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Naphthalene-Catalysed Lithiation of Functionalized Chloroarenes: Regioselective Preparation and Reactivity of Functionalized Lithioarenes

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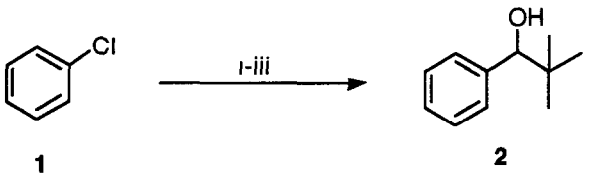
Abstract: *The lithiation of different functionalized chloroarenes (dichlorobenzenes* ***1*** *and* ***3****, mono and dichlorophenols* ***9*** *and* ***14****, and chloropivalanilides* ***18****) in the presence of a catalytic amount of naphthalene leads to the corresponding functionalized lithioarenes, which react with electrophiles to give the expected polyfunctionalized aromatic molecules* ***2****,* ***4****,* ***10****,* ***19****,* ***21****,* ***22*** *and* ***24*** *in a regioselective manner. In the case of starting from chlorinated phenols or anilides a deprotonation of the functional group is carried out prior to the lithiation process; only for 2-chloropivalanilide* ***18a*** *a coupling reaction leading to 2-*n*-butylpivalanilide is observed when an excess of* n*-butyllithium is used in the deprotonation step.*

Introduction

Functionalized organolithium compounds[1] are useful intermediates for the construction of organic molecules because their reaction with electrophilic reagents usually yields polyfunctionalized structures. In the case of functionalized aromatic organolithium derivatives, the most common methodology for their preparation consists in the bromine/lithium exchange between the appropriate brominated precursor and an alkyllithium reagent as lithiating agent[2]. Another possibility, limited to the preparation of lithioarenes functionalized at the *ortho* position, involves the so called "ortho-lithiation", in which a proton at this position is removed by means of a strong base, usually an alkyllithium reagent[3,4]. However, although chlorinated arenes are in general more available, cheaper and more stable than the corresponding brominated compounds, they have been scarcely used[5] as starting materials for functionalized lithioarenes, probably due to their low reactivity compared to the bromine-containing analogues. On the other hand, we have recently described[6] that the chlorine/lithium exchange can be effectively carried out under very mild reaction conditions in the presence of a catalytic amount of an arene, naphthalene being the most generally used[7]. We explore in this paper the naphthalene-catalysed lithiation of functionalized chloroarenes and its application to the preparation of polyfunctionalized aromatic compounds.

Results and Discussion

We first studied the direct lithiation of chlorobenzene (**1**)[8] with lithium powder in THF at -78°C: after four hours under these reaction conditions the lithiation failed (Scheme 1 and Table 1, entry 1). The reaction took place at -55°C, and after one hour a 76% of the reaction product with pivalaldehyde (**2**) was isolated (Table 1, entry 3). However, in the presence of a catalytic amount (3%) of naphthalene the process yielded 98% of compound **2** after 45 min at -78°C (Table 1, entry 2).



1 **2**

Scheme 1. *Reagents*: i, Li or Li-$C_{10}H_8$ cat. (3%; see Table 1); ii, Bu^tCHO; iii, H_2O-HCl.

Table 1. Lithiation of Chlorobenzene (**1**) and Reaction with Pivalaldehyde.

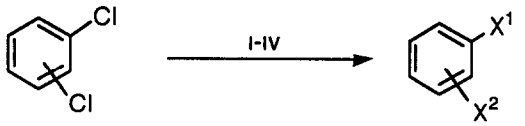
Entry	Starting material	Reaction conditions			Product[a]	
		T (°C)[b]	t (h)[c]	naphthalene (%)	no.	yield (%)[d]
1	**1**	-78	4	-	**2**	0[e]
2	**1**	-78	0.75	3	**2**	98
3	**1**	-55	1	-	**2**	76

[a] Compound **2** was >95% pure by g.l.c. [b] Bath temperature corresponding to the lithiation step. [c] Reaction time in the lithiation process. [d] Isolated yield after flash chromatography base on the starting material **1**. [e] Only the starting material **1** was isolated (>90%).

Catalytic Lithiation of Dichlorobenzenes

We then studied the lithiation of the three dichlorobenzenes **3** (Scheme 2). In the case of **3*o*** we never observed the incorporation of two electrophiles into the aromatic ring (Table 2, entries 1 and 2); thus, even at -105°C only the first electrophile,cyclohexanone or pivalaldehyde, reacted yielding compounds **4a** and **2**, respectively, in which no incorporation of deuterium -coming from deuterium oxide used as a second electrophile- was observed. Two possible explanations can be given: (a) the monolithiated species **5** reacts rapidly with the first electrophile to give compound **6**, which very fast suffers lithiation to **7** followed by proton abstraction from

the reaction media[9] to yield products **4a** or **2**; (b) the intermediate **5** abstracts rapidly a proton yielding chlorobenzene (**1**), which behaves as above. This last possibility is more probable than the evolution of **5** to the intermediate **8**[10], which could give phenyllithium by proton abstraction. Since we never detected compound of the type **6** we find more probable the way (b).



3o: 1,2-
3m: 1,3-
3p: 1,4-

2, 4a-e

Scheme 2. *Reagents and conditions*: i, Li, $C_{10}H_8$ cat. (3%), -78°C; ii, E^1=BuᵗCHO, $(\overline{CH_2)_5}\overline{CO}$, -78°C; iii, E^2=H_2O, D_2O, Et_2CO, -78 to 20°C; iv, H_2O-HCl.

5 **6** **7** **8**

In the case of the starting material **3*m***, we think that the lithiation occurs in two steps. Thus, when the excess of lithium powder was filtered off at low temperature after the first lithiation, the reaction with pivalaldehyde gave the corresponding chloroderivative **4c** (Table 2, entry 7). This fact allowed us the use of two different electrophiles in a two-steps process to give compounds **2** or **4b** (Table 2, entries 4-6). In order to compare the catalytic effect of naphthalene, the same process was carried out with or without catalyst (Table 2, entries 5 and 6): in absence of naphthalene the temperature should be around -55°C and the yield was lower (32%) than in the catalytic process (56%).

The behaviour of *p*-dichlorobenzene (**3*p***) was similar to that of compound **3*m***: the reaction could be stopped after the first step (Table 2, entry 10) and the use of two different electrophiles yielded the expected products **2** and **4** (Table 2, entries 8 and 9).

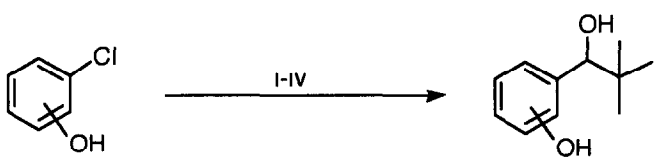
Catalytic Lithiation of Chlorophenols

The lithiation of *o*-, *m*- and *p*-chlorophenol (**9**) was carried out at 0°C after treating the starting material with *n*-butyllithium in order to form the corresponding phenolate (Scheme 3); the reaction of the lithiated phenoxide **11** with pivalaldehyde afforded the expected products **10**. Interesting features of this reaction are: (a) the yield in the

Table 2. Lithiation of Dichlorobenzenes **3** and Reaction with Electrophiles (E^1 and E^2). Obtention of Compounds **4**.

Entry	Dichloro-benzene	Lithiation T (°C)	Electrophiles E1	Electrophiles E2	Product[a] no.	Product[a] X1	Product[a] X2	Product[a] yield (%)[b]
1[c]	**3*o***	-78	$(CH_2)_5CO$	D_2O	**4a**	$(CH_2)_5COH$	H[d]	64[d]
2[e]	**3*o***	-105	ButCHO	D_2O	**2**	ButCHOH	H[d]	63[d]
3[f]	**3*m***	-78	ButCHO	H_2O	-[g]	-	-	>90[g]
4	**3*m***	-78	ButCHO	H_2O	**2**	ButCHOH	H	95
5[f]	**3*m***	-55	ButCHO	Et_2CO	**4b**	ButCHOH	Et_2COH	32
6	**3*m***	-78	ButCHO	Et_2CO	**4b**	ButCHOH	Et_2COH	56
7	**3*m***	-78	ButCHO	-	**4c**	ButCHOH	Cl[h]	61
8	**3*p***	-78	ButCHO	H_2O	**2**	ButCHOH	H	96
9	**3*p***	-78	ButCHO	Et_2CO	**4d**	ButCHOH	Et_2COH	42
10	**3*p***	-78	ButCHO	-	**4e**	ButCHOH	Cl[h]	56

[a] All isolated products were >95% pure by g.l.c. [b] Isolated yield after flash chromatography based on the starting dichlorobenzene **3**. [c] Cyclohexanone was added before the starting material **3*o***. [d] No deuterium incorporation was observed. [e] A mixture of diethyl ether and THF (9/1) was used as solvent. [f] Only lithium powder, without naphthalene, was used in the lithiation step. [g] Starting material **3*m*** was the only reaction product isolated. [h] The excess of lithium powder was filtered off at -78°C before adding pivalaldehyde: under these reaction conditions only one Cl/Li exchange took place.



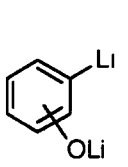
9*o* 1,2-
9*m* 1,3-
9*p* 1,4-

10a-c

Scheme 3: *Reagents and conditions*: I, Bu^nLi; II, Li, $C_{10}H_8$ cat. (3%), 0°C; III, ButCHO, 0 to 20°C, IV, H_2O-HCl.

case of the *o*-derivative is very poor (Table 3, entry 1), due to the decomposition of the corresponding dianion of the type **11**, mainly by proton abstraction; (b) when the process was carried out without using a catalytic amount of naphthalene the reaction did not work (Table 3, entry 2); (c) alternatively, the reaction can be performed

"directly" without adding *n*-butyllithium in the first step, the yield being in this case lower (Table 3, entries 3 and 4). The problem with the *o*-intermediate can be easily overcome by transforming the starting material **9*o*** into its MEMO-derivative **12**[11] and performing the tandem lithiation-reaction with pivalaldehyde as above to yield compound **13** (90%), which was finally hydrolyzed with 6 N HCl to give the corresponding product **10a** in 93%. Anyhow, this last process is not too interesting because it is just in this case that the direct *o*-deprotonation[3] of phenol derivatives has found the best synthetic applications[12]. On the other side, the bromine/lithium exchange has been also used for the preparation of *o*-lithiated phenol derivatives[13].



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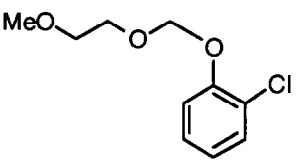

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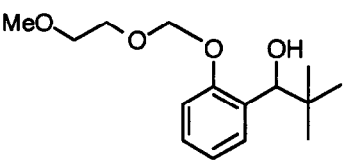

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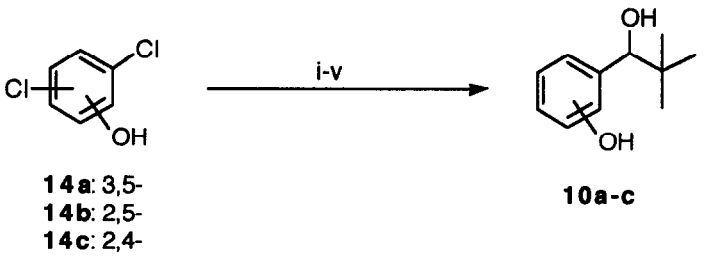
Table 3. Lithiation of Chlorophenols **9** and Reaction with Pivalaldehyde. Obtention of Compounds **10**.

Entry	Chloro-phenol	Lithiation time (h)	Product[a]	
			no.	yield (%)[b]
1	**9*o***	6	**10a**	10
2[c]	**9*m***	7	**10b**	0[d]
3[e]	**9*m***	3	**10b**	45
4	**9*m***	1	**10b**	78
5	**9*p***	5	**10c**	45

[a] All isolated products **10** were >95% pure by g.l.c. [b] Isolated yield after flash chromatography based on the starting chlorophenols **9**. [c] Only lithium powder was used in the lithiation step. [d] The starting material **9*m*** was the only reaction product isolated (>95%). [e] This reaction was performed without using *n*-butyllithium in the first step.

We have also studied the lithiation of dichlorophenols **14** using also pivalaldehyde as standard electrophile, under the above described reaction conditions (Scheme 4). In the three cases tried we never got the expected reaction products arisen from the corresponding trianions of the type **15**; instead of them, compounds **10** were isolated as the only reaction products. Since we never could detect products of monosubstitution of the type **16**, we think that the first dianion **17** took a proton from the solvent to give the corresponding phenoxide derived

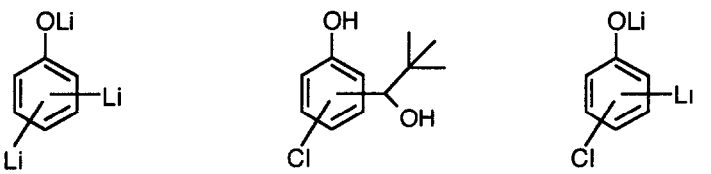
from **9**, which suffered lithiation to **11** as above, and finally reacted with pivalaldehyde to give products **10**. As expected, only the symmetric dichlorophenol **14a** affords a sole product **10b**; in the other cases mixtures of the corresponding regioisomers (**10a+10b** or **10a+10c**) were obtained (Table 4, entries 2 and 3).



14a: 3,5-
14b: 2,5-
14c: 2,4-

10a-c

Scheme 4. *Reagents and conditions*: i, Bu^{n}Li; ii, Li, $C_{10}H_8$ cat. (3%), 0°C; iii, Bu^{t}CHO, 0 to 20°C; iv, D_2O; v, H_2O-HCl.



15 **16** **17**

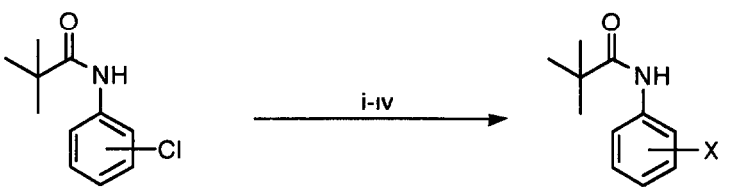
Table 4. Lithiation of Dichlorophenols **14** and Reaction with Electrophiles. Obtention of Compounds **10**.

Entry	Dichloro-phenol	Lithiation time (h)	Product[a]	
			no.	yield (%)[b]
1	**14a**	1	**10b**	72
2	**14b**	1	**10b+10a**	60+20
3	**14c**	3	**10c+10a**	59+3

[a] All isolated products were >95% pure by g.l.c. [b] Isolated yield after flash chromatography based on the starting dichlorophenols **14**.

Catalytic Lithiation of Chloropivalanilides

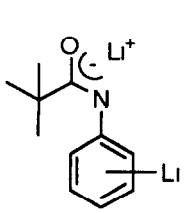
In the last part of this study we first attempted transformation of chloroanilines into the corresponding dianions, but the reaction failed: under different reaction conditions tried either the chlorine/lithium exchange did not take place or when the lithiation occurred (after 2-3 days) a lithium/hydrogen exchange took place yielding aniline as the reaction product. We then tried the lithiation of the corresponding amides. As expected[14], the acidity of hydrogen atoms at the α-position in the amide group was incompatible with the carbon-lithium bond. Thus, chlorinated formanilides, benzanilides and pivalanilides were tested; in the two first cases deprotection of the amide group or deprotonation on the aromatic ring and decomposition took place preventing the formation of the expected dilithiated amides. However, pivalanilides **18** were adequate starting materials for the reaction; thus, the deprotonation of compounds **18** with *n*-butyllithium followed by catalytic lithiation at low temperature led to the formation of the corresponding dianion of the type **20**, which by reaction with different electrophiles yielded the expected compounds **19** (Scheme 5 and Table 5). As electrophiles carbonyl compounds, benzonitrile or phenyl isocyanate were used; in the last two cases it is necessary to filter off the excess of lithium prior to the addition of the electrophile in order to avoid undesirable by-processes. Another important aspect of this reaction is that the catalytic amount of naphthalene should be bigger (~12%) than in the above described cases in order to get the yields shown in Table 5.



18 *o* : 2-
18 *m* : 3-
18 *p* : 4-

19a-j

Scheme 5. *Reagents and conditions*: i, Bu^nLi; ii, Li, $C_{10}H_8$ cat. (12%), -78°C; iii, E+=Pr^nCHO, Bu^tCHO, Et_2CO, $(\overline{CH_2)_5}CO$, PhCN, PhNCO, -78 to 20°C; iv, H_2O.



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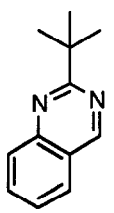

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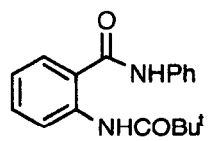

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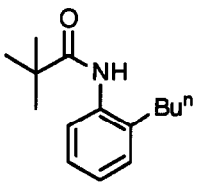

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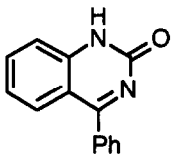

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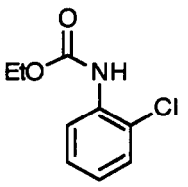

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Table 5. Lithiation of Chloroanilides **18** and Reaction with Electrophiles. Obtention of Compounds **19**, **21** and **22**.

Entry	Chloro-anilide	Electrophile E+	Product[a] no.	Product[a] X.	Product[a] yield (%)[b]
1	**18*o***	Bu^tCHO	**19a**	2-(Bu^tCHOH)	75
2	**18*o***	Et_2CO	**19b**	2-(Et_2COH)	90
3	**18*o***	PhCN	**21**	-	75
4	**18*o***	PhNCO	**22**	-	40
5	**18*m***	Pr^nCHO	**19c**	3-(Pr^nCHOH)	65
6	**18*m***	Bu^tCHO	**19d**	3-(Bu^tCHOH)	68
7	**18*m***	$(CH_2)_5CO$	**19e**	3-[$(CH_2)_5COH$]	71
8	**18*m***	PhCN	**19f**	3-(PhCO)	60
9	**18*p***	Pr^nCHO	**19g**	4-(Pr^nCHOH)	71
10	**18*p***	Bu^tCHO	**19h**	4-(Bu^tCHOH)	70
11	**18*p***	Et_2CO	**19i**	4-(Et_2COH)	70
12	**18*p***	PhCN	**19j**	4-(PhCO)	60

[a] All isolated products **19**, **21** and **22** were >95% pure by g.l.c. [b] Isolated yield after flash chromatography based on the starting chloroanilide **18**.

Only starting from compound **18*o*** we found a rare behaviour depending on the amount of *n*-butyllithium added in the deprotonation step: using an excess of the deprotonating agent (>2 eq) the reaction product was, after hydrolysis, the corresponding *alkylated product* **23** in 90% isolated yield[15]. Considering that no reaction was found in the presence of several nucleophiles (sodium amide, sodium methoxide, lithium diisopropylamide, or the lithium enolate of acetone), we discard a $S_{RN}1$ mechanism or the participation of an aryne as intermediate. On

the other hand, a S_NAr mechanism is not probable due to the negative charge borne by the amide group before the attack of the nucleophile. So. we do not find any satisfactory explanation for this observed fact.

From the results obtained in this part, the *o*-functionalized systems[14,16] are the most interesting ones for obtaining benzo-fused compounds; thus, with benzonitrile or phenyl isocyanate compounds **21** or **22** [precursor of 4-(3*H*)quinazolinones[17]] were directly isolated, respectively, after work-up. Finally, we could prepare the compound **24** (80%) by the same methodology[18] starting from **25** (easily prepared from *o*-chloroaniline and ethyl chloroformate) and using benzonitrile as electrophile. Compounds of the type **24** have been used as antiinflamatory agents[19].

Conclusions

From the results described in this paper we conclude that naphthalene is an efficient catalyst for the lithiation of functionalized chloroarenes with lithium powder and under mild reaction conditions. This methodology is adequate for preparing (regioselectively) functionalized lithioarenes, which by reaction with electrophiles give polyfunctionalized arenes.

Experimental Part

General- M.p.s are uncorrected and were measured on a Reichert thermovar apparatus. I.r. spectra were determined with a Pye Unicam SP3-200 spectrometer. ^1H and ^{13}C n.m.r. spectra were recorded in a Bruker AC-300 using $CDCl_3$ as solvent (unless otherwise stated) and $SiMe_4$ as internal standard; chemical shifts are given in δ (ppm) and the coupling constants (*J*) are measured in Hz. M.s. (e.i.) were recorded with a Hewlett Packard EM/GC HP-5988A spectrometer. Microanalysis were performed by the Microanalyses Service of the University of Alicante. The purity of volatile distilled products and the chromatographic analysis (g.l.c.) were determined with a Hewlett Packard HP-5990 or a Konik Kromatix KNK- 2000 instrument, both equipped with a flame ionization detector. Thin layer chromatography (t.l.c.) was carried out on Scheleicher & Schnell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel using different mixtures of hexane/ethyl acetate as eluent; R_f values are given under these conditions. Starting chloroarenes **1**, **3**, **9** and **14**, naphthalene, lithium powder and the electrophiles were comercially available (Fluka, Aldrich). Starting compounds **12**[11g] and chloroanilides **19*o***[20], **19*m***[21], **19*p***[20,22] and **26**[23] were prepared according to the literature procedures. Solvents were dried as usually.

Catalytic Lithiation of Chloroarenes **1** *and* **3** *and Reaction with Electrophiles . General Procedure for Compounds* **2** *and* **4**.- To a cooled (-78 °C) green suspension of lithium powder (14 mmol) and naphtalene (0.06 mmol) in THF (10 ml) was added the corresponding chlorinated aromatic compound **1** or **3** (2,5 mmol), and the mixture was stirred at the same temperature for a period of 0.75-1.25 h. Then the corresponding electrophile was added (2.5 mmol). In the case of compound **3**, after 0.5 h stirring at -78°C the excess of lithium powder was filtered off at the same temperature and the second electrophile (3.0 mmol) was added (see Table 2)[24]. In both cases, the reaction mixture was stirred allowing the temperature to rise to 20°C during *ca.* 3h. The resulting mixture was then hydrolysed with methanol, neutralized with 2N hydrochloric acid and extracted with ether (2x10 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvents were evaporated (15 Torr) to give a residue, which was chromatographied (silica gel; hexane/ethyl acetate) to yield the corresponding products **2** and **4**. Yields are given in Tables 1 and 2. Physical and spectroscopic data follow.

2,2-Dimethyl-1-phenyl-1-propanol (**2**)[25]: R_f=0.40 (hexane/ethyl acetate: 9/1); ν (film) 3440 (OH), 3060, 3040, 1600 (Ph), and 1050 cm^{-1} (C-O); δ_H 0 90 (s, 9 H, $3xCH_3$), 2.00 (s, 1 H, OH), 4,35 (s, 1 H, CHO), and 7.25 (s, 5 H, Ph); δ_C 25.75, 35.3, 81.95, 126.9, 127.2, 127.45, and 142.15; *m/z* 165 (M^{+}+1, 1%), 164 (M^{+}, 10), 108 (10), 107 (100), 105 (15), 79 (77), 78 (14), 77 (61), 57 (13), 51 (15), and 41 (22).

1-Phenyl-1-cyclohexanol (**4a**)[26]: R_f=0.56 (hexane/ethyl acetate: 4/1); m.p. 60-62°C (hexane/ether); ν (melted) 3340 (OH), 3040, 1600 (Ph), and 970 cm^{-1} (C-O), δ_H 1.30-2.20 (m, 11 H, $5xCH_2$, OH), and 7.00-7.50 (m,

5H, Ph); δ_C 22.15, 25.45, 38.8, 73.1, 124.55, 126.65, 128.15, and 149.4; *m/z* 177 (M++1, 10%), 176 (M+, 71), 134 (24), 133 (100), 120 (62), 115 (16), 105 (71), 91 (21), 78 (24), 77 (48), 55 (47), and 51 (15).

3-[3-(2,2-Dimethyl-1-hydroxypropyl)phenyl]-3-pentanol (**4b**): R_f=0.27 (hexane/ethyl acetate: 4/1); ν (film) 3420 (OH), 3020, 1600 (Ph), 1040, and 1000 cm^{-1} (C-O); δ_H 0.75 (t, *J*=7.25, 6 H, 2xCH_3CH_2), 0.90 [s, 9 H, $(CH_3)_3C$], 1.80 (q, *J*=7.25, 2 H, 2xCH_2), 2.10 (s, 2 H, 2xOH), 4.35 (s, 1 H, CHO), and 7.10-7.30 (m, 4 H, Ph); δ_C 7.75, 25.95, 35.0, 35.65, 77.35, 82.45, 124.45, 124.8, 125.45, 127.15, 141.75, and 144.9; *m/z* 250 (M+, <1%), 221 (40), 194 (16), 193 (100), 105 (12), 91 (14), 87 (20), and 57 (29).

1-(3-Chlorophenyl)-2,2-dimethyl-1-propanol (**4c**)[27]: R_f=0.53 (hexane/ethyl acetate: 4/1); b.p. 75-78°C at 0.01 Torr; ν (film) 3420 (OH), 3040, 1590 (Ph), and 1000 cm^{-1} (C-O); δ_H 0.90 (s, 9 H, 3xCH_3), 2.20 (s, 1 H, OH), 4.33 (s, 1H, CHO), and 7.10-7.35 (m, 4 H, Ph); δ_C 25.8, 35.6, 81.7, 125.8, 127.35, 127.65, 128.7, 135.5, and 144.21; *m/z* 200 (M++2, 5%), 198 (M+, 14), 144 (20), 143 (64), 142 (63), 141 (100), 139 (12), 115 (16), 113 (44), 107 (14), 77 (76), 57 (65), 51 (15), and 41 (25).

3-[4-(2,2-Dimethyl-1-hydroxypropyl)phenyl]-3-pentanol (**4d**): R_f=0.36 (hexane/ethyl acetate: 4/1); ν (film) 3420 (OH), 3040, 1600 (Ph), 1040, and 1000 cm^{-1} (C-O); δ_H 0.75 (t, *J*=7.4, 6 H, 2xCH_3CH_2), 0.90 [s, 9 H, $(CH_3)_3C$], 1.80 (q, *j*=7.4, 4 H, 2xCH_2), 2.25 (s, 2 H, 2xOH), 4.35 (s, 1 H, CHO), 7,23, and 7.28 (2 d, *J*=8.1, 4 H, Ph); δ_C 7.75, 25.85, 35.5, 77.25, 82.05, 124.55, 127.1, 140.05, and 144.6; *m/z* 250 (M+, <1%), 194 (12), 193 (100), 137 (51), 136 (14), 107 (11), 79 (18), 57 (18), and 41 (10).

1-(4-Chlorophenyl)-2,2-dimethyl-1-propanol (**4e**)[28]: R_f=0.59 (hexane/ethyl acetate: 4/1); b.p. 90-93°C at 0.01 Torr; ν (film) 3420 (OH), 3020, 1600 (Ph), and 1000 cm^{-1} (C-O); δ_H 0.90 (s, 9 H, 3xCH_3), 2.25 (s, 1 H, OH), 4.30 (s, 1H, CHO), 7.20, and 7.27 (2 d, *J*=8.45, 4 H, Ph); *m/z* 200 (M++2, 1%), 198 (M+, 3), 143 (31), 141 (100), 113 (16), and 77 (40).

Catalytic Lithiation of Chlorophenols **9** *and* **14** *and Reaction with Electrophiles. General procedure for compounds* **10**.- To a solution of the corresponding chlorophenol **9** or **14** (2.5 mmol) in THF (5 ml) was added a 1.6 M hexane solution of butyllithium (2.6 mmol) at 0°C and the corresponding mixture was stirred during 15 min at the same temperature. The resulting solution was added to a green suspension of lithium powder (14 mmol) and naphthalene (0.06 mmol) in THF (5 ml) at 0°C and the mixture was stirred for 1-7 h (see Tables 3 and 4) at the same temperature. Then the corresponding electrophile (2.5 mmol) was added. In the case of dichlorophenols **14** after 2 h stirring deuterium oxide was added (0.3 ml) and the temperature was allowed to rise to 20°C overnigth. In both cases, the corresponding reaction mixture was worked up as above for compounds **2** and **4** to give products **10**. Products **10a**, **10b**, and **10c**, obtained of a mixture in the case of starting from materials **14b** and **14c**, could be easily separated by flash chromatography (silica gel; hexane/ethyl acetate). Yields for compounds **10** are given in tables 3 and 4. Analytical, physical and spectroscopic data follow.

2-(2,2-Dimethyl-1-hydroxypropyl)phenol (**10a**): R_f=0.67 (hexane/ethyl acetate: 3/2); ν (film) 3340 (OH), 3040, 1580 (Ph), 1030, and 1000 cm^{-1} (C-O); δ_H 0.95 (s, 9 H, 3xCH_3), 3.15 (s, 1 H, CHO*H*), 4,50 (s, 1 H, CHO), 6.75-6.90, 7.10-7.20 (2 m, 4 H, Ph), and 8.50 (s, 1 H, OH); δ_C 26.0, 37.2, 84.8, 117.15, 118.7, 123.9, 128.6, 129.65, and 156.1; *m/z* 181 (M++1, 2%), 180 (M+, 16), 147 (14), 124 (12), 123 (100), 95 (32), and 77 (27).

3-(2,2-Dimethyl-1-hydroxypropyl)phenol (**10b**): R_f=0.74 (hexane/ethyl acetate: 1/4); m.p. 156-159°C (hexane/ether); ν (melted) 3400, 3180 (OH), 3040, 1600 (Ph), 1040, and 1000 cm^{-1} (C-O); δ_H (CD_3COCD_3) 0.90 (s, 9 H, 3xCH_3), 4.10 (s, 1 H, CHO*H*), 4,30 (s, 1 H, CHO), 6.70, 6.75, 6.80, 7.05 (d, d, s, t, respectively, *J*=7.8, 4 H, Ph), and 8.20 (s, 1 H, COH); δ_C (CD_3COCD_3) 26.5, 36.1, 81.9, 114.4, 115.6, 119.9, 128.7, 145.9, and 157.35; *m/z* 181 (M++1, 2%), 180 (M+, 16), 124 (28), 123 (100), 95 (90), 77 (31), and 41 (10); Anal. calcd for $C_{11}H_{16}O_2$· C, 73.30; H, 8.95. Found: C, 73.2; H, 9.0.

4-(2,2-Dimethyl-1-hydroxypropyl)phenol (**10c**) R_f=0.68 (hexane/ethyl acetate: 1/4); m.p. 147-150°C (hexane/ether); ν (KBr) 3380, 3240 (OH), 3040, 1600 (Ph), 1040, and 1000 cm^{-1} (C-O); δ_H (CD_3COCD_3) 0.90 (s, 9 H, 3xCH_3), 4.00 (s, 1 H, CHO*H*), 4,30 (s, 1 H, CHO), 6.75, 7.15 (2 d, *J*=8.45, 4 H, Ph), and 8.20 (s, 1 H, COH); δ_C (CD_3COCD_3) 26.4, 36.15, 81.7, 114.7, 129.45, 134.9, and 156.95; *m/z* 181 (M ++1, 1%), 180

(M+, 9), 124 (18), 123 (100), 95 (37), and 77 (21); Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.3; H, 9.2.

Catalitic Lithiation of Compound **12** *and Reaction with Pivalaldehyde. Isolation of compound* **13** *and Hydrolysis to* **10a**.- To a green suspension of lithium powder (14 mmol) and naphthalene (0.06 mmol) in THF (10 ml) was added the compound **12**[11] (2.5 mmol) at -78°C and the mixture was stirred for 45 min at the same temperature. Then, pivalaldehyde (3.0 mmol) was added and stirring was continued allowing the temperature to rise to 20°C during *ca.* 4 h. The resulting mixture was then worked up as for compounds **2, 4** or **10**, yielding *2,2-Dimethyl-1-[2-(2-methoxy)methoxyphenyl]-1-propanol* (**13**): R_f=0.78 (hexane/ethyl acetate: 3/2); ν (film) 3440 (OH), 3040, 1600 (Ph), 1090, 1080, and 1000 cm^{-1} (C-O); δ_H 0.95 [s, 9 H, $(CH_3)_3C$], 2.80 (s,1 H, OH), 3.35 (s, 3 H, CH_3O), 3.55, 3.75 (2 t, *J*=4.55, 4 H, OCH_2CH_2O), 4.80 (s, 1 H, CHO), 5.25 (s, 2 H, OCH_2O), 6.95, 7.12, 7.17, and 7.35 (t, d, t, d, respectively, *J*=6.85, 7.25, 6.85, 7.25, respectively, 4 H, Ph); δ_C 25.75, 36.25, 58.7, 67.6, 71.35, 93.6, 113.65, 121.0, 127.85, 128.8, 131.0, and 154.65; *m/z* 268 (M+, <1%), 211 (22), 135 (13), 121 (13), 89 (100), and 59 (70).

A solution of compound **13** (2 mmol) in THF (5 ml) was treated with 6 N HCl (5 ml) and the mixture was refluxed for 2 h, yielding after the above described work up compound **10a** (93 %).

Catalitic Lithiation of Chloroanilides **18** *and* **25** *and Reaction with Electrophiles. General Procedure for Compounds* **19, 21, 22**, *and* **24**.-To a solution of the corresponding chloroanilide **18** or **25** (2.0 mmol) in THF (5 ml) at 0°C was added a 1.6 M hexane solution of butyllithium (2.0 mmol) and the mixture was stirred for 10 min. This solution was then added to a green suspension of lithium (14 mmol) and naphthalene (0.23 mmol) in THF (10 ml) at -78°C and the mixture was stirred at the same temperature for 3-4 h . Then, the corresponding electrophile (2.2 mmol) was added to the reaction mixture and stirring was continued for *ca.* 1h allowing the temperature to rise to 20°C. In the case of using benzonitrile or phenyl isocyanate as electrophile the excess of lithium powder was filtered off at low temperature prior the addition of the electrophile. The resulting mixture was then worked up as above[29] for compounds **2**, **4**, or **10**, yielding compounds **19, 21, 22**, and **24**. Yields are given in Table 5. Analytical, physical, and spectroscopic data follow.

N-*[2-(1-Hydroxy-2,2-dimethylpropyl)phenyl]pivalamide* (**19a**): R_f 0.53 (hexane/ethyl acetate: 3/2); m.p. 125-126°C (hexane/dichloromethane); ν ($CHCl_3$) 3300 (NH, OH), 1650 (C=O), and 1515 cm^{-1} (NH, C-N); δ_H 0.90 [s, 9 H, $(CH_3)_3CCHOH$], 1.23 [s, 9 H, $(CH_3)_3CCO$], 4 20 (br s, 1 H, OH), 4.48 (s, 1 H, CHOH), 6.93, 7.15 (2 m, 3 H, ArH), 8.24 (d, *J*=8.1, 1 H, ArH), and 10.06 (br s, 1 H, NH); δ_C 26.45, 27.4, 37.3, 39.65, 84.8, 122.0, 122.5, 127.5, 128.6, 130.1, 138.7, and 176.85; *m/z* 264 (M+·+1, 4%), 263 (M+·, 20), 206 (52), 132 (21), 122 (81), 93 (15), 85 (47), 57 (100), and 41 (38).

N-*[2-(1-Ethyl-1-hydroxyethyl)phenyl]pivalamide* (**19b**). R_f 0.54 (hexane/ethyl acetate: 3/2); m.p. 137-138°C (hexane/dichloromethane); ν ($CHCl_3$) 3340 (OH, NH), 1650 (C=O), and 1520 cm^{-1} (NH, C-N); δ_H 0.83 (t, *J*=7.4, 6 H, CH_3CH_2), 1.27 [s, 9 H, $(CH_3)_3C$], 1.92 (m, 4 H, 2xCH_2), 3.08 (br s, 1 H, OH), 6.95-7.07 (m, 2 H, ArH), 7.20 (dt, *J*=7.0, 0.65, 1 H, ArH), 8.38 (dd, *J*=8.2, 1.2, 1 H, ArH), and 10.40 (br s, 1 H, NH); δ_C 8.0, 27.55, 32.6, 39.8, 80.55, 122.25, 122.65, 126.95, 127.4, 131.1, 138.5, and 176.7; *m/z* 264 (M+·+1, 5%), 263 (M+·, 25), 234 (34), 160 (33), 150 (39), 132 (37), 120 (15), 85 (24), 57 (100), and 41 (16); Anal. calcd for $C_{16}H_{25}NO_2 \cdot 1/2\ H_2O$: C, 70.55; H, 9.62; N, 5.14. Found: C, 70.9; H, 9.7; N, 5.1.

N-*[3-(1-Hydroxy-2-methylpropyl)phenyl]pivalamide* (**19c**)· R_f 0.34 (hexane/ethyl acetate: 3/2); syrup; ν ($CHCl_3$) 3320 (NH, OH), 1650 (C=O), and 1520 cm^{-1} (NH, C-N); δ_H 0.78, 0.96 (2d, *J*=6.6, 6 H, 2xCH_3CH), 1.29[s, 9 H, $(CH_3)_3C$], 1.93 [m, 1 H, $(CH_3)_2CH$], 2.70 (br s, 1 H, OH), 4.28 (d, *J*=6.6, 1 H, CHOH), 7.02 (deformed d, 1 H, ArH), 7.25 (deformed t, 1 H, ArH), 7.42 (deformed d, 1 H, ArH), 7.43 (s, 1 H, ArH), and 7.50 (br s, 1 H, NH), δ_C 18 0, 19 0, 27.5, 35.1, 39.5, 79.5, 118.4, 119.15, 122.6, 128.5, 137.7, 144.7, and 176.85; *m/z* 250 (M+·+1, 4%), 249 (M+·, 28), 207 (25), 206 (100), 94 (20), and 57 (48).

N-*[3-(1-Hydroxy-2,2-dimethylpropyl)phenyl]pivalamide* (**19d**): R_f 0.43 (hexane/ethyl acetate: 3/2); syrup; ν ($CHCl_3$) 3430, 3350 (NH, OH), 1655 (C=O), and 1520 cm^{-1} (NH, C-N); δ_H 0.91 [s, 9 H, $(CH_3)_3CCHOH$], 1.29 [s, 9 H, $(CH_3)_3CCO$], 2.41 (br s, 1 H, OH), 4.30 (s, 1 H, CHOH), 7.00 (d, *J*=7.7, 1 H, ArH), 7.21 (t,

J=7.7, 1 H, ArH), 7.40 (s, 1 H, ArH), 7.45 (d, *J*=7.7, 1 H, ArH), and 7.47 (s, 1 H, NH); δ_C 25.9, 27.5, 35.5, 39.5, 81.95, 119.0, 119.4, 123.65, 127.85, 137.3, 143.2, and 176.65; *m/z* 264 (M++1, 2%), 263 (M+, 12), 208 (17), 207 (100), 206 (91), 94 (25), 77 (12), 57 (87), and 41 (30).

N-*[3-(1-Hydroxycyclohexyl)phenyl]pivalamide* (**19e**): R_f 0.37 (hexane/ethyl acetate : 3/2); m.p. 130°C (hexane/dichloromethane); ν ($CHCl_3$) 3350 (NH, OH), 1650 (C=O), and 1525 cm^{-1} (NH, C-N); δ_H 1.30 [s, 9 H, $(CH_3)_3C$], 1.52-1.90 (m, 10 H, 5xCH_2), 2.11 (br s, 1 H, OH), 7.19-7.29 (m, 2 H, ArH), 7.42 (m, 1 H, ArH), 7.44 (br s, 1 H, NH), and 7.66 (m, 1 H, ArH); δ_C 22.0, 25.35, 27.5, 38.65, 39.5, 73.05, 116.6, 118.3, 120.5, 128.65, 137.8, 150.55, and 176.65; *m/z* 276 (M++1, 8%), 275 (M+, 46), 232 (75), and 57 (100). Anal. calcd for $C_{17}H_{25}NO_2 \cdot 1/2\ H_2O$: C, 71.80; H, 9.21; N, 4.92. Found: C, 71.9; H, 9.2; N, 4.8.

3-Benzoylpivalanilide (**19f**): R_f 0.50 (hexane/ethyl acetate : 3/2); m.p. 139°C (hexane/dichloromethane); ν ($CHCl_3$) 3440, 3360 (NH), 1650 (C=O), and 1520 cm^{-1} (NH, C-N); δ_H 1.32 [s, 9 H, $(CH_3)_3C$], 7.39-7.51 (m, 4 H, ArH), 7.50 (br s, 1 H, NH), 7.59 (deformed t, 1 H, ArH), 7.78 (s, 1 H, ArH), 7.80 (deformed d, 2 H, ArH), and 8.00 (deformed d, 1 H, ArH); δ_C 27.55, 39.65, 121.0, 124.15, 127.85, 128.3, 128.9, 130.05, 132.55, 137.3, 138.25, 138.3, 176.8 and 196.3; *m/z* 282 (M++1, 5%), 281 (M+, 30), 197 (42), 120 (11), 105 (31), 77 (36), 57 (100), and 41 (20). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.97. Found: C, 76.7; H, 6.8; N, 4.9.

N-*[4-(1-Hydroxy-2-methylpropyl)phenyl]pivalamide* (**19g**): R_f 0.31 (hexane/ethyl acetate: 3/2); ν ($CHCl_3$) 3420 (NH, OH), 1650 (C=O), and 1510 cm^{-1} (NH, C-N); δ_H 0.76, 0.97 (2d, *J*=6.7, 6 H, 2xCH_3CH), 1.30 [s, 9 H, $(CH_3)_3C$], 1.91 [m, 1 H, $(CH_3)_2CH$], 2.26 (br s, 1 H, OH), 4.30 (d, *J*=6.9, 1 H, CHOH), 7.21, 7.46 (2d, *J*=8.5, 4 H, ArH), and 7.45 (br s, 1 H, NH); δ_C 18.2, 18.8, 27.5, 35.15, 39.45, 76.4, 119.85, 127.0, 137.0, 139.5, and 176.7; *m/z* 249 (M+, 5%), 207 (14), 206 (100), 123 (23), 122 (26), 94 (10), 77(10), 57 (41), and 41 (13). Anal. calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.3; H, 9.3; N, 5.4.

N-*[4-(1-Hydroxy-2,2-dimethylpropyl)phenyl]pivalamide* (**19h**): R_f 0.36 (hexane/ethyl acetate: 3/2); m.p. 158-159°C (hexane/dichloromethane); ν ($CHCl_3$) 3400 (NH, OH), 1640 (C=O), and 1510 cm^{-1} (NH, C-N); δ_H 0.89 [s, 9 H, $(CH_3)_3$CCHOH], 1.30 [s, 9 H, $(CH_3)_3$CCO], 2.10 (br s, 1 H, OH), 4.34 (s, 1 H, CHOH), 7.22, 7.45 (2d, *J*=7.5, 4 H, ArH), and 7.41 (br s, 1 H, NH); δ_C 25.8, 27.55, 35.6, 39.5, 81.85, 119.15, 128.0, 137.0, 138.05, and 176.6; *m/z* 263 (M+, 6%), 207 (28), 206 (100), 123 (34), 122 (33), 94 (15), 77(11), and 57 (64). Anal. calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.5; H, 9.6; N, 5.4.

N-*[4-(1-Ethyl-1-hydroxyethyl)phenyl]pivalamide* (**19i**): R_f 0.36 (hexane/ethyl acetate : 3/2); m.p. 165-166°C (hexane/dichloromethane); ν ($CHCl_3$) 3425, 3300 (NH, OH), 1640 (C=O), and 1510 cm^{-1} (NH, C-N); δ_H 0.74 (t, *J*=7.4, 6 H,2xCH_3CH_2), 1.31 [s, 9 H, $(CH_3)_3C$], 1.81 (m, 4 H, 2xCH_2), 1.81 (br s, 1 H, OH), 7.31, 7.49 (2d, *J*=8.6, 4 H, ArH), and 7.40 (br s, 1 H, NH); δ_C 7.85, 27.7, 35.0, 39.6, 77.3, 119.7, 126.15, 136.25, 141.75, and 176.65; *m/z* 245 (M^+-H_2O, 73%), 161 (28), 160 (19), 132 (39), and 57 (100). Anal. calcd for $C_{16}H_{25}NO_2 \cdot 1/2\ H_2O$: C, 70.55; H,9.62; N, 5.14. Found: C, 70.7; H, 9.7; N, 5.1.

4-Benzoylpivalanilide (**19j**): R_f 0.45 (hexane/ethyl acetate: 3/2); m.p. 128-129°C (hexane/dichloromethane); ν ($CHCl_3$) 3345 (NH), 1640 (C=O), and 1510 cm^{-1} (NH, C-N); δ_H 1.32 [s, 9 H, $(CH_3)_3C$], 7.45 (t, *J*=7.6, 2 H, ArH), 7.56 (t, *J*=7.6, 1 H, ArH), 7.65-7.85 (m, 6 H, ArH), and 7.97 (br s, 1H, NH); δ_C 27.3, 39.7, 119.05, 128.1, 129.65, 131.3, 132.05, 132.55, 137.7, 142.2, 177.1, and 195.7; *m/z* 282 (M++1, 5%), 281 (M+, 24), 197 (21), 120 (29), 77 (17), 57 (100), and 41 (15). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.8; H, 6.8; N, 5.0.

2-tert-Butyl-4-phenylquinazoline (**21**): R_f 0 68 (hexane/ethyl acetate: 3/2); m.p. 96°C (hexane/dichloromethane); ν ($CHCl_3$) 1610, 1560, and 1540 cm^{-1} (C=N, C=C); δ_H 1.55 [s, 9 H, $(CH_3)_3C$], 7.45-7.55 , 7.78-7.83, and 8 03-8.08 (3 m, 9 H, ArH); δ_C 29.7, 39.6, 120.85, 126.4, 126.65, 128.4, 128.9, 129.6, 130.2, 132.85, 137.95, 151.4, 167.35, and 172.85; *m/z* 263 (M++1, 12%), 262 (M+, 50), 261 (21), 247 (100), 220 (48), 205 (20), 123 (11), and 77 (13). Anal. calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.4; H, 7.0;

N, 10.6.

2-Phenylaminocarbonylpivalanilida (**22**): R_f 0.48 (hexane/ethyl acetate: 3/2); m.p. 227°C (hexane/dichloromethane); ν ($CHCl_3$) 3420, 3300 (NH), 1650 (C=O), and 1510 cm^{-1} (N-H, C-N); δ_H 1.33 [s, 9 H, $(CH_3)_3C$], 7.00 (t, *J*=7.6, 1 H, ArH), 7.19 (t, *J*=7.4, 1 H, ArH), 7.31 (t, *J*=7.9, 1 H, ArH), 7.40 (t, *J*=7.6, 2 H, ArH), 7.49 (d, *J*=7.9, 1 H, ArH), 7.71 (d, *J*=8.1, 2 H, ArH), 8.37 (d, *J*=8.4, 1 H, ArH), 8.61 (br s, 1 H, NH), and 10.90 (br s, 1 H, NH); δ_C 27.55, 40.0, 120.5, 122.0, 122.15, 122.8, 124.8, 126.95, 129.10, 132.1, 137.85, 139.25, 167.15, and 178.0; *m/z* 239 (M^+-C_4H_9, 1%), 204 (28), 146 (10), 120 (22), 93 (100), 92 (12), 90 (11), 65 (13), 57 (48), and 41 (25). Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45.Found: C, 72.4; H, 6.8; N, 9.2.

4-Phenyl-2-(1H)-quinazolinone (**24**)[16b]: R_f 0.28 (hexane/ethyl acetate : 1/4); m.p. 262-263°C (hexane/dichloromethane); ν (Nujol) 3140 (NH), 1650, and 1590 cm^{-1} (C=O, C=N, C=C); δ_H 7.22-7.27, 7.53-7.75 (2 m, 6 H, ArH), 7.80-7.90 (2 d, *J*=6.8, 8.2, 3 H, ArH), and ≈9.50 (br s, 1 H, NH); δ_C 115.35, 116.8, 123.05, 128.4, 128.8, 129.8, 130.75, 135.3, 136.5, 143.4, 158.35, and 176.65; *m/z* 224 (M^++2, 29%), 223 (M^++1, 30), 222 (M^+, 53), 221 (100), 180 (22), 147 (87), 77(36), 63 (13), 51 (24), and 50 (12). Anal. calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 74 7; H, 4.5; N, 12.4

Reaction of 2-Chloropivalanilide (**18***o*) *with an Excess of Butyllithium. Isolation of 2-Butylpivalanilide* (**23**).- The reaction was carried out as it was described for compounds **19**, starting from **18***o* but using an excess of butyllithium (1:2.5 molar ratio) at -78°C with or without lithium powder/naphthalene cat.[30], and hydrolyzed and worked up as for compounds **19** to yield the title compound **23**: R_f 0.70 (hexane/ethyl acetate: 4/1); m.p. 71-72°C (hexane/dichloromethane); ν ($CHCl_3$) 3300 (NH) and 1650 cm^{-1} (C=O); δ_H 0.95 (t, *J*=7.2, 3 H, CH_3CH_2), 1.34 [s, 9 H, $(CH_3)_3C$], 1.39, 1.58 (2 m, 4 H, CH_2CH_3), 2.56 (t, *J*=7.7, 2 H, CH_2Ar), 7.05-7.26 (m, 3 H, Ar), 7.30 (br s, 1 H, NH), and 7.88 (d, *J*=8.0, 1 H, ArH); δ_C 13.95, 22.7, 27.7, 31.45, 32.05, 39.7, 123.35, 124.95, 126.75, 129.55, 133.2, 135.3, and 176.15; *m/z* 234 (M^++1, 7%), 233 (M^+, 45), 204 (3[3]), 176 (58), 106 (77), and 57 (100).

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