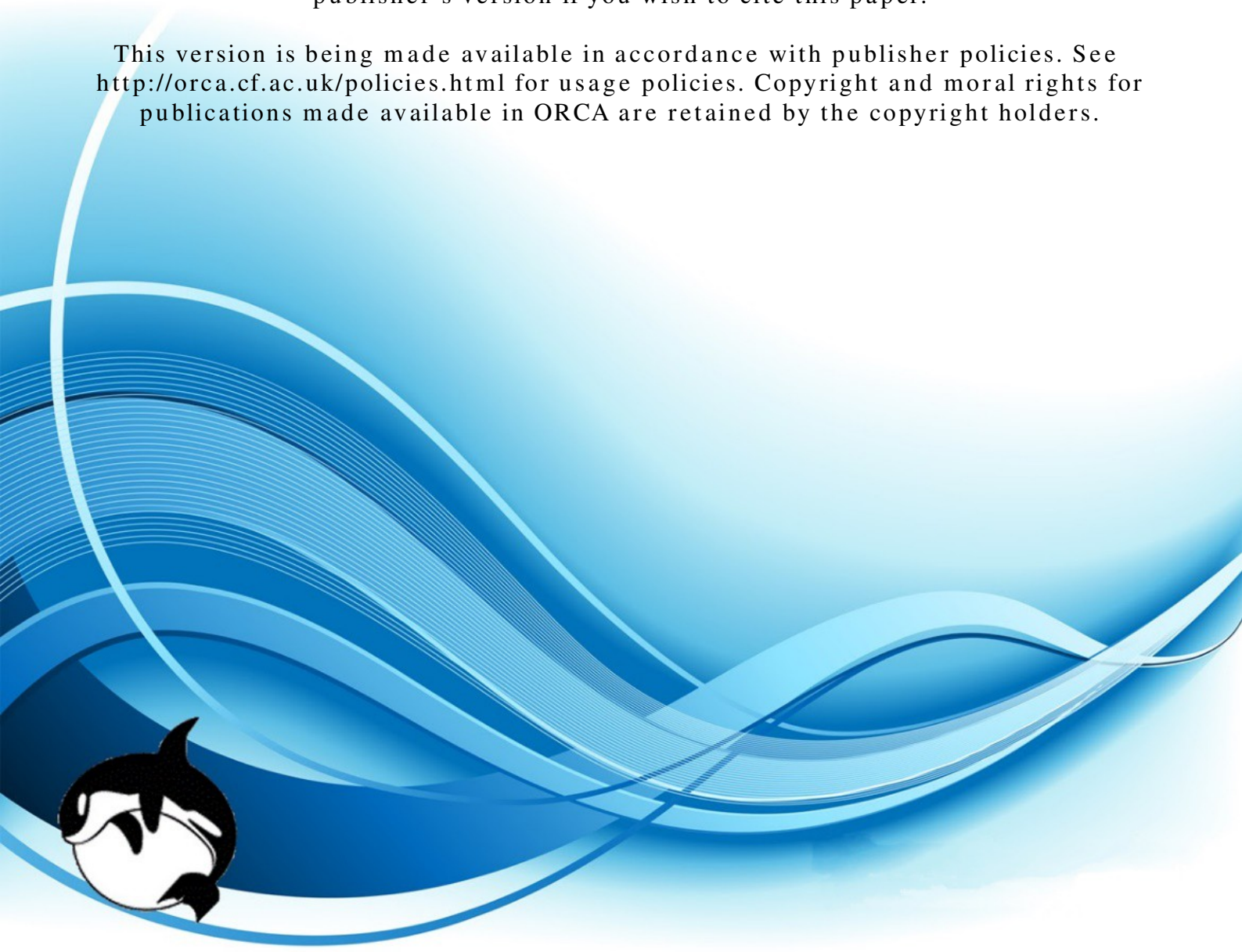

Unravelling Factors Affecting Directed Lithiation of Acylaminoaromatics

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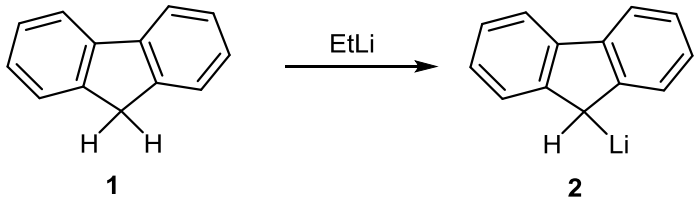
Abstract Ureas, pivalamides and carbamates are widely used as directing metalation groups (DMGs) due to their good directing ability, low cost, ease of access and ease of removal. Lithiation of substituted benzenes having such directing metalation groups using various alkyllithiums in anhydrous solvent at low temperature provides the corresponding lithium intermediates, but lithiation may take place at various sites. Reactions of the lithium reagents obtained *in-situ* with various electrophiles give the corresponding derivatives, typically substituted at the site(s) where initial lithiation occurred, often in high yields. However, it is often difficult to predict what reagents and/or conditions might be needed to give specific products or to draw general conclusions about the factors that influence the reactions, especially when the reagents, temperature and solvents used in reported reactions are not directly comparable. In this review, therefore, we attempt to unravel the various factors that influence the lithiation of various simple aromatic compounds containing urea, pivalamide and carbamate groups.

Keywords lithium reagents, directed lithiation, ureas, pivalamides, carbamates, electrophiles, lateral lithiation

1. Introduction

Traditional electrophilic aromatic substitution reactions were once the mainstay for synthesis of pharmaceutical and other valuable aromatic compounds, and were extremely thoroughly studied.[1] However, such reactions often suffer from serious disadvantages such as elevated temperatures, low regioselectivity and/or use of stoichiometric quantities of Lewis acids or other activators. Solid catalysts offer a possible route for improving the selectivity towards *para*-substitution,[2] but for preparation of *ortho*-disubstituted aromatics, directed *ortho* metalation (DoM), and particularly directed lithiation, is often now the method of choice.[3–7]

Lithiation was reported for the first time in 1928 by Schlenk and Bergmann who deprotonated fluorene (**1**) with ethyllithium (Scheme 1).[8]



Scheme 1 Lithiation of fluorene (1) using ethyllithium by Schlenk and Bergmann[8]

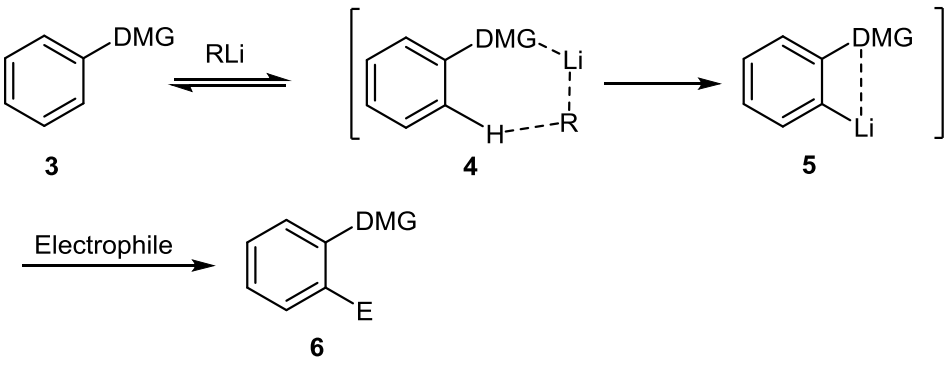
In 1939–1940, Gilman[9] and Wittig[10] independently discovered that *n*-butyllithium (*n*-BuLi) brought about *ortho* deprotonation of anisole, which heralded a new concept in synthetic aromatic chemistry, the ability of a substituent to direct lithiation to a particular location. The same scientists also discovered halogen–metal exchange reactions, which could be used for the production of lithium reagents when lithiation failed.[11,12] Although the field of organolithium chemistry continued to advance following those pioneering discoveries, it was not until some simple organolithium reagents became commercially available in the 1970s,[13] as a result of their use as polymerization catalysts,[14] that lithiation became a standard part of the toolkit of synthetic chemists. Following seminal work by notables such as Schlosser, Beak, Hoppe, Snieckus, and others, the *ortho*-lithiation reaction has evolved to become a significant fundamental methodology for the regiospecific construction of polysubstituted aromatic and heteroaromatic compounds and has become one of the most widely used processes for synthesis of organic compounds.

Simple organolithium reagents such as the various isomeric butyllithiums are soluble in organic solvents (*e.g.* hexane and ethers), and are more reactive than comparable organomagnesium reagents but less reactive than organosodium and organopotassium reagents.[15] Several organolithium reagents are made commercially, and *n*-BuLi, *sec*-BuLi and *t*-BuLi are sold as solutions in hydrocarbon solvents in tonnage quantities due to their reasonable stability at room temperature. The reagents are aggregates (typically hexamers or tetramers) in hydrocarbon solvents,[16] but the degree

of aggregation tends to be lower (and the reactivity somewhat higher in consequence) in the presence of coordinating ligands such as ether solvents or *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), which provide electron density to the electron deficient lithium atom *via* coordination. Alternative lithiating reagents include lithium amides such as lithium diisopropylamide (LDA), which are less basic than alkyllithium reagents but also less nucleophilic, and mixtures of alkyllithiums with potassium alkoxides (so-called LICKOR reagents or Schlosser's base)[17] or related species, which are very reactive reagents often referred to as "super-bases".

The lithiation of benzene, naphthalene or other simple arenes does not occur with simple hydrocarbon solutions of alkyllithium reagents because although protons attached to sp^2 carbons are more acidic than protons attached to unactivated sp^3 carbons, the reactivity of simple unsubstituted arenes is not great enough. In some substituted aromatic rings, however, alkyllithium reagents can deprotonate an sp^2 hybridized carbon atom on the ring, because of the activating effect of the substituent or a heteroaromatic ring. Factors which increase the acidity of the hydrogens, such as electron-withdrawing groups (*e.g.* nitrile and carboxyl) facilitate lithiation,[18] while methyl and other alkyl groups deactivate the ring towards lithiation.[19] However, in addition to any effects on the thermodynamic acidity of the hydrogens on the ring, various substituents exert a kinetic enhancement of removal of particular protons, apparently through a direct proximity effect. For this reason, such groups are described as directing metalation groups (DMGs) and the process is referred to as directed metalation (specifically DoM when the proton removed is *ortho* to the DMG), and in particular directed lithiation when the metal is lithium.

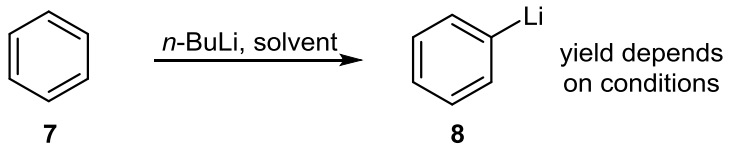
Scheme 2 shows directed lithiation of a substituted benzene (**3**) possessing a DMG, which directs the attack of an organolithium reagent to the *ortho* positions of the benzene ring. The DMG has to possess a donor substituent containing a coordinating atom such as oxygen or nitrogen to form a complex **4** with the Lewis acidic organolithium reagent and direct the nucleophile to the neighboring proton that is to be removed. Removal of the proton leads *in-situ* to production of new lithium reagent **5**, which on reaction with an electrophile gives the corresponding 2-substituted derivatives **6**.



Scheme 2 Directed lithiation of substituted benzene **3** and reaction with an electrophile

This latter process is of enormous utility and is widely used, but there are many potential variables that can influence the course of any particular metalation reaction, including the nature of the metal or metals, the ligands attached to those metals, the solvent, the temperature, the underlying structure of the substrate, the nature of any directing groups or other groups forming part of the substrate, the distance between the directing group and any hydrogen atom to be replaced, and so on.

Aggregation brings down the reactivity of organolithium reagents, but the aggregates can be broken up and the reagent activated by complexation with an electron donor such as a Lewis basic solvent (*e.g*. diethyl ether or THF) or an additive (*e.g*. TMEDA, 1,4-diazabicyclo[2.2.2]octane (DABCO), or potassium *tert*-butoxide (*t*-BuOK)), which also enhance the reactivity of organolithiums by increasing the ionic character of the Li–C bond (increased negative charge on carbon). For example, whereas lithiation of benzene (**7**) does not take place using *n*-BuLi in hydrocarbon solvent, where the *n*-BuLi exists as a hexamer, in diethyl ether and/or THF, where the *n*-BuLi exists as a tetramer, lithiation occurs to a modest extent (greater in THF than in diethyl ether), while in the presence of TMEDA or DABCO, where the *n*-BuLi exists as either a dimer or monomer, a good yield of phenyllithium can be achieved (Scheme 3).



Scheme 3 Lithiation of benzene (**7**) using *n*-BuLi in different conditions

The increased reactivity resulting from the complexation between a lithium reagent and a solvent can be deleterious under certain conditions (*e.g*. higher temperature or longer time), because the reagent and solvent may react with each other. For example, one typical pathway for a reaction of an organolithium reagent with an ether solvent involves ether cleavage leading to an alkene and a lithium alkoxide.

Additives can also affect the regioselectivity of lithiation reactions. For example, during lithiation of 4-methoxy-(*N,N*-dimethylaminomethyl)benzene (**9**, Figure 1) with *n*-BuLi, the nitrogen atom binds to the Li (Lewis acid), and directs deprotonation to the position *ortho-* to the dimethylaminomethyl group, *i.e. meta* to the methoxy group. On the other hand, in the presence of TMEDA or *t*-BuOK, which increase the basicity of the metalating agent, the more acidic proton, next to the methoxy group, is removed.[20]

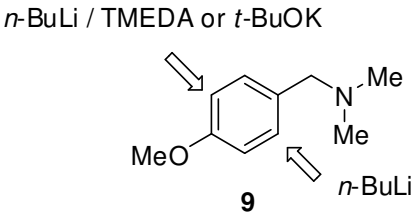


Figure 1 Regioselective lithiation of 4-methoxy-(*N,N*-dimethylaminomethy)lbenzene (**9**)

In another example, lithiation of *tert*-butyl *N*-2-(3-methoxyphenyl)ethylpivalamide (**10**, Figure 2) with *n*-BuLi takes place at the 2-position, powered by coordination from both the methoxy and pivaloylamino groups. The use of *t*-BuLi diverts lithiation to the less hindered benzylic site (α-lithiation), where it still benefits from coordination with the pivaloylamino group. When the Lewis acidity of the Li atom in *t*-BuLi is decreased and the basicity of the reagent increased by the addition of a Lewis base such as TMEDA, the most acidic and less hindered proton, at position 4, is removed.[21]

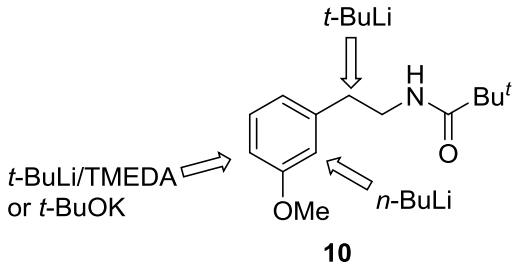
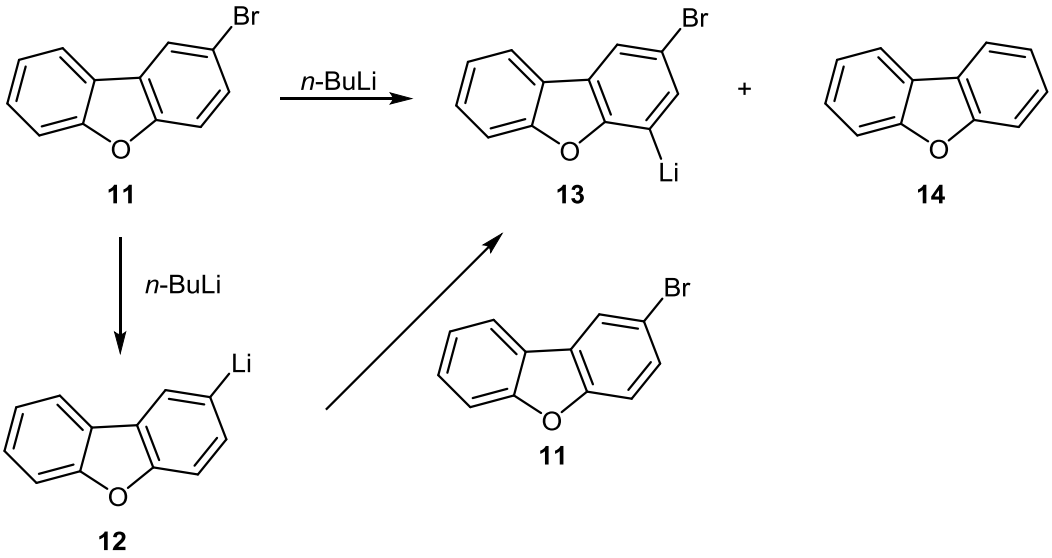


Figure 2 Regioselective lithiation of *N*-2-(3-methoxyphenyl)ethylpivalamide (**10**)

The temperature can also have a significant effect in lithiation reactions. It can affect the reaction rate or regioselectivity, the stability of the intermediates, or the tendency for isomerization, as well as creating or preventing side products.

In some cases, the lithiation product does not reflect where lithiation initially occurs during the course of a reaction. For example, lithiation of 2-bromodibenzofuran (**11**) with *n*-BuLi initially undergoes halogen–metal exchange to give 2-lithiodibenzofuran (**12**), which then lithiates unreacted 2-bromodibenzofuran to give 2-bromo-4-lithiodibenzofuran (**13**) along with dibenzofuran (**14**; Scheme 4), as inferred from the structure of the carboxylation product obtained.[22,23]



Scheme 4 Reaction of 2-bromodibenzofuran (**11**) with *n*-butyllithium

Despite the electronegativity of oxygen and nitrogen atoms, lithiation at a carbon atom attached to an NMe_2 or OMe group is disfavored as a result of the destabilizing interaction of the lone pairs of electrons on N or O with the electrons of the C–Li bond (Figure 3). However, such α-lithiation may be favored when the lone pairs are delocalized by conjugation with a carbonyl group, which reduces the repulsive interaction and provides an attractive interaction between the Li and O atoms (Figure 3).

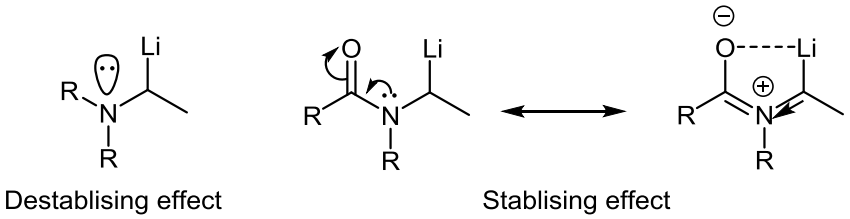


Figure 3 Stabilizing and destabilizing effects of lithium intermediates

Clearly, there is significant understanding of many of the individual factors that influence lithiation reactions and in many specific cases conditions have been optimized for the production of particular products. However, it is unusual for several different factors to be addressed simultaneously within any single study, so it is difficult to gauge the relative importance of the various factors. Consequently, when attempting a new lithiation reaction it is frequently necessary to resort to trial and error approaches in order to determine how to conduct the desired reaction.

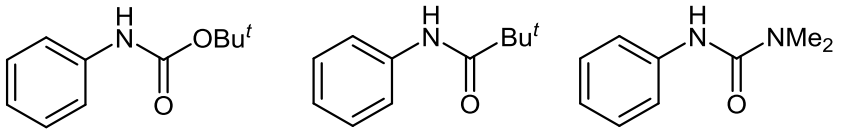
The widespread presence of nitrogen in molecules with important properties means that there is always need for methods of synthesis and elaboration of compounds containing an amino group. We have been interested in substitution of (hetero)aromatic rings containing an amino group *via*

lithiation (*i.e.* the replacement of hydrogen by lithium) of protected derivatives thereof and for some time we have been attempting to disentangle some of the variables by looking systematically at lithiation reactions of substrates possessing the same set of DMGs (specifically *tert*-butoxycarbonylamino, pivaloylamino and dimethylaminocarbonylamino groups)[24–28] with a limited range of lithiating agents (mostly *n*-BuLi, *s*-BuLi and *t*-BuLi, with occasional comparisons with lithium amides such as LDA, superbasic reagents such as LICKOR reagents, and alkyllithium reagents in the presence of Lewis base additives). Clearly, it is not possible to look at the systematic effects of all variables within a short timescale, but we have varied the DMG attached to an aromatic ring, the substituents around that ring, and the location of the DMGs in relation to the ring, all under a limited range of conditions. We have published individual studies of specific systems, but in this review for the first time we bring all our information together, along with information in articles published by others for reactions conducted under broadly similar conditions, in an attempt to clarify the relative importance of the different parameters.

2. Lithiation with DMG Attached Directly to Aromatic Ring

2.1. Influence of the DMG

All three DMGs of interest for this study can be cleaved to give an amino group, and can therefore all be considered as masked amino groups. In order to assess the relative influences of the three DMGs, the conditions necessary to bring about *ortho*-lithiation of the appropriate *N*-phenyl derivatives **15**–**17** (Figure 4) can be compared. Unfortunately, the conditions reported for lithiation of the three compounds are not always directly comparable, but some general conclusions are nevertheless possible.



15 **16** **17**

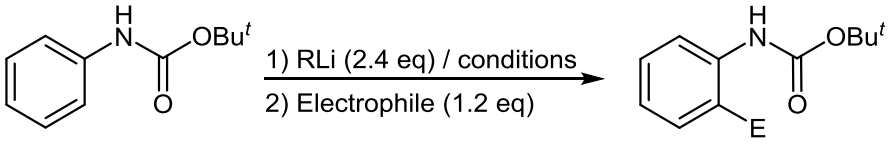
Figure 4 Structures of compounds **15–17**

All of the compounds readily give up the NH proton when reacted with one equivalent of an alkyllithium, but the important lithiation step is removal of a second (CH) proton. Therefore, while we may refer to lithiation of the parent compounds, it should be recognized that it is really lithiation of the metalated functionality that is meant.

Although the carbamate **15** has been reported to undergo lithiation with *t*-BuLi in THF at temperatures as low as –75 °C,[29] the optimum temperature for lithiation using this reagent and solvent

is reported to be –20 °C, which enables high yields of substitution products **18** (Table 1) to be achieved routinely.[30–33] Lithiation with *t*-BuLi in ether is also possible,[34,35] but the reported yield of one product when the reaction was conducted in ether as solvent under comparable conditions was somewhat lower.[36] Use of *s*-BuLi in THF was reported not to be successful,[30] but in the presence of TMEDA good yields could be obtained.[37]

Table 1 Synthesis of Various *t*-Butyl (2-Substituted phenyl)carbamates **18** *via* Lithiation



15 **18**

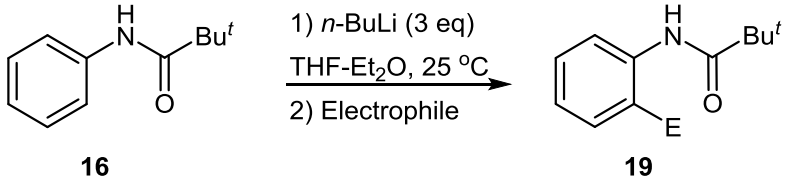
RLi	Conditions	Electrophile	E	Yield (%)	Ref
t-BuLi	THF, –50 °C	CBr_4	Br	78	29
t-BuLi	THF, –20 °C	MeI	Me	59[a]	30
t-BuLi	THF, –20 °C	$(PhS)_2$	PhS	91	30
t-BuLi	THF, –20 °C	PhCHO	PhCH(OH)	67	30
t-BuLi	THF, –20 °C	Ph_2CO	$Ph_2C(OH)$	78	30
t-BuLi	THF, –20 °C	Me_2NCHO	CHO	65	30
t-BuLi	THF, –20 °C	CO_2	CO_2H	73	30
t-BuLi	THF, –20 °C	PhNCS	PhNHCS	69	30
t-BuLi	Et_2O, –10 °C	PhOCN	CN	68	34
t-BuLi	THF, –20 °C	Me_3SnCl	$SnMe_3$	82	31
t-BuLi	THF, –20 °C	$B(OMe)_3/H_2O_2$	OH	52	36
t-BuLi	Et_2O, –20 °C	$B(OMe)_3/H_2O_2$	OH	47	36
s-BuLi[b]	THF, –20 °C	PhCH=NS(O)^{t}Bu	CHPhNHS(O)Bu^t	61	37

[a] Dimethylated product was obtained in 82% yield when excess MeI (4 equivalent) was used. [b] TMEDA was also present.

No lithiation was reported with *n*-BuLi, in the presence or absence of TMEDA,[30] but later work suggested that by use of *n*-BuLi in the presence of TMEDA modest levels of lithiation could be achieved provided that the concentration of substrate and excess of *n*-BuLi were carefully controlled so as to reduce or compensate the loss of *n*-BuLi by reaction with solvent over the necessary prolonged reaction times.[26]

From the above results it is clear that to achieve good *ortho*-lithiation of compound **15** it is necessary to use a fairly basic reagent system such as *t*-BuLi in an ether solvent or *s*-BuLi in the presence of TMEDA. Even with such a reagent, a lithiation temperature around –20 °C is typically required.

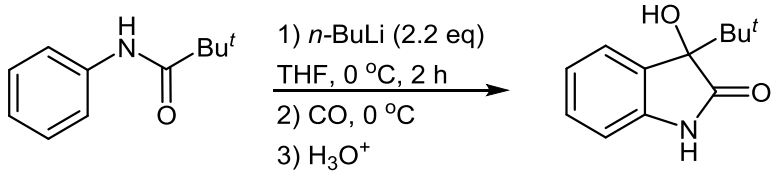
Lithiation appears to be much easier for *N*-phenylpivalamide, which can be *ortho*-lithiated in a THF–diethyl ether mixture using excess *n*-BuLi (the excess being necessary to account for some reaction of the organolithium reagent with the solvent) at 25 °C for 20 h (Scheme 5).[38] Treatment with dimethyl disulfide gave *N*-(2-(methylthio)phenyl)pivalamide in 78% yield, while reaction with DMF gave the corresponding aldehyde in 53% yield.



16 **19**

Scheme 5 Lithiation of *N*-phenylpivalamide and subsequent reaction with electrophiles

One particularly interesting electrophile used in another study is carbon monoxide, which gave rise to 3-*t*-butyldioxindole (**20**) in 77% yield (Scheme 6).[39,40] The reaction involves intramolecular trapping of the incipient acyllithium and subsequent rearrangement before work up leads to the observed product. Interestingly, lithiation occurred efficiently in 2 h at 0 °C in THF alone, so that a smaller excess of organolithium reagent could be used.



16 **20** (77%)

Scheme 6 Lithiation of *N*-phenylpivalamide followed by reaction with carbon monoxide[39,40]

The situation relating to ring-lithiation of *N′*-phenyl-*N,N*-dimethylurea (**17**) is more difficult to assess. As expected, the NH proton could easily be removed with *n*-BuLi at low temperature,[41] but further lithiation on carbon was not successful using *n*-BuLi and starting materials could be recovered quantitatively after attempted trapping.[42] Double lithiation could be achieved using *t*-BuLi, but the products obtained depended on the temperature of lithiation. At 0 °C a mixture of products derived from ring-lithiation (**21**; Figure 5), lithiation on an NMe group (**22**), and lithiation at both positions **23** resulted, but at −20 °C for 2 h the reaction was much more selective, giving almost exclusively the product of lithiation on an NMe group (Scheme 7). However, by use of 3 equivalents of *t*-BuLi and 2 equivalents of benzophenone a good yield of the doubly-substituted product **23** (Figure 5; E = C(OH)Ph$_2$) could be obtained under otherwise similar conditions.

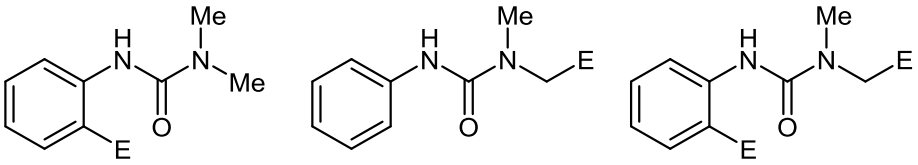
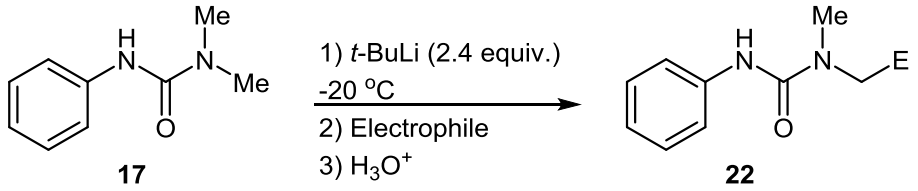


Figure 5 Structures of compounds **21–23**



Scheme 7 Side-chain lithiation of *N*′-phenyl-*N*,*N*-dimethylurea **17**

The 2-lithiophenyl derivative of **17** can be obtained by bromine-lithium exchange of the 2-bromo analogue,[42] but it is clear that direct lithiation of **17** leads preferentially to substitution at an NMe group. The generation of an alternative organolithium reagent of unknown lithiation properties prevents proper comparison with *ortho*-lithiation of **15** and **16**. Thus, while it is evident that it is easier to lithiate at the 2-position of pivaloylaminobenzene than of *t*-butoxycarbonylaminobenzene, it is hard to decide where to place dimethylaminocarbonylaminobenzene on this spectrum. The effectiveness of the various DMGs may become clearer when other factors are also considered.

2.2. Influence of Substitution on the Phenyl Ring

There are several ways in which a substituent on the phenyl ring of **15**, **16** or **17** can potentially influence the course of lithiation, notably: (a) changing the electron distribution around the ring and in consequence influencing the acidity of hydrogens *ortho* to the DMG as well as other ring hydrogens; (b) changing the steric situation in the vicinity of any possible lithiation site; (c) providing an alternative site for attack by the lithiating agent, resulting in lithiation on the substituent group or some other process such as bromine-lithium exchange; or (d) acting as a DMG in its own right, thereby being in competition with the already present acylamino substituent. When the substituent is located in the 4-position of the ring, the level of complication is somewhat reduced because there is no additional steric hindrance to lithiation at the 2-position, so in the first instance these are considered.

Table 2 shows some results of reported lithiations of 4-substituted 1-acylaminobenzenes **24**, **25** and **26**. Some caution must be exercised when interpreting the results in Table 2, because the individual reactions have generally not been optimized; instead, conditions have often been optimized

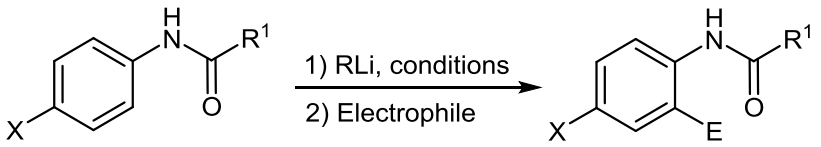
for the unsubstituted analogue and then the conditions standardized for the substituted examples. Nevertheless, some general conclusions can be drawn.

For example, reactions involving most electron-withdrawing groups at the 4-position gave good yields of products having the new substituent in the 2-position for all three DMG types when an appropriate lithiating agent was used (the trifluoromethyl substituted urea (**26c**) gave a more modest yield in a reaction with benzophenone, although **29c-ket** was still the only product, the remainder being unreacted **26c**).[42] However, Schlosser has shown that the position of lithiation of the 4-fluorophenyl carbamate (**24b**) can be completely inverted, to put Li at the position next to F, by use of a LICKOR super base.[27,43] Production of 2-substituted products with an alkyllithium base is particularly noteworthy for the ureas **26a**, **26b** and **26c**, because with such reagents the unsubstituted parent compound **17** preferentially gave lithiation on the dimethylamino group.[42] However, simple lithiation of *N*′-(4-nitrophenyl)-*N*,*N*-dimethylurea was unsuccessful with *n*-BuLi or *t*-BuLi under various reaction conditions.[42]

By contrast, compounds with electron donating groups (Me or OMe) at the 4-position were lithiated in a less consistent way that was more dependent on the nature of the DMG.[44–46] The 4-methylphenyl urea (**26e**) behaved in the same way as the unsubstituted analogue **17**, involving lithiation on an *N*-methyl group under mild conditions but allowing further lithiation at the ring 2-position with excess *t*-BuLi, while the 4-methoxyphenyl urea (**26f**) gave no substitution at the 2-position of the ring at all. Under the standard conditions used for the other ureas the major product involved lithiation on an *N*-methyl group, but there was some lithiation also at the 3-position of the ring (next to the methoxy group) and some product derived from lithiation at both positions, which could be maximized by use of excess *t*-BuLi.[42]

The corresponding 4-methoxyphenylpivalamide (**25f**) could be lithiated using *n*-BuLi and on reaction with dimethyl disulfide gave a 38% yield of the product of lithiation at the 2-position, but also gave a significant amount (21% yield) of a disubstituted product, with the second new substituent located at the 3-position (next to the methoxy group). The 4-methoxy carbamate **24f** required the more basic *t*-BuLi for lithiation, but gave exclusively the product of lithiation at the 2-position.

Table 2 Lithiation of 4-Substituted 1-Acylaminobenzenes **24–26**



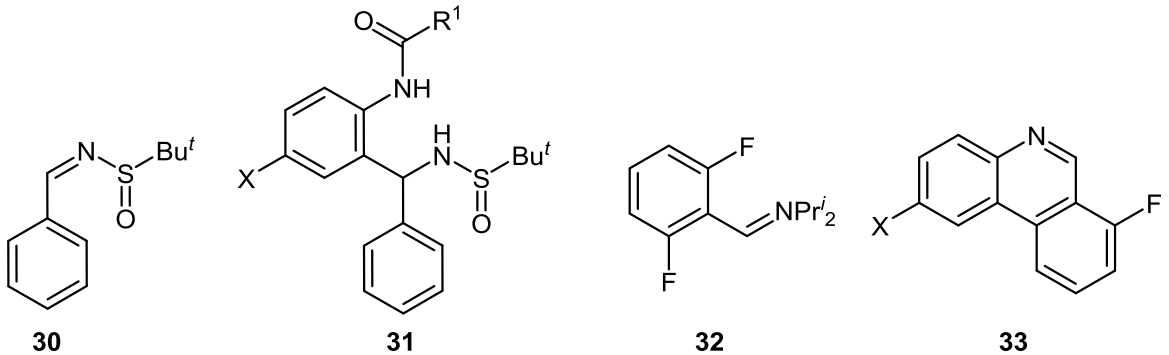
24, $R^1 = OBu^t$
25, $R^1 = Bu^t$
26, $R^1 = NMe_2$

27, $R^1 = OBu^t$
28, $R^1 = Bu^t$
29, $R^1 = NMe_2$

X: a = Cl, b = F, c = CF_3, d = OCF_3, e = Me, f = OMe

X	**24–26**	RLi	Conditions	Electrophile	E	Product	Yield[a] (%)	Ref
Cl	**24a**	*s*-BuLi	–20 °C, THF[b]	**30**	See **31**	**31a**	79	37
Cl	**25a**	*n*-BuLi	0 °C, THF	$(MeS)_2$	SMe	**28a-SMe**	79	38
Cl	**25a**	*n*-BuLi	0 °C, THF	MeI	Me	**28a-Me**	71	38
Cl	**26a**	*n*-BuLi	0 °C, THF	D_2O	D	**29a-D**	83	42
Cl	**26a**	*n*-BuLi	0 °C, THF	$(Ph)_2CO$	$(Ph)_2C(OH)$	**29a-ket**	82	42
Cl	**26a**	*n*-BuLi	0 °C, THF	PhCHO	PhCH(OH)	**29a-ald**	78	42
Cl	**26a**	*n*-BuLi	0 °C, THF	PhNCO	PhNHCO	**29a-cy**	80	42
Cl	**26a**	*n*-BuLi	0 °C, THF	PhNCS	PhNHCS	**29a-Scy**	72	42
F	**24b**	*s*-BuLi	–20 °C, THF[b]	**30**	See **31**	**31b**	74	37
F	**24b**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**27b-Br**	66	29
F	**26b**	*t*-BuLi	0 °C, THF	D_2O	D	**29b-D**	88	42
F	**26b**	*t*-BuLi	0 °C, THF	$(Ph)_2CO$	$(Ph)_2C(OH)$	**29b-ket**	78	42
F	**26b**	*t*-BuLi	0 °C, THF	PhCHO	PhCH(OH)	**29b-ald**	77	42
CF_3	**24c**	*s*-BuLi	–20 °C, THF[b]	**30**	See **31**	**31c**	81	37
CF_3	**24c**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**27c-Br**	94	29
CF_3	**26c**	*n*-BuLi	0 °C, THF	$(Ph)_2CO$	$(Ph)_2C(OH)$	**29c-ket**	31[c]	42
OCF_3	**24d**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**27d-Br**	81	29
Me	**24e**	*t*-BuLi	–30 °C, Et_2O	**32**/TFA	See **33**	**33b**	49	46
Me	**26e**	*t*-BuLi	–20 °C, THF	$(Ph)_2CO$	$(Ph)_2C(OH)$	**29e-ket**	0[d]	42
OMe	**24f**	*s*-BuLi	–20 °C, THF[b]	**30**	See **31**	**31f**	30	37
OMe	**24f**	*t*-BuLi	–30 °C, Et_2O	**32**/TFA	See **33**	**33b**	74	46
OMe	**24f**	*t*-BuLi	–20 °C, Et_2O	ICH_2CH_2I	I	**27f-I**	86	45
OMe	**25f**	*n*-BuLi	0 °C, THF	$(MeS)_2$	SMe	**28f-SMe**	38[e]	38
OMe	**26f**	*t*-BuLi	–20 °C, THF	$(Ph)_2CO$	$(Ph)_2C(OH)$	**29f-ket**	0[d]	42

[a] Yield of pure isolated products. [b] TMEDA was also present. [c] Starting material (61%) was recovered. [d] Other products formed (see discussion). [e] 21% of disusbtituted product (next to directing group and the methoxy group) was obtained.



30 **31** **32** **33**

X: a = Cl, b = F, c = CF_3, d = OCF_3, e = Me, f = OMe

Figure 6 Structures of compounds **30–33**

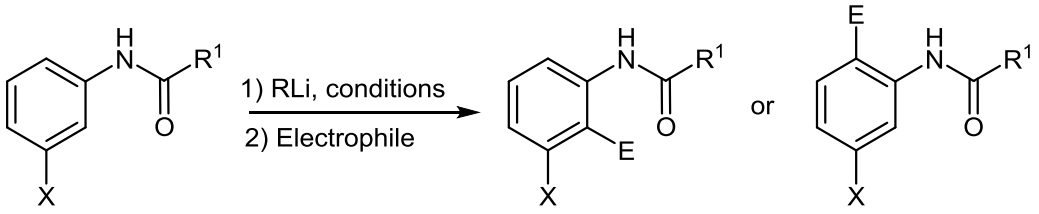
From a detailed inspection of the results some other interesting features emerge. The ***power of the DMGs to influence selectivity*** for lithiation at the 2-position (next to the DMG) of the 4-methoxyphenyl derivatives **24f**, **25f** and **26f** decreases in the order $NHCO_2Bu^t$ > $NHCOBu^t$ > $NHCONMe_2$, although $NHCO_2Bu^t$ is not the best ***DMG for increasing the ease*** of lithiation in these cases. It is reasonable to assume that complexation with the organolithium reagent is strongest for the urea (ureas have the lowest IR carbonyl bond frequencies, suggesting higher electron density on oxygen) and weakest for the carbamate (carbamates have the highest carbonyl group frequencies).[47] Stronger complexation should increase the basicity and decrease the level of aggregation of the organolithium reagent, and the results suggest that the ureas and pivalamides are indeed more readily lithiated than the analogous carbamates. However, the results also suggest that the more strongly complexed reagents tend to deprotonate at the more acidic sites, whereas the less basic carbamate complexed reagent is more likely to deprotonate *ortho* to the DMG, which is kinetically favored. Therefore, the *t*-butoxycarbonylamino group is the more powerful ***directing*** group in these cases even though it is the least powerful ***activator***.

The ability of the various ureas **26a-f** to be lithiated at the 2-position decreases in the following order: CF_3, Cl > F > OMe, H, Me. Although these results cannot be used to verify a linear free energy relationship, it is nevertheless tempting to see if there is a trend that can be compared qualitatively to a trend in Hammett sigma values. The trends for σ_m (CF_3 0.43; Cl 0.37; F 0.34; OMe 0.12; H 0.00; Me −0.07) and for σ_p (CF_3 0.54; Cl 0.23; F 0.06; H 0.00; Me −0.17; OMe −0.27)[48] would both be consistent with the observations, but the values of σ_p^+ and σ_p^- of the F substituent would both be out of line with the unsubstituted compound in terms of relative facility of lithiation next to the DMG.

Lithiation of 3-substituted acylaminobenzenes **34**, **35** and **36** introduces a further complication, since the two locations *ortho* to the DMG are no longer identical, leading to the possibility of formation of either 2-substituted compounds **37–39** or 6-substituted compounds **40–42**. There are not so many examples of lithiation of 3-substituted compounds **34–36** but some representative examples are recorded in Table 3. In view of the previously discussed results with carbamates, it is not surprising that the 3-trifluoromethyl compound **34c** and the 3-trifluoromethoxy compound **34d** should be lithiated *ortho* to the DMG; in the case of the trifluoromethyl compound **34c**, lithiation occurred at the less hindered of the two possible sites, resulting in the 1,2,4-trisubstitued product, **40c-Br**,[29] but the situation was different for the 3-trifluoromethoxy carbamate **34d**[49] and 3-methoxy carbamate **34f**, which resulted in the products of lithiation between the two substituents, presumably because of synergistic directing effects from both and reduced steric hindrance compared to the CF_3 compound.[46] The same kind of synergy seems to apply in the case of the 3-methoxyphenylpivalamide (**35f**).[38] However, even the presence of a 3-methoxyphenyl group was not enough to divert initial lithiation of the urea **36f** from the NMe_2 group.[50] In the cases of the

3-chloro derivatives **34a**[51] and **35a**,[52,53] lithiation again occurs between the two substituents, but the lithio compounds thus generated eliminate LiCl to give benzynes, which cyclize to lithiobenzoxazoles and reactions with electrophiles then give the corresponding substituted benzoxazoles (see compounds **47-49**, Figure 7). Similar reactions have been conducted with compounds having an extra Cl or F substituent at the 4-position of the phenyl ring of compound **35**.[52]

Table 3 Lithiation of 3-Substituted 1-Acylaminobenzenes **34–36**



34, R^1 = OBu^t
35, R^1 = Bu^t
36, R^1 = NMe_2

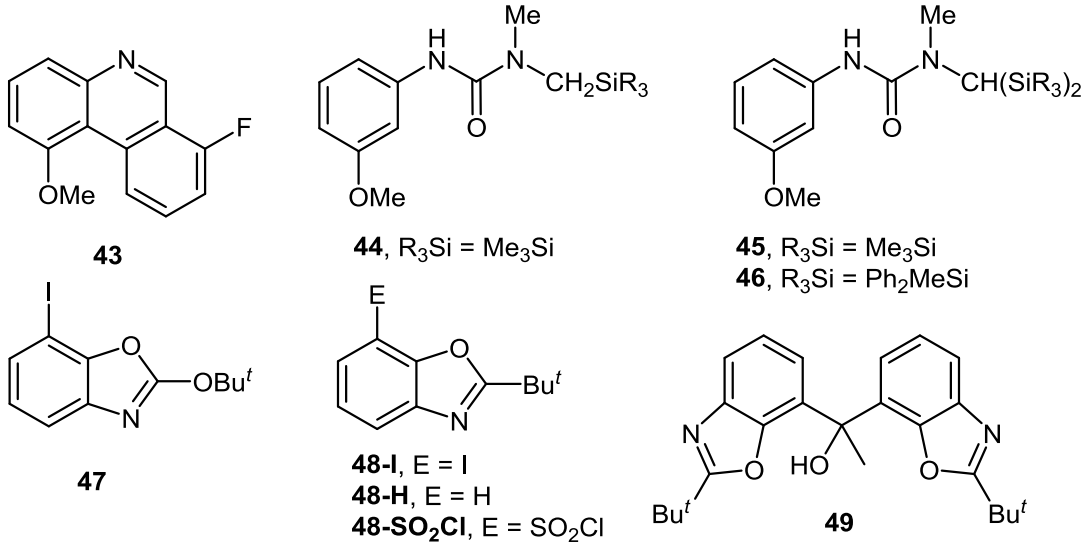
37, R^1 = OBu^t
38, R^1 = Bu^t
39, R^1 = NMe_2

40, R^1 = OBu^t
41, R^1 = Bu^t
42, R^1 = NMe_2

X: a = Cl, b = F, c = CF_3, d = OCF_3, e = Me, f = OMe

X	**34–36**	RLi	Conditions	Electrophile	E	Product	Yield[a] (%)	Ref
Cl	**34a**	*t*-BuLi	–20 °C, THF	I_2	I	**47**	38	51
Cl	**35a**	*n*-BuLi	–10 °C, THF	I_2	I	**48-I**	68	52
Cl	**35a**	*n*-BuLi	–10 °C, THF	AcOH	H	**48-H**	81	52
Cl	**35a**	*n*-BuLi	–10 °C, THF	EtOAc	See **49**	**49**	70	52
Cl	**35a**	*n*-BuLi	–45 °C, THF	SO_2Cl_2	SO_2Cl	**48-SO_2Cl**	50	53
CF_3	**34c**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**40c-Br**	77	29
OCF_3	**34d**	*t*-BuLi	–50 °C, THF	Me_2SO_4	Me	**37c-Me**	66	49
OMe	**34f**	*t*-BuLi	–30 °C, Et_2O	**32**/TFA	See **43**	**43**	15	46
OMe	**35f**	*n*-BuLi	0 °C, THF	$(MeS)_2$	SMe	**38f-SMe**	82	38
OMe	**35f**	*n*-BuLi	0 °C, THF	PhCHO	PhCH(OH)	**38f-ald**	79	38
OMe	**36f**	*t*-BuLi	–78 °C, THF	R_3SiCl	SiR_3	**39f-SiR_3**	0[b]	50

[a] Yield of pure isolated products. [b] Other products formed (**44** (15%) and **45** (25%) for reaction with Me_3SiCl; **46** (35%) for $Ph_2MeSiCl$; Figure 7).



43

44, R_3Si = Me_3Si

45, R_3Si = Me_3Si
46, R_3Si = Ph_2MeSi

47

48-I, E = I
48-H, E = H
48-SO_2Cl, E = SO_2Cl

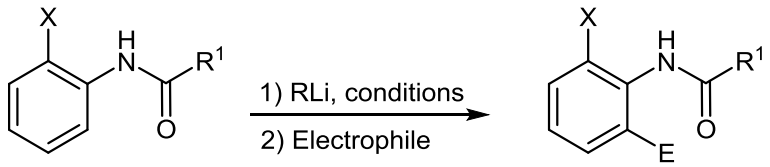
49

Figure 7 Structures of compounds **43–49**

Lithiation of various *tert*-butyl (2-substituted phenyl)carbamates **50** followed by reaction with CBr_4 gave the corresponding products bearing a bromo substituent at the 6-position (Table 4).[29] The examples cited all involved electron-withdrawing substituents, which should enhance the ease of lithiation, but since the unsubstituted carbamate undergoes lithiation under similar conditions to those reported for the substituted compounds it is not possible to draw such a conclusion from the direct evidence. Although the 2-fluorophenyl)carbamate **50b** behaved like the other 2-substituted carbamates, the limited information available for 2-halophenyl pivalamide and urea substrates reveals a more complex situation. Lithiation at the 6-position of the phenyl ring in (2-chlorophenyl)pivalamide can be accomplished in reasonable yield using *n*-BuLi in *t*-BuOMe containing TMEDA (Table 4; Entry 1), but in THF the major products result from benzyne formation, suggesting initial lithiation next to Cl.[54] The final entry in Table 4 shows that at least for the case of urea derivative **52i** no lithiation at the 6-position of the 2-bromophenyl group takes place. Instead, Br-Li exchange occurs by direct reaction of the lithium reagent at the bromine atom, and the corresponding 1-(2-substituted phenyl)-3,3-dimethylureas can be obtained by treatment with electrophiles.[42]

Most other reports of lithiation of 2-substituted-1-acylaminobenzenes deal with 2-alkyl substituents.[55–60] Modest yields of the corresponding 6-substitued products **53h** and **54h** were reported for 2-isopropylphenyl carbamate and pivalamide compounds, respectively, and the low yields were said to result from a combination of low solubility and low reaction rates rather than lithiation at alternative positions.[60] Lithiations of the 2-methylphenyl derivatives **50e**, **51e** and **52e** and 2-ethylphenyl derivatives **50f** and **51f**, however, take a completely different course, since the methyl or ethyl groups offer more favorable sites for lithiation.[50,55–59] For example, treatment of the lithiated derivative of **50e** with a ketone gives rise to the corresponding products substituted at the benzylic position (Scheme 8). In a similar way, treatment of the lithiated intermediates with dimethylformamide (DMF) gives rise to the products **57** and **58**.[58] This preferential ***lateral*** lithiation is an important process in its own right.

Table 4 Lithiation of 2-Substituted 1-(Acylamino)benzenes **47–49**



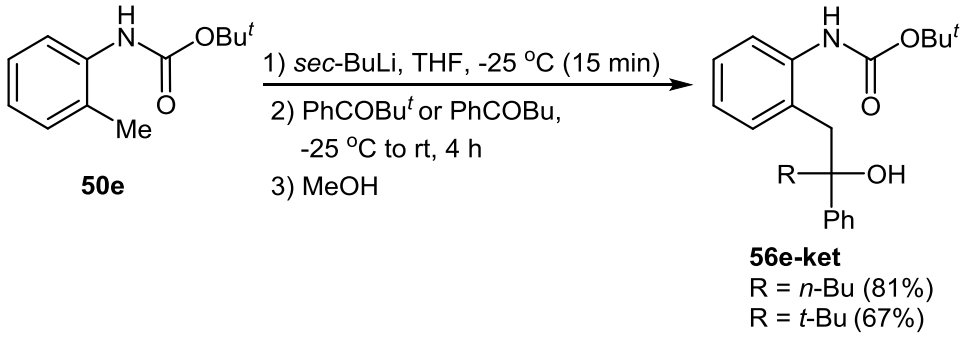
50, R^1 = OBu^t
51, R^1 = Bu^t
52, R^1 = NMe_2

53, R^1 = OBu^t
54, R^1 = Bu^t
55, R^1 = NMe_2

X: b = F, c = CF_3, d = OCF_3, e = Me, g = Et, h = *i*-Pr, i = Br

X	**50–52**	RLi	Conditions	Electrophile	E	Product	Yield[a] (%)	Ref
Cl	**51a**	*n*-BuLi	–5 °C, *t*-BuOMe[c]	MeI	Me	**54a-Me**	81	54
F	**50b**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**53b-Br**	82	29
CF_3	**50c**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**53c-Br**	64	29
OCF_3	**50d**	*t*-BuLi	–50 °C, THF	CBr_4	Br	**53d-Br**	46	29
Me	**50e**	*s*-BuLi	–25 °C, THF	PhCOR	PhCR(OH)	**53e-ket**	0[b]	55,56
Me	**50e**	*t*-BuLi	–40 °C, THF	CO_2	CO_2H	**53e-CO_2H**	0[b]	57
Me	**50e**	*s*-BuLi	–40 °C, THF	Me_2NCHO	See **57**	**53e-CHO**	0[b]	58
Me	**51e**	*n*-BuLi	0 °C, THF	Me_3SiCl	$SiMe_3$	**54e-$SiMe_3$**	0[b]	38
Me	**52e**	*t*-BuLi	–30 °C, THF[c]	Ph_2CO	$Ph_2C(OH)$	**55e-ket**	0[b]	59
Et	**50g**	*t*-BuLi	–40 °C, THF[c]	Me_2NCHO	See **58**	**53g-CHO**	0[b]	55
Et	**51g**	*t*-BuLi	–10 °C, Et_2O	$(MeS)_2$	SMe	**54g-SMe**	0[b]	60
i-Pr	**50h**	*t*-BuLi	–10 °C, Et_2O	$(MeS)_2$	SMe	**53h-SMe**	25–30[d]	60
i-Pr	**51h**	*t*-BuLi	–10 °C, Et_2O	$(MeS)_2$	SMe	**54h-SMe**	35	60
Br	**52i**	MeLi/*t*-BuLi	0 °C, THF	Ph_2CO	$Ph_2C(OH)$	**55i-ket**	0[b]	42

[a] Yield of pure isolated products. [b] Other products formed (see discussion). [c] TMEDA was used. [d] According to NMR of the crude reaction mixture.



Scheme 8 Lateral lithiation and substitution of *tert*-butyl (2-methylphenyl)carbamate (**50e**)[55,56]

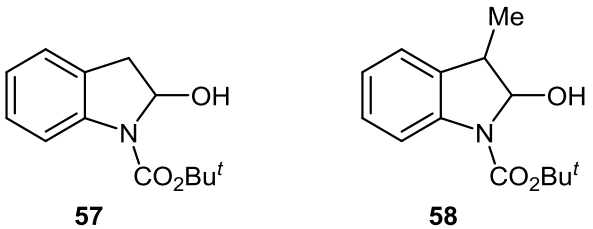
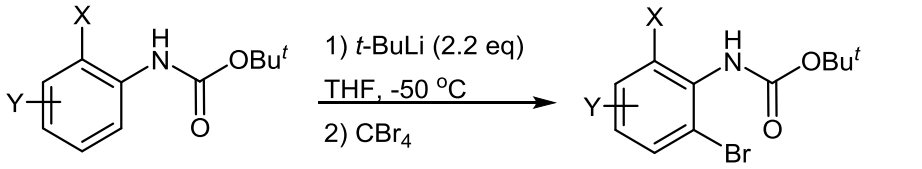


Figure 8 Structures of compounds **57** and **58**

There are some examples of lithiations of carbamates bearing more than one substituent in the phenyl ring (Scheme 9).[29] However, the examples reported do not throw much extra light on the factors that influence the lithiation process.



59, X = F, Y = 3-OMe
60, X = CF_3, Y = 4-CF_3

61, X = F, Y = 3-OMe (62%)
62, X = CF_3, Y = 4-CF_3 (63%)

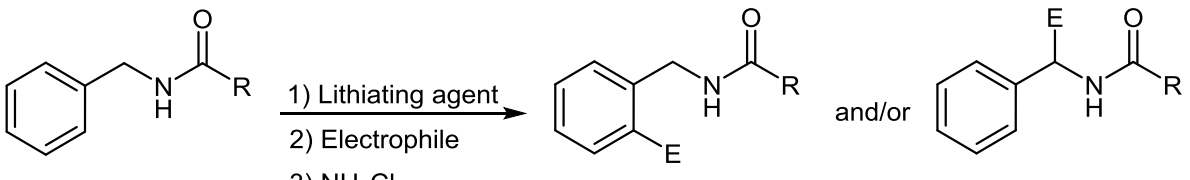
Scheme 9 Lithiation of disubstituted *tert*-butyl phenylcarbamates **59** and **60**[29]

3. Lithiation with the DMG Separated by a CH_2 Group from the Aryl Ring

3.1 Effect of the DMG

As with the simple acylaminobenzenes, the first deprotonation of (acylaminomethyl)benzenes is at nitrogen, and by use of one equivalent of lithiating agent and a suitable electrophile, the *N*-substituted products can be obtained.[61,62] Two or more equivalents of lithiating agent are required to bring about additional *C*-lithiation and in this case there is an additional potential site (α) for lithiation compared to the acylaminobenzenes. Examples of lithiations of the three parent (acylaminomethyl)benzenes of interest are shown in Table 5.[63–69] All three substrates are lithiated readily by *sec*-BuLi or *t*-BuLi at low temperature, but in contrast to the situation when the urea group is attached directly to the ring, lithiation does not occur to any significant extent on the *N*-methyl groups. Also, for substrates **63–65** there is a clear trend in the regioselectivity of lithiation as the DMG is varied. The urea (substrate **63**) is substituted at the *ortho*-position in high yield,[63,64] whereas the carbamate (substrate **65**) is substituted substantially at the α-position.[63,66–69] The amide (substrate **64**) gives a mixture of the two substitution products,[64,65] but increasing the basicity of the lithiating agent by addition of TMEDA or KOBu^t shifts the selectivity to the α-substituted product.[65]

Table 5 Lithiation of (Acylaminomethyl)benzenes **63–65**



63, R = NMe_2
64, R = Bu^t
65, R = OBu^t

66, R = NMe_2
67, R = Bu^t
68, R = OBu^t

69, R = NMe_2
70, R = Bu^t
71, R = OBu^t

63–**65**	RLi	Conditions	Electrophile	E	**66**–**68** (%)[a]	**69**–**71** (%)[a]	Ref

63	*sec*-BuLi	–50°C, THF	CO_2	CO_2H	82	–	63
63	*t*-BuLi	–78 °C, THF	CO_2	CO_2H	90	–	63
63	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	86	–	64
63	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	82	–	64
63	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	84	–	64
63	*t*-BuLi	–78 °C, THF	MeI	Me	80	–	64
63	*t*-BuLi	–78 °C, THF	D_2O	D	89	–	64
64	*sec*-BuLi	–50 °C, THF	CO_2	CO_2H	36	20	65
64	*t*-BuLi	0 °C, THF	Ph_2CO	$Ph_2C(OH)$	34	37	64
64	*sec*-BuLi[b]	–50 °C, THF	CO_2	CO_2H	–	'excl'	65
65	*sec*-BuLi	–50 °C, THF	CO_2	CO_2H	–	79	63
65	*sec*-BuLi[c]	–78 °C, THF	CO_2	CO_2H	–	54[d]	66
65	*sec*-BuLi[b]	–78 °C, THF	CH_2=CHCHO	CH_2=CHCH(OH)	–	49	69

[a] Yield of pure isolated products. [b] TMEDA also present. [c] (–)Sparteine also present. [d] 54:46 ratio *R:S*.

These trends can be understood in terms of two properties of the carbonyl groups in the three DMGs, namely their ability to withdraw electron density from the α-attached nitrogen atom (carbamate > amide > urea) and the strength of their ability to complex an organolithium reagent (urea > amide > carbamate), which trends correlate with the carbonyl group stretching frequencies of such groups (carbamate > amide > urea). The stronger the electron-withdrawal, the greater the acidity of the α-protons and the more likely it is that substitution will occur at that position. The stronger the complexation of an organolithium reagent, the more likely it is that directed lithiation (leading to *ortho*-substitution) will take place. However, increasing the basicity of the reagent by complexation (to the DMG or an added nucleophile) also renders acidity of the protons to be removed more important and directed lithiation less important.

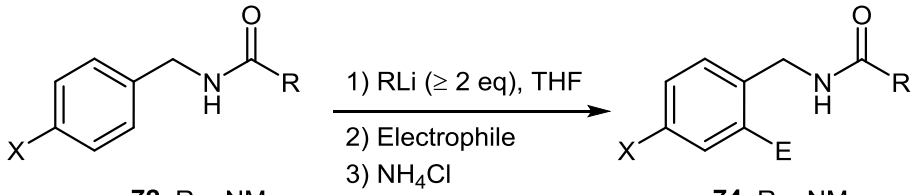
There is one report of lithiation of **65** at the *ortho*-position with *t*-BuLi, but no yield or spectral data were recorded for the product and the report acknowledges that the crude product, used directly for further reactions, was impure[70] so it is likely that the amount of product **68** formed was modest.

3.2. Influence of Substitution on the Phenyl Ring

N'-(*p*-Substituted benzyl)-*N,N*-dimethylureas (**72**) and *N*-(*p*-substituted benzyl)pivalamides (**73**) are lithiated rapidly at −78 °C with *t*-BuLi, at −50 °C with *sec*-BuLi, or at 0 °C with *n*-BuLi to give products substituted at the position *ortho*- to the DMG in high yield irrespective of the nature of the substituent, at least for the four substituents studied (Table 6). This is somewhat surprising for some of the pivalamides in view of the low yield and the mixture of products obtained on direct lithiation of the unsubstituted *N*-benzylpivalamide **64** (Table 5). It would appear that the presence of a substituent in the 4-position inhibits deprotonation at the α-position while promoting deprotonation at the 2-position. Given the different natures of the substituents (electron-donating as well as electron-withdrawing) and the relatively small effects those substituents have on ^{1}H and ^{13}C NMR chemical shifts at positions *meta* to them, it is not immediately obvious why this should be. However, perhaps

the electron-withdrawing substituents enhance the acidity of the *ortho*-protons, while the electron-donating substituents exert a greater influence at the α-position by decreasing the acidity of the α-protons and/or enhancing the ability of the DMG to coordinate to the organolithium reagent. It is noteworthy that both DMGs act as stronger directing groups than a 4-methoxy group.

Table 6 Substitution of *N*-Acyl-(4-substituted benzyl)amines **72** and **73**



72, R = NMe_2
73, R = *t*-Bu

74, R = NMe_2
75, R = *t*-Bu

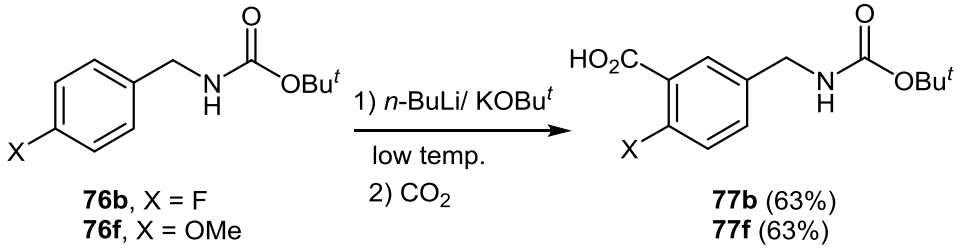
X: a = Cl, b = F, e = Me, f = OMe

X	**72/ 73**	RLi	Conditions	Electrophile	E	**74/75**	Yield (%)[a]	Ref
Cl	**72a**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**74a*1***	79	64
Cl	**73a**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**75a*1***	83	64
Cl	**72a**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**74a*2***	79	64
Cl	**73a**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**75a*2***	82	64
Cl	**72a**	*t*-BuLi	–78 °C, THF	EtI	Et	**74a*3***	78	64
Cl	**73a**	*t*-BuLi	–78 °C, THF	EtI	Et	**75a*3***	79	64
Cl	**72a**	*t*-BuLi	–78 °C, THF	D_2O	D	**74a*4***	79	64
Cl	**73a**	*t*-BuLi	–78 °C, THF	D_2O	D	**75a*4***	88	64
Cl	**73a**	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	**75a*5***	79	64
Cl	**73a**	*t*-BuLi	–78 °C, THF	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**75*a6***	73	64
Cl	**73a**	*n*-BuLi	0 °C, THF	CO_2	CO_2H	**75a*7***	46	65
F	**72b**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**74b*1***	83	64
F	**73b**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**75b*1***	78	64
F	**72b**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**74b*2***	83	64
F	**73b**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**75b*2***	79	64
F	**73b**	*t*-BuLi	–78 °C, THF	EtI	Et	**75b*3***	82	64
F	**73b**	*t*-BuLi	–78 °C, THF	D_2O	D	**75b*4***	85	64
F	**73b**	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	**75b*5***	76	64
F	**73b**	*t*-BuLi	–78 °C, THF	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**75b*6***	82	64
F	**72b**	*sec*-BuLi	–50 °C, THF	CO_2	CO_2H	**74b*7***	87	63
Me	**72e**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**74e*1***	76	64
Me	**73e**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(Oh)$	**75e*1***	81	64
Me	**72e**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**74e*2***	70	64
Me	**73e**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**75e*2***	79	64
Me	**72e**	*t*-BuLi	–78 °C, THF	EtI	Et	**74e*3***	80	64
Me	**73e**	*t*-BuLi	–78 °C, THF	EtI	Et	**75e*3***	81	64
Me	**72e**	*t*-BuLi	–78 °C, THF	D_2O	D	**74e*4***	86	64
Me	**73e**	*t*-BuLi	–78 °C, THF	D_2O	D	**75e*4***	88	64
Me	**72e**	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	**74e*5***	72	64
Me	**73e**	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	**75e*5***	81	64
Me	**73e**	*t*-BuLi	–78 °C, THF	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**75e*6***	82	64
Me	**73e**	*t*-BuLi	–78 °C, THF	MeI	Me	**75e*8***	80[b]	64
OMe	**72f**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**74f*1***	85	64
OMe	**73f**	*t*-BuLi	–78 °C, THF	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**75f*1***	82	64
OMe	**72f**	*t*-BuLi	–78 °C, THF	PhCHO	PhCH(OH)	**74f*2***	89	64
OMe	**72f**	*t*-BuLi	–78 °C, THF	EtI	Et	**74f*3***	88[b]	64
OMe	**72f**	*t*-BuLi	–78 °C, THF	D_2O	D	**74f*4***	86	64
OMe	**73f**	*t*-BuLi	–78 °C, THF	D_2O	D	**75f*4***	88	64
OMe	**72f**	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	**74f*5***	84	64
OMe	**73f**	*t*-BuLi	–78 °C, THF	Ph_2CO	$Ph_2C(OH)$	**75f*5***	80	64

OMe	**73f**	*t*-BuLi	–78 °C, THF	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**75f*6***	77	64
OMe	**72f**	*sec*-BuLi	–50 °C, THF	CO_2	CO_2H	**74f*7***	85	63
OMe	**73f**	*n*-BuLi	0 °C, THF	CO_2	CO_2H	**75f*7***	64	65
OMe	**73f**	*t*-BuLi	–78 °C, THF	MeI	Me	**75f*8***	81[c]	64
OMe	**73f**	*t*-BuLi	–78 °C, THF	MeCOBu	MeC(OH)Bu	**75f*9***	78	64

[a] Yield of pure isolated products.

It appears that no comparable lithiations with simple alkyllithium reagents have been reported for *tert*-butyl (4-substituted benzyl)carbamates, but with a superbasic reagent the fluoro and methoxy derivatives both give substitution next to the 4-substituent rather than next to the *tert*-butoxycarbonylaminomethyl group (Scheme 10).[63]

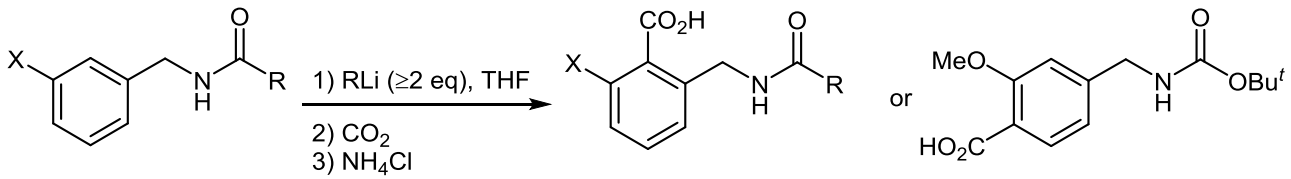


76b, X = F
76f, X = OMe

77b (63%)
77f (63%)

Scheme 10 Lithiation of *tert*-butyl (4-substituted benzyl)carbamates (**76**)

There are few reports of lithiation of *m*-substituted derivatives of acylaminomethylbenzenes (Scheme 11). The urea derivatives **78b** and **78f**[63] and the pivaloyl derivative **79f**[65] are lithiated by alkyllithium reagents in THF at the position between the acylaminomethyl group and the substituent, presumably because the two groups act synergistically as directing groups. The 3,4-methylenedioxy-substituted pivalamide derivative behaves similarly, giving a 65% yield of the corresponding 2-carboxylic acid.[63] However, the only report of lithiation of a *m*-substituted (*tert*-butoxycarbonylaminomethyl)benzene (the methoxy derivative **80f**) involved a superbasic reagent, which resulted in substitution next to the methoxy group (Scheme 11).[63] It is not clear whether the result would have been different with a simple alkyllithium reagent.



78, R = NMe_2
79, R = Bu^t
80, R = OBu^t
X: b = F, f = OMe

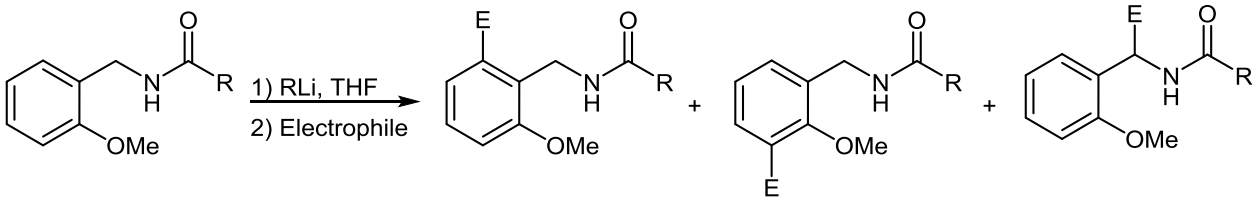
81, R = NMe_2
(**81b7**, 94%, *n*-BuLi, -75 °C)
(**81f7**, 86%, *sec*-BuLi, -50 °C)
81, R = Bu^t
(**82f7**, 61%, *n*-BuLi, 0 °C)

83f7
(57%, *n*-BuLi/ $KOBu^t$, -50 °C)

Scheme 11 Lithiation and substitution of *N*-acyl (3-substituted benzyl)amines **78–80**

There are also few reports of lithiation of 2-substituted (acylaminomethyl)benzenes. The most widely studied examples are the 2-methoxy derivatives **84–86**, for which products result from lithiation at three different positions (*ortho* to either the acylaminomethyl or methoxy groups or at the α-position) (Table 7). Interpretation of the results is clouded by the fact that the information available relates to different reaction conditions, but some trends are discernible. Thus, at –20 °C the urea **84** gives mixtures of the products **87** and **90** from lithiation *ortho* to the two functionalities (the urea and methoxy groups), with **87** predominating slightly over **90**, and there is no evidence for lithiation at the α-position.[64] Lithiation of the pivalamide **85** invariably leads to some of the α-product **94**, but the proportions of the other two products **88** and **91** vary considerably depending on the reagent and temperature, with the more hindered and more powerful *t*-BuLi favoring lithiation at the more acidic and less hindered site next to the MeO group, especially at low temperature, but the less hindered, less powerful alkyllithium reagents favoring lithiation next to the pivaloylaminomethyl group. By contrast, the carbamate **86** lithiates only next to the methoxy group to give **95** even with less powerful *sec*-BuLi.

Table 7 Substitution of *N*-Acyl-(2-methoxybenzyl)amines **84–86**



84, R = NMe_2
85, R = Bu^t
86, R = OBu^t

87, R = NMe_2
88, R = Bu^t
89, R = OBu^t

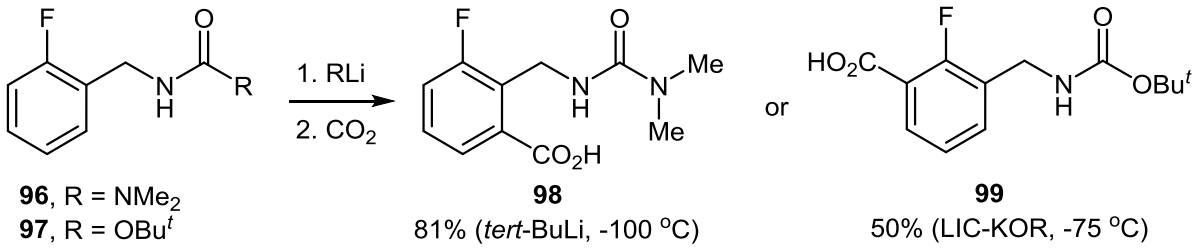
90, R = NMe_2
91, R = Bu^t
92, R = OBu^t

93, R = NMe_2
94, R = Bu^t
95, R = OBu^t

84–86	RLi	T (°C)	Electrophile	E	Yields (%) **87/88/89**	**90/91/92**	**93/94/95**	Ref
84	*t*-BuLi	–20	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	49 (**87-*1***)	40 (**90-*1***)	–	64
84	*t*-BuLi	–20	PhCHO	PhCH(OH)	50 (**87-*2***)	48 (**90-*2***)	–	64
84	*t*-BuLi	–20	D_2O	D	51 (**87-*4***)	38 (**90-*4***)	–	64
84	*t*-BuLi	–20	Ph_2CO	$Ph_2C(OH)$	47 (**87-*5***)	30 (**90-*5***)	–	64
84	*t*-BuLi	–20	MeI	Me	51 (**87-*8***)	40 (**90-*8***)	–	64
85	*t*-BuLi	–78	CO_2	CO_2H	–	87 (**91-*7***)	7	**Erro**
85	*t*-BuLi	0	CO_2	CO_2H	19 (**88-*7***)	49 (**91-*7***)	26 (**94-*7***)	64
85	*sec*-BuLi	–78	CO_2	CO_2H	36 (**88-*7***)	–	34 (**94-*7***)	64
85	*sec*-BuLi	0	CO_2	CO_2H	48 (**88-*7***)	–	38 (**94-*7***)	64
85	*n*-BuLi	–78	CO_2	CO_2H	–	–	–	64
85	*n*-BuLi	0	CO_2	CO_2H	30 (**88-*7***)	8 (**91-*7***)	40 (**94-*7***)	64
85	*n*-BuLi	0	CO_2	CO_2H	10 (**88-*7***)	–	14 (**94-*7***)	64
86	*sec*-BuLi	–50	CO_2	CO_2H	–	46 (**92-*7***)	–	63

The result with the carbamate possibly signifies that this group is a significantly weaker DMG than methoxy, so that neither of the positions it might be expected to activate are lithiated in competition with the one activated by methoxy. With a comparable reagent (*t*-BuLi), the pivaloyl derivative gives predominant attack next to the MeO group, while the more powerful urea DMG gives predominant attack *ortho* to the DMG. Also, as seen with the unsubstituted compounds **63-65**, the urea directs lithiation to the *ortho*-position while the pivalamide directs both to this and the α-position. The explanation is presumably the same (see Section 3.1).

The 2-fluoro substituted urea **96** is lithiated *ortho* to the urea unit with *t*-BuLi at −100 °C (Scheme 12),[63] compared to competitive lithiation adjacent to MeO seen with **84**, which is consistent with F being a poorer DMG than MeO. There are no reports of lithiation of the pivalamide or carbamate 2-fluoro derivatives with simple alkyllithiums, but with a superbase the carbamate **97** is lithiated *ortho* to F (Scheme 12),[36] which is presumably the most acidic position.



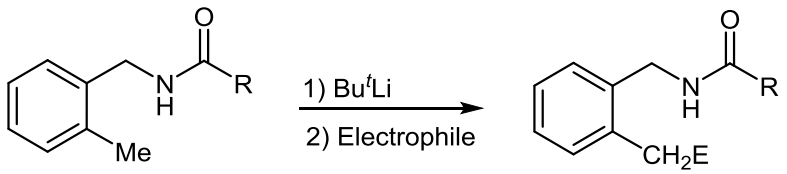
96, R = NMe_2
97, R = OBu^t

98
81% (*tert*-BuLi, -100 °C)

99
50% (LIC-KOR, -75 °C)

Scheme 12 Lithiation and substitution of *N*-acyl-(2-fluorobenzyl)amines **96** and **97**

2-Methyl derivatives of all three (acylaminomethyl)benzenes (**100-102**) undergo lateral lithiation on the methyl group with *t*-BuLi to give high yields of the corresponding substituted derivatives **103-105** (Scheme 13),[62,71] and in the case of the carbamate the same process has been shown to occur also with other lithiating agents.[62] Clearly the DMGs influence this process, since *o*-xylene is not lithiated under such conditions, but lithiation at the methyl group is favored even over the other activated positions (*ortho* to the acylaminomethyl group or α).



100, R = NMe_2
101, R = Bu^t
102, R = OBu^t

103, R = NMe_2
104, R = Bu^t
105, R = OBu^t

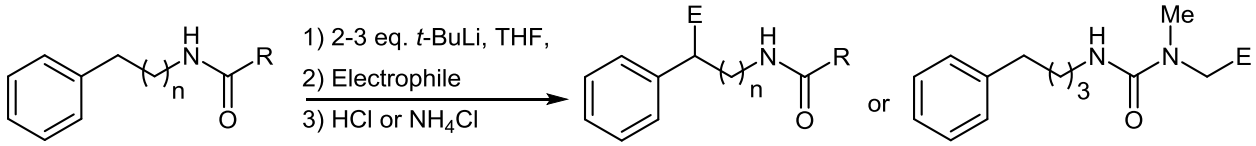
Scheme 13 Lithiation and substitution of *N*-acyl-(2-methylbenzyl)amines **100–102**

4. Lithiation with the Aryl Ring and DMG Separated by Two or More CH2 Groups

4.1 Effect of the DMG and its Distance from the Aryl Group

Unlike the situation on lithiation of (acylaminomethyl)benzenes with alkyllithium reagents, where the urea derivative gives *ortho*-lithiation, the carbamate derivative gives α-lithiation, and the pivalamide gives a mixture of the products of lithiation at the two positions, the corresponding (2-(acylamino)ethyl)benzenes and (3-(acylamino)propyl)benzenes all consistently give the products of lithiation at the α-position, at least for the examples reported (Table 8), all of which make use of *t*-BuLi as lithiating agent.[21,72,73] Since both the benzyl and (3-phenylpropyl) carbamates (**65** and **109**, respectively) give α-lithiation, it is reasonable to assume that the (2-phenylethyl) carbamate would also be lithiated at the α- position with similar reagents. Presumably, an alkyllithium reagent that is complexed to any of the DMGs can be delivered readily to the modestly acidic protons at the α-positions, but less readily to the protons at the more remote *ortho*-positions. The data in Table 8 do not provide much information about the relative activities of the different DMGs in these systems, but the different temperatures used may suggest that the further away that the DMG is from the α-position, the less effective it is at promoting lithiation at that position. Indeed, for the one example reported for a (4-(acylamino)butyl)benzene (**110**), lithiation does not occur at the α-position, but at one of the methyl groups of the urea unit.[72]

Table 8 Substitution of *N*-Acyl-(ω-phenylalkyl)amines **106–110**



106, n = 1, R = NMe_2
107, n = 1, R = Bu^t
108, n = 2, R = NMe_2
109, n = 2, R = OBu^t
110, n = 3, R = NMe_2

111, n = 1, R = NMe_2
112, n = 1, R = Bu^t
113, n = 2, R = NMe_2
114, n = 2, R = OBu^t

115
(from **110**)

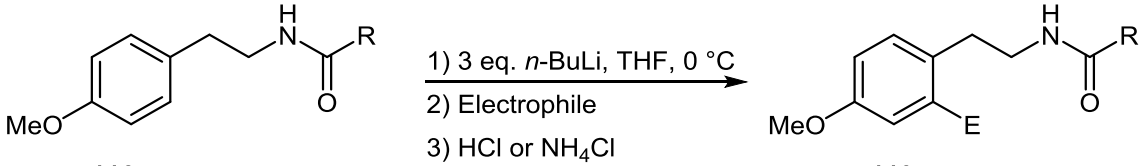
106–110	T (°C)	Electrophile	E	Product	Yield (%)	Ref
106	–78	PhCHO	PhCH(OH)	**111**	97[a]	**Error! Bookmark not defined.**72
106	–78	PhCOMe	PhC(OH)Me	**111**	96[a]	**Error! Bookmark not defined.**72
106	–78	Ph_2CO	$Ph_2C(OH)$	**111**	98	72
106	–78	Me_2CO	$Me_2C(OH)$	**111**	98	72
106	–78	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**111**	98	72
106	–78	EtI	Et	**111**	86	72
106	–78	D_2O	D	**111**	99	72
107	–50	CO_2	CO_2H	**112**	72	21
108	0	Ph_2CO	$Ph_2C(OH)$	**113**	89	72
109	–30	CO_2/CH_2N_2	CO_2Me	**114**	65	73
110	0	Ph_2CO	$Ph_2C(OH$	**115**	89	72

[a] Mixture of diastereoisomers

4.2 Effect of Substituents on the Aryl Ring

Relatively few lithiation reactions of ring-substituted ω-(acylamino)alkylbenzenes have been reported, but the ones reported do show some interesting characteristics. For example, all three types of 1-(2-(acylamino)ethyl)-4-methoxybenzenes **116–118** on lithiation with *n*-BuLi at 0 °C in THF give good yields of products substituted on the ring *ortho* to the DMG-containing substituent (Table 9),[74,75] in contrast to the α-substitution products obtained on lithiation with *t*-BuLi of the corresponding substrates lacking the methoxy substituent (Table 8).[21a,72]

Table 9 Substitution of *N*-Acyl-(ω-phenylalkyl)amines **116–118**



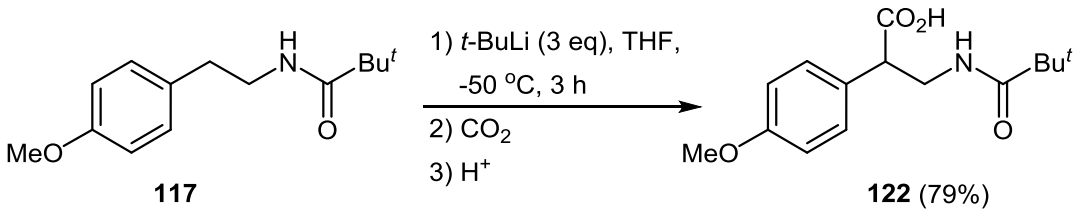
116, R = NMe_2
117, R = Bu^t
118, R = OBu^t

119, R = NMe_2
120, R = Bu^t
121, R = OBu^t

116–118	Electrophile	E	Product	Yield (%)	Ref
116	PhCHO	PhCH(OH)	**119**	82	**Error! Bookmark not defined.**74
116	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$)	**119**	80	74
116	4-$MeOC_6H_4COMe$	4-$MeOC_6H_4C(OH)Me$	**119**	82	74
116	Ph_2CO	$Ph_2C(OH)$	**119**	85	74
116	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**119**	77	74
116	EtI	Et	**119**	86	74
116	Me_2NCHO	CHO	**119**	90	74
117	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$)	**120**	90	**Error! Bookmark not defined.**75
117	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**120**	80	75
117	Ph_2CO	$Ph_2C(OH)$	**120**	92	75
117	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**120**	88	75
117	EtCOMe	EtC(OH)Me	**120**	95	75
117	Me_2NCHO	CHO	**120**	98	75
117	I_2	I	**120**	89	75
118	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$)	**121**	93	74
118	Ph_2CO	$Ph_2C(OH)$	**121**	89	74
118	Me_2NCHO	CHO	**121**	87	74
118	EtI	Et	**121**	90	74

The urea products **119** are generally accompanied by a small amount (0-17%) of a product resulting from lithiation at a *N*-methyl group or in the case of EtI as electrophile by some diethyl

product having an extra ethyl group on nitrogen.[74]**Error! Bookmark not defined.** The pivaloyl substrate **117** can be diverted to α-substituted product by use of *t*-BuLi at low temperature (Scheme 14).[21a,75]



Scheme 14 Lithiation of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide **117**

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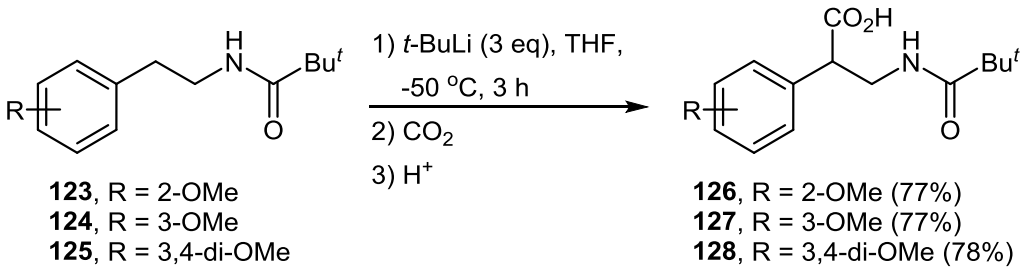
Indeed, the same conditions also lead to α-lithiation in the cases of *N*-(2-(2-methoxyphenyl)ethylpivalamide (**123**), *N*-(2-(3-methoxyphenyl)ethylpivalamide (**124**) and *N*-(2-(3,4-dimethoxyphenyl)ethylpivalamide (**125**) (Scheme 15).[21]



Scheme 15 Lithiation of substituted *N*-phenethylpivalamides **17**[17]

However, in the case of *N*-(2-(3-methoxyphenyl)ethyl)pivalamide (**124**) it has been shown that it can be controlled to give three different types of product **127**, **129** or**-130**, depending on the type of lithium reagent used and the reaction temperature (Figure 9).[21]

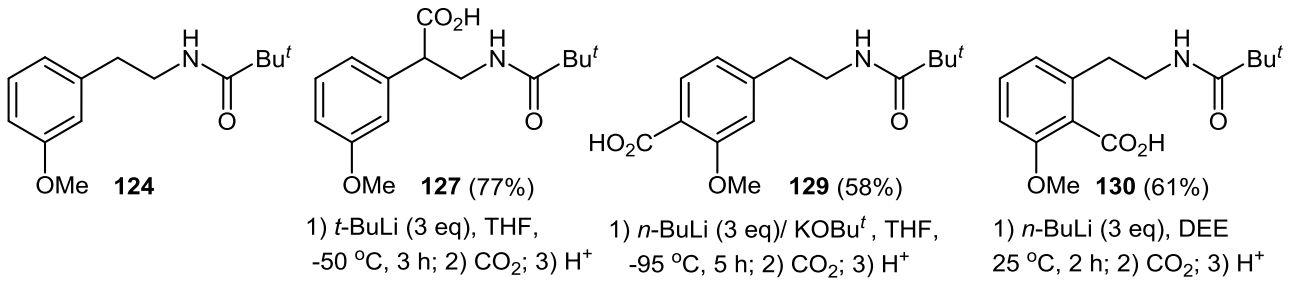
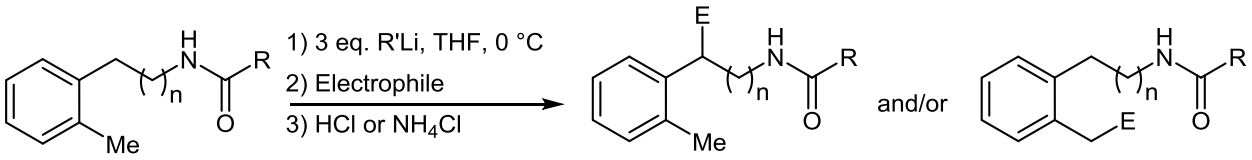


Figure 9 Products of the lithiation of **124** under various conditions[21]

The situation with 2-methylphenyl derivatives is also interesting. With two methylene groups between the DMG and the aryl ring, the urea and pivalamide are lithiated cleanly in the α-position, whereas the carbamate is lithiated cleanly on the methyl group (lateral lithiation)[73,76] (Table 10). For

the corresponding compounds with three or four methylene groups between the DMG and the aryl ring, only the carbamates have been reported. For *tert*-butyl *N*-(3-(2-methylphenyl)propylcarbamate (**134**), the major product results from lateral lithiation, but there is a small proportion of product from α-lithiation, whereas for the compound with the longer spacer group, only products derived from lateral lithiation are observed, albeit in quite modest yields (Table 10).[73]

Table 10 Substitution of *N*-Acyl-(ω-(2-methylphenyl)alkyl)amines **131–135**



131, n = 1, R = NMe_2
132, n = 1, R = Bu^t
133, n = 1, R = OBu^t
134, n = 2, R = OBu^t
135, n = 3, R = OBu^t

136, n = 1, R = NMe_2
137, n = 1, R = Bu^t
138, n = 2, R = OBu^t

139, n = 1, R = OBu^t
140, n = 2, R = OBu^t
141, n = 3, R = OBu^t

131–135	R'Li, Conditions	Electrophile	E	Product	Yield (%)	Ref
131	*n*-BuLi, THF, 0 °C	PhCHO	PhCH(OH)	**136**	82	**Error! Bookmark not defined.** 76
131	*n*-BuLi, THF, 0 °C	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**136**	78	76
131	*n*-BuLi, THF, 0 °C	4-$MeOC_6H_4COMe$	4-$MeOC_6H_4C(OH)Me$	**136**	82	76
131	*n*-BuLi, THF, 0 °C	Ph_2CO	$Ph_2C(OH)$	**136**	93	76
131	*n*-BuLi, THF, 0 °C	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	**136**	90	76
131	*n*-BuLi, THF, 0 °C	Me_2NCHO	CHO	**136**	84	76
132	*n*-BuLi, THF, 0 °C	Ph_2CO	$Ph_2C(OH)$	**137**	86	76
133	*n*-BuLi, THF, 0 °C	Ph_2CO	$Ph_2C(OH)$	**139**	13	76
133	*t*-BuLi, THF, –60 °C	Ph_2CO	$Ph_2C(OH)$	**139**	88	76
133	*t*-BuLi, THF, –30 °C	MeI	Me	**139**	80	73
133	*t*-BuLi, THF, –30 °C	CO_2/CH_2N_2	CO_2Me	**139**	67	73
134	*t*-BuLi, THF, –30 °C	MeI	Me	**138 + 140**	16 + 66	73
134	*t*-BuLi, THF, –30 °C	CO_2/CH_2N_2	CO_2Me	**138 + 140**	11 + 45	73
135	*t*-BuLi, THF, –25 °C	MeI	Me	**141**	<40	73
135	*t*-BuLi, THF, –25 °C	CO_2/CH_2N_2	CO_2Me	**141**	<40	73

5. Conclusions

This review of lithiation of aromatic compounds containing one of three types of DMG, namely dimethylaminocarbonylamino (abbreviated to urea), *tert*-butylcarbonylamino (abbreviated to pivalamide) and *tert*-butoxycarbonylamino (abbreviated to carbamate), has revealed several factors that influence how readily and at what location(s) lithiation occurs. The basicity of the lithiating agent (LICKOR > RLi + TMEDA > *tert*-BuLi > *sec*-BuLi > *n*-BuLi) is one significant factor, with the most

basic of lithiating agents bringing about removal of the most acidic protons, irrespective of the DMG, while the least basic reagents are most likely to be influenced by the DMG in terms of both ease and selectivity of proton removal.

Where the available evidence reveals significant differences between the three types of DMG, it suggests that ease of deprotonation decreases in the order urea > pivalamide > carbamate, which correlates with the nucleophilicity of the carbonyl oxygen atoms according to the carbonyl stretching frequencies. However, where the complex of the organolithium with the DMG is stronger, the influence of the DMG on selectivity is less, since the RLi-DMG complex is more basic.

Substituents on the aromatic ring influence the regioselectivity of deprotonation. Compounds with electron-donating substituents such as alkyl or methoxy groups at the 4-position tend to behave like the unsubstituted analogues, while electron-withdrawing substituents in the 4-position of the aromatic ring tend to enhance the reactivity of the 2-position towards deprotonation, presumably by enhancing the acidity of the relevant protons. Many substituents in the 3-position also enhance reactivity at the 2-position, while such substituents at the 2-position may enhance the reactivity at the 6-position. However, 2-methyl or 2-ethyl derivatives are often more readily deprotonated at the benzylic position of the 2-alkyl group (lateral lithiation), particularly when the DMG is close to the aromatic ring.

Insertion of methylene groups between the DMG and the aromatic ring diminishes the likelihood of *ortho*-lithiation and increases the likelihood of α-lithiation. A similar trend is seen for the urea and pivalamide 2-methylphenyl derivatives as the DMG is moved further from the ring, with a shift from lateral lithiation to α-lithiation as the number of intervening methylene groups is increased, but the carbamate consistently favors α-lithiation for up to four methylene groups.

Some of the results of all of these factors are manifested in the primary lithiation selectivities recorded in Figure 10 (U represents urea, P pivalamide and C carbamate).

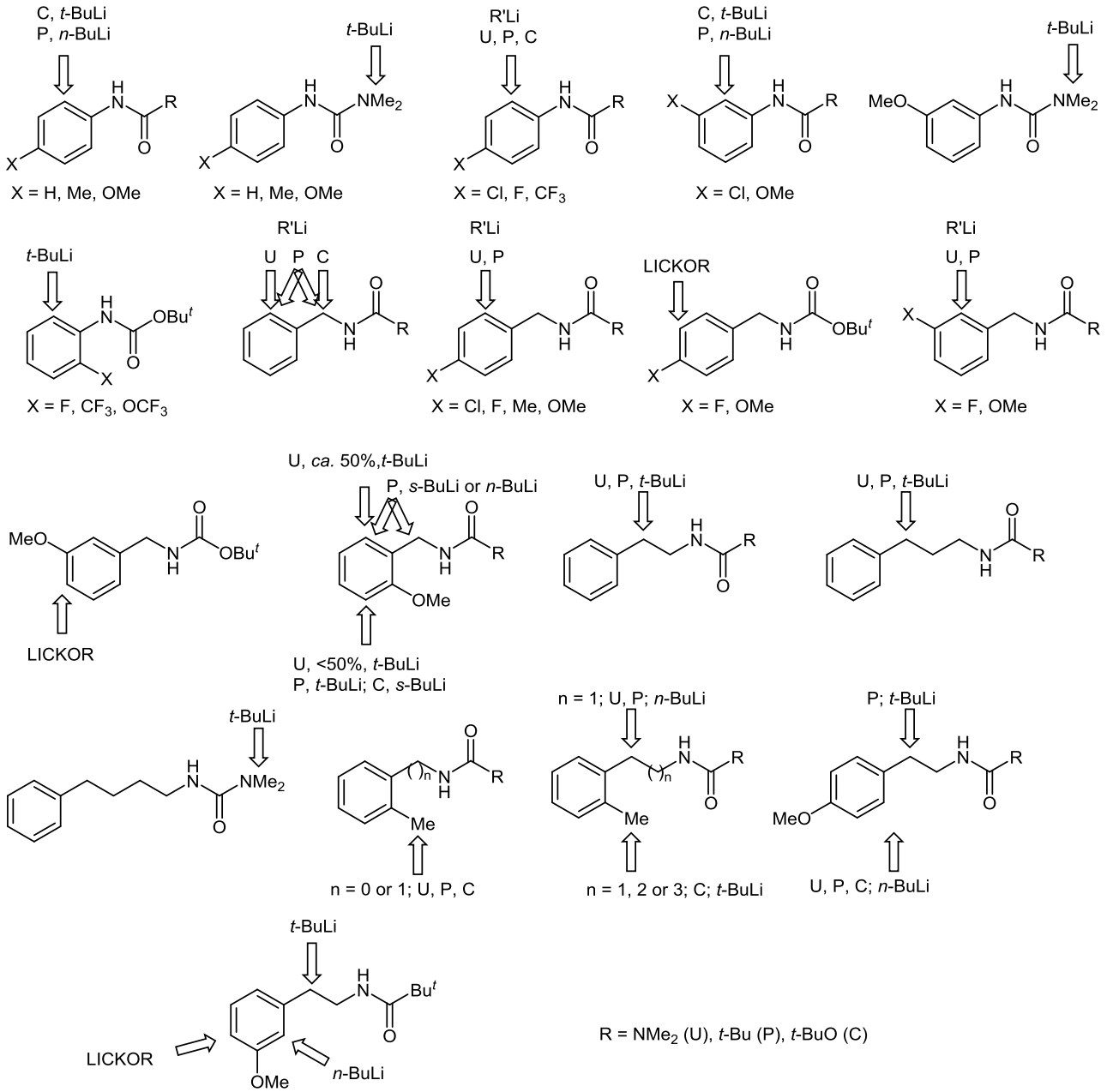


Figure 10 Primary lithiation sites of compounds relevant to this review

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Biographical Sketches

Keith Smith received his PhD degree from Manchester University in 1971 (Professor A. Pelter). Royal Society European Exchange Fellow, ETH Zürich (1971–1972; Professor A. Eschenmoser, chlorophyll derivatives). Lecturer, Swansea University (1972–1980). Visiting Research Associate, Purdue University West Lafayette IN USA (1978–1979; Professor H. C. Brown). Senior Lecturer and Reader Swansea University (1980-1988) and promoted to personal chair (1988). Head of Chemistry Department (1990-1993; 2001–2007). Professor of Organic Chemistry, Cardiff University (2007–2013). Managing Director of CatCelt Ltd since 2006. He is currently an Emeritus Professor, since 2013, at Cardiff University, UK, and a Fellow and Council member of the Learned Society of Wales.

Mohammed B. Alshammari received his B.Sc. and M.Sc. degrees in Chemistry from King Saud University, Saudi Arabia. He received his Ph.D. degree from Cardiff University, UK, in 2013 under the supervision of Professor Keith Smith. Currently, he is working as Assistant Professor of Organic Chemistry, since 2013, at Prince Sattam bin Abdulaziz University, Saudi Arabia. Also, he is acting as the Dean for the College of Computer Engineering and Sciences at Prince Sattam bin Abdulaziz University.

Gamal A. El-Hiti received his BSc and MSc degrees from Tanta University, Egypt. He received his PhD degree from Tanta University in 1996 including two years at Swansea University, UK (Professor K. Smith). Lecturer (1996), Associate Professor (2001) and Professor (2006–2013), Tanta University (was on sabbatical leave to the UK; 1993–1995, 1998–1999 and 2002–2013). Academic Visitor, Swansea University (1998–1999). Lecturer and Research Officer, Swansea University (2002–2007). Research Fellow, Research Associate and Teacher in Organic Chemistry, Cardiff University (2007–2013). Technical Director of CatCelt Limited since 2006. He is currently a Professor, since 2013, at King Saud University, Saudi Arabia.

Graphical Abstract

Synthesis
Synthesis **2018**, *50*, xxx–xxx
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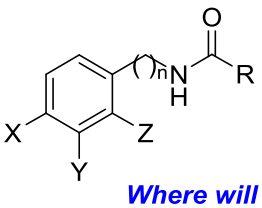
Unravelling Factors Affecting Directed Lithiation of Acylaminoaromatics

Review

xxx



R = NMe_2, Bu^t or OBu^t
n = 0-3
X, Y, Z = H, Me, OMe, Cl, F or CF_3

Where will lithiation occur predominantly?