman rearrangement.[18] In addition, regioselective 1,4- or 1,5-O→C shifts to an *o*-alkenyl group have also been reported by Snieckus et al. depending on the substitution of the alkene moiety.[19] Furthermore, hetero-Fries rearrangements 1,3-X→C (X = N, C, S) are also known.[20] However, the corresponding O→X (X ≠ C) carbamoyl migrations are much less developed and only few examples of 1,5-O→O carbamoyl transfer reactions have been previously described.[21]

In the last years, we have been interested in the use of D*o*M reactions for the synthesis of functionalized heterocyclic compounds.[22] In this field, we have recently reported a new pattern of the A*o*F rearrangement consisting on a 1,5-O→N carbamoyl rearrangement that takes place in the reactions of *o*-lithiated *O*-arylcarbamates with nitriles.[23] Herein, we wish to report a detailed study of this reaction, both experimental and computational, as well as about the related processes of these organolithium intermediates with a variety of unsaturated C–N based electrophilic reagents.

Scheme 1. Carbamoyl Rearrangements of Lithiated *N,N*-Diethylcarbamates

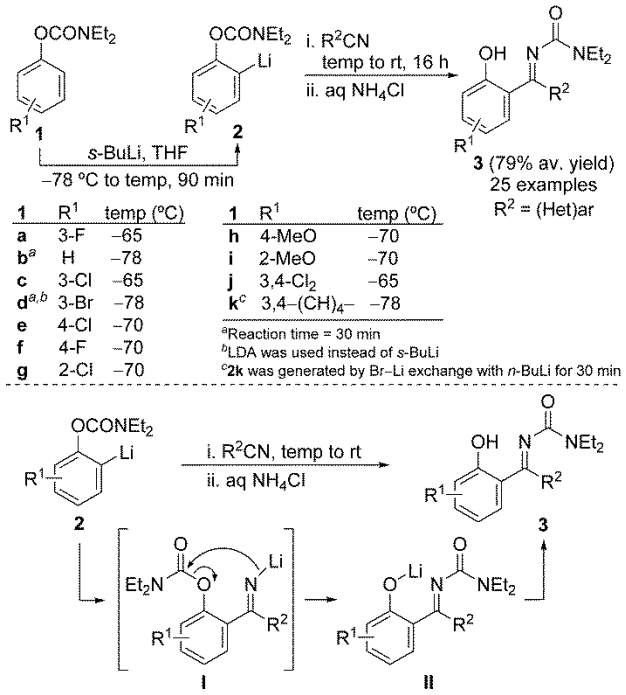


RESULTS AND DISCUSSION

Reaction of *o*-lithiated *O*-aryl carbamates 2 with nitriles. Looking for a suitable method for the preparation of 6-halo-2-hydroxybenzophenone derivatives, we found that the reaction of *o*-lithiated *O*-arylcarbamates **2**, readily generated by *o*-lithiation of *N*,*N*-diethylcarbamates **1**, with (hetero)aromatic nitriles gave rise to salicylidene urea derivatives **3** in high yields after hydrolysis with aqueous NH_4Cl (Scheme 2).[23] Starting from *O*-3-fluorophenyl carbamate **1a**, a wide variety of (hetero)aromatic nitriles were shown to participate in this 1,5-O→N carbamoyl translocation, although nitriles bearing α-hydrogens, such as MeCN or *c*-C_3H_5CN, underwent competitive acid-base reaction leading to the hydrolysis of **2** and the recovery of the starting carbamate.[24] Regarding the scope of the *O*-aryl carbamate partner **1**, we demonstrated that the rearrangement is quite general as carbamates bearing no functional group, halogens, or methoxy substituents at different positions efficiently underwent the translocation. In addition, the *O*-*o*-lithioarylcarbamate could also be generated by bromine-lithium exchange instead of hydrogen abstraction as shown with *O*-(1-bromo-2-naphthyl) *N*,*N*-diethylcarbamate **1k**. Our mechanistic proposal for this new carbamoyl shift is shown in Scheme 2.

Treatment of organolithium **2** with the nitrile would lead to *N*-lithiated intermediate **I**, which evolves through an intramolecular 1,5-O→N carbamoyl rearrangement giving rise to lithium aryloxide **II**. The subsequent hydrolysis releases the final salicylidene urea derivative **3** (Scheme 2).

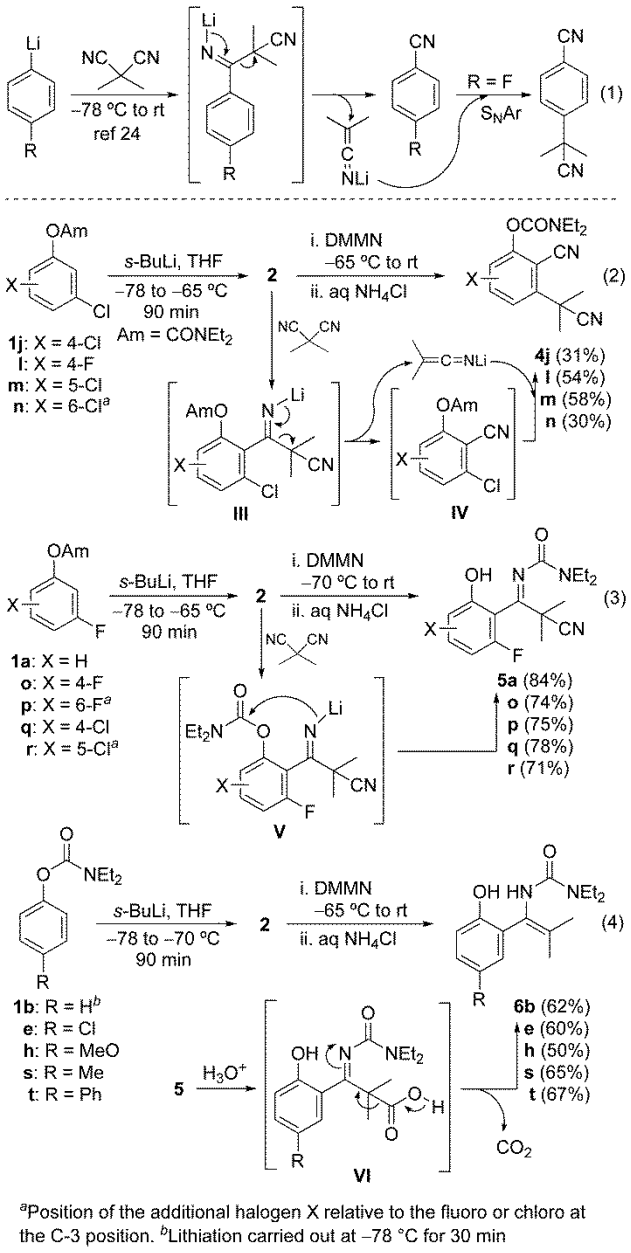
Scheme 2. Reactions of *o*-Lithiated *N*,*N*-Diethylcarbamates 2 with Nitriles. Synthesis of Salicylidene Urea Derivatives 3 and Mechanistic Proposal



Dimethylmalononitrile (DMMN) and related dinitriles are a particular type of cyano compounds that have been described by Reeves and co-workers as useful transnitrilation reagents for the electrophilic cyanation of aryl Grignard or lithium compounds through a retro-Thorpe reaction.[25] The same authors have also described a tandem transnitrilation/S_NAr reaction, which leads to 1,4-difunctionalization of 4-fluorophenyl magnesium or lithium reagents, due to the generation of isobutyronitrile anion and electronically activated *p*-fluorobenzonitrile after the transnitrilaton. However 3-fluoro or 4-chloroaryl organometallics do not undergo the tandem process and 2-fluorophenyl Grignard reagent failed to afford either cyanation or difunctionalization (Scheme 3, eq 1).[26]

Thus, we decided to study the reactivity of DMMN with *o*-lithiated carbamates **2**. Surprisingly, we obtained different products depending on the carbamate substitution pattern. For *O*-3-chlorophenyl carbamates bearing an additional halogen substituent, such as **1j,l,m,n**, their reaction with DMMN led to the isolation of compounds **4** bearing two different cyano groups.[22f] Their formation could be understood by an initial transnitrilation reaction that led to the carbamate **IV** through unstable intermediate **III**. Cyano-functionalized **IV** would undergo a S_NAr reaction with the released isobutyronitrile anion, likely favored by the additional electron-withdrawing effect of the second halogen. Although with low to moderate yields, the overall process implies an interesting 2,3-difunctionalization of the starting carbamate (Scheme 3, eq 2). Surprisingly, when we tried to extend this reactivity to *O*-3-fluorophenyl carbamates **1a,o-r** more favoured, a priori, to undergo the subsequent S_NAr reaction we did not obtain the same result. In theses cases DMMN behaves as the (hetero)aromatic nitriles described in Table 1. Thus, the intermediate lithiated imine **V**, generated by reaction of the corresponding *o*-lithiated carbamate **2** with DMMN, evolves through the 1,5-O→N carbamoyl rearrangement leading to the cyano-functionalized urea derivatives **5** in high yields (Scheme 3, eq 3).[23] Moreover, with carbamates **1** that do not possess an halogen at the *meta*-position, such as unfunctionalized **1b** and *p*-substituted **1e,h,s,t**, the reactions of their *o*-lithiated anions **2** with DMMN afforded new enamide derivatives **6** in moderate to good yields after purification. For their formation we propose that the corresponding rearranged product **5** is initially generated,[27] which upon acid hydrolysis in the purification process by silica gel column chromatography leads to unstable intermediate **VI** that easily releases CO_2 giving rise to the isolated enamide **6** (Scheme 3, eq 4). The structure of **6b** was further confirmed by X-ray analysis.[28] These results show that, except for *O*-3-chlorophenyl carbamates, the carbamoyl migration is faster than the competitive retro-Thorpe-type process that release the isobutyronitrile anion leaving behind the cyano group.

Scheme 3. Different Reactivity of *o*-Lithiated Carbamates 2 with Dimethylmalononitrile (DMMN). Synthesis of 4-6

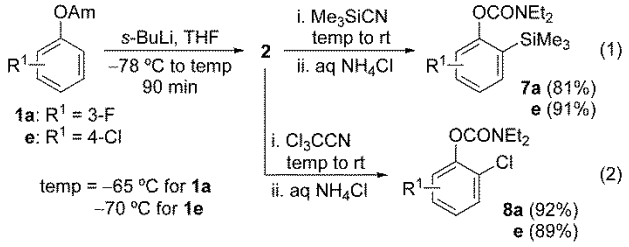


[a]Position of the additional halogen X relative to the fluoro or chloro at the C-3 position. [b]Lithiation carried out at –78 °C for 30 min

At this point, we wondered about the behaviour of other cyano-containing electrophilic reagents. When we faced selected *O*-3-fluorophenyl and *O*-4-chlorophenyl carbamates, **1a** and **1e**, with trimethysilyl cyanide (Me_3SiCN), *o*-silylated carbamates **7** were obtained in high yields (Scheme 4, eq 1). This result showed that the cyanide behaves as a leaving group instead of being attacked by the organolithium. This is not unexpected as it had been described the use of alkylsilyl cyanides as

silylating reagents for accessing C-trimethylsilylated compounds from organometallics including organolithiums.[29] In the same way, when the *o*-lithiated derivatives from the same starting materials **1a,e** were treated with trichloroacetonitrile (Cl_3CCN), the chloro-functionalized carbamates **8** were isolated in high yields (Scheme 4, eq 2). In this case, an electrophilic chlorine atom is preferentially attacked instead of the cyanide in Cl_3CCN, with the concurrent releasing of weak dichloroacetonitrile anion.[30] Of course these TMS- or chloro-functionalized compounds could also be obtained by treatment of the intermediate organolithiums with TMSCl or "Cl^+"-type electrophiles such as C_2Cl_6.

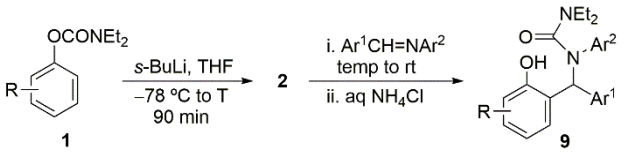
Scheme 4. Reaction of Selected *o*-Lithiated Carbamates 2 with Me_3SiCN and Cl_3CCN



Reaction of *o*-lithiated *O*-aryl carbamates 2 with imines. After having established the reactivity of *o*-lithiated *O*-aryl carbamates **2** with nitriles, leading to the description of a new 1,5-O→N carbamoyl rearrangement, we focused our attention on imines as electrophilic reagents. The presence of a C=N functionality in these electrophiles suggests that they could behave in an analogous way as nitriles undergoing the same type of carbamoyl shift. In a first experiment, unfunctionalized *O*-phenyl carbamate **1b** was *o*-lithiated and treated with commercially available *N*-benzylidene aniline. This reaction affords, after acid hydrolysis, the phenol derivative **9ba** in which the carbamoyl group was shifted from the oxygen to the nitrogen atom (Table 1, entry 1). To test the scope of this process, a selection of starting *N*,*N*-diethyl carbamates **1**, possessing electron-rich as well as electron-withdrawing groups, were treated with different aldimines that can also be functionalized with halogens. In all cases the *o*-functionalized phenol derivatives **9** were obtained in high yields (entries 2–8). Their structure, further confirmed by X-ray analysis of **9ba**,[28] suggests that, after initial attack of

the organolithium to the imine, the 1,5-O→N carbamoyl migration takes place efficiently. This result shows that the O→N migration does not require that the N atom to be bonded to a sp^2 carbon to take place.

Table 1. Reactions of *O*-Aryl *N*,*N*-Diethylcarbamates 1 with Imines. Synthesis of Derivatives 9



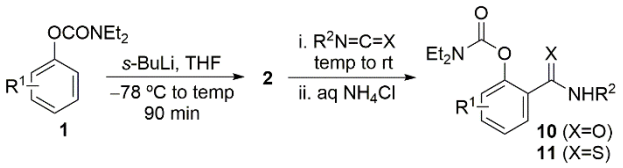
entry	**1**	R	temp (ºC)	Ar^1	Ar^2	product	yield (%)[a]
1[b]	**1b**	H	–78	Ph	Ph	**9ba**	79
2	**1c**	3-Cl	–65	Ph	Ph	**9ca**	85
3	**1c**	3-Cl	–65	Ph	4-BrC_6H_4	**9cb**	87
4	**1c**	3-Cl	–65	4-MeC_6H_4	4-BrC_6H_4	**9cc**	81
5	**1e**	4-Cl	–70	Ph	Ph	**9ea**	81
6	**1e**	4-Cl	–70	4-MeC_6H_4	3-Cl-5-FC_6H_3	**9ed**	83
7	**1i**	2-MeO	–70	Ph	Ph	**9ia**	84
8	**1q**	3-F-4-Cl	–65	Ph	Ph	**9qa**	76

[a]Isolated yield of product based on starting material **1**. [b]Reaction time = 30 min.

Reaction of *o*-lithiated *O*-aryl carbamates 2 with iso(thio)cyanates. At this point we wondered if other electrophilic reagents bearing the C=N fragment as reactive moiety would also undergo the 1,5-O→N carbamoyl shift. In addition, if the rearrangement takes place an additional regiochemical issue would arise as two heteroatoms (N,O and N,S) are present in the electrophile. We anticipated that N would likely be the preferred nucleophilic center attending to the corresponding resonance structures (computed charges obtained in preliminary calculations for these anions also assigned more negative charge to the N than the O/S atoms). First, a variety of isocyanates (R^2N=C=O), including aromatic ones and *p*-toluenesulfonyl isocyanate, were allowed to react with organolithium **2e**, easily generated by *o*-lithiation of carbamate **1e** (Table 2, entries 1–6). In these cases, the *O*-(2-carbamoylaryl) carbamates **10** were selectively obtained in high yields. Their structures show that no

carbamoyl migration has taken place, as it was confirmed by X-ray crystallography of **10eb**.[28] In an analogous way, a selection of *o*-lithiated carbamates **2** were treated with different isothiocyanates ($R^2N=C=S$) as electrophilic counterparts (Table 2, entries 7–18). Again, the structure of the thioamide derivatives obtained **11** reveal that no rearrangement of the *N*,*N*-diethylcarbamoyl group has occurred. To confirm this, X-ray analysis of **11eb** and **11ha** was carried out.[28] Apart from aromatic isothiocyanates, an alkyl derivative like *i*-propylisothiocyanate could be used as electrophile giving rise to the thioamide **11ef** in high yield (entry 14). Thus, the reaction *o*-lithiated *O*-aryl carbamates **2** with both isocyanates and isothiocyanates afford the expected amide **10** and thioamide derivative **11**, respectively, with no carbamoyl transfer between the phenolic oxygen and any of the heteroatoms from the electrophile. According to our preliminary simulations the isocyanate product was expected to rearrange from a thermodynamic point of view. To discard that the migration did not occur only due to kinetic issues we tried several experiments at higher temperature, but we never observed migration. This apparent contradiction triggered a detailed computational work on the reaction mechanism (see below).

Table 2. Reactions of *O*-Aryl *N*,*N*-Diethylcarbamates 1 with Iso(thio)cyanates. Synthesis of (thio)amide derivatives 10 and 11



entry	**1**	R^1	temp (ºC)	X	R^2	product	yield (%)[a]
1	**1e**	4-Cl	–70	O	Ph	**10ea**	82
2	**1e**	4-Cl	–70	O	3-ClC_6H_4	**10eb**	79
3	**1e**	4-Cl	–70	O	3-BrC_6H_4	**10ec**	76
4	**1e**	4-Cl	–70	O	4-$MeOC_6H_4$	**10ed**	82
5	**1e**	4-Cl	–70	O	4-*n*-BuC_6H_4	**10ee**	81
6	**1e**	4-Cl	–70	O	SO_2*p*-Tol	**10ef**	86
7[b]	**1b**	H	–78	S	Ph	**11ba**	86

8	**1c**	3-Cl	–65	S	2-FC_6H_4	**11cb**	83
9	**1e**	4-Cl	–70	S	Ph	**11ea**	86
10	**1e**	4-Cl	–70	S	2-FC_6H_4	**11eb**	80
11	**1e**	4-Cl	–70	S	3-ClC_6H_4	**11ec**	84
12	**1e**	4-Cl	–70	S	4-BrC_6H_4	**11ed**	79
13	**1e**	4-Cl	–70	S	3,4-$(MeO)_2C_6H_3$	**11ee**	80
14	**1e**	4-Cl	–70	S	*i*-Pr	**11ef**	90
15	**1h**	4-MeO	–70	S	Ph	**11ha**	85
16	**1i**	2-MeO	–70	S	Ph	**11ia**	84
17[c]	**1k**	3,4–$(CH)_4$–	–78	S	Ph	**11ka**	81
18	**1l**	3-Cl-4-FC_6H_3	–65	S	Ph	**11la**	77

[a]Isolated yield of product based on starting carbamate **1**. [b]Reaction time = 30 min. [c]*O*-(1-bromo-2-naphthyl) *N*,*N*-diethylcarbamate **1k** was used as starting material and the corresponding intermediate *o*-lithiated carbamate **2k** was generated by bromine-lithium exchange with *n*-BuLi for 30 min.

Reactivity model via computational simulations. Once armed with a plethora of experimental results we set out to rationalize the observations and, if possible, provide a model that could anticipate the migratory behaviour of these substrates. Initially, two possible scenarios can be proposed for the governing effects on the migratory ability of the *o*-lithiated *N*,*N*-diethyl *O*-arylcarbamates **2** upon nucleophilic attack to the series of electrophiles explored experimentally: 1- some intermediates rearrange and some do not because of kinetic control, or 2- the eventual migration depends only on the relative stability of the anions involved in the process, hence thermodynamic control is operating. As a corollary, the first scenario would involve a competition between the nucleophilic character of both anions whereas the second cause would rely on their basicity. In order to provide in our simulations with a chemical representation of the system as accurate as possible, while still maintaining computational efficiency, we decided to keep structural truncations to the reacting substrates to a minimum. Hence for the reaction with nitriles we employed benzonitrile, *N*-benzylideneaniline was used to simulate the reaction with imines, and phenylisocyanate and phenylisothiocyanate were used to simulate the reactions of substrates featuring the corresponding functional groups. The reaction counterpart used was always *N*,*N*-dimethyl *O*-phenylcarbamate. This essentially means that the only

truncation applied to the reaction with respect to the experimentally probed substrates is the shortening of the ethyl to methyl groups at the amide fragment. This should have minimum impact on the reaction profiles but restricts to some degree the conformational space of the already rather flexible coupled product. The lithium counterion was taken into account explicitly and solvation (THF) was modelled implicitly via a continuum solvation model. A detailed description of the methodology can be found in the Supporting Information.

According to these simulations the benzonitrile and imine derived adducts (**R**, in Figure 1) have a strong driving force toward migration (the final rearranged product **P** lie at –33 and –21 kcal mol^{-1} with respect to the initial adduct **R**, which is compatible with the observed behaviour). However, when considering the isocyanate and isothiocyanate derivatives some unexpected trends were obtained. Our results, if we consider the thermodynamics of the reaction, indicate that the isothiocyanate derivative should not migrate (as it is observed in the experiment), but the isocyanate derivative shows a migrated product, **P**, which is 3.9 kcal mol^{-1} more stable than the starting compound **R**. This latter result suggests that isocyanate derivatives would migrate, but they never do in our experiments. An extensive conformational search for a more stable isomer resulted in ca. 9 structures, none of which resulted more stable than the rearranged product. It seemed therefore clear that the thermodynamic balance of this last reaction was such that did not fit with the observations. Intriguingly, and despite being in contradiction with our experimental observations, these results do bear some chemical logic since the pKa of these species in DMSO are: 23 for the amide, 17 for the thioamide and 18 for the phenol. Hence, from this perspective, it can be expected that the phenolate is released through nucleophilic attack by the amidate anion but not by the thioamidate one (it is worth noting however that this pKa values are not measured in THF, and due to the last two substrates being rather close in basicity, a solvent change could reverse the relative order). To address this contradictory result, we explored the possibility of kinetic control governing the output of these reactions. Our hypothesis being that perhaps this migration is not observed due to high barriers hampering the reaction, despite the potential thermal stability of the rearranged product. We therefore

computed the full profiles for the migration of these four types of substrates: nitrile, imide, isocyanate and isothiocyanate. The results are summarized in Figure 1.

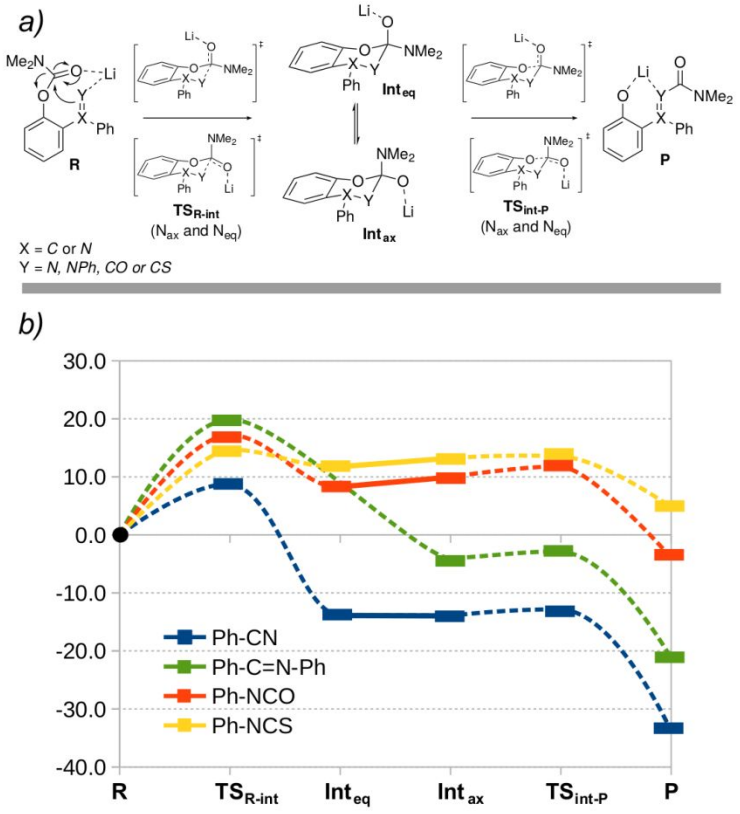


Figure 1. a) Reaction scheme for the proposed 1,5-O→N carbamoyl rearrangement mechanism starting from the migration adducts and considering the chair-like conformations of transition states and intermediates. b) Relative Gibbs free energies (in kcal mol^{-1}) for the structures involved in the migration illustrated on top. Solid lines represent conformational relations since both NEt_2 equatorial and axial intermediates are considered, only the lowest energy transition states are shown. Other conformers explored for transition state structures and intermediates can be found in the SI

We are hereby only showing the lowest energy transition states and intermediates. These systems have significant conformational freedom, and for instance, different transition states can be located in which the NEt_2 fragment of the carbamate is poised in pseudo-axial of pseudo-equatorial orientations. Additionally, for some reacting systems, the adduct features alternative nucleophilic sites and in these

cases all the alternatives were explored as a benchmark to our calculations (i.e. to verify that in all cases a non-observed reaction product is simulated as a non-competitive path in our simulations). An illustrative example can be found in Figure 2 where the initial rearrangement for the isocyanate adduct can be initiated via nucleophilic attack by the N or O site in two possible chair-like structures. These and other alternative conformations for all the substrates included in this work along with energy data can be found in the SI.

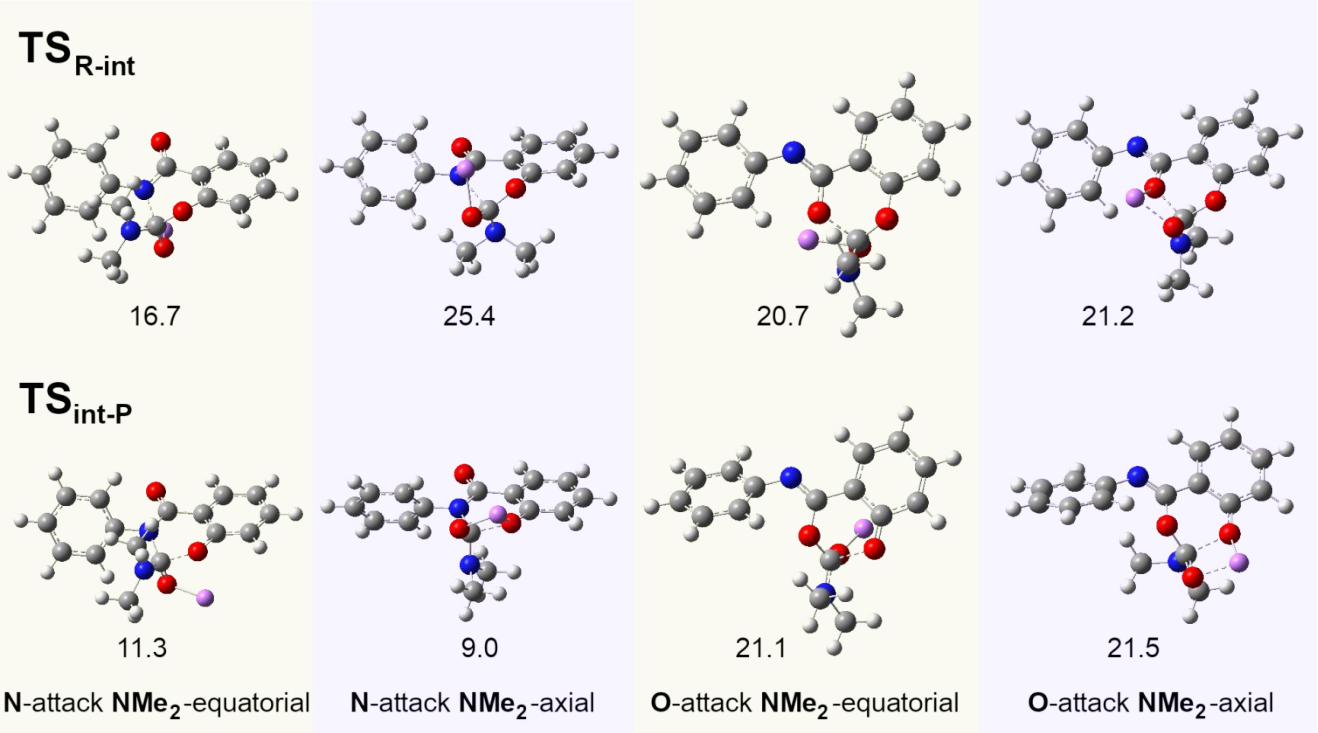


Figure 2. Isomeric possibilities for the rearrangement of the isocyanate complex including N and O attacks onto the carbamoyl group. Initial transition state alternatives $TS_{R\text{-}int}$ (top), second transition state alternatives $TS_{int\text{-}P}$ (bottom), activation free energies (in kcal mol^{-1}) relative to the initial adduct **R** are reported with each structure.

It is interesting to note that, in all cases, the rate-limiting transition state is the nucleophilic attack, and the subsequent release of the phenolate is almost barrierless, even in the case of the endergonic reaction found for the isothiocyanate substrate. Actually, the four reactions feature a second barrier

that is approximately only 1 kcal mol^{-1} above the six-member ring intermediate. All the rate-limiting barriers are surmountable at room temperature, and the results obtained for the kinetics of these reactions therefore do not justify the unobserved rearrangement of the isocyanate derivative.

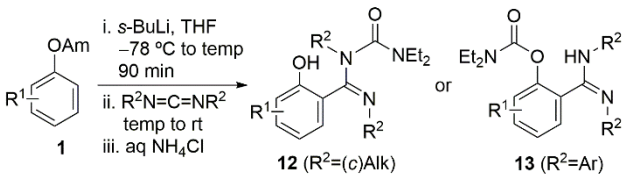
We therefore decided to look back into the chemical model used for these simulations. Due to the minimal amount of simplifications that we applied when building our simulation model, there was not much that could be added to it to make it more realistic. We considered including explicit solvent, but this is a rather brute force approach for such an apparently simple governing effect (relative pKa values are rather accurately computed with continuum solvent models).[31] For this reason we focused on what could have been added "in excess" to our model. In this regard we noticed that perhaps the counterion effect was being overestimated since Li^+ can be quite efficiently solvated in THF and may not be chelating the substrate. In such a case this counterion effect would be screened by the surrounding solvent. This scenario is actually quite appropriate for a continuum dielectric model.[32] We therefore removed the explicit lithium cation and let the PCM model to mirror the negative charge of the reacting molecule. After this minor modification to our model, we repeated the thermodynamic simulations. Gratifyingly the four systems provided energetics according to the experimental observations. The migrated products formed with benzonitrile and *N*-benzylideneaniline are more stable than the non-migrated precursor by –36.1 and –15.1 kcal mol^{-1}, respectively. On the contrary, both iso(thio)cyanate derivatives feature endergonic migration steps (3.7 and 6.3 kcal mol^{-1}). Actually, in these cases we also computed the possible, although unexpected, migrations due to an initial S/O nucleophilic attack (with relative energies of 12.6 and 17.8 kcal mol^{-1} for the isocyanate and isothiocyanate derivatives, respectively). It does seem, therefore, that the governing factor of these reactions is the relative basicity of the involved anions in the migrated vs. non migrated products. Interestingly the fact that these latter results fit better with our observations provide some evidence suggesting that the lithium cation under experimental conditions is only loosely bound to the organic substrate, or perhaps even completely dissociated and stabilized by solvation with THF.

Finally, we explored other potential candidates for which this migration could provide interesting molecular scaffolds. Some substrates that, on paper or on preliminary simulations, seemed promising did not furnish the desired product, mostly because they were excessively reactive and unstable, like unsaturated nitrocompounds and allenoates. However, one derivative that also caught our attention was the carbodiimide fragment. Initial exploratory work through computational simulations suggested that aliphatic carbodiimides were good candidates to suffer nucleophillic attack by the *o*-lithiated carbamate and undergo subsequent migration (the migrated product being ca. 16 kcal mol^{-1} more stable when using dimethyl carbodiimide). Surprisingly, when aromatic carbodiimides were considered, most of the driving force for the migration vanished, and the reaction was anticipated to be not far from equilibrium (the energy difference between migrated and non-migrated product lie within only 2 kcal mol^{-1} when diphenyl carbodiimide was simulated), so a question remained on what would happen to this last kind of substrates under laboratory conditions. Another promising candidate that was found during this exploratory work in the space of functional groups was *N*-sulfonylimines. Our simulations yielded interesting results when compared with those obtained above for the imine functional group. Unlike *N*-aryl imines, *N*-sulfonyl imines presented an energy balance that strongly suggested non-migratory abilities: the non-migrated substrate was computed to be 3.5 kcal mol^{-1} more stable than the migrated alternative. The latter functional groups, carbodiimides (in their aliphatic and aromatic form) and *N*-sulfonyl imines, can therefore serve as a litmus test for our calculations if these reactions can be run in the laboratory.

Reaction of *o*-lithiated *O*-aryl carbamates 2 with carbodiimides. Inspired by the preliminary computational results with carbodiimides we proceeded to study the behavior of selected *o*-lithiated *O*-aryl carbamates **2** with this type of C=N based electrophilic reagents (Table 3). Carbodiimides have been previously reported to react with organolithium reagents, however the focus was on the structure of the amidinate complexes formed after treatment with different metallic salts.[33] Initially, when we

treated the *o*-lithiated carbamates **1a,b** with di(*c*)alkylcarbodiimides, such as dicyclohexylcarbodiimide and di-*i*-propylcarbodiimide, *o*-hydroxy-*N,N′*-di(*c*)alkylbenzimidamide derivatives **12** were selectively obtained (entries 1 and 2). Their structure, further confirmed with X-ray analysis of **12bb**,[28] demonstrates that the carbamoyl transfer from O→N has occurred. Gratifyingly, in excellent agreement with the predictions posed through our computational results, the reaction of **2b** with di-*p*-tolylcarbodiimide afforded the *O*-2-(N,N′-ditolylcarbamimidoyl)phenyl carbamate **13bc** instead of the corresponding derivative **12** (entry 3). This behavior in which the success of the 1,5-O→N carbamoyl rearrangement seems to depend on the aryl or (*c*)alkyl nature of the *N*-substituents of the carbodiimide was reproduced with different substituted starting carbamates **1** and the selected (*c*)alkyl or arylcarbodiimides. Thus, phenol derivatives **12** were obtained for (*c*)alkylcarbodiimides (entries 4,5,7–9) whereas non-rearranged carbamate **13ec** was isolated when using di-*p*-tolylcarbodiimide (entry 6). Its structure was again further confirmed by X-ray analysis.[28]

Table 3. Reactios of *O*-Aryl *N,N*-Diethylcarbamates 1 with Carbodiimides. Synthesis of Derivatives 12 and 13



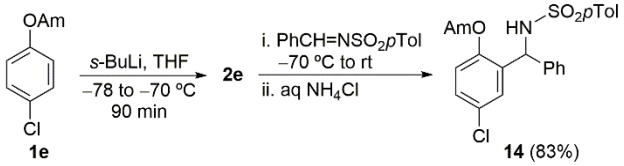
entry	**1**	R^1	temp (ºC)	R^2	product	yield (%)[a] **12**	**13**
1	**1a**	3-F	–65	*c*-C_6H_{11}	**aa**	79	–
2[b]	**1b**	H	–78	*i*-Pr	**bb**	88	–
3[b]	**1b**	H	–78	*p*-Tol	**bc**	–	81
4	**1c**	3-Cl	–65	*i*-Pr	**cb**	83	–
5	**1e**	4-Cl	–70	*c*-C_6H_{11}	**ea**	78	–
6	**1e**	4-Cl	–70	*p*-Tol	**ec**	–	88
7	**1h**	4-MeO	–70	*i*-Pr	**hb**	76	–
8	**1i**	2-MeO	–70	*i*-Pr	**ib**	78	–
9	**1u**	2-Me	–70	*i*-Pr	**ub**	77	–

[a]Isolated yields referred to the starting carbamate **1**. [b]Reaction time = 30 min.

These results show that amidinates having a higher degree of delocalization due to the presence of aryl substituents favour the formation of carbamates **13**, in which no rearrangement has taken place**.** As predicted by our simulations and taking into account these findings, stabilized C=N electrophiles, such as *N*-sulfonyl imines are expected to have no migratory abilities. This behaviour would contrast with the results shown in Table 2 regarding reactions of *o*-lithiated *O*-aryl *N*,*N*-diethylcarbamates **2** with imines. To check this, *N*-benzylidene *p*-toluenesulfonamide was also explored as electrophile by reaction with **2e**, derived from *O*-4-chlorophenyl carbamate **1e**. As anticipated, no carbamoyl migration occurred and carbamate **14**, whose structure was confirmed by X-ray analysis,[28] was obtained in high yields (Scheme 5).

This latter result, together with the experiments performed on carbodiimides, strongly suggest that the dissociated model eventually employed in our simulations is correct and it provides us with rather powerful predictive power based on a simple energy balance between the migrated and non-migrated substrates.

Scheme 5. Reaction of *o*-Lithiated Carbamate 2e with a *N*-sulfonyl Imine

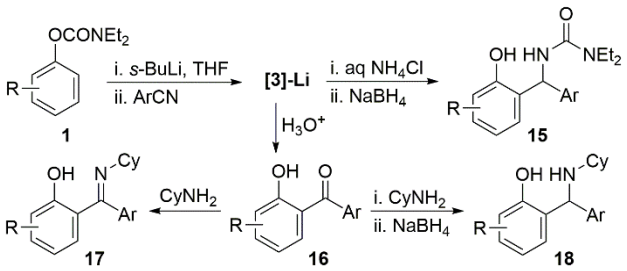


Further transformations. Finally, we decided to prove the usefulness of benzylidene urea derivatives **3** that were easily obtained from the reaction of *o*-lithiated carbamates **2** with (hetero)aromatic nitriles (see Scheme 1). We focused our attention in the development of procedures that avoid the isolation of compounds **3** in pure form (Table 4). First, when a selection of crude ureas **3** were treated with $NaBH_4$ the corresponding *o*-(α-amidobenzyl)phenol derivatives **15** were obtained

in good overall yields (entries 1–3). In addition, if the acid hydrolysis is carried out with mineral acid (HCl) instead of softer aqueous NH_4Cl, the lithium phenoxide intermediate **[3]-Li** is directly transformed into *o*-hydroxybenzophenones **16** (entries 4–11). Due to the interest of these structural motifs, which are included in several biologically active compounds and serve as useful synthetic intermediates for the preparation of *O*-heterocycles like benzofurans, benzoxazoles, or coumarines,[34] we synthesized a variety of these *o*-hydroxybenzophenone derivatives **16** further functionalized with halogens, alkoxy or thioether groups in high overall yields. Interestingly, few general methods are available for synthesizing 6-halo-2-hydroxybenzophenones such as **16aa** and **16ad** (entries 4 and 5).[35] Moreover, 2-hydroxybenzophenones bearing an *o*-fluorine substituent at the other aromatic ring, such as **16ek**, are easily transformed into xanthones under soft basic conditions.[36]

Having efficiently accessed to benzophenones **16**, we also took advantage from the known favorable effect of 2-hydroxyphenyl groups for ketimine formation of benzophenone derivatives,[37] and applied it to the preparation of 2-(imino)benzyl phenol and 2-(α-alkylamino)benzyl phenol derivatives **17** (entries 12 and 13) and **18** (entries 14 and 15), respectively.

Table 4. Synthetic Applications of Urea Derivatives 3



entry	carbamate	R	Ar	product	yield (%)[a]
1	**1a**	3-F	4-ClC_6H_4	**15aa**	77
2	**1a**	3-F	2-BrC_6H_4	**15af**	76
3	**1g**	2-Cl	2-FC_6H_4	**15gk**	80
4	**1a**	3-F	4-ClC_6H_4	**16aa**	85
5	**1a**	3-F	4-$MeSC_6H_4$	**16ad**	83
6	**1e**	4-Cl	4-$EtOC_6H_4$	**16ej**	88
7	**1e**	4-Cl	2-FC_6H_4	**16ek**	83

8	**1f**	4-F	4-ClC_6H_4	**16fa**	80
9	**1h**	4-MeO	4-ClC_6H_4	**16ha**	81
10	**1i**	2-MeO	4-ClC_6H_4	**16ia**	81
11	**1j**	2-Cl	4-ClC_6H_4	**16ja**	84
12	**1h**	4-MeO	4-ClC_6H_4	**17ha**	91
13	**1i**	2-MeO	4-ClC_6H_4	**17ia**	90
14	**1h**	4-MeO	4-ClC_6H_4	**18ha**	85
15	**1i**	2-MeO	4-ClC_6H_4	**18ia**	88

[a]Isolated yields of products **15** and **16** referred to the starting carbamate **1**. Isolated yields of products **17** and **18** referred to *o*-hydroxyketones **16**.

CONCLUSIONS

In summary, we have reported a new type of the carbamoyl Snieckus–Fries rearrangement in which the carbamoyl group migrates from oxygen to nitrogen (1,5-O→N). This type of reactivity is observed in the reactions of *o*-lithioaryl *N,N*-diethylcarbamates with nitriles, imines, and alkylcarbodiimides, whereas the corresponding electrophilic trappings with iso(thio)cyanates and aromatic carbodiimides give rise to the non-rearranged *o*-functionalized *O*-arylcarbamates. Particularly, dimethylmalononitrile, which has been described as an electrophilic cyano source, presents different reactivity patterns depending on the carbamate moiety. A computational model is provided that reveals how the relative basicity of the competing products is the governing factor in this chemistry. Additionally, interesting implications on the non-direct participation of lithium in these reactions have been derived from simulations with explicit and implicit counterion effects. It is also worthy to note that the reactions of *o*-lithiated carbamates with nitriles led to new and interesting salicylidene urea derivatives that have been further transformed into different highly functionalized phenol derivatives, including the useful structural motifs 2-hydroxybenzophenones.

EXPERIMENTAL SECTION

General Methods. 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 F254 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. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-Plus (300 MHz ^{1}H; 75.4 MHz ^{13}C) or Bruker Avance (300 MHz ^{1}H; 75.4 MHz ^{13}C) spectrometers at room temperature. NMR splitting pattern abbreviations are: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. Chemical shifts are reported in ppm using residual solvent peak as reference ($CDCl_3$: ^{1}H δ = 7.26 ppm; ^{13}C δ = 77.16 ppm; DMSO-d_6: ^{1}H δ = 2.50 ppm; ^{13}C δ = 39.50 ppm) and the multiplicities of ^{13}C signals were determined by DEPT experiments. High resolution mass spectra (HRMS) were obtained on a Micromass Autospec spectrometer using EI at 70 eV or on an Agilent 6545 Q-TOF mass spectrometer using electrospray ionization (ESI). Melting points were measured on a Gallenkamp apparatus using open capillary tubes and are uncorrected. 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. Single crystal X-ray diffraction analysis data collection was done on a Bruker D8 Venture Dual source configuration diffractometer from Bruker using Photon III detector or alternatively on a Bruker APEX-II CCD detector from Bruker. Microfocus IμS Cu/Mo X-ray sources were used.

General Procedure for the Synthesis of *O*-Aryl-*N*,*N*-Diethylcarbamates 1. To a 50 mL flask, NaOH (2 g, 50 mmol) was added to a solution of the corresponding phenol (20 mmol) in THF (10 mL) and the mixture was stirred at rt for 10 min. Then, diethylcarbamoyl chloride (2.54 mL, 20 mmol) was added, and the resulting mixture was stirred at rt for 24 h. H_2O (5 mL) was added to the reaction mixture and most of the solvent was removed under reduced pressure. More water was added, and the aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried

over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained crude products **1** were used without further purification. Characterization and spectral data for **1a**, **1c-f**, **1h-r** have been previously reported in our previous works.[22a,f,23] **1g,u** have been reported by Snieckus and co-workers.[7f] Finally, **1b,s,t** have also been previously reported.[38]

General Procedure for the Synthesis of Urea Derivatives 3. A solution of the corresponding carbamate **1** (1 mmol, 1 equiv) in THF (2 mL) at –78 ºC under nitrogen, was treated with a solution of *s*-BuLi (1.1 to 1.3 equiv, 1.4 M solution in cyclohexane) or LDA (1.1 equiv for **1d**) or *n*-BuLi (1.1 equiv for **1k**). The reaction mixture was allowed to reach to temp for 5 min, and stirred at this temperature for 90 min (30 min for **1b,d,k**) [temp = –78 ºC for **1b,d**; temp = –70 ºC for **1e-i**; temp = –65 ºC for **1a,c,j**]. Then, the corresponding nitrile is added (same equivalents as the employed base) and allowed to stir at temp for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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 silica gel column chromatography, and recrystallization in some cases, affording the corresponding 1,1-diethyl-3-(2-hydroxyphenyl)(aryl)methylene ureas **3**.Characterization and spectral data of **3** have been previously reported in our previous communication.[23]

General Procedure for the Synthesis of Dicyano-Functionalized *O*-Aryl Carbamates Derivatives 4 and Urea Derivatives 5 and 6. A solution of the corresponding *O*-aryl *N,N*-diethylcarbamate **1** (1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with a solution of *s*-BuLi (1.4 M solution in cyclohexane, 1.1 mmol for **1a,j-n,o-r** or 1.2–1.3 mmol for **1b,e,h,s,t**). The reaction mixture was allowed to reach to temp for 5 min [temp = –78 ºC for **1b**; temp = –70 ºC for **1e,h,s,t**; temp = –65 ºC for **1a,j-n,o-r**], and stirred at this temperature for 90 min (30 min for **1b**). Then, dimethylmalononitrile (DMMN) (same amount as the employed base, 1.1–1.3 mmol) is added and allowed to stir at temp for 60 min. The reaction mixture was allowed to warm to rt and stirred for

16 h. 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 silica gel column chromatography, and recrystallization in some cases, affording the corresponding 2-cyano-3-(2-cyanopropan-2-yl)phenyl *N,N*-diethylcarbamates **4**, (*E*)-3-(2-cyano-1-(2-fluoro-6-hydroxyphenyl)-2-methylpropylidene)-1,1-diethylurea derivatives **5** or 1,1-diethyl-3-(1-(2-hydroxyphenyl)-2-methylprop-1-en-1-yl)urea derivatives **6**. Characterization and spectral data of compounds **4**[22f] and **5**[23] have been previously reported.

*1,1-Diethyl-3-(1-(2-hydroxyphenyl)-2-methylprop-1-en-1-yl)urea (**6b**).* The reaction of *O*-phenyl *N,N*-diethylcarbamate (**1b**) (193 mg, 1 mmol), *s*-BuLi (0.86 mL, 1.2 mmol) and DMMN (113 mg, 1.2 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **6b** after recrystallization in $CHCl_3$/hexane (1:10), as a colorless solid (163 mg, 62% yield): mp 109–111 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.39 (s, 1H), 7.22–7.16 (m, 1H), 6.97–6.91 (m, 2H), 6.83–6.78 (m, 1H), 5.48 (s, 1H), 3.30 (q, J = 7.2 Hz, 4H), 1.83 (s, 3H), 1.60 (s, 3H), 1.17 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 157.9, 155.7, 137.0, 130.0, 129.3, 126.8, 124.5, 119.1, 117.0, 41.7, 20.8, 19.2, 13.8. LRMS (EI) *m/z* (%): 262 (M^+, 1), 189 (100), 174 (50), 145 (40), 132 (60). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_2$, 263.1754; found, 263.1759.

*3-(1-(5-Chloro-2-hydroxyphenyl)-2-methylprop-1-en-1-yl)-1,1-diethylurea (**6e**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and DMMN (122 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **6e** after recrystallization in $CHCl_3$/hexane (1:10), as a yellow solid (178 mg, 60% yield): mp 130–132 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.14 (dd, J = 8.7, 2.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.51 (s, 1H), 3.32 (q, J = 7.1 Hz, 4H), 1.83 (s, 3H), 1.61 (s, 3H), 1.19 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 157.9, 154.5, 138.0, 129.5, 129.1, 128.2, 123.44, 123.42, 118.4, 41.7, 20.8, 19.2, 13.8.

LRMS (EI) *m/z* (%): 298 (M^++2, 1), 296 (M^+, 2), 251 (73), 233 (100), 205 (44). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{22}ClN_2O_2$, 297.1364; found, 297.1371.

*1,1-Diethyl-3-(1-(2-hydroxy-5-methoxyphenyl)-2-methylprop-1-en-1-yl)urea (**6h**)*. The reaction of *O*-4-methoxyphenyl *N,N*-diethylcarbamate (**1h**) (227 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and DMMN (122 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **6h** as a red oil (146 mg, 50% yield), R_f = 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.8, 3.0 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 5.55 (s, 1H), 3.72 (s, 3H), 3.29 (q, J = 7.1 Hz, 4H), 1.81 (s, 3H), 1.59 (s, 3H), 1.15 (t, J = 7.1 Hz, 6H), the OH signal does not appear. ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 157.8, 152.4, 149.5, 136.7, 127.2, 124.4, 117.4, 115.2, 114.4, 55.8, 41.6, 20.7, 19.2, 13.8. LRMS (EI) *m/z* (%): 292 (M^+, 1), 219 (100), 161 (91). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_3^+$, 293.1860; found, 293.1865.

*1,1-Diethyl-3-(1-(2-hydroxy-5-methylphenyl)-2-methylprop-1-en-1-yl)urea (**6s**)*. The reaction of *O*-4-methylphenyl *N,N*-diethylcarbamate (**1s**) (207 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and DMMN (122 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **6s** after recrystallization in $CHCl_3$/hexane (1:10), as a colorless solid (180 mg, 65% yield): mp 120–122 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.19 (s, 1H), 6.98 (dd, J = 8.2, 1.8 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 1.8 Hz, 1H), 5.54 (s, 1H), 3.29 (q, J = 7.2 Hz, 4H), 2.24 (s, 3H), 1.82 (s, 3H), 1.59 (s, 3H), 1.16 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 157.8, 153.2, 136.4, 130.2, 129.7, 128.0, 126.5, 124.6, 116.6, 41.5, 20.7, 20.4, 19.1, 13.8. LRMS (EI) *m/z* (%): 276 (M^+, 1), 203 (100), 184 (44), 159 (55), 145 (82). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_2$, 277.1911; found, 277.1914.

*1,1-Diethyl-3-(1-(4-hydroxy-[1,1'-biphenyl]-3-yl)-2-methylprop-1-en-1-yl)urea (**6t**)*. The reaction of *O*-(1,1'-biphenyl)-4-yl *N,N*-diethylcarbamate (**1t**) (269 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and DMMN (122 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **6t** as a colorless solid (227 mg, 67% yield): mp

138–140 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.55 (s, 1H), 7.55–7.51 (m, 2H), 7.46–7.42 (m, 1H), 7.41–7.36 (m, 2H), 7.30–7.24 (m, 1H), 7.21 (t, J = 2.9 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.49 (s, 1H), 3.30 (q, J = 7.1 Hz, 4H), 1.84 (s, 3H), 1.64 (s, 3H), 1.17 (t, J = 7.1, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$) δ (ppm): 157.9, 155.4, 140.8, 137.1, 132.0, 128.64, 128.58, 127.8, 127.0, 126.45, 126.36, 124.5, 117.3, 41.5, 20.8, 19.1, 13.7. LRMS (EI) *m/z* (%): 338 (M^+, 1), 265 (100), 207 (67). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_2$, 339.2067; found, 339.2071.

General Procedure for the Synthesis of *O*-2-(Trimethylsilyl)aryl *N,N*-Diethyl Carbamates 7 and *O*-2-Chloroaryl *N,N*-Diethyl Carbamates 8. A solution of the corresponding carbamate **1** (1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with *s*-BuLi (1.4 M solution in cyclohexane). The reaction mixture was allowed to reach to temp (temp = –65 ºC for **1a**; temp = –70 ºC for **1e**) for 5 min and stirred at this temperature for additional 90 min. Then, trimethylsilyl cyanide (TMSCN) or trichloroacetonitrile (Cl_3CCN) is added and allowed to stir at temp for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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 silica gel column chromatography affording the *O*-2-(trimethylsilyl)aryl *N,N*-diethylcarbamate derivatives **7** or the *O*-2-chloroaryl *N,N*-diethylcarbamate derivatives **8**.

*O-3-Fluoro-2-(trimethylsilyl)phenyl N,N-diethylcarbamate (**7a**).* The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (211 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and TMSCN (109 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **7a** as a yellowish liquid (230 mg, 81% yield), R_f= 0.32 (hexane/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.29 (m, 1H), 7.00–6.81 (m, 2H), 3.53–3.39 (m, 4H), 1.32–1.19 (m, 6H), 0.40–0.35 (m, 9H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 167.3 (d, J = 242.3 Hz), 156.8 (d, J = 14.6 Hz), 154.3, 131.1 (d, J = 10.5 Hz), 119.3 (d, J = 31.8 Hz), 118.5 (d, J = 3.3 Hz), 112.1 (d, J = 27.1

Hz), 42.0, 41.7, 14.2, 13.3, 0.5 (d, J = 3.5 Hz). LRMS (EI) *m/z* (%): 283 (M^+, 1), 268 (55), 100 (100), 72 (30). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{23}FNO_2Si$, 284.1477; found, 284.1489.

*O-4-Chloro-2-(trimethylsilyl)phenyl N,N-diethylcarbamate (**7e**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and TMSCN (129 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **7e** as a colorless solid (273 mg, 91% yield): mp 53–55 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, J = 2.6 Hz, 1H), 7.33 (dd, J = 8.6, 2.6 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 3.52–3.37 (m, 4H), 1.29–1.19 (m, 6H), 0.32 (s, 9H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 154.6, 154.0, 134.2, 134.1, 130.4, 130.1, 123.8, 41.6, 41.5, 14.1, 13.2, –1.1. LRMS (EI) *m/z* (%): 301 (M^++2, 1), 299 (M^+, 3), 284 (59), 100 (100), 72 (69). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{23}ClNO_2Si$, 300.1181; found, 300.1187.

*O-2-Chloro-3-fluorophenyl N,N-diethylcarbamate (**8a**).* The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (211 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and Cl_3CCN (159 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **8a** as a yellowish liquid (226 mg, 92% yield), R_f= 0.21 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.21 (m, 1H), 7.14–7.01 (m, 2H), 3.55–3.38 (m, 4H), 1.35–1.22 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 158.9 (d, J = 249.1 Hz), 152.8, 149.2 (d, J = 2.2 Hz), 127.1 (d, J = 9.1 Hz), 119.5 (d, J = 3.4 Hz), 115.6 (d, J = 18.9 Hz), 113.2 (d, J = 21.1 Hz), 42.6, 42.2, 14.1, 13.3. LRMS (EI) *m/z* (%): 247 (M^++2, 1), 245 (M^+, 3), 100 (100), 72 (42). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{14}ClFNO_2$, 246.0692; found, 246.0696.

*O-2,4-Dichlorophenyl N,N-diethylcarbamate (**8e**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and Cl_3CCN (188 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **8e** as a yellowish liquid (233 mg, 89% yield), R_f = 0.20 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 3.50–3.38 (m, 4H), 1.32–1.19 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 152.8, 146.5, 131.0,

129.8, 128.1, 127.7, 125.1, 42.5, 42.1, 14.1, 13.3. LRMS (EI) *m/z* (%): 265 (M^++4, 1), 263 (M^++2, 3), 261 (M^+, 6), 100 (100), 72 (51). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{14}Cl_2NO_2$, 262.0396; found, 262.0397.

General Procedure for the Synthesis of Urea Derivatives 9. A solution of the corresponding carbamate **1** (1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with *s*-BuLi (1.4 M solution in cyclohexane). The reaction mixture was allowed to reach to temp (see Table 1) for 5 min and stirred at this temperature for additional 90 min (30 min for **1b**). Then, the corresponding imine is added and allowed to stir at temp for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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, the residue was purified by silica gel column chromatography and further recrystallized in pentane/CH_2Cl_2 (5:1), affording the 1,1-diethyl-3-((2-hydroxyphenyl)(phenyl)methyl)-3-phenylurea derivatives **9**.

*1,1-Diethyl-3-((2-hydroxyphenyl)(phenyl)methyl)-3-phenylurea (**9ba**)*. The reaction of *O*-phenyl *N,N*-diethylcarbamate (**1b**) (193 mg, 1 mmol), *s*-BuLi (0.86 mL, 1.2 mmol) and *N*-benzylideneaniline (217 mg, 1.2 mmol), following the general procedure (purification by column chromatography in hexane/MeOH/CH_2Cl_2 = 10:2:1), yielded **9ba** as a colorless solid (296 mg, 79% yield): mp 136–138 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.61 (s, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.37–7.30 (m, 1H), 7.17–7.04 (m, 4H), 6.99–6.94 (m, 4H), 6.51–6.46 (m, 2H), 3.48–3.27 (m, 4H), 0.94 (t, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.6, 156.8, 143.6, 140.2, 131.6, 129.2, 129.0, 128.1, 127.8, 126.8, 126.2, 125.8, 123.4, 118.2, 117.6, 62.8, 42.2, 12.3. LRMS (EI) *m/z* (%): 374 (M^+, 1), 257 (100), 181 (36). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_2$, 375.2067; found, 375.2072.

*1-((2-Chloro-6-hydroxyphenyl)(phenyl)methyl)-3,3-diethyl-1-phenylurea (**9ca**)*. The reaction of *O*-3-chlorophenyl *N,N*-diethylcarbamate (**1c**) (228 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and *N*-benzylideneaniline (199 mg, 1.1 mmol), following the general procedure (purification by column

chromatography in hexane/EtOAc = 4:1), yielded **9ca** as a colorless solid (348 mg, 85% yield): mp 149–151 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.82 (s, 1H), 7.38–7.24 (m, 9H), 7.13–7.03 (m, 3H), 6.86 (dd, J = 8.2, 1.2 Hz, 1H), 6.77 (dd, J = 8.2, 1.2 Hz, 1H), 3.33–3.13 (m, 4H), 0.84 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 161.5, 158.3, 143.9, 137.4, 135.5, 129.8, 129.6, 128.6, 127.6, 127.5, 125.3, 124.6, 120.8, 120.3, 117.7, 64.2, 42.0, 12.3. LRMS (EI) *m/z* (%): 410 (M^++2, 2), 408 (M^+, 6), 291 (100), 215 (52). HRMS (ESI/Q-TOF) *m/z*: [M – H]$^-$ calcd for $C_{24}H_{24}ClN_2O_2$, 407.1532; found 407.1537.

1-(4-Bromophenyl)-1-((2-chloro-6-hydroxyphenyl)(phenyl)methyl)-3,3-diethylurea ***(9cb)***. The reaction of *O*-3-chlorophenyl *N,N*-diethylcarbamate (**1c**) (228 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and *N*-(4-bromophenyl)-1-phenylmethanimine (286 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **9cb** as a colorless solid (424 mg, 87% yield): mp 171–173 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.65 (s, 1H), 7.43–7.27 (m, 7H), 7.14–7.07 (m, 3H), 6.99 (s, 1H), 6.89–6.81 (m, 2H), 3.34–3.14 (m, 4H), 0.88 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 160.9, 158.0, 142.9, 136.8, 135.3, 132.61, 132.59, 130.0, 128.6, 127.68, 127.66, 125.1, 120.3, 117.8, 117.7, 63.7, 41.9, 12.3. LRMS (EI) *m/z* (%): 450 (M^++4, 1), 488 (M^++2, 1), 486 (M^+, 3), 415 (18), 215 (100). HRMS (ESI/Q-TOF) *m/z*: [M + H]$^+$ calcd for $C_{24}H_{25}BrClN_2O_2$, 487.0782; found, 487.0787.

1-(4-Bromophenyl)-1-((2-chloro-6-hydroxyphenyl)(p-tolyl)methyl)-3,3-diethylurea ***(9cc)*****.** The reaction of *O*-3-chlorophenyl *N,N*-diethylcarbamate (**1c**) (228 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and *N*-(4-methoxyphenyl)-1-(*p*-tolyl)methanimine (248 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/MeOH/CH_2Cl_2 = 10:2:1), yielded **9cc** as a colorless solid (406 mg, 81% yield): mp 175–177 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.57 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.13–7.03 (m, 7H), 6.91 (s, 1H), 6.84–6.77 (m, 2H), 3.24–3.17 (m, 4H), 2.32 (s, 3H), 0.87 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 161.0, 158.0, 143.0, 137.3, 135.3, 133.8, 132.6, 129.9, 129.4, 127.6, 125.1, 120.6, 120.4, 117.78, 117.75, 63.6, 41.9, 21.2, 12.3.

LRMS (EI) *m/z* (%): 502 (M^++2, 1), 500 (M^+, 3), 429 (17), 215 (100). HRMS (ESI/Q-TOF) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{27}BrClN_2O_2$, 501.0939; found, 501.0934.

*1-((5-Chloro-2-hydroxyphenyl)(phenyl)methyl)-3,3-diethyl-1-phenylurea (**9ea**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and *N*-benzylideneaniline (236 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded the product as a colorless solid (331 mg, 81% yield): mp 151–153 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.75 (s, 1H), 7.51–7.36 (m, 5H), 7.21–7.10 (m, 3H), 7.05–7.01 (m, 1H), 6.95 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 9.1 Hz, 2H), 6.41 (s, 1H), 3.45–3.29 (m, 4H), 0.93 (t, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.6, 155.6, 143.2, 139.5, 131.0, 129.2, 129.1, 128.3, 127.8, 127.1, 126.1, 126.0, 125.3, 122.9, 119.0, 62.4, 42.3, 12.2. LRMS (EI) *m/z* (%): 410 (M^++2, 1), 408 (M^+, 3), 208 (100). HRMS (ESI/Q-TOF) *m/z*: [M + H]$^+$ calcd for $C_{24}H_{26}ClN_2O_2$, 409.1677; found, 409.1681.

*1-((5-Chloro-2-hydroxyphenyl)(p-tolyl)methyl)-1-(3-chloro-5-fluorophenyl)-3,3-diethylurea (**9ed**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and *N*-(3-chloro-5-fluorophenyl)-1-(*p*-tolyl)methanimine (328 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/MeOH/CH_2Cl_2 = 10:2:1), yielded **9ed** as a colorless solid (395 mg, 83% yield): mp 150–152 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.67 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.22–7.17 (m, 3H), 7.11 (dd, J = 8.7, 2.6 Hz, 1H), 7.04–6.94 (m, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.66 (s, 1H), 6.46 (d, J = 2.6 Hz, 1H), 3.32 (q, J = 7.1 Hz, 4H), 2.39 (s, 3H), 0.89 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.0, 158.2 (d, J = 253.8 Hz), 155.8, 137.1, 135.3, 133.4 (d, J = 10.0 Hz), 130.6, 129.8 (d, J = 11.1 Hz), 129.60, 129.56, 129.2, 127.6, 125.2 (d, J = 3.5 Hz), 124.6, 123.2, 119.6, 117.4 (d, J = 24.0 Hz), 62.9, 42.4, 21.1, 12.4. LRMS (EI) *m/z* (%): 476 (M^++2, 1), 474 (M^+, 3), 254 (36), 100 (100). HRMS (ESI/Q-TOF) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{26}Cl_2FN_2O_2$, 475.1350; found, 475.1352.

*1,1-Diethyl-3-((2-hydroxy-3-methoxyphenyl)(phenyl)methyl)-3-phenylurea (**9ia**).* The reaction of *O*-2-methoxyphenyl *N,N*-diethylcarbamate (**1i**) (223 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and

N-benzylideneaniline (236 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/MeOH/CH_2Cl_2 = 10:2:1), yielded **9ia** as a colorless solid (340 mg, 84% yield): mp 145–147 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.49 (d, J = 7.1 Hz, 2H), 7.40–7.30 (m, 3H), 7.16–7.11 (m, 2H), 7.06–6.99 (m, 3H), 6.93 (s, 1H), 6.73 (d, J = 7.7 Hz, 1H), 6.48 (t, J = 7.7 Hz, 1H), 6.23 (d, J = 7.7 Hz, 1H), 3.88 (s, 3H), 3.40–3.25 (m, 4H), 0.90 (t, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.0, 148.2, 145.8, 143.7, 140.1, 128.8, 127.88, 127.86, 126.6, 126.0, 125.3, 124.3, 123.3, 117.6, 110.6, 62.5, 55.7, 41.9, 12.1. LRMS (EI) *m/z* (%): 404 (M^+, 1), 327 (63), 325 (100), 327 (36). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_3$, 405.2173; found, 405.2176.

*1-((3-Chloro-2-fluoro-6-hydroxyphenyl)(phenyl)methyl)-3,3-diethyl-1-phenylurea (**9qa**).* The reaction of *O*-4-chloro-3-fluorophenyl *N,N*-diethylcarbamate (**1q**) (246 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and *N*-benzylideneaniline (199 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/MeOH/CH_2Cl_2 = 10:2:1), yielded **9qa** as a yellowish solid (324 mg, 76% yield): mp 133–135 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.88 (s, 1H), 7.42–7.29 (m, 7H), 7.23–7.14 (m, 4H), 6.83 (s, 1H), 6.75 (dd, J = 8.9, 1.0 Hz, 1H), 3.37–3.17 (m, 4H), 0.86 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 162.0, 156.9 (d, J = 3.8 Hz), 156.8 (d, J = 247.1 Hz), 143.8, 137.6, 130.3 (d, J = 2.1 Hz), 129.7, 128.5, 127.4, 126.8, 126.0, 125.4, 114.8 (d, J = 3.4 Hz), 113.1 (d, J = 12.5 Hz), 110.1 (d, J = 20.6 Hz), 60.0 (d, J = 6.4 Hz), 42.2, 12.2. LRMS (EI) *m/z* (%): 428 (M^++2, 1), 426 (M^+, 3), 233 (100). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{24}H_{23}ClFN_2O_2$, 425.1438; found, 425.1438.

General Procedure for the Synthesis of Benzamide Derivatives 10. A solution of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with *s*-BuLi (0.93 mL, 1.4 M solution in cyclohexane, 1.3 mmol). The reaction mixture was allowed to reach to –70 ºC for 5 min and stirred at this temperature for additional 90 min. Then, the corresponding isocyanate (1.3 mmol) is added and allowed to stir at –70 ºC for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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, the residue was purified by silica gel column chromatography and further recrystallized in hexane/$CHCl_3$ (10:1), affording the *O*-2-(arylcarbamoyl)phenyl *N,N*-diethylcarbamate derivatives **10**.

*O-4-Chloro-2-(phenylcarbamoyl)phenyl N,N-diethylcarbamate (**10ea**)*. The reaction with phenyl isocyanate (155 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **10ea** as a colorless solid (284 mg, 82% yield): mp 76–78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.72–7.67 (m, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.43–7.29 (m, 3H), 7.14 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 3.46–3.34 (m, 4H), 1.20–1.11 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.1, 154.1, 146.7, 137.9, 131.8, 131.3, 131.2, 129.4, 128.8, 124.5, 124.4, 119.8, 42.4, 42.1, 14.0, 13.2. LRMS (EI) *m/z* (%): 348 (M^++2, 1), 346 (M^+, 3), 254 (22), 100 (100), 72 (36). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}ClN_2O_3$, 347.1157; found, 347.1161.

*O-4-Chloro-2-((3-chlorophenyl)carbamoyl)phenyl N,N-diethylcarbamate (**10eb**)*. The reaction with 3-chlorophenyl isocyanate (200 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **10eb** as a colorless solid (301 mg, 79% yield): mp 131–133 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.71–7.66 (m, 2H), 7.46 (dd, J = 8.1, 0.8 Hz, 1H), 7.40 (dd, J = 8.7, 2.6 Hz, 1H), 7.32–7.22 (m, 1H), 7.15–7.10 (m, 1H), 7.07 (d, J = 8.7 Hz, 1H), 3.50–3.39 (m, 4H), 1.25–1.17 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.4, 154.2, 146.8, 139.1, 134.4, 131.5, 131.3, 131.2, 129.8, 129.3, 124.4, 120.0, 118.0, 42.5, 42.2, 14.0, 13.3. LRMS (EI) *m/z* (%): 384 (M^++4, 1), 382 (M^++2, 3), 380 (M^+, 6), 100 (100), 72 (32). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}Cl_2N_2O_3$, 381.0767; found, 381.0770.

*O-2-((3-Bromophenyl)carbamoyl)-4-chlorophenyl N,N-diethylcarbamate (**10ec**)*. The reaction with 3-bromophenyl isocyanate (257 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **10ec** as a colorless solid (324 mg, 76%

yield): mp 91–93 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.80 (d, J = 1.7 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.6, 2.4 Hz, 1H), 7.31–7.16 (m, 2H), 7.06 (d, J = 8.6 Hz, 1H), 3.49–3.38 (m, 4H), 1.24–1.16 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.3, 154.3, 146.7, 139.3, 131.6, 131.4, 131.3, 130.2, 129.4, 127.4, 124.5, 122.8, 122.5, 118.4, 42.6, 42.2, 14.1, 13.4. LRMS (EI) *m/z* (%): 428 (M^++4, 1), 426 (M^++2, 1), 424 (M^+, 3), 254 (10), 100 (100), 72 (31). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}BrClN_2O_3$, 425.0262; found, 425.0283.

*O-4-Chloro-2-((4-methoxyphenyl)carbamoyl)phenyl N,N-diethylcarbamate (**10ed**)*. The reaction with 4-methoxyphenyl isocyanate (194 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **10ed** as a yellowish solid (309 mg, 82% yield): mp 127–129 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.71 (d, J = 2.6 Hz, 1H), 7.53–7.48 (m, 2H), 7.41 (dd, J = 8.7, 2.6 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 6.91–6.86 (m, 2H), 3.82 (s, 3H), 3.48–3.32 (m, 4H), 1.23–1.09 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 162.9, 156.7, 154.6, 146.6, 132.4, 131.8, 131.5, 131.2, 129.8, 124.8, 121.5, 114.3, 55.6, 42.7, 42.3, 14.2, 13.4. LRMS (EI) *m/z* (%): 378 (M^++2, 4), 376 (M^+, 12), 254 (54), 100 (100), 72 (38). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+ - H_2O$ calcd for $C_{19}H_{20}ClN_2O_3$, 359.1157; found, 359.1160.

*O-2-((4-Butylphenyl)carbamoyl)-4-chlorophenyl N,N-diethylcarbamate (**10ee**)*. The reaction with 4-butylphenyl isocyanate (228 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **10ee** as a colorless solid (326 mg, 81% yield): mp 148–150 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.70 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.39 (dt, J = 6.1, 3.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.05 (dd, J = 8.7, 3.1 Hz, 1H), 3.44–3.33 (m, 4H), 2.61–2.55 (m, 2H), 1.63–1.51 (m, 2H), 1.34 (dq, J = 14.3, 7.3 Hz, 2H), 1.20–1.09 (m, 6H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 163.0, 154.3, 146.6, 139.3, 135.5, 132.1, 131.5, 131.4, 129.6, 128.8, 124.6, 119.9, 42.5, 42.2, 35.1, 33.7, 22.3, 14.1, 14.0, 13.2. LRMS (EI) *m/z* (%): 404 (M^++2, 2), 402 (M^+, 6), 285 (15), 254 (39), 100 (100), 72 (27).

*O-4-Chloro-2-(tosylcarbamoyl)phenyl N,N-diethylcarbamate (**10ef**)*. The reaction with *p*-toluenesulfonyl isocyanate (355 mg, 1.3 mmol), following the general procedure (purification by

column chromatography in hexane/EtOAc = 4:1), yielded **10ef** as a colorless solid (365 mg, 86% yield): mp 164–166 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (bs, 1H), 8.01–7.91 (m, 2H), 7.63 (d, J = 2.6 Hz, 1H), 7.43 (dd, J = 8.7, 2.7 Hz, 1H), 7.36–7.29 (m, 2H), 7.04 (d, J = 8.7 Hz, 1H), 3.48 (q, J = 7.1 Hz, 2H), 3.40 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 2H). ^{13}C{^{1}H} NMR (75.4 MHz, dmso-d_6): δ 163.0, 152.3, 148.0, 144.2, 136.6, 132.2, 129.4, 129.1, 128.9, 127.9, 125.4, 41.7, 41.4, 21.1, 13.8, 13.1, an aromatic C signal does not appear due to overlapping. LRMS (EI/QQQ) *m/z* (%): 426 (M^++2, 1), 424 (M^+, 3), 308 (33), 154 (100), 126 (36), 100 (100), 72 (36). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{22}ClN_2O_5S$, 425.0932; found, 425.0935.

General Procedure for the Synthesis of Benzothioamide Derivatives 11. A solution of the corresponding carbamate **1** (1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with *s*-BuLi (1.4 M solution in cyclohexane). The reaction mixture was allowed to reach to temp (see Table 2) for 5 min and stirred at this temperature for additional 90 min (30 min for **1b**). Then, the corresponding isothiocyanate is added and allowed to stir at temp for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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, the residue was purified by silica gel column chromatography and further recrystallized in hexane/$CHCl_3$ (10:1), affording the 2-(arylcarbamothioyl)phenyl *N,N*-diethylcarbamate derivatives **11**.

*O-2-(Phenylcarbamothioyl)phenyl N,N-diethylcarbamate (**11ba**)*. The reaction of *O*-phenyl *N,N*-diethylcarbamate (**1b**) (193 mg, 1 mmol), *s*-BuLi (0.86 mL, 1.2 mmol) and phenyl isothiocyanate (162 mg, 1.2 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ba** as a yellow solid (282 mg, 86% yield): mp 110–112 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.95 (d, J = 7.8 Hz, 2H), 7.75 (dd, J = 7.7, 1.6 Hz, 1H), 7.45–7.40 (m, 3H), 7.35–7.27 (m, 2H), 7.07 (dd, J = 8.0, 0.8 Hz, 1H), 3.45–3.31 (m, 4H), 1.17 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 194.4, 155.8, 145.2, 139.2, 139.0,

130.8, 130.6, 128.9, 126.6, 126.4, 123.1, 122.2, 42.5, 42.3, 14.1, 13.2. LRMS (EI) *m/z* (%): 328 (M^+, 30), 196 (100), 100 (50), 72 (34). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2S$, 329.1318; found, 329.1323.

*O-3-Chloro-2-((2-fluorophenyl)carbamothioyl)phenyl N,N-diethylcarbamate (**11cb**).* The reaction of *O*-3-chlorophenyl *N,N*-diethylcarbamate (**1c**) (228 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and 2-fluorophenyl isothiocyanate (227 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11cb** as a yellowish solid (316 mg, 83% yield): mp 119–121 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.04 (s, 1H), 7.58 (t, J = 7.1 Hz, 1H), 7.45–7.30 (m, 6H), 3.40–3.30 (m, 4H), 1.17–1.10 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 193.2, 156.1 (d, J = 249.7 Hz), 152.4, 147.6, 135.6, 129.3, 129.2, 128.1, 126.22 (d, J = 12.6 Hz), 126.18 (d, J = 23.0 Hz), 126.0, 124.5, 122.5, 116.4 (d, J = 19.3 Hz), 41.7, 41.5, 14.1, 13.1. LRMS (EI) *m/z* (%): 382 (M^++2, 1), 380 (M^+, 3), 100 (100), 72 (39). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}ClFN_2O_2S$, 381.0834; found, 381.0838.

*O-4-Chloro-2-(phenylcarbamothioyl)phenyl N,N-diethylcarbamate (**11ea**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and phenyl isothiocyanate (176 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ea** as a yellow solid (312 mg, 86% yield): mp 140–142 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.91 (d, J = 7.7 Hz, 2H), 7.72 (d, J = 2.5 Hz, 1H), 7.48–7.26 (m, 4H), 7.02 (d, J = 8.6 Hz, 1H), 3.44–3.31 (m, 4H), 1.17 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 192.4, 155.2, 143.8, 139.9, 138.8, 131.5, 130.4, 129.8, 128.8, 126.8, 124.5, 122.3, 42.5, 42.2, 14.0, 13.1. LRMS (EI) *m/z* (%): 364 (M^++2, 8), 366 (M^+, 22), 230 (73), 100 (100), 72 (53). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}ClN_2O_2S$, 363.0929; found, 363.0934.

*O-4-Chloro-2-((2-fluorophenyl)carbamothioyl)phenyl N,N-diethylcarbamate (**11eb**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and 2-fluorophenyl isothiocyanate (269 mg, 1.3 mmol), following the general procedure (purification by

column chromatography in hexane/EtOAc = 4:1), yielded **11eb** as a yellow solid (305 mg, 80% yield): mp 130–132 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.33 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.40–7.15 (m, 4H), 7.03 (d, J = 8.6 Hz, 1H), 3.47–3.31 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 193.7, 154.24 (d, J = 249.3 Hz), 154.17, 143.3, 138.2, 130.6, 129.8, 129.2, 127.4 (d, J = 7.6 Hz), 125.7 (d, J = 10.9 Hz), 124.6, 123.7, 123.2, 114.9 (d, J = 19.4 Hz), 41.6, 41.3, 13.1, 12.0. LRMS (EI) *m/z* (%): 382 (M^++2, 1), 380 (M^+, 3), 273 (9), 100 (100), 72 (34). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}ClFN_2O_2S$, 381.0834; found, 381.0836.

*O-4-Chloro-2-((3-chlorophenyl)carbamothioyl)phenyl N,N-diethylcarbamate (**11ec**)*. The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and 3-chlorophenyl isothiocyanate (221 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ec** as a yellow solid (334 mg, 84% yield): mp 148–150 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.05 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.44–7.27 (m, 3H), 7.02 (d, J = 8.6 Hz, 1H), 3.45–3.34 (m, 4H), 1.24–1.07 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 193.0, 155.6, 143.8, 140.0, 139.9, 134.6, 131.9, 130.8, 130.2, 130.0, 126.9, 124.6, 122.2, 120.4, 42.6, 42.3, 14.1, 13.3. LRMS (EI) *m/z* (%): 400 (M^++4, 1), 398 (M^++2, 1), 396 (M^+, 3), 207 (58), 100 (100), 72 (29). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}Cl_2N_2O_2S$, 397.0539; found, 397.0539.

*O-2-((4-Bromophenyl)carbamothioyl)-4-chlorophenyl N,N-diethylcarbamate (**11ed**)*. The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and 4-bromophenyl isothiocyanate (278 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ed** as a yellow solid (349 mg, 79% yield): mp 150–152 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 2.5 Hz, 1H), 7.57–7.52 (m, 2H), 7.38 (dd, J = 8.6, 2.5 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 3.44–3.31 (m, 4H), 1.19–1.07 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 192.6, 155.4, 143.8, 139.8, 137.9, 131.9, 131.7, 130.7, 130.0, 124.5, 123.7, 119.5, 42.6, 42.3, 14.1, 13.3. LRMS (EI) *m/z* (%): 402

(M^++2, 1), 400 (M^+, 1), 281 (30), 207 (100), 100 (74), 72 (19). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}BrClN_2O_2S$, 441.0034; found, 441.0034.

*O-4-Chloro-2-((3,4-dimethoxyphenyl)carbamothioyl)phenyl N,N-diethyl carbamate (**11ee**)*. The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and 3,4-dimethoxyphenyl isothiocyanate (254 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ee** as a yellow solid (338 mg, 80% yield): mp 133–135 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.88 (s, 1H), 7.71 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 3.92 (s, 6H), 3.46–3.31 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 191.2, 155.3, 148.6, 147.4, 143.8, 139.9, 132.4, 131.6, 130.4, 129.9, 124.5, 114.6, 110.7, 106.3, 56.0, 42.5, 42.2, 14.1, 13.2. LRMS (EI) *m/z* (%): 424 (M^++2, 1), 422 (M^+, 3), 406 (20), 254 (60), 207 (85), 100 (100), 72 (36). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{24}ClN_2O_4S$, 423.1140; found, 423.1145.

*O-4-Chloro-2-(isopropylcarbamothioyl)phenyl N,N-diethylcarbamate (**11ef**)*. The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and isopropyl isothiocyanate (132 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ef** as a yellow solid (296 mg, 90% yield): mp 130–132 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.33 (dd, J = 8.6, 2.6 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 4.78–4.65 (m, 1H), 3.49–3.37 (m, 4H), 1.31–1.21 (m, 12H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 192.8, 155.5, 143.9, 139.2, 131.6, 130.3, 130.0, 124.5, 47.7, 42.5, 42.2, 21.0, 14.2, 13.4. LRMS (EI) *m/z* (%): 330 (M^++2, 14), 328 (M^+, 41), 100 (100), 72 (41). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{22}ClN_2O_2S$, 329.1085; found, 329.1092.

*O-4-Methoxy-2-(phenylcarbamothioyl)phenyl N,N-diethylcarbamate (**11ha**)*. The reaction of *O*-4-methoxyphenyl *N,N*-diethylcarbamate (**1h**) (223 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and phenyl isothiocyanate (176 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ha** as a yellow solid (305 mg, 85% yield): mp

118–120 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.11 (s, 1H), 7.94 (dd, J = 8.5, 0.9 Hz, 2H), 7.44–7.39 (m, 2H), 7.29–7.25 (m, 2H), 6.96 (t, J = 1.7 Hz, 2H), 3.85 (s, 3H), 3.43–3.30 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 194.2, 157.5, 156.3, 139.6, 139.2, 138.6, 128.9, 126.7, 124.1, 122.2, 117.3, 114.6, 55.9, 42.5, 42.2, 14.1, 13.2. LRMS (EI) *m/z* (%): 358 (M^+, 28), 226 (85), 225 (100), 100 (52), 72 (35). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_3S$, 359.1424; found, 359.1431.

*O-2-Methoxy-6-(phenylcarbamothioyl)phenyl N,N-diethylcarbamate (**11ia**).* The reaction of *O*-2-methoxyphenyl *N,N*-diethylcarbamate (**1i**) (223 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and phenyl isothiocyanate (176 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ia** as a yellow solid (301 mg, 84% yield): mp 116–118 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.23 (s, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.44–7.35 (m, 3H), 7.29–7.22 (m, 2H), 6.99 (dd, J = 8.2, 1.2 Hz, 1H), 3.87 (s, 3H), 3.47–3.39 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 194.0, 156.0, 151.9, 140.2, 139.4, 134.8, 128.9, 126.6, 126.5, 122.2, 122.2, 113.0, 56.3, 42.5, 42.4, 13.8, 13.2. LRMS (EI/QQQ) *m/z* (%): 358 (M^+, 24), 226 (100), 100 (41), 72 (30). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_3S$, 359.1424; found, 359.1430.

*O-1-(Phenylcarbamothioyl)naphthalen-2-yl N,N-diethylcarbamate (**11ka**).* The reaction of *O*-1-bromonaphthalen-2-yl *N,N*-diethylcarbamate (**1k**) (322 mg, 1 mmol), *n*-BuLi (0.44 mL of a 2.5 M solution in hexane, 1.1 mmol) and phenyl isothiocyanate (149 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11ka** as a yellowish solid (307 mg, 81% yield): mp 102–104 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.23 (dd, J = 8.2, 1.3 Hz, 1H), 8.06–7.94 (m, 2H), 7.94–7.83 (m, 2H), 7.64–7.40 (m, 4H), 7.34–7.30 (m, 1H), 7.26 (d, J = 8.9 Hz, 1H), 3.53–3.38 (m, 2H), 3.34 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 193.0, 152.8, 143.0, 139.4, 132.6, 130.7, 129.7, 128.6, 128.5, 127.9, 127.1, 126.4, 125.7, 124.6, 123.0, 122.7, 41.7, 41.6, 14.1, 13.2. LRMS (EI)

m/z (%): 378 (M^+, 12), 246 (100), 207 (20), 100 (24), 72 (20). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_2S$, 379.1475; found, 379.1481.

*O-3-Chloro-4-fluoro-2-(phenylcarbamothioyl)phenyl N,N-diethylcarbamate (**11la**).* The reaction of *O*-3-chloro-4-fluorophenyl *N,N*-diethylcarbamate (**1s**) (246 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and phenyl isothiocyanate (149 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **11la** as a yellow solid (393 mg, 77% yield): mp 133–135 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.26 (s, 1H), 7.94–7.91 (m, 2H), 7.50–7.43 (m, 3H), 7.37–7.27 (m, 2H), 3.31–3.20 (m, 4H), 1.07–0.98 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 188.4, 154.6 (d, J = 244.8 Hz), 152.4, 143.1 (d, J = 3.0 Hz), 139.0, 137.4, 128.7, 126.6, 123.7 (d, J = 7.9 Hz), 122.6, 116.3 (d, J = 20.3 Hz), 115.5 (d, J = 23.0 Hz), 41.8, 41.6, 14.0, 13.0. LRMS (EI) *m/z* (%): 382 (M^++2, 9), 380 (M^+, 27), 248 (100), 100 (98), 72 (50). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}ClFN_2O_2S$, 381.0834; found, 381.0834.

General Procedure for the Synthesis of *o*-Hydroxybenzimidamide Derivatives 12 and *O*-2-*N,N′*-Diarylcarbamimidoyl Carbamates 13. A solution of the corresponding carbamate **1** (1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with *s*-BuLi (1.4 M solution in cyclohexane). The reaction mixture was allowed to reach to temp (see Table 3) for 5 min and stirred at this temperature for additional 90 min (30 min for **1b**). Then, the corresponding carbodiimide is added and allowed to stir at temp for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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 silica gel column chromatography, and recrystallization in some cases, affording the (*E*)-*N*-(diethylcarbamoyl)-2-hydroxy-*N,N′*-dialkylbenzimidamide derivatives **12** or (*E*)-2-(*N,N′*-diarylcarbamimidoyl)phenyl diethylcarbamates **13**. In some cases, the signals of ^{1}H and ^{13}C NMR appear poorly resolved, or do not appear, due to restricted rotation of the molecules. The structures have been confirmed by X-ray analysis.

O-(E)-N,N′-Dicyclohexyl-N-(diethylcarbamoyl)-2-fluoro-6-hydroxybenzimidamide ***(12aa)***. The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (211 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and *N,N′*-dicyclohexylcarbodiimide (227 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12aa**, after recrystallization in hexane/Et_2O (10:1), as a colorless solid (330 mg, 79% yield): mp 121–123 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.29 (s, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.91 (dd, J = 19.7, 8.0 Hz, 2H), 3.57–2.89 (m, 4H), 2.64–2.53 (m, 2H), 2.16–0.61 (m, 26H). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 156.9, 156.0, 151.6 (d, J = 246.2 Hz), 132.0, 130.6, 119.6 (d, J = 12.9 Hz), 114.3, 58.2, 56.6, 39.8, 34.7, 25.9, 25.5, 25.1, 24.1, 12.9. LRMS (EI) *m/z* (%): 417 (M^+, 1), 398 (100), 317 (36), 100 (43), 72 (23). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{37}FN_3O_2$, 418.2864; found, 418.2866.

O-(E)-N-(Diethylcarbamoyl)-2-hydroxy-N,N′-diisopropylbenzimidamide ***(12bb)***. The reaction of *O*-phenyl *N,N*-diethylcarbamate (**1b**) (193 mg, 1 mmol), *s*-BuLi (0.84 mL, 1.2 mmol) and *N,N′*-diisopropylcarbodiimide (151 mg, 1.2 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12bb** as a colorless solid (281 mg, 88% yield): mp 18–20 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.00 (s, 1H), 7.53 (dd, J = 8.0, 1.6 Hz, 1H), 7.30 (ddd, J = 8.3, 1.6, 0.8 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 4.05–3.97 (m, 1H), 3.77–3.68 (m, 1H), 3.20–3.06 (m, 4H), 1.44 (d, J = 6.8 Hz, 6H), 1.28–1.23 (m, 6H), 1.00 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 162.7, 159.3, 158.3, 132.6, 128.6, 118.2, 117.9, 117.0, 53.1, 49.1, 41.8, 24.9, 22.9, 20.8, 20.0, 12.8. LRMS (EI) *m/z* (%): 319 (M^+, 38), 318 (53), 220 (62), 203 (100), 120 (49), 100 (82), 72 (40). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{18}H_{28}N_3O_2$, 318.2187; found, 318.2193.

O-(E)-2-Chloro-N-(diethylcarbamoyl)-6-hydroxy-N,N′-diisopropylbenzimidamide ***(12cb)***. The reaction of *O*-3-chlorophenyl *N,N*-diethylcarbamate (**1c**) (228 mg, 1 mmol), *s*-BuLi (0.78 mL, 1.1 mmol) and *N,N′*-diisopropylcarbodiimide (139 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12cb** as a colorless oil (294 mg, 83% yield), R_f = 0.23 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.35 (s, 1H), 7.19

(t, *J* = 8.1 Hz, 1H), 6.89 (dd, *J* = 16.6, 8.1 Hz, 2H), 3.68–3.15 (m, 4H), 3.09–2.86 (m, 1H), 2.53–2.50 (m, 1H), 1.28–0.77 (m, 18H). $^{13}C\{^1H\}$ NMR (75.4 MHz, DMSO-d_6): δ 156.8, 156.1, 150.0, 131.9, 130.6, 119.6, 119.5, 114.4, 50.2, 48.1, 40.1, 24.9, 21.4, 12.9. LRMS (EI) *m/z* (%): 355 (M^++2, 2), 353 (M^+, 6), 318 (100), 237 (36), 154 (35), 100 (67), 72 (27). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{29}ClN_3O_2$, 354.1943; found, 354.1941.

O-(E)-5-Chloro-N,N′-dicyclohexyl-N-(diethylcarbamoyl)-2-hydroxybenzimidamide ***(12ea)***. The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and *N,N′*-dicyclohexylcarbodiimide (268 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12ea** as a yellow oil (339 mg, 78% yield), R_f = 0.32 (hexane/EtOAc, 10:1). ^1H NMR (300 MHz, $CDCl_3$): δ 15.19 (s, 1H), 7.54 (d, *J* = 2.6 Hz, 1H), 7.27 (dd, *J* = 8.8, *J* = 2.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.81–3.65 (m, 1H), 3.40–2.98 (m, 5H), 2.19 (s, 2H), 1.88–1.14 (m, 18H), 1.01 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 161.6, 159.3, 158.1, 132.6, 128.1, 122.4, 119.9, 118.4, 62.0, 57.1, 42.2, 26.7, 25.7, 25.5, 24.2, 12.8. LRMS (EI) *m/z* (%): 435 (M^++2, 5), 433 (M^+, 15), 317 (100), 207 (82), 100 (78), 72 (38). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{37}ClN_3O_2$, 434.2569; found, 434.2575.

O-(E)-N-(Diethylcarbamoyl)-2-hydroxy-N,N′-diisopropyl-5-methoxybenzimidamide ***(12hb)***. The reaction of *O*-4-methoxyphenyl *N,N*-diethylcarbamate (**1h**) (223 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.1 mmol) and *N,N′*-diisopropylcarbodiimide (164 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12hb** as a yellowish oil (266 mg, 76% yield), R_f= 0.18 (hexane/EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ 14.30 (s, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 6.94–6.88 (m, 2H), 3.99 (dt, *J* = 12.1, 6.1 Hz, 1H), 3.78–3.70 (m, 4H), 3.14 (d, *J* = 9.6 Hz, 4H), 1.45 (d, *J* = 6.8 Hz, 6H), 1.24 (s, 6H), 1.01 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 159.5, 157.9, 156.9, 151.5, 120.4, 119.1, 116.9, 111.8, 55.9, 53.1, 49.4, 41.9, 25.0, 23.1, 21.0, 20.3, 13.1. LRMS (EI) *m/z* (%): 349 (M^+, 43), 348 (46), 233 (100), 100 (62), 72 (28). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{32}N_3O_3$, 350.2438; found, 350.2444.

O-(E)-N-(Diethylcarbamoyl)-2-hydroxy-N,N′-diisopropyl-3-methoxybenzimidamide ***(12ib)***. The reaction of *O*-2-methoxyphenyl *N,N*-diethylcarbamate (**1i**) (223 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.1 mmol) and *N,N′*-diisopropylcarbodiimide (164 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12ib** as a yellowish oil (273 mg, 78% yield), R_f= 0.16 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.54 (s, 1H), 6.90 (dd, J = 8.2, 1.3 Hz, 1H), 6.66 (dd, J = 8.2, 1.1 Hz, 1H), 6.49 (t, J = 8.2 Hz, 1H), 3.81–3.76 (m, 1H), 3.63 (s, J = 4.3 Hz, 3H), 3.56–3.46 (m, 1H), 3.03–2.76 (m, 4H), 1.20 (t, J = 7.1 Hz, 6H), 1.01–0.93 (m, 6H), 0.75 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 158.93, 158.86, 153.7, 149.3, 119.8, 116.32, 116.29, 113.3, 60.0, 55.7, 53.0, 48.6, 41.5, 24.4, 20.7, 12.5. LRMS (EI) *m/z* (%): 349 (M^+, 26), 348 (27), 233 (100), 150 (32), 100 (52), 72 (35). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{32}N_3O_3$, 350.2438; found, 350.2444.

O-(E)-N-(Diethylcarbamoyl)-2-hydroxy-N,N′-diisopropyl-3-methylbenzimidamide ***(12ub)***. The reaction of *O*-2-methylphenyl *N,N*-diethylcarbamate (**1u**) (207 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.1 mmol) and *N,N′*-diisopropylcarbodiimide (164 mg, 1.1 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **12ub** as a yellowish oil (257 mg, 77% yield), R_f= 0.26 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 15.38 (s, 1H), 7.43–7.37 (m, 1H), 7.22–7.18 (m, 1H), 6.74 (t, J = 7.7 Hz, 1H), 4.02 (dt, J = 12.1, 6.1 Hz, 1H), 3.74 (dt, J = 12.1, 6.1 Hz, 1H), 3.21–3.09 (m, 4H), 2.29 (s, 3H), 1.45 (d, J = 6.7 Hz, 6H), 1.31–1.21 (m, 6H), 1.02 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 161.3, 159.5, 158.7, 133.5, 127.1, 126.4, 117.2, 116.2, 53.3, 49.1, 41.9, 25.1, 23.0, 20.9, 20.1, 16.1, 13.0. LRMS (EI) *m/z* (%): 333 (M^+, 26), 332 (28), 233 (56), 217 (100), 134 (44), 100 (69), 72 (37). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{32}N_3O_2$, 333.2489; found, 333.2496.

O-(E)-2-(N,N′-Di-p-tolylcarbamimidoyl)phenyl N,N-diethylcarbamate ***(13bc)***. The reaction of *O*-phenyl *N,N*-diethylcarbamate (**1b**) (193 mg, 1 mmol), *s*-BuLi (0.84 mL, 1.2 mmol) and bis(4-methylphenyl)carbodiimide (267 mg, 1.2 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **13bc** after recrystallization in DMSO as a

colorless solid (337 mg, 81% yield): mp 137–139 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–6.46 (m, 12H), 3.46–3.31 (m, 4H), 2.28 (s, 6H), 1.20–1.07 (m, 6H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 154.9, 151.4, 149.0, 131.5, 130.2, 129.7, 129.1, 125.8, 123.4, 42.4, 42.1, 20.9, 14.0, 13.3. LRMS (EI) *m/z* (%): 415 (M^+, 27), 310 (28), 309 (100), 100 (26), 72 (16). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{30}N_3O_2$, 416.2333; found, 416.2341.

*O-(E)-4-Chloro-2-(N,N'-di-p-tolylcarbamimidoyl)phenyl N,N-diethylcarbamate (**13ec**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (228 mg, 1 mmol), *s*-BuLi (0.93 mL, 1.3 mmol) and bis(4-methylphenyl)carbodiimide (289 mg, 1.3 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 4:1), yielded **13ec** as a colorless solid (396 mg, 88% yield): mp 143–145 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–6.78 (m, 11H), 3.41–3.31 (m, 4H), 2.28 (s, 6H), 1.18–1.06 (m, 6H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 154.5, 150.0, 147.5, 132.0, 131.1, 130.3, 129.9, 129.3, 124.8, 120.8, 42.5, 42.2, 20.9, 14.1, 13.3. LRMS (EI) *m/z* (%): 451 (M^++2, 7), 449 (M^+, 21), 345 (33), 343 (100), 100 (38), 72 (20). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{29}ClN_3O_2$, 450.1943; found, 450.1949.

General Procedure for the Synthesis of *O*-2-(α-Amidobenzyl)phenyl Carbamate Derivative 14. A solution of the carbamate **1e** (228 mg, 1 mmol) in THF (2 mL) at –78 ºC under nitrogen, was treated with s-BuLi (0.93 mL of a 1.4 M solution in cyclohexene, 1.3 mmol). The reaction mixture was allowed to reach to –70 ºC for 5 min and stirred at this temperature for additional 90 min. Then, *N*-benzylidene-4-methyl benzenesulfonamide (337 mg, 1.3 mmol) is added and allowed to stir at –70 ºC for 60 min. The reaction mixture was allowed to warm to rt and stirred for 16 h. 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, the residue was purified by silica gel column chromatography in hexane/EtOAc (5:1) and further recrystallized in pentane/CH_2Cl_2 (5:1), affording the *N,N*-diethylcarbamate **14**.

O-4-Chloro-2-(((4-methylphenyl)sulfonamido)(phenyl)methyl)phenyl N,N-diethylcarbamate ***(14)***. Colorless solid (404 mg, 83% yield): mp 136–138 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 8.3 Hz, 2H), 7.25–7.20 (m, 3H), 7.17–7.12 (m, 5H), 6.95 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 5.86 (d, J = 8.1 Hz, 1H), 5.69 (d, J = 8.1 Hz, 1H), 3.38–3.17 (m, 2H), 3.12–2.99 (m, 2H), 2.39 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 153.4, 147.4, 143.3, 139.1, 137.4, 133.7, 130.5, 129.4, 129.2, 128.5, 128.4, 127.6, 127.1, 127.0, 124.7, 56.9, 42.3, 41.7, 21.5, 14.0, 13.2. LRMS (EI) *m/z* (%): 488 (M^++2, 1), 486 (M^+, 3), 331 (36), 100 (100), 72 (25). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}ClN_2O_4S$, 487.1453; found, 487.1453.

General Procedure for the Synthesis of Urea Derivatives 15. After following the general procedure for the synthesis of **3** but starting from the corresponding carbamate **1** (0.2 mmol), the residue was dissolved in MeOH (3 mL) and treated with $NaBH_4$ (11.3 mg, 0.3 mmol). The reaction mixture was stirred at rt for 16 h. The resulting solution was quenched with H_2O (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography affording the corresponding 1,1-diethyl-3-(2-hydroxybenzyl)ureas **15**.

3-((4-Chlorophenyl)(2-fluoro-6-hydroxyphenyl)methyl)-1,1-diethylurea ***(15aa)***. The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (42.2 mg, 0.2 mmol), *s*-BuLi (0.16 mL, 0.22 mmol) and 4-chlorobenzonitrile (30.3 mg, 0.22 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **15aa** as a colorless solid (54 mg, 77% yield): mp 157–159 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.52 (bs, 1H), 7.33 (dd, J = 6.4, 4.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.12 (dd, J = 15.2, 8.2 Hz, 1H), 6.70–6.63 (m, 3H), 6.43 (d, J = 9.1 Hz, 1H), 3.26–3.18 (m, 4H), 1.04 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 160.2 (d, J = 241.5 Hz), 156.4 (d, J = 7.5 Hz), 155.8, 141.9, 131.1, 129.1 (d, J = 11.0 Hz), 128.1, 127.8, 115.9 (d, J = 17.0 Hz), 112.2, 106.2 (d, J = 23.2 Hz), 47.7 (d, J = 5.1 Hz), 40.6, 13.9. LRMS (EI) *m/z* (%): 352 (M^++2,

1), 350 (M^+, 3), 233 (20), 199 (100). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}ClFN_2O_2$, 351.1270; found, 351.1267.

*3-((2-Bromophenyl)(2-fluoro-6-hydroxyphenyl)methyl)-1,1-diethylurea (**15af**)*. The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (42.2 mg, 0.2 mmol), *s*-BuLi (0.16 mL, 0.22 mmol) and 2-bromobenzonitrile (40 mg, 0.22 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **15af** as a colorless solid (59 mg, 76% yield): mp 138–140 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.29 (s, 1H), 7.57–7.50 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.14 (dt, J = 15.1, 7.7 Hz, 2H), 6.69 (d, J = 8.1 Hz, 1H), 6.62–6.48 (m, 3H), 3.23 (q, J = 6.9 Hz, 4H), 1.04 (t, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 161.5 (d, J = 244.3 Hz), 157.4 (d, J = 7.8 Hz), 156.1, 141.8, 133.1, 129.9, 129.5 (d, J = 11.2 Hz), 129.0, 127.5, 123.1, 115.4 (d, J = 15.1 Hz), 112.2, 106.6 (d, J = 23.0 Hz), 49.7 (d, J = 3.3 Hz), 40.8, 14.3. LRMS (EI) *m/z* (%): 396 (M^++2, 1), 394 (M^+, 3), 240 (100). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}BrFN_2O_2$, 395.0765; found, 395.0763.

*3-((4-Chlorophenyl)(2-fluoro-6-hydroxyphenyl)methyl)-1,1-diethylurea (**15gk**)*. The reaction of *O*-2-chlorophenyl *N,N*-diethylcarbamate (**1g**) (45.5 mg, 0.2 mmol), *s*-BuLi (0.18 mL, 0.26 mmol) and 2-fluorobenzonitrile (31.5 mg, 0.26 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **15gk** as a colorless solid (56 mg, 80% yield): mp 172–174 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (bs, 1H), 7.40–7.25 (m, 3H), 7.22–7.15 (m, 2H), 6.82 (dt, J = 7.8, 1.7 Hz, 1H), 6.70 (t, J = 7.8 Hz, 1H), 6.51 (d, J = 9.2 Hz, 1H), 5.85 (dd, J = 9.1, 5.5 Hz, 1H), 3.40–3.24 (m, 4H), 1.17 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 160.8 (d, J = 243.7 Hz), 157.8, 151.3, 129.7, 129.54 (d, J = 13.1 Hz), 129.52, 129.46, 127.3 (d, J = 12.5 Hz), 126.7 (d, J = 2.0 Hz), 124.8 (d, J = 3.2 Hz), 122.4, 120.0, 116.3 (d, J = 22.5 Hz), 51.4, 41.7, 13.7. LRMS (EI) *m/z* (%): 352 (M^++2, 1), 350 (M^+, 3), 229 (31), 157 (100), 58 (37). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}ClFN_2O_2$, 351.1270; found, 351.1269.

General Procedure for the Synthesis of 2-Hydroxybenzophenones 16. After following the general procedure for the synthesis of **3** but starting from the corresponding carbamate **1** (0.5 mmol),

the reaction mixture was treated with HCl (3 M, 4 mL) and stirred for 16 h, instead of 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 affording the corresponding 2-hydroxybenzophenones **16**.

*(4-Chlorophenyl)(2-fluoro-6-hydroxyphenyl)methanone (**16aa**)*. The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (106 mg, 0.5 mmol), *s*-BuLi (0.39 mL, 0.55 mmol) and 4-chlorobenzonitrile (76 mg, 0.55 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16aa** as a yellow solid (107 mg, 85% yield): mp 78–80 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.98 (s, 1H), 7.71–7.66 (m, 2H), 7.51–7.44 (m, 3H), 6.92 (d, J = 8.5 Hz, 1H), 6.69–6.62 (m, 1H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 196.6, 162.4 (d, J = 3.9 Hz), 161.5 (d, J = 255.7 Hz), 139.2, 137.9 (d, J = 2.9 Hz), 136.2 (d, J = 11.8 Hz), 130.2, 130.1, 128.5, 114.1 (d, J = 3.2 Hz), 110.3 (d, J = 14.7 Hz), 106.7 (d, J = 23.0 Hz). LRMS (EI) *m/z* (%): 252 (M^++2, 18), 250 (M^+, 69), 249 (100), 215 (95), 139 (99), 111 (44). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{13}H_7ClFO_2$, 249.0124; found 249.0130.

*(2-Fluoro-6-hydroxyphenyl)(4-(methylthio)phenyl)methanone (**16ad**)*. The reaction of *O*-3-fluorophenyl *N,N*-diethylcarbamate (**1a**) (106 mg, 0.5 mmol), *s*-BuLi (0.39 mL, 0.55 mmol) and 4-(methylthio)benzonitrile (82 mg, 0.55 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16ad** as a yellow solid (109 mg, 83% yield): mp 55–57 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.87 (s, 1H), 7.71–7.67 (m, 2H), 7.49–7.42 (m, 1H), 7.33–7.29 (m, 2H), 6.91 (d, J = 8.4 Hz, 1H), 6.69–6.63 (m, 1H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 196.5, 162.1 (d, J = 4.1 Hz), 161.4 (d, J = 255.1 Hz), 146.2, 135.7 (d, J = 11.6 Hz), 135.4 (d, J = 2.9 Hz), 129.6, 129.5, 124.6, 114.0 (d, J = 3.3 Hz), 110.7 (d, J = 15.2 Hz), 106.8 (d, J = 23.2 Hz), 14.8. LRMS (EI) *m/z* (%): 262 (M^+, 100), 215 (87), 151 (50), 124 (72). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{12}FO_2S$, 263.0537; found, 263.0541.

*(5-Chloro-2-hydroxyphenyl)(4-ethoxyphenyl)methanone (**16ej**).* The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (114 mg, 0.5 mmol), *s*-BuLi (0.46 mL, 0.65 mmol) and 4-ethoxybenzonitrile (96 mg, 0.65 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16ej** as a yellow solid (122 mg, 88% yield): mp 92–94 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.87 (s, 1H), 7.76–7.71 (m, 2H), 7.64–7.63 (m, 1H), 7.48–7.44 (m, 1H), 7.06–7.01 (m, 3H), 4.17 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 198.8, 162.8, 161.4, 135.6, 132.5, 131.9, 129.4, 123.2, 120.1, 120.0, 114.4, 63.9, 14.7. LRMS (EI) *m/z* (%): 278 (M^++2, 18), 276 (M^+, 70), 122 (100), 94 (44). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{15}H_{12}ClO_3$, 275.0480; found, 275.0490.

*(5-Chloro-2-hydroxyphenyl)(2-fluorophenyl)methanone (**16ek**).*[36] The reaction of *O*-4-chlorophenyl *N,N*-diethylcarbamate (**1e**) (114 mg, 0.5 mmol), *s*-BuLi (0.46 mL, 0.65 mmol) and 2-fluorobenzonitrile (79 mg, 0.65 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16ek** as a yellow solid (104 mg, 83% yield): mp 76–78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$: δ 11.90 (s, 1H), 7.63–7.55 (m, 1H), 7.52–7.44 (m, 2H), 7.40–7.20 (m, 3H), 7.04 (d, J = 8.9 Hz, 1H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 197.8, 161.6, 159.2 (d, J = 252.1 Hz), 137.0, 133.5 (d, J = 8.2 Hz), 132.2 (d, J = 2.5 Hz), 130.0 (d, J = 2.7 Hz), 125.7 (d, J = 15.5 Hz), 124.7 (d, J = 3.6 Hz), 123.9, 120.4, 120.1, 116.6 (d, J = 21.3 Hz). LRMS (EI) *m/z* (%): 252 (M^++2, 33), 250 (M^+, 100), 231 (41), 155 (47), 154 (61), 123 (162), 95 (39). HRMS (ESI) could not be recorded.

*(4-Chlorophenyl)(5-fluoro-2-hydroxyphenyl)methanone (**16fa**).*[39] The reaction of *O*-4-fluorophenyl *N,N*-diethylcarbamate (**1f**) (105.61 mg, 0.5 mmol), *s*-BuLi (0.46 mL, 0.65 mmol) and 4-chlorobenzonitrile (89 mg, 0.65 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16fa** as a colorless solid (100 mg, 80% yield): mp 97–99 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.63 (s, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.33–7.24 (m, 2H), 7.08 (dd, J = 8.9, 4.5 Hz, 1H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 199.1 (d, J = 2.5 Hz), 159.3 (d, J = 1.3 Hz), 154.5 (d, J = 238.9 Hz), 138.8, 135.5, 133.4, 130.6, 129.7, 128.9,

124.1 (d, J = 23.6 Hz), 119.9 (d, J = 7.2 Hz), 118.4 (d, J = 6.3 Hz), 117.9 (d, J = 23.8 Hz). LRMS (EI) *m/z* (%): 250 (M^++2, 33), 250 (M^+, 100), 249 (91), 215 (97), 139 (99), 111 (63). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_9ClFO_2$, 251.0270; found, 251.0265.

*(4-Chlorophenyl)(2-hydroxy-5-methoxyphenyl)methanone (**16ha**)*. The reaction of *O*-4-methoxyphenyl *N,N*-diethylcarbamate (**1h**) (112 mg, 0.5 mmol), *s*-BuLi (0.46 mL, 0.65 mmol) and 4-chlorobenzonitrile (89 mg, 0.65 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16ha** as a colorless solid (106 mg, 81% yield): m.p 88–90 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.04 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 8.2 Hz, 2H), 6.84 (t, J = 8.2 Hz, 1H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 200.4, 153.3, 149.1, 138.5, 136.3, 130.8, 128.7, 124.4, 119.2, 118.3, 117.2, 56.3. LRMS (EI) *m/z* (%): 264 (M^++2, 33), 262 (M^+, 100), 151 (44), 139 (41), 122 (46). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{14}H_{10}ClO_3$, 261.0324; found, 261.0326.

*(4-Chlorophenyl)(2-hydroxy-3-methoxyphenyl)methanone (**16ia**)*. The reaction of *O*-2-methoxyphenyl *N,N*-diethylcarbamate (**1i**) (112 mg, 0.5 mmol), *s*-BuLi (0.46 mL, 0.65 mmol) and 4-chlorobenzonitrile (89 mg, 0.65 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16ia** as a colorless solid (106 mg, 81% yield): mp 83–85 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.16 (dd, J = 9.1, 3.0 Hz, 1H), 7.04–6.99 (m, 2H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 199.8, 157.5, 151.6, 138.5, 136.2, 130.7, 128.8, 124.4, 119.5, 118.5, 115.9, 56.0. LRMS (EI) *m/z* (%): 264 (M^++2, 33), 262 (M^+, 100), 150 (94). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{14}H_{10}ClO_3$, 261.0324; found, 261.0325.

*(3-Chloro-2-hydroxyphenyl)(4-chlorophenyl)methanone (**16ja**)*. The reaction of *O*-2-chlorophenyl *N,N*-diethylcarbamate (**1j**) (114 mg, 0.5 mmol), *s*-BuLi (0.46 mL, 0.65 mmol) and 4-chlorobenzonitrile (89 mg, 0.65 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 10:1), yielded **16ja** as a yellowish solid (112 mg, 84% yield): mp 60–62 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.41 (s, 1H), 7.69–7.60 (m, 3H), 7.54–7.49 (m, 3H), 6.88 (t,

J = 7.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 200.0, 158.8, 139.0, 136.6, 135.7, 131.8, 130.8, 128.9, 123.2, 120.0, 119.0. LRMS (EI) *m/z* (%): 270 (M^++4, 15), 268 (M^++2, 60), 266 (M^+, 100), 231 (73), 155 (80), 154 (80), 139 (94), 111 (53). HRMS (ESI/Q-TOF) *m/z*: $[M - H]^-$ calcd for $C_{13}H_7Cl_2O_2$, 264.9829; found, 264.9833.

General Procedure for the Synthesis of (2-Cyclohexylimino)phenol Derivatives 17.[37] A solution of the corresponding 2-hydroxybenzophenone **16** (0.25 mmol) in MeOH (2 mL) was treated with cyclohexylamine (30 mg, 0.3 mmol), and the mixture was stirred at 50 ºC in an oil bath for 24 h. After cooling to rt all volatile residues were removed under reduced pressure affording the 2-((cyclohexylimino)(aryl)methyl)phenol derivatives **17**, which were obtained in pure form without further purification.

*(E)-2-((4-Chlorophenyl)(cyclohexylimino)methyl)-4-methoxyphenol (**17ha**).* The reaction of (4-chlorophenyl)(2-hydroxy-5-methoxyphenyl)methanone (**16ha**) (66 mg, 0.25 mmol), following the general procedure, yielded **17ha** as a colorless solid (78 mg, 91 % yield): mp 93–95 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 16.12 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.58–6.42 (m, 1H), 6.19 (d, *J* = 8.1 Hz, 1H), 3.75 (s, 3H), 1.71–1.09 (m, 11H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 170.9, 154.6, 149.0, 134.0, 132.0, 129.2, 128.9, 122.6, 118.6, 116.0, 114.6, 58.1, 55.9, 33.2, 25.5, 25.0, 24.7, 23.3. LRMS (EI) *m/z* (%): 345 (M^++2, 5), 343 (M^+, 15), 260 (100), 229 (21). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}ClNO_2$, 344.1412; found, 344.1419.

*(E)-2-((4-Chlorophenyl)(cyclohexylimino)methyl)-6-methoxyphenol (**17ia**).* The reaction of (4-chlorophenyl)(2-hydroxy-3-methoxyphenyl)methanone (**16ia**) (66 mg, 0.25 mmol), following the general procedure, yielded **17ia** as a colorless solid (77 mg, 90 % yield): mp 100–102 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 14.87 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 1H), 6.13 (d, *J* = 3.0 Hz, 1H), 3.50 (s, 3H), 1.71–1.38 (m, 8H), 1.27–1.10 (m, 3H). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 169.9, 156.2, 150.5, 133.9, 132.1, 129.1, 128.9, 119.1, 118.6, 118.0, 115.4, 59.0, 55.3, 33.3, 25.0, 23.4. LRMS (EI) *m/z* (%): 345 (M^++2, 2),

343 (M^+, 6), 260 (100), 229 (72). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}ClNO_2$, 344.1412; found, 344.1421.

General Procedure for the Synthesis of 2-((Dyclohexylamino)benzyl)phenol Derivatives 18. A solution of the corresponding 2-hydroxybenzophenone derivative **16** (0.2 mmol) in MeOH (2 mL) at 50 ºC in an oil bath was treated with cyclohexylamine (24 mg, 0.24 mmol), and the reaction mixture was stirred 24 h at this temperature. After cooling to rt the reaction mixture was treated with $NaBH_4$ (15 mg, 0.4 mmol) and further stirred for 24 h. The resulting solution was quenched with H_2O. The aqueous phase was extracted with EtOAc (3 × 6 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, affording the 2-((cyclohexylamino)(aryl)methyl)phenol derivatives **18**.

*2-((4-Chlorophenyl)(cyclohexylamino)methyl)-4-methoxyphenol (**18ha**)*. The reaction of (4-chlorophenyl)(2-hydroxy-5-methoxyphenyl)methanone (**16ha**) (53 mg, 0.2 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **18ha** as a colourless oil (59 mg, 85% yield), R_f = 0.23 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.27 (m, 4H), 6.81 (d, J = 7.9 Hz, 1H), 6.71 (t, J = 7.9 Hz, 1H), 6.48 (d, J = 7.9 Hz, 1H), 5.14 (s, 1H), 3.91 (s, 3H), 2.61 (s, 1H), 2.12–1.99 (m, 2H), 1.76–1.58 (m, 3H), 1.30–1.13 (m, 6H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 148.7, 147.5, 140.8, 133.7, 129.2, 129.0, 125.0, 120.7, 118.8, 110.7, 63.5, 55.9, 54.6, 33.2, 32.8, 25.9, 24.9, 24.9. LRMS (EI) *m/z* (%): 347 (M^++2, 4), 345 (M^+, 12), 330 (14), 262 (80), 247 (100), 197 (32). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}ClNO_2$, 346.1568; found, 346.1567.

*2-((4-Chlorophenyl)(cyclohexylamino)methyl)-6-methoxyphenol (**18ia**)*. The reaction of (4-chlorophenyl)(2-hydroxy-3-methoxyphenyl)methanone (**16ia**) (53 mg, 0.2 mmol), following the general procedure (purification by column chromatography in hexane/EtOAc = 8:1), yielded **18ia** as a colourless oil (61 mg, 88% yield), R_f = 0.19 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 4H), 6.80 (d, J = 8.8 Hz, 1H), 6.72 (dd, J = 8.8, 2.9 Hz, 1H), 6.37 (d, J = 2.9 Hz, 1H), 5.05 (s, 1H), 3.67 (s, 3H), 2.56 (s, 1H), 2.07–1.95 (m, 2H), 1.75–1.54 (m, 3H), 1.29–1.09 (m, 6H). ^{13}C{^{1}H}

NMR (75.4 MHz, $CDCl_3$): δ 152.5, 151.8, 140.6, 133.7, 129.2, 129.0, 125.5, 117.7, 114.6, 113.8, 63.7, 55.7, 54.6, 33.2, 32.9, 25.9, 24.9, 24.9. LRMS (EI) *m/z* (%): 347 (M^++2, 11), 345 (M^+, 33), 330 (31), 262 (98), 247 (100), 197 (21). HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}ClNO_2$, 346.1568; found, 346.1567.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc. Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra for all new compounds and DFT computational details (PDF).

FAIR data, including the primary NMR FID files, for compounds **6b-6t**, **7a**, **7e**, **8a**, **8e**, **9ba-9qa**, **10ea-10ef**, **11ba-11la**, **12aa-12ub**, **13bc**, **14**, **15aa-15gk**, **16aa-16ja**, **17ha**, **17ia**, **18ha**, **18ia** (ZIP)

Crystallographic data for **6b** (CIF)

Crystallographic data for **9ba** (CIF)

Crystallographic data for **10eb** (CIF)

Crystallographic data for **11eb** (CIF)

Crystallographic data for **11ha** (CIF)

Crystallographic data for **12bb** (CIF)

Crystallographic data for **13ec** (CIF)

Crystallographic data for **14** (CIF)

ACKNOWLEDGMENTS

We gratefully acknowledge Junta de Castilla y León and FEDER (BU291P18) and Ministerio de Ciencia e Innovación and FEDER (CTQ2016-75023-C2-1-P and 2-P) for financial support. C.F. and C.S. thank Universidad de Burgos and Ministerio de Educación y Ciencia (FPU), respectively, for predoctoral contracts. S.S.-P. thanks Junta de Castilla y León and FEDER for a postdoctoral contract.

We also thank the Centro de Supercomputación de Galicia (CESGA) for the allocation of computational resources.

REFERENCES

(1) (a) Hartung, C. G.; Snieckus, V. The Directed *ortho* Metalation Reaction–A Point of Departure for New Synthetic Aromatic Chemistry, in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, **2002**, pp. 330–367. (b) Board, J.; Cosman, J. L.; Rantanen, T.; Singh, S. P.; Snieckus, V. The Directed *ortho* Metallation-Cross-Coupling Fusion: Development and Application in Synthesis. *Platin. Met. Rev.* **2013**, *57*, 234–258. (c) Leroux, F. R.; Mortier, J. Directed Metalation of Arenes with Organolithiums, Lithium Amides, and Superbases, in *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds* (Ed.: J. Mortier), John Wiley & Sons, **2016**, pp. 743–776. (d) For directed remote metalation, see: Tilly, D.; Magolan, J.; Mortier, J. Directed Remote Aromatic Metalations: Mechanisms and Driving Forces. *Chem. Eur. J.* **2012**, *18*, 3804–3820.

(2) (a) Gilman, H.; Bebb, R. L. Relative Reactivities of Organometallic Compounds. XX.* Metalation. *J. Am. Chem. Soc.* **1939**, *61*, 109–112. (b) Wittig, G.; Fuhrman, G. Über das Verhalten der halogenierten Anisole gegen Phenyl-lithium (V. Mitteil. Über die Reaktionsweise des Phenyl-lithiums). *Chem. Ber.* **1940**, *73*, 1197–1218. (c) Snieckus, V. Directed Ortho Metalation. Tertiary Amide and O-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics. *Chem. Rev.* **1990**, *90*, 879–933. (d) Clayden, J. in *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, **2002**, pp. 9–109. (e) El-Hiti, G. A.; Smith, K.; Hegazy, A. S.; Alshammari, M. B.; Masmali, A. M. Directed lithiation of simple aromatics and heterocycles for synthesis of substituted derivatives. *Arkivoc*, **2015**, (*iv*), 19–47. (f) Florio, S.; Salomone, A. Heterocycle-Mediated *ortho*-Functionalization of Aromatic Compounds: The DoM Methodology and Synthetic Utility. *Synthesis* **2016**, *48*, 1993–2008.

(3) (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C–H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879–5918. (b) Gensch, T.; Hopkinson, M. N.; Glorius,

F.; Wencel-Delord, J. Mild Metal-Catalyzed C–H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936.

(4) (a) Stern, R.; English, J.; Cassidy, H. G. Diastereomeric Tetrahydropyranyl Ethers of Hydroquinone. *J. Am. Chem. Soc.* **1957**, 79, 5797–5800. (b) Posner, G. H.; Canella, K. A. Phenoxide-Directed Ortho Lithiation. *J. Am. Chem. Soc.* **1985**, *107*, 2571–2573; (c) M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki and S. Furukawa, Ortho-Lithiation of phenols using the bis(dimethylamino)phosphoryl group as a directing group. *Chem. Pharm. Bull.* **1989**, *37*, 2564–2566. (d) Sengupta, S.; Snieckus, V. The 2-(trimethylsilyl)ethoxymethoxy (OSEM) directed ortho metalation group. New regiospecific synthetic routes to substituted benzenes and pyridines. *Tetrahedron Lett.* **1990**, *31*, 4267–4270. (e) Watanabe, M.; Date, M.; Kawanishi, K.; Hori, T.; Furukawa, S. The Directed *ortho*-Lithiation of Aryl Tetramethylphosphorodiamidates. *Chem. Pharm. Bull.* **1990**, *38*, 2637–2643. (f) Zacharie, B.; Attardo, G.; Barriault, N.; Penney, C. Regioselective synthesis of 6-substituted 2-hydroxybenzaldeehyde: efficient synthesis of the immunomodulator tucaresol and related analogues. *J. Chem. Soc., Perkin Trans 1*, **1997**, 2925–2929. (g) Alessi, M.; Patel, J. J.; Zumbansen, K.; Snieckus, V. The Tetraethylphosphorodiamidate ($OP(O)(NEt_2)_2$ Directed Metalation Group (DMG). Directed *ortho* and Lateral Metalation and the Phospha Anionic Fries Rearrangement. *Org. Lett.* **2020**, *22*, 2147–2151.

(5) (a) Sibi, M. P.; Snieckus, V. The Directed Ortho Lithiation of *O*-Aryl Carbamates. An Anionic Equivalent of the Fries Rearrangement. *J. Org. Chem.* **1983**, *48*, 1935–1937. For the *ortho*-sodiation of aryl carbamates, see: (b) Ma, Y.; Woltornist, R. A.; Algera, R. F.; Collum, D. B. Aryl Carbamates: Mechasnisms of Orthosodiations and Snieckus-Fries Rearrangement. *J. Org. Chem.* **2019**, *84*, 9051–9057.

(6) (a) Metallinos, C.; Nerdinger, S.; Snieckus, V. *N*-Cumyl Benzamide, Sulfonamide, and Aryl *O*-Carbamate Directed Metalation Groups. Mild Hydrolytic Lability for Facile Manipulation of Directed Ortho Metalation Derived Aromatics. *Org. Lett.* **1999**, *1*, 1183–1186. (b) Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J.-P. New Synthesis of Benzoquinone Primin and its Water-Soluble Analog

Primin Acid via Heck Reactions. *Synthesis* **1999**, 1127–1134. (c) Kauch, M.; Hoppe, D. Synthesis of substituted phenols by directed *ortho*-lithiation of in situ *N*-silyl-protected *O*-aryl *N*-monoalkylcarbamates. *Can. J. Chem.* **2001**, *79*, 1736–1746. (d) Kauch, M.; Snieckus, V.; Hoppe, D. Substitution of Hydroxybiaryls via Directed *ortho*-Lithiation of *N*-Silylated *O*-Aryl *N*-Isopropylcarbamates. *J. Org. Chem.* **2005**, *70*, 7149–7158. (e) Kauch, M.; Hoppe, D. Efficient Two-Step Synthesis of Salicylaldehydes via Directed *ortho*-Lithiation of in situ *N*-Silylated *O*-Aryl *N*-Isopropylcarbamates. *Synthesis* **2006**, 1575–1577. (f) Kauch, M.; Hoppe, D. Synthesis of Halogenated Phenols by Directed *ortho*-Lithiation and *ipso*-Iododesilylation Reactions of *O*-Aryl *N*-Isopropylcarbamates. *Synthesis* **2006**, 1578–1590. (g) Morin, J.; Zhao, Y.; Snieckus, V. Reductive Cleavage of Aryl *O*-Carbamates to Phenols by the Schwartz Reagent. Expedient Link to the Directed *Ortho* Metalation Strategy. *Org. Lett.* **2013**, *15*, 4102–4105.

(7) See, for instance: (a) Parsons, A. S.; García, J. M.; Snieckus, V. A. Directed *ortho* metalation reactions. Expedient synthesis of 3,3'-disubstituted 1,1'-bi-(2-phenols) (BIPOLS). *Tetrahedron Lett.* **1994**, *35*, 7537–7540. (b) Griffen, E. J.; Roe, D. G.; Snieckus, V. Benzenoid Ring Functionalization of Indoles and Tryptophols via Combined Directed Ortho Metalation-Cross Coupling Methodology. *J. Org. Chem.* **1995**, *60*, 1484–1485. (c) Milburn, C.; Milburn, R. R.; Snieckus, V. Directed *ortho* Metalation Reaction of Aryl *O*-Carbamates on Solid Support. *Org. Lett.* **2005**, *7*, 629–631. (d) Miller, R. E.; Rantanen, T.; Ogilvie, K. A.; Groth, U.; Snieckus, V. Combined Directed *ortho* Metalation-Halogen Dance (HD) Synthetic Strategies. HD-Anionic *ortho* Fries Rearrangement and Double HD Sequences. *Org. Lett.* **2010**, *12*, 2198–2201. (e) Groom, K.; Hussain, S. M. S.; Morin, J.; Nilewski, C.; Rantanen, T.; Snieckus, V. Directed *ortho* Metalation Strategies. Effective Regioselective Routes to 1,2-, 2,3-, and 1,2,3-Substituted Naphthalenes. *Org. Lett.* **2014**, *16*, 2378–2381. (f) Miah, M. A. J.; Sibi, M. P.; Chattopadhyay, S.; Familoni, O. B.; Snieckus, V. Directed *ortho*-Metalation of *O*-Aryl *N,N*-Dialkylcarbamates: Methodology, Anionic *ortho*-Fires Rearrangement, and Lateral Metalation. *Eur. J. Org. Chem.* **2018**, 440–446. (g) Kancherla, S.; Lorentzen, M.; Snieckus, V.; Jorgensen, K. B.

Directed *ortho*-Metalation and Anionic *ortho*-Fries Rearrangement of Polycyclic Aromatic *O*-Carbamates: Regioselective Synthesis of Substituted Chrysenes. *J. Org. Chem.* **2018**, *83*, 3590–3598.

(8) (a) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. Suzuki-Miyaura Coupling of Aryl Carbamates, Carbonates, and Sulfamates. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *N,N*-Diethyl *O*-Carbamate: Directed Metalation Group and Orthogonal Suzuki-Miyaura Cross-Coupling Partner. *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752. (c) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. Nickel-Catalyzed Efficient and Practical Suzuki-Miyaura Coupling of Alkenyl and Aryl Carbamates with Aryl Boroxines. *Org. Lett.* **2010**, *12*, 884–887. (d) Guo, L.; Hsiao, C.-C.; Yue, H.; Liu, X.; Rueping, M. Nickel-Catalyzed C_{sp2}-C_{sp3} Cross-Coupling via C-O Bond Activation. *ACS Catal.* **2016**, *6*, 4438–4442. (e) Ogawa, H.; Yang, Z.-K.; Minami, H.; Kojima, K.; Saito, T.; Wang, C.; Uchiyama, M. Revisitation of Organoaluminum Reagents Affords a Versatile Protocol for C-X (X = N, O, F) Bond-Cleavage Cross-Coupling: A Systematic Study. *ACS Catal.* **2017**, *7*, 3988–3994.

(9) Fries, K.; Finck, G. Über Homologe des Cumaranons und ihre Abkömmlinge. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4271–4284.

(10) For the first example of an *o*-litioaryl ester Fries rearrangement, see: (a) Miller, J. A. The Metal-Promoted Fries Rearrangement. *J. Org. Chem.* **1987**, *52*, 322–323. For the anionic thia-Fries rearrangement, see: (b) Charmant, J. P. H.; Dyke, A. M.; Lloyd-Jones, G. C. The anionic thia-Fries rearrangement of aryl triflates. *Chem. Commun.* **2003**, 380–381. For the anionic sila-Fries rearrangement, see: (c) Speier, J. L. The Preparation and Properties of (Hydroxyorgano)-silanes and Related Compounds. *J. Am. Chem. Soc.* **1952**, *74*, 1003–1010. For the anionic phospho-Fries rearrangement, see: (d) Melvin, L. S. An efficient synthesis of 2-hydroxyphenylphosphonates. *Tetrahedron Lett.* **1981**, *22*, 3375–3376. For a comprehensive recent review on the A*o*F, see: Korb, M.; Lang, H. The anionic Fries rearrangement: a convenient route to *ortho*-functionalized aromatics. *Chem. Soc. Rev.* **2019**, *48*, 2829–2882.

(11) See, for instance: (a) Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. Combinational O-aryl carbamates and benzamide directed ortho metalation reactions. Synthesis of ochratoxin A and ochratoxin B. *J. Am. Chem. Soc.* **1985**, *107*, 6312–6315. (b) Dennis, M. R.; Woodward, S. Enantiopure 3-amido or 3,3'-bisamido substituted 1,1'-bi-2-naphtol by anionic Fries rearrangements. *J. Chem. Soc., Perkin Trans 1*, **1998**, 1081–1085. (c) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. Harnessing Anionic Rearrangements on the Benzenoid Ring of Quinoline for the Synthesis of 6,6'-Disubstituted 7,7'-Dihydroxy-8,8'-biquinolyls. *J. Org. Chem.* **2005**, *70*, 373–376. (d) Assimomytis, N.; Sariyannis, Y.; Stavropoulos, G.; Tsoungas, P. G.; Varvounis, G.; Cordopatis, P. Anionic *ortho*-Fries Rearrangement, a Facile Route to Arenol-Based Mannich Bases. *Synlett* **2009**, 2777–2782. (e) Chang, C.-W.; Chein, R.-J. Absolute Configuration of Anti-HIV-1 Agent (–)-Concentricolide: Total Synthesis of (+)-(R)-Concentricolide. *J. Org. Chem.* **2011**, *76*, 4154–4157. (f) Schneider, C.; David, E.; Toutov, A. A.; Snieckus, V. In Situ Anionic Schielding for Regioselective Metalation: Directed *peri* and Iterative Metalation Routes to Polyfunctionalized 7-Azaindoles. *Angew. Chem. Int. Ed.* **2012**, *51*, 2722–2726. (g) Lo, H.-J.; Lin, C.-Y.; Tseng, M.-C.; Chein, R.-J. Lithiation of a Silyl Ether: Formation of an ortho Fries Hydroxyketone. *Angew. Chem. Int. Ed.* **2014**, *53*, 9026–9029. (h) Kumar, S. N.; Bavikar, S. R.; Kumar, C. N. S. S. P.; Yu, I. F.; Chein, R.-J. From Carbamate to Chalcone: Consecutive Anionic Friess Rearrangement, Anionic Si→C Alkyl Rearrangement, and Claisen-Schmidt Condensation. *Org. Lett.* **2018**, *20*, 5362–5366.

(12) For mechanistic studies of the A*o*F rearrangements, see: (a) Singh, K. J.; Collum, D. B. Lithium Diisopropylamide-Mediated Ortholithiation and Anionic Fries Rearrangement of Aryl Carbamates: Role of Aggregates and Mixed Aggregates. *J. Am. Chem. Soc.* **2006**, *128*, 13753–13760. (b) Riggs, J. C.; Singh, K. J.; Yun, M.; Collum, D. B. Anionic Snieckus-Fries Rearrangement: Solvent Effects and Role of Mixed Aggregates. *J. Am. Chem. Soc.* **2008**, *130*, 13709–13717.

(13) For the suppression or careful control of the 1,3-O→C A*o*F, see: (a) Kim, H.; Min, K.-I.; Inoue, K.; Im, D. J.; Kim, D.-P.; Yoshida, J.-i. Submillisecond organic synthesis: Outpacing Fries rearrangement through microfluidic rapid mixing. *Science* **2016**, *352*, 691–694. (b) Kim, H.; Inoue,

K.; Yoshida, J.-i. Harnessing [1,4], [1,5], and [1,6] Anionic Fries-type Rearrangements by Reaction-Time Control in Flow. *Angew. Chem. Int. Ed.* **2017**, *56*, 7863–7866.

(14) Kalinin, A. V.; Miah, M. A. J.; Chattopadhyay, S.; Tsukazaki, M.; M. Wicki, M.; Nguen, T.; Coelho, A. L.; Kerr, M.; Snieckus, V. Anionic Homologous Fries Rearrangement of O-(2-Methylaryl)carbamates. A Regiospecific Route to Benzo[*b*]furan-2(*3H*)-ones including an Unnamed Metabolite from *Helenium* Species. *Synlett* **1997**, 839–841.

(15) 1,4-O→C_{sp}^2: Zhang, P.; Gawley, R. E. Directed Metalation/Snieckus Rearrangement of *O*-Benzylic Carbamates. *J. Org. Chem.* **1993**, *58*, 3223–3224.

(16) Wang, W.; Snieckus, V. Remote Directed Metalation of Biaryl *o*-Carbamates. Ring to Ring Carbamoyl Transfer Route to Biaryl, Dibenzo[*b,d*]pyranones, and the Natural Fluorenone Dengibsin. *J. Org. Chem.* **1992**, *57*, 424–426.

(17) 1,4-O→C_{sp}^3: (a) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. The First Lateral Functionalization of Calix[4]arenes by a Homologous Anionic Ortho-Fries Rearrangement. *J. Org. Chem.* **2000**, *65*, 667–675. (b) Azzena, U.; Pisano, L.; Pittalis, M. Application of the anionic homologous Fries-rearrangement to synthesis of 3-alkylbenzofuran-2(*3H*)-ones. *Appl. Organometal. Chem.* **2008**, *22*, 523–528. 1,4-O→C_{sp}^2: (c) Alves Slana, G. B. C.; Soares de Azevedo, M.; Capella Lopes, R. S.; Cerqueira Lopes, C.; Nobrega Cardoso, J. Total synthesis of oxygenated brazaquinones via regioselective homologous anionic Fries rearrangement of benzylic *O*-carbamates. *Beilstein J. Org. Chem.* **2006**, *2*, No. 1. 1,5-O→C_{sp}^2: (d) Mohri, S.; Stefinovic, M.; Snieckus, V. Combined Directed *Ortho*-, Remote-Metalation and Cross-Coupling Strategies- Concise Syntheses of the Kinamycin Biosynthetic Grid Antibiotics Phenanthroviridin Aglycon and Kinobscurinone. *J. Org. Chem.* **1997**, *62*, 7072–7073. (e) Macklin, T. K.; Panteleev, J.; Snieckus, V. Carbamoyl Translocation by an Anionic *ortho*-Fries and Cumulenolate α–Acylation Pathway: Regioselective Synthesis of Polysubstituted Chromone 3- and 8-Carboxamides. *Angew. Chem. Int. Ed.* **2008**, *47*, 2097–2101. (f) James, C. A.; Snieckus, V. Combined Directed Remote Metalation-Transition Metal Catalyzed Cross Coupling Strategies: The Total Synthesis of the Aglycones of the Gilvocarcins V, M, and E and

Arnottin I. *J. Org. Chem.* **2009**, *74*, 4080–4093. (g) James, C. A.; Coelho, A. L.; Gevaert, M.; Forgione, P.; Snieckus, V. Combined Directed ortho and Remote Metalation-Suzuki Cross-Coupling Strategies. Efficient Synthesis of Heteroaryl-Fused Benzopyranones from Biaryl *O*-Carbamates. *J. Org. Chem.* **2009**, *74*, 4094–4103.

(18) (a) Kalinin, A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. Directed *ortho* Metalation–Cross Coupling Links. Carbamoyl Rendition of the Baker-Venkataraman Rearrangement. Regiospecific Route to Substituted 4-Hydroxycoumarins. *Tetrahedron Lett.* **1998**, *39*, 4995–4998. For a review, see (b) Ameen, D.; Snape, T. J. Mechanism and Application of Baker-Venkataraman O→C Acyl Migration Reactions. *Synthesis* **2015**, 141–158.

(19) Reed, M. A.; Chang, M. T.; Snieckus, V. Anionic O→α- and β-Vinyl Carbamoyl Translocation of 2-(*O*-Carbamoyl)Stilbenes. *Org. Lett.* **2004**, *6*, 2297–2300.

(20) N→C: (a) MacNeil, S. L.; Wilson, B. J.; Snieckus, V. Anionic *N*-Fries Rearrangement of *N*-Carbamoyl Diarylamines to Anthranilamides. Methodology and Application to Acridone and Pyranoacridone Alkaloids. *Org. Lett.* **2006**, *8*, 1133–1136. (b) Zhao, Z.; Jaworski, A.; Piel, I.; Snieckus, V. Anionic Indole *N*-Carbamoyl N→C Translocation. A Directed remote Metalation Route to 2-Aryl- and 2-Heteroarylindoles. Synthesis of Benz[*a*]carbazoles and Indeno[1,2-*b*]indoles. *Org. Lett.* **2008**, *10*, 2617–2620. (c) Costil, R.; Dale, H. J. A.; Fey, N.; Whitcombe, G.; Matlock, J. V.; Clayden, J. Heavily Substituted Atropisomeric Diarylamines by Unactivated Smiles Rearrangement of *N*-Aryl Anthranilamides. *Angew. Chem. Int. Ed.* **2017**, *56*, 12533–12537. C→C: (d) Wykypiel, W.; Lohmann, J. J.; Seebach, D. Laser Flash Photolysis of Phthalocyanines in Solution and Microemulsion. *Helv. Chim. Acta* **1981**, *64*, 1337–1346. S→C: (e) Bennett, S. M. W.; Brown, S. M.; Conole, G.; Dennis, M. R.; Fraser, P. K.; Radojevic, S.; McPartlin, M.; Topping, C. M.; Woodward, S. Catalytic conjugate addition promoted by the copper(I)-monothiobinaphthol system. Part 3.1 Comparison of three thiolate-based catalytic systems. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3127–3132.

(21) (a) Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. Directed Metalation Linked to Transition Metal Catalyzed Cascade Reactions: Two Total syntheses of Plicadin, the Alleged Coumestan from *Psoralea plicata. Angew. Chem. Int. Ed.* **1999**, *38*, 1435–1438. (b) Chauder, B. A.; Kalinin, A. V.; Snieckus, V. Directed *ortho* Metalation Reactions of Aryl *O*-Carbamates; A Regiospecific Synthesis of 2,2-Disubstituted 2*H*-1-Benzopyrans. *Synthesis* **2001**, 140–144.

(22) (a) Sanz, R.; Castroviejo, M. P.; Fernández, Y.; Fañanás, F. J. A New and Efficient Synthesis of 4-Functionalized Benzo[*b*]furans from 2,3-Dihalophenols. *J. Org. Chem.* **2005**, *70*, 6548–6551. (b) Sanz, R.; Castroviejo, M. P.; Guilarte, V.; Pérez, A.; Fañanás, F. J. Regioselective Synthesis of 4- and 7-Alkoxyindoles from 2,3-Dihalophenols: Application to the Preparation of Indole Inhibitors of Phospholipase A_2. *J. Org. Chem.* **2007**, *72*, 5113–5118. (c) Sanz, R.; Guilarte, V.; Hernando, E.; Sanjuán, A. M. Synthesis of Regioselectively Functionalized Benzo[*b*]thiophenes by Combined *ortho*-Lithiation–Halocyclization Strategies. *J. Org. Chem.* **2010**, *75*, 7443–7446. (d) Sanz, R.; Guilarte, V.; García, N. Synthesis of 4-functionalized-1*H*-indoles from 2,3-dihalophenols. *Org. Biomol. Chem.* **2010**, *8*, 3860–3864. (e) Guilarte, V.; Castroviejo, M. P.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. Approaches to the Synthesis of 2,3-Dihaloanilines. Useful Precursors of 4-Functionalized-1*H*-indoles. *J. Org. Chem.* **2011**, *76*, 3416–3437. (f) Feberero, C.; Velasco, R.; Sanz, R. *ortho*-Lithiation Reactions of *O*-(3,*n*-Dihalophenyl) *N,N*-Diethylcarbamates: Synthesis of Dihalosalicylamides and 2,3,*n*-Trihalophenol Derivatives. *Eur. J. Org. Chem.* **2016**, 5519–5528.

(23) Feberero, C., Suárez-Pantiga, S.; Cabello, Z.; Sanz, R. 1,5-O→N Carbamoyl Snieckus–Fries-Type Rearrangement. *Org. Lett.* **2018**, *20*, 2437–2440.

(24) Other nitriles, such as *t*-BuCN o 9-anthracenecarbonitrile, have also been demonstrated as not suitable electrophiles for organolithiums. See: Korb, M.; Mahrholdt, J.; Lang, H. (Planar-Chiral) Ferrrocenylmethanols: From Anionic Homo Phospho-Fries Rearrangements to α-Ferrocenyl Carbenium Ions. *Eur. J. Inorg. Chem.* **2017**, 4028–4048.

(25) Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H. Transnitrilation from Dimethylmalononitrile to Aryl

Grignard and Lithium Reagents: A Practical Method for Aryl Nitrile Synthesis. *J. Am. Chem. Soc.* **2015**, *137*, 9481–9488.

(26) Malapit, C. A.; Luvaga, I. K.; Reeves, J. T.; Volchkov, I.; Busacca, C A.; Howell, A. R.; Senanayake, C. H. 1,4-Dicarbofunctionalization of 4-Fluoroaryl Grignard and Lithium Reagents with Disubstituted Malononitriles. *J. Org. Chem.* **2017**, *82*, 4993–4997.

(27) NMR spectra of the crude reaction mixture posses the signals characteristic from compounds **5**.

(28) CCDC 2000234 (**6b**), 2000258 (**9ba**), 2002768 (**10eb**), 2001029 (**11eb**), 2002776 (**11ha**), 2000295 (**12bb**), 2001045 (**13ec**), and 2000155 (**14**) contain the crystallographic data for this work.

(29) Mai, K.; Patil, G. Alkylsilyl Cyanides as Silylating Agents. *J. Org. Chem.* **1986**, *51*, 3545–3548.

(30) For a related example with a Grignard reagent, see ref. 25.

(31) (a) Schüürmann, G.; Cossi, M.; Barone, V.; Tomasi, J. Prediction of the pKa of Carboxylic acids Using the ab Initio Continuum-Solvation Model PCM-UAHF. *J. Phys. Chem. A* **1998**, *102*, 6706–6712. (b) Trummal, A.; Rummel, A.; Lippmaa, E.; Burk, P.; Koppel, I. A. IEF-PCM Calculations of Absolute pKa for Substituted Phenols in Dimethyl Sulfoxide and Acetonitrile Solutions. *J. Phys. Chem. A* **2009**, *113*, 6206–6212.

(32) Bo, C.; Poblet, J. M. Electronic Properties and Molecular Simulations of Polyoxometalates. *Isr. J. Chem.* **2011**, *51*, 228–237.

(33) See, for instance: (a) Clare, B.; Sarker, N.; Shoemaker, R.; Hagadorn, J. R. Synthesis and Characterization of Binucleating Bis(amidinate) Ligands and Their Dialuminum Complexes. *Inorg. Chem.* **2004**, *43*, 1159–1166. (b) Sinenkov, M.; Kirillov, E.; Roisnel, T.; Fukin, G.; Trifonov, A.; Carpentier, J.-F. Rare-Earth Complexes with Multidentate Tethered Phenoxy-Amidinate Ligands: Synthesis, Structure, and Activity in Ring-Opening Polymerization of Lactide. *Organometallics* **2011**, *30*, 5509–5523.

(34) See, for instance: (a) Clive, D. L. J.; Cheng, P. The marinopyrroles. *Tetrahedron* **2013**, *69*, 5067–5078. (b) Shan, G.; Han, X.; Lin, Y.; Yua, S.; Rao, Y. Broadening the catalyst and reaction scope of regio- and chemoselective C–H oxygenation: a convenient and scalable approach to 2-

acylphenols by intriguing Rh(II) and Ru(II) catalysis. *Org. Biomol. Chem.* **2013**, *11*, 2318–2322. (c) Yoo, H. J.; Youn, S. W. Zn(II)-Catalyzed One-Pot Synthesis of Coumarins from Ynamides and Salicylaldehydes. *Org. Lett.* **2019**, *21*, 3422–3426. (d) Tong, Z.; Tang, Z.; Au, C.-T.; Qiu, R. Nickel-Catalyzed Decarbonyloxidation of 3-Aryl Benzofuran-2(3*H*)-ones to 2-Hydroxybenzophenones. *J. Org. Chem.* **2020**, *85*, 8533–8543.

(35) For the metal-catalyzed C–H oxygenation of aryl ketones, see: Shan, G.; Yang, X.; Ma, L.; Rao, Y. Pd-Catalyzed C–H Oxygenation with TFA/TFAA: Expedient Access to Oxygen-Containing Heterocycles and Late-Stage Drug Modification. *Angew. Chem. Int. Ed.* **2012**, *51*, 13070–13074.

(36) Zhou, C.; Larock, R. C. Synthesis of Aryl Ketones or Ketimines by Palladium-Catalyzed Arene C–H Addition to Nitriles. *J. Org. Chem.* **2006**, *71*, 3551–3558.

(37) Seo, M. S.; Jang, S.; Jung, H.; Kim, H. Hydrogen-Bonding-Assisted Ketimine Formation of Benzophenone Derivatives. *J. Org. Chem.* **2018**, *83*, 14300–14306.

(38) Xiong, W.; Qi, C.; Guo, T.; Zhang, M.; Chen, K.; Jiang, H. A copper-catalyzed oxidative coupling reaction of arylboronic acids, amines and carbon dioxide using molecular oxygen as the oxidant. *Green. Chem*. **2017**, *19*, 1642–1646.

(39) Kaplan, J.-P.; Raizon, B. M. New anticonvulsants: Schiff bases of gamma-aminobutyric acid and gamma-aminobutyramide. *J. Med. Chem.* **1980**, *23*, 702–704.